A Common Disease with Uncommon Treatment

Background Data for a 12-country survey of guidelines for the use of biologics in the treatment of rheumatoid arthritis

June 2012

<table>
<thead>
<tr>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
</tr>
<tr>
<td>England</td>
</tr>
<tr>
<td>France</td>
</tr>
<tr>
<td>Germany</td>
</tr>
<tr>
<td>Greece</td>
</tr>
<tr>
<td>Ireland</td>
</tr>
<tr>
<td>Italy</td>
</tr>
<tr>
<td>Netherlands</td>
</tr>
<tr>
<td>Poland</td>
</tr>
<tr>
<td>Slovenia</td>
</tr>
<tr>
<td>Spain</td>
</tr>
<tr>
<td>Sweden</td>
</tr>
</tbody>
</table>

Note
This document comprises largely unedited papers produced in the development of the report on European guidelines. The material has not undergone secondary checks or editing, and readers are advised to refer to available primary sources before citing or using any of the data provided. The data was mostly gathered between January and March 2012. Interview data has been anonymised.

Funding
This research was commissioned and funded by Merck Sharp & Dohme Ltd. MSD reviewed the report prior to publication in line with the ABPI Code of Practice. The authors had full editorial control of the content.

Policy Analysis Centre Limited
Belgium

Belgian health system
The basics of the Belgian health system (FPS Social Security, Jan 2011):

Belgian health system coverage:
The entire Belgian population is entitled to medical care, with a few exceptions. But a number of conditions have to be met to obtain health insurance benefits:

- All the persons entitled to the compulsory insurance for medical care must affiliate or register with a health insurance fund (either a mutual insurance fund or a regional service of the Auxiliary fund for sickness and invalidity insurance)
- Contributions have to be paid up to date and equal a minimum amount
- In principle, you do not have to achieve a six-month qualifying period before medical care can be reimbursed by the insurance for medical care

Types of medical care:
Medical care covers preventative and curative care. It is divided in 27 different categories, most importantly:

- Ordinary care (GP, specialized practitioners, physiotherapists, etc.)
- Dental care
- Deliveries
- Dispensation of pharmaceutical products
- Hospital care
- Care required for revalidation

Reimbursement
All the medical dispensations that can be (partly or completely) reimbursed are listed in a so-called nomenclature of medical dispensations. The nomenclature is a positive list which does not only mention the relative value of dispensations, but also specific rules of application, requirements about the competence of care providers, etc. There is also a list with pharmaceutical specialties that are reimbursed.

Full amount of medical treatment is paid by the patient and partly reimbursed by the insurance institution.
The insurance refund varies primarily with the nature of the treatment, the status of the insured and the care provider’s capacity. Often, you have to pay a sum yourself, called personal fee or patient fee, which generally accounts for 25%. Higher reimbursement is obtained if:

- Eligible for granted social benefit (RVV/BIM status)
- On the basis of a personal situation and an income screening performed by the insurance institutions (RVV/BIM status)
- On the basis of an income screening performed by the insurance institutions (OMNIO status)

Pharmaceutical costs. If you have a prescription of an acknowledged practitioner, you do not have to pay the full amount at the chemist’s, but the reimbursement rates are applied directly (third payer’s scheme). Reimbursable pharmaceutical specialties are
divided into five reimbursement categories. For the calculation, the following maximum patient fee amounts are taken into account:

**Table 1 Belgium reimbursement categories and maximum prices to be paid by patients, modified from (Österreichisches Bundesinstitut für Gesundheitswesen, ÖBIG Health Economics, 2006)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Type of pharmaceutical</th>
<th>Examples</th>
<th>Patient fee for the preferential category (outpatients)</th>
<th>Patient fee for ordinary beneficiaries (outpatients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Life saving pharmaceuticals</td>
<td>Cancer treatment, HIV/AIDS, diabetes</td>
<td>No patient fee</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Important therapeutic pharmaceuticals</td>
<td>Antibiotics, cardiovascular disease treatment</td>
<td>15% Max 7.30€ (large packages max 9.00€)</td>
<td>25% Max 11.00€ (large packages max 13.70€)</td>
</tr>
<tr>
<td>C</td>
<td>Pharmaceuticals for symptomatic treatment of chronic diseases</td>
<td>Combined painkillers, vaccines</td>
<td>50% Max 9.00€</td>
<td>Max 13.00€</td>
</tr>
<tr>
<td>Cs</td>
<td></td>
<td>Antihistamines, flu vaccines</td>
<td>60% - unlimited patient fee</td>
<td></td>
</tr>
<tr>
<td>Cx</td>
<td></td>
<td>Antipasmodics, migraine treatment, oral contraceptives</td>
<td>80% - unlimited patient fee</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Non-reimbursed pharmaceuticals</td>
<td>Sedatives and sleeping pills</td>
<td>100% - no reimbursement and unlimited</td>
<td></td>
</tr>
</tbody>
</table>

In case of hospitalization in a general hospital, a lump sum of 0.62 € per care day is invoiced for the reimbursable pharmaceutical specialties.

**Reimbursement of RA biologics. List of medicines** (inami.fgov.be, 2012) (if administered at hospital or ambulatory care no payment for the patient. Usually home administration is only initial conditioning for treatment, in the case of home administration, only B-category fees are paid). Biologics are classified as:

- **Group B-255.** Analgesic and anti-inflammatory medicines for internal use. DMARD from the following group: selective immunosuppressants. Arava (leflunomide), Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), Leflunomide Apotex/Demac/Sandoz (leflunomide), Mabthera (rituximab), Simponi (golimumab), Ocrevus (abatacept)

- **Group B-253.** Analgesic and anti-inflammatory medicines for internal use. DMARD from the following group: Anti-TNF. Remicade (infliximab): administered at hospital so no payment.
Group B-305. Analgesic and anti-inflammatory medicines for internal use. DMARD from the following group: interleukin inhibitor. RoActemra (Tocilizumab).

Group B-230. For osteoporosis only. Prolia (denosumab)

**Table 2 Biologics DMARD treatments and their reimbursement category (created from diverse sources)**

<table>
<thead>
<tr>
<th>molecule</th>
<th>Brand</th>
<th>Target</th>
<th>Reimbursement group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>Enbrel /</td>
<td>TNFα</td>
<td>B-255. Payment only if admin at home</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>TNFα</td>
<td>B-253. Admin at hospital/ambulatory care</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td>TNFα</td>
<td>B-255. Payment only if admin at home</td>
</tr>
<tr>
<td>Anankira</td>
<td>Kineret</td>
<td>IL-1R antagonist</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>Mabthera</td>
<td>B-cells anti CD-20</td>
<td>A-28, for RA : B-255. Admin at hospital/ambulatory care</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Oencia</td>
<td>T-cells</td>
<td>B-255. Admin at hospital/ambulatory care</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>RoActemra</td>
<td>IL-6</td>
<td>B-305. Admin at hospital/ambulatory care</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Cimzia</td>
<td>TNFα</td>
<td>B-255. Payment only if admin at home</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Simponi</td>
<td>TNFα</td>
<td>B-255. Payment only if admin at home</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Prolia</td>
<td>Anti-RANKL</td>
<td>B-230. Only for osteoporosis</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td></td>
<td>B-cells anti CD-20</td>
<td></td>
</tr>
</tbody>
</table>

**A solution to high patient fees: Maximum billing**

The amount that remains to be paid after the reimbursement by the mutual insurance funds (i.e. the personal share or patient fee) can still be high in case of a long-term or serious illness. Maximum billing provides a solution to this problem. It gives the beneficiary and his family the guarantee that only a fixed amount (this amount is determined on the basis of the family's incomes) of the medical costs has to be paid. As soon as the amount of the personal share of a beneficiary or a member of his family for certain types of medical care reaches a fixed ceiling, the costs for further care are entirely reimbursed by the mutual insurance funds.

**Treatment and reimbursement guidelines** (Österreichisches Bundesinstitut für Gesundheitswesen, ÖBIG Health Economics, 2006)
Since 1974, the Belgian Center for Pharmacotherapeutic Information (Centre Belge d’Information Pharmacothérapeutique, CBIP/ BCFI, \texttt{http://www.cbip.be/}) has been providing systematic, independent information on pharmaceuticals in the form of:

- The \textit{Folia Pharmacotherapeutica}, a monthly journal containing information on pharmaceuticals
- Information cards (Fiches) providing information on recently authorized active ingredients
- A yearly updated, commented list of pharmaceuticals available on the market and their prices (Répertoire Commenté des Médicaments). Published by BCNI since 1977, the list provides essential information about pharmaceutical specialties, and to help physicians in choosing the most suitable pharmaceutical
- The transparency-cards (fiches de transparence), which provide comparisons of different treatment alternatives for a number of diseases. These transparency-cards aim to help physicians and pharmacists in weighing the pros and cons of different treatment options

The guidelines are continuously updated with new information on new or existing drugs being published in the \textit{Folia Pharmacotherapeutica}.

Several reports in the \textit{folia pharmacotherapeutica} tackle RA treatments, as will be described beneath. No transparency cards were found.

\textbf{Pharmaceutical system and pricing} (Österreichisches Bundesinstitut für Gesundheitswesen, ÖBIG Health Economics, 2006)

In Belgium there is a formalized decision-making process where economic evaluation and the issue of cost-effectiveness play an important role (European Health Economics and i3 Innovus, 2009). Control is exercised over the prices of all pharmaceuticals, in the form of either price fixing or price notification, depending on the type of pharmaceutical. In the case of pharmaceuticals seeking reimbursement, prices are fixed. Institution in charge of pricing: Public Service for Economy, SMEs, self-employed and Energy, based on advice of the Medicines Pricing Commission (Commission des Prix des Spécialités Pharmaceutiques, CPSP). The application dossier for pricing must contain the following documentation:

- A description of the product
- A copy of the market authorization
- Company financial records for the past three years
- A proposed price and a justification for this price
- A price comparison with other EU Member States
- A market and competition research report

As part of the new reimbursement system, which was introduced in 2002, pharmaco-economic analysis and budgetary consequences are included in the decision making process. For pharmaceuticals with a proven improvement in therapeutic benefit (therapeutic value class 1 (cf. 3.3.1.2)) manufacturers must provide pharmaco-economic information for decision on the reimbursement price and for re-evaluation. Official guidelines state that the manufacturer should demonstrate total costs, effectiveness, cost-benefit ratio and target population. Pharmaco-economic requirements are not mandatory for other pharmaceuticals.
Prescription of biological DMARDs (andar, 2011)
The health authorities have established medical criteria to be eligible to receive biological treatment for RA. Rheumatologists are the only physicians allowed to prescribe biologic DMARDs to RA patients. The specialist has to ensure the patient fulfills the criteria if they want to be reimbursed. Once the specialist has identified the patient as eligible he has to make a petition to the medical council from the insurance fund, who will grant (or not) their approval. In short, to receive reimbursement for biological treatment, a set of criteria has to be fulfilled and the medical council has to grant approval.

1. Belgian Demographics and stakeholders
General prevalence and access to specialists
Belgium has an adult population (>19 years of age) of 8.1 million. With a prevalence of 0.48% of RA in the population, the approximate number of RA patients (>19 years of age) is 39,209 (European Health Economics and i3 Innovus, 2009). The age structure of the disease is as follows: 10% of patients are between 20 and 44, 42% are between 45 and 64, and the remaining 48% if over 64.

The estimated number of patients per rheumatologist is 150 (calculated with data prior to 2007). Nevertheless, the number of rheumatologists does not seem to influence the use of biologics in a country (European Health Economics and i3 Innovus, 2009).

Table 3 Prevalence of RA in Belgium and number of patients. Inferred from (European Health Economics and i3 Innovus, 2009). The data from prevalence and number of patients with RA has to be interpreted carefully since different studies show very different results.

<table>
<thead>
<tr>
<th>Population &gt;19</th>
<th>8.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients &gt;19</td>
<td>39,209</td>
</tr>
<tr>
<td>Prevalence &gt;19 (%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Aged 20-44 (%)</td>
<td>10</td>
</tr>
<tr>
<td>Aged 45-64 (%)</td>
<td>42</td>
</tr>
<tr>
<td>Aged &gt;64 (%)</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 4 Total number of rheumatologists and number of patients per rheumatologist from (European Health Economics and i3 Innovus, 2009).

<table>
<thead>
<tr>
<th>Adult population</th>
<th>8.1m (19+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number rheumatologists</td>
<td>Approx. 260 (190 stated by interviewee)</td>
</tr>
<tr>
<td>Adult pop/rheumatologists</td>
<td>31,600</td>
</tr>
<tr>
<td>Patient/rheumatologists</td>
<td>150</td>
</tr>
<tr>
<td>Number Patients &gt;19</td>
<td>39,209</td>
</tr>
<tr>
<td>Prevalence % &gt;19</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Use of biologics for the treatment of RA

With approximately 8000 patients treated with RA, Belgium has the largest market for biologics of all small Western European countries compared in the report (Austria, Belgium, Greece, Ireland, Luxembourg, Netherlands, Portugal, Switzerland) (European Health Economics and i3 Innovus, 2009). However, in percentage of RA patients treated with biologics the difference is not so clear, Ireland is very close to the figures of Belgium.
### Table 5 Uptake from biologics. Inferred from (European Health Economics and i3 Innovus, 2009)

<table>
<thead>
<tr>
<th>Sales biologics/100000 pop (€, m)</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number patients treated with biologics (2008)</td>
<td>8,000 (20%)</td>
</tr>
</tbody>
</table>

**Costs**

The total costs of RA for Belgium in 2008 have been estimated to be 618,317,047 € (European Health Economics and i3 Innovus, 2009). Westhovens et al calculated the total direct cost per patient to be 8,240 € (Westhovens, et al., 2005). The report by European Health Economics and i3 innovus revised these figures and reported 15,770 € annual cost per patient (including direct costs –excl. biologics- of 3,959€, informal care costs of 4,606€ and indirect costs of 4,983), the same report estimated the costs of biologics per patient to be 2,222€ (European Health Economics and i3 Innovus, 2009).

### Table 6 Total costs of RA in Belgium and annual costs per patient in €. From diverse sources

<table>
<thead>
<tr>
<th>From (OECD, 2011). Data for 2009</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Health expenditure per capita ($USD)</td>
<td>3,946</td>
</tr>
<tr>
<td>Total health expenditure (% GDP)</td>
<td>10.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From (European Health Economics and i3 Innovus, 2009), €</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost of RA (2008)</td>
<td>618,317,047</td>
</tr>
<tr>
<td>Total costs /patient</td>
<td>15,770</td>
</tr>
<tr>
<td>Direct costs (excl biologics)</td>
<td>3,959</td>
</tr>
<tr>
<td>Biologics cost/ patient</td>
<td>2,222</td>
</tr>
<tr>
<td>Informal care</td>
<td>4,606</td>
</tr>
<tr>
<td>Indirect cost</td>
<td>4,983</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From (Westhovens, et al., 2005), €</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual direct costs/patient</td>
<td>8,240</td>
</tr>
</tbody>
</table>

**List of RA related associations**

- Belgium Royal association of Rheumatology (SRBR / KBVR) [Error! Hyperlink reference not valid.](http://example.com)
- CLAIR (Confédération pour la Lutte contre les Affections Inflammatoires Rhumatismales) Confederation for the fight against inflammatory rheumatic conditions. [www.claire.be](http://www.claire.be)
2. Treatment guidelines affecting patients’ access to biologics for RA

There are active guidelines regulating the reimbursement of biologic therapies in Belgium (could be better referred to as ‘reimbursement criteria’). The relevant document is found in the Folia Pharmacotherapeutica 38 “Traitement de fond de la Polyarthrite Rhumatoïde” (‘DMARD treatment for RA’) (cbip.be). The report was published in September 2011, prior to that there was a working document published in March 2005: Folia Pharmacotherapeutica - March 2005 "Traitement de la polyarthrite rhumatoïde : état de la question" (‘treatment of RA: state of the question’).

No treatment guidelines for RA exist in Belgium. The above mentioned guidelines only refer to the reimbursement conditions, which have to be applied if the patient wants the costs of biologics to be covered by social insurance fund (INAMI). Therefore, these conditions only affects poor patients’ access to biologics since they will only reimburse them under certain conditions, should the patient be rich and wish to pay the full cost of treatment with biologics, the doctor can decide to prescribe biologic DMARD treatment at any time (information summarized from interview).

Reimbursement criteria revision. The revision process is constant with any new data on pharmaceuticals published in their cbip website, and on Folia Pharmacotherapeutica. There is no specific date published for the review of the RA reimbursement guidelines; however, since they have been published in the past year it should not be expected to have a new report published in the next year.

Additional recommendations. Other recommendations, relating to specific drugs, that were published in the Folia Pharmacotherapeutica are described beneath.

International inspiration. The reimbursement criteria constantly refer to the UK NICE guidelines and the EULAR guidelines. Some of the points of Belgium’s paper seem to be heavily inspired by both NICE and EULAR guidelines, and where these differ they recommend to consider the specific reimbursement conditions set by INAMI.

Reimbursement. Drugs are reimbursed by the social insurance fund, given that they have approved the petition to treat the specific RA patient from the specialist rheumatologist. Patients still have to pay a percentage of the treatment (unless it is administered ambulatory or at the hospital) (see tables 1 and 2). Specific parts of the population are entitled to an increased exemption from out of pocket payment as previously described. The INAMI takes action in the reimbursement of most DMARD RA treatments (given that its guidelines are followed and the patients are eligible).

Within country differences. Differences within the country have not been found, it may be that different doctors apply different strategies, although the fact that they have to get approval by the insurance fund is likely to reduce the variations.
Specifications of the 2011 guideline (CBIP, 2011)
This guideline (or reimbursement criteria) considers early treatment with DMARDs as the most important part of RA drug treatment. It recommends early and intensive treatment to reach the goal of "obtain remission or low disease activity at 3-6 first months". However, the exact timing for early treatment is not specified. Referral to the specialist is recommended immediately.

First treatment choice is methotrexate (MTX) at high dosage as monotherapy. For early stage treatment of active RA forms (no specification on what conditions apply to account as active form of RA) combination of various classical DMARDs, with or without glucocorticoids (GC), may be necessary. For patients that are intolerant to MTX other synthetic DMARDs, such as Leflunomide and sulfasalazine, can be used. In January 2010 the Sels d'or was denied market access in Belgium.

Treatment revision is recommended every 2 months, with adaptation to achieve the treatment goal previously mentioned. Revision of treatment with biologics is advised after 3-6 months.

The first treatment recommended for severe forms of RA is the combination of synthetic DMARDs with or without GC. Biologic DMARDs are not accepted as first treatment, the guideline specifies that "there is insufficient scientific prove that the use of biologics (such as anti-TNF α) in combination with synthetic DMARDs at this early stage is more beneficial than the use of synthetic DMARDs + GC".

Conditions to be eligible for biologic DMARD treatment. "Considering the high price of biologic DMARDs and their reimbursement conditions, the use of biological DMARD is reserved to patients with active and advanced forms of RA, having had insufficient response to two alternative classical DMARD treatment (one of them MTX)". The minimum total time on treatment before being eligible for biologics is 6 months.

In the treatment of patients suffering from severe RA, the guidelines state that they cannot decide between NICE and EULAR recommendations, therefore doctors are advised to consider the reimbursement policies from INAMI when making a decision. Should it be the third treatment on a patient with severe RA, the introduction of anti-TNFα biologic DMARDs (in combination with MTX) is allowed. Other biologic compounds, such as abatacept or tocilizumab (having the same reimbursement conditions as anti-TNFαs), can be used. If the treatment with the first biologic is not successful another anti-TNFα or alternative biologic DMARD can be used. The use of rituximab is allowed if the disease progression is not stopped by at least one treatment round with a biologic DMARD compound.

Treatment termination. "Progressive and slow treatment termination (is recommended) only if long and stable remission is observed (>6 months) and after consultation with rheumatologist and patient".

Specific Guidelines on biologics for RA treatment in Belgium (previous to 2011 general guideline; all from cbip.be searches) (CBIP, 2012)
2005 Mar First guidelines on RA, they only offer a proposition of the problem

2008 Feb They refer to the publication of a paper (Ann Intern Med 2007; 146: 406-15) that shows how early treatment of RA can control the disease, whether with monotherapy or combined therapy. Considering the adverse reactions and the high costs, it seems reasonable, after consultation with a rheumatologist, to start treating patients with DMARDs in monotherapy (often MTX) and adapt the treatment individually and progressively. As another paper shows (Brit Med J 2007; 335: 56-6) it
may be beneficial to put patients with more severe RA prognosis on combined therapy of two synthetic DMARDs

2009 Nov Tocilizumab (RoActemra) is a new immunosuppressor to be used in hospitals, in combination with MTX, against RA in patients that have an active form of moderate to severe RA, and who are irresponsive or intolerant to other DMARD and TNF inhibitors.

2010 Jan Pharmacovigilance. FDA concern of cancer and psoriasis risk with TNF inhibitors (concerning adalimumba, etanercept and infliximab)

2010 May Golimumab (Simponi) is a new TNF inhibitor to treat moderate to severe forms of RA in case of irresponsiveness to other antirheumatic drugs. It is administered once a month in a subcutaneous injection. There is no evidence for superiority over other immunosuppressants.

2010 Jun Certolizumab (Cimzia) is a new TNF inhibitor to treat moderate to severe forms of RA, in association to MTX or as monotherapy, in case of irresponsiveness to a synthetic DMARD treatment. It is administered every two weeks in a subcutaneous injection. There is no evidence for superiority over other immunosuppressants.

3. Differences with other countries
If you consider their 2008 recommendation, you can observe that the early use of synthetic DMARDs combination therapy in treating RA patients is widely spread in Belgium, with very positive results. Together with The Netherlands, they are the only European country that applies such early DMARD treatment (from interview).

Comparison with France. Even though Belgium has a higher percentage of patients treated with biologic DMARDs (20% against 13% in France), French guidelines (before their cancellation in 2011) allows patients to access biologic treatment after only one alternative synthetic DMARD treatment, and after a minimum time of 3 months.

Considering the common and widespread practice of early treatment with combination of synthetic DMARDs, RA patients in Belgium are not disadvantaged in the access to biologics since by the time their rheumatologists consider it appropriate to treat them with biologic DMARDs they would have most likely already been through two alternative synthetic DMARD treatment (from interview).

Belgium’s reimbursement guidelines for biological DMARDs are inspired by NICE guidelines and they have many similarities. However, NICE requires patients to be on two alternative DMARD treatment for 6 month each (if no adverse reactions to treatments are experienced) whereas in Belgium the minimum previous treatment time is 6 months in total.

4. Extracts from an interview with a rheumatologist
"I don’t think our patients are suffering from unnecessary delays in access to the drugs (biologic DMARDs) when they need them compared to other countries”

Synthesis of main points:

- There are no treatment guidelines, just reimbursement criteria, which affect
the access to biologic DMARDs as these are expensive drugs.

- Belgium (together with The Netherlands) has an established tradition of using synthetic DMARDs therapy often in combination therapy, as first treatment for RA patients. Combination therapies appear less frequently used in other countries.
- Rheumatologists in Belgium do not observe their reimbursement conditions as limiting since by the time they consider using biologic DMARDs patients will have most likely already received 2 synthetic DMARDs before.
- There is no specific need for RA treatment guidelines in Belgium. The community uses EULAR and ACR guidelines. Rheumatology specialists are a small community that knows each other; they have a shared and established treatment protocol that the majority follows. Prescription of biologic DMARDs is restricted to Rheumatologists.

**Specifics on the guidelines**

*we (rheumatologists in Belgium) agree with the setting*. The interviewee explained that there are no guidelines as issued by NICE or EULAR, they only have reimbursement criteria, set by the government and the social security offices, based on what companies propose and experts’ opinion. Prescription for RA is limited to rheumatologists, which ensures there is a certain experience in diagnoses and in picking the right moment when or not to start biologics. Rheumatologists do not have to adhere to the reimbursement criteria for all patients, only if the patients want their treatment to be reimbursed.

The interviewee expressed that the approval process for reimbursement from the ‘medecin conseil’ is a difficult exercise. Previously, the reimbursement criteria for biologic DMARDs was based on level of eroding disease, now it has been changed to DAS score, in accordance with EULAR guidelines. The final decision is technical, with budget considerations and that takes into account other factors in addition to the scientific criteria.

**On treatment strategy**

*we (rheumatologists in Belgium) –and in The Netherlands tend to use combination DMARD therapies fairly early on, which have been established for a long time in Belgium, but have not been followed in other EU countries* “This also means that the patients that you are considering for biologics will have seen 2 DMARDs by the time you want to use biologic DMARDs”

The interviewee explained his views on the reasons why other European countries have not adopted combination therapy, the most important being the fact that it is a difficult strategy, hard to explain to the patient and with difficult compliance. The rationale followed by rheumatologists in Belgium for the early use of DMARD combination therapy is to achieve early and quick remission of disease.

Regarding patient’s access to biologics in Belgium, the interviewee stated “I don’t think our patients are suffering from unnecessary delays in access to the drugs (biologic DMARDs) when they need them compared to other countries”.

12
On the need of guidelines in Belgium

“To do the guidelines you need the adequate audience, nobody is really waiting for the Belgium treatment guidelines”. It was made clear that Belgium does not need independent national guidelines for the treatment of RA. It is a small community of rheumatologists that know each other well and communicate often on treatment strategies, if one tries a new protocol it is communicated to everybody. The specialists are there, and they would be able to create a set of guidelines, but it may not be worth spending time to try and improve the available guidelines from EULAR, NICE (UK) or HAS (FR).

5. Comments from stakeholders
Due to the fact that treatment guidelines as such do not exist, there are no specific comments from the stakeholders on them. Patient groups, some of the list presented above, are worried with the access of patients to adequate treatment being biologics or not.

François Dessy from the Belgium Association POLYARTHRITE, claims in an interview published in the andar website, that patients can only access biologic DMARD treatment if the reimbursement criteria is fulfilled (andar, 2011).

Patient associations have as goals to break the isolation of RA patients, to inform the patients on treatments and life-styles, to represent the patients by the authorities and to allow the social integration of patients by doing public awareness campaigns.

6. Summary
What guidelines affect the use of biologic therapies for the treatment of RA?

The reimbursement criteria published by the INAMI in the pholia pharmaceutica in September 2011. And the previous recommendations published in pholia pharmacotherapeutica.

How do these affect patients’ access to these therapies?

Patients who seek the reimbursement of biologic DMARDs are only allowed to access them after having had two synthetic DMARD treatments of at least 6 month duration (in total). Patients who are willing to fully cover the expenses of their treatment can access them before

How are the guidelines reviewed?

No specific review process has been found. Reimbursement conditions are set by the government and the social security offices, based on what companies propose and experts’ opinion. New information on pharmaceuticals that should be taken into account by physicians is published in their cibp.be website and in the pholia pharmacotherapeutica.

What comments have the guidelines provoked (from patients, clinicians, and other opinion leaders)?

The only clear statement that can be used is from the interview with Rik Lories where he states that there is not need for Belgian RA treatment guidelines, they
have a well established treatment protocol with early use of combination therapy of synthetic DMARD, and their patients are not disadvantaged compared to other EU countries in relation to the access to biologic treatment.

**Abreviations**

CBIP/BCFI: Belgian Centre for Pharmacotherapeutic Information (Centre Belge d'information Pharmacothérapeutic)
DMARD: Disease Modifying Arthritic Drug
EU: European Union
EULAR: European League Against Rheumatism
GC: Glucocorticoid
INAMI: National Institute for the insurance of disease-invalidity (Institut national d'assurance maladie-invalidité)
MTX: Methotrexate
NICE: National Institute for Health and Clinical Excellence
RA: Rheumatoid Arthritis
UK: United Kingdom

**References**


FPS Social Security, Jan 2011. *Social Security. Everything you have always wanted to know,* s.l.: s.n.


OECD, 2011. *OECD Health Data*, s.l.: OECD.


Pubmed, 2012. [Online]
[Accessed 16 02 2012].

Rheumatoid arthritis in adults: review of the guidelines in England

This paper is intended to provide material relating to health care in England for a comparative review of guidelines across several European countries on the use of biological therapies in the treatment of rheumatoid arthritis (RA) in adults.

The care pathway for adults with RA consists of four key elements:

1. early identification of the problem;
2. pharmacological management;
3. ongoing monitoring of the patient; and,
4. timing and referral for surgery.

Although ongoing monitoring and surgery are important aspects of the care pathway, they are not discussed in this paper. In addition other key aspects of care include good communication with and appropriate education of the patient, the use of a multi-disciplinary team, good symptom control, and the use of diet and complementary therapies where considered appropriate.

Early identification

It is important that recent-onset RA is identified as soon as possible and that the patient is referred for specialist opinion. Key to identification is to establish the existence of synovitis (inflammation of the membrane lining the inside of synovial joints which is revealed in pain, swelling, heat, loss of function and stiffness). Early recognition of RA is important as left untreated it can result in substantial damage to the joints which may otherwise be avoided. Thus, the NICE guidelines (NICE 2009) recommend,

Referral for specialist opinion [for] any person with suspected persistent synovitis of undetermined cause, [and] ... urgently if any of the following apply:

- The small joints of the hands or feet are affected
- More than one joint is affected;
- There has been a delay of 3 months or longer between onset of symptoms and seeking medical advice.

2.2 Pharmacological management

The key intervention for people with RA is the use of DMARDs (disease-modifying anti-rheumatic drugs). There is a consensus that DMARD therapy should be started as soon as possible. NICE reported that early introduction of drugs is beneficial in terms of joint
damage, function and quality of life (NCCCC 2009). However, the key questions are which DMARD to use, and whether one drug or a combination should be used.

A key distinction is made in the guidance between ‘conventional’ DMARDs and biological therapies. It is to the latter group that this paper is directed although an understanding of the general guidelines is helpful. The full NICE guidelines (NCCCC 2009) define biological drugs as,

*a type of DMARD which targets pro-inflammatory cytokines that are involved in joint destruction (particularly TNF-α and IL-1).*

All DMARDs can be helpful in slowing down the damaging component of the disease process although it is widely recognised that biologics can act more quickly and be more successful (NAO 2009).

### 3 Developing guidelines

Conventional DMARDs include six main drugs: methotrexate, sulphasalazine, hydroxychloroquine, leflunomide, ciclosporin and gold injections.

Biologic drugs include the five TNF-α inhibitors (also known as anti-TNF (tumour necrosis factor)): etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab.

Additional biological drugs that are licensed for use include: rituximab, a chimeric monoclonal antibody that depletes B-cells; abatacept, a selective T-cell co-stimulation modulator that blocks a key co-stimulatory signal required for T-cell activation; and tocilizumab which is a humanised monoclonal antibody that inhibits cytokine interleukin-6 (IL-6).

The optimal sequencing of DMARDs remains a source of debate; whether patients should be started on combinations of therapies or single DMARDs is also contentious. NICE decided this was an important area for detailed health-economic analysis in an attempt to determine which DMARD strategy was most cost effective (NCCCC 2009 p6). As the NICE guidelines point out, biological drugs are substantially more expensive than conventional DMARDs (p141); this is clearly why the distinction is so crucial.

NICE found there was evidence that methotrexate is at least as effective as other DMARD monotherapies (p126), and thus recommends that methotrexate is tried before anti-TNF therapies (biological drugs) are considered. A key recommendation from the NICE guidelines is that, in people with newly diagnosed active RA, a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) should be offered as a first-line treatment as soon as possible, ideally within three months of the onset of persistent symptoms (NCCCC 2009, p128). NICE thus excludes the possibility of using a biological therapy before treatment with methotrexate has been tried.
NICE also recommended that in people with newly diagnosed RA for whom combination DMARD therapy is not appropriate (for example due to co-morbidities) then DMARD monotherapy should be offered, with a greater emphasis placed on fast escalation to a clinically effective dose rather than on the choice of DMARD (NCCCC 2009, p128).

Finally, in people with recent-onset RA receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control had been achieved, NICE recommended the cautious reduction of drug doses to levels that still maintain disease control (NCCCC 2009, p128).

NICE’s recommendations with respect to the use of biological therapies are discussed in the next section.

4 Development of guidelines on the use of biological drugs for RA

The development of biological therapies over the last ten years has seen their increasing use in the treatment of RA. This group of drugs consist of monoclonal antibodies and soluble receptors that specifically modify the disease process by blocking key protein messenger molecules (such as cytokines) or cells (such as B-lymphocytes). The development of biological drugs has been based on an increasing understanding of the disease pathology. The key drivers of RA include cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) (NCCCC 2009, p6).

As discussed above, NICE has produced guidelines relating to the overall management of RA in adults; it has also produced specific guidelines (technology appraisals) concerning the use of biological therapies in adults. NICE considered studies that looked at the efficacy and safety of biological drugs compared with other DMARDs either singly or in combination, with respect to symptoms, joint damage, function and quality of life in patients with established RA.

NICE found that in patients with established active disease, the addition of a biological therapy adds significant benefits in terms of symptom control, function and quality of life. In addition there was some evidence that in direct comparisons of biological drugs against conventional, biologics were superior (NCCCC 2009, p156). Over the last ten years NICE has produced a series of TAs (technology appraisals) regarding the use of various non-conventional RA drug therapies. In some cases later publications have overridden the findings of earlier ones.

NICE recommends the use of rituximab in combination with methotrexate for adults with severe RA (defined as DAS-28 (the 28-joint version of the disease activity score) > 5.1) who have an inadequate response to, or are intolerant to, other DMARDs including at least one α-TNF inhibitor. This was based on the estimated cost-effectiveness of rituximab (NICE 2010b).

Etanercept, adalimumab, atanercept and infliximab are each recommended in combination with methotrexate only for adults with severe RA (again DAS-28 > 5.1) who have an inadequate response to, or are intolerant to, other DMARDs including at least one TNF inhibitor, and who cannot take rituximab either because of a contra-
indication or an adverse event. Rituximab is found to be more effective and less costly than these four, but for people who are unable to take either rituximab or methotrexate, then these four biological therapies are more cost-effective than other conventional DMARDs (NICE 2010b).

5 Review of guidelines

NICE carried out some early technology appraisals relating to RA. Thus in 2001 NICE produced ‘Cox-II inhibitors for the treatment of osteoarthritis and rheumatoid arthritis’ (NICE 2001). This was subsequently superseded by the NICE clinical guidelines discussed above (NICE 2009). In 2002 NICE produced ‘The clinical effectiveness and cost effectiveness of etanercept and infliximab for rheumatoid arthritis and juvenile poly-articular idiopathic arthritis’ (NICE 2002). This was replaced by TA130 and TA195.

NICE is committed to review its guidelines on a regular basis. Thus the guidelines issued in February 2009 are subject to a 3-year review: hence 2012. In November 2011 NICE issued a consultation document recommending there should be no change in the current guideline recommendations (NCCP 2011). In 2012 NICE announced that the result of the review was that there would be no changes (NCCP 2012). Hence the 2009 guidelines stand.

NICE also reviews technology appraisals on an ongoing basis. Thus, TA198 (tocilizumab for RA) is due for review in August 2013; TA195 (Adalimumab, etanercept, infliximab, rituximab and abatacept for RA after failure of a TNF inhibitor) is due for review in June 2013; and, TA234 (abatacept for RA after failure of conventional DMARDs) is due for review in July 2014.

At the same time professional bodies and academics continue a process of research and development and critique of existing guidelines. Their views are discussed in the next section.

6 Other views of clinical guidelines for adults with RA

The main commentary on NICE guidelines is from professional rheumatologists, and in particular the BSR. The National Rheumatoid Arthritis Society (NRAS) is the society in the UK that aims to provide information and support for people with RA. It does not produce its own guidelines, but provides some commentary on what patients might expect, and refers to the NICE guidelines as well as the guidelines produced by the BSR.

The NRAS while not questioning the detail of NICE guidelines relating to RA are concerned that NICE does not consider all the costs that are involved when people have RA. Thus the NRAS claim that NICE does not look at the impact of newer drugs on: keeping people at work; not needing the support of family and carers; not claiming benefits; and, allowing people to feel that they are contributing fully in society. NRAS campaigns for the inclusion of the wider costs to society in NICE evaluations.
6.1 BSR guidelines

The BSR had produced guidelines in 2000 relating to eligibility for anti-TNFs (biological therapies) which were adopted within NICE TA36 (NICE 2002) and became part of the NICE guidelines in 2009 (Deighton et al. 2010). NICE’s TA36 (NICE 2002) retained the eligibility criteria and stiffened the response criterion by requiring six-monthly assessments to demonstrate maintenance of response. These guidelines as discussed above were that an adult patient would be eligible for the use of biological therapies only if the following criteria were satisfied:

- DAS-28 > 5.1 on two occasions one month apart;
- where patients have failed to respond to two DMARDs one of which is methotrexate; and,
- successful response demonstrated by drop in DAS-28 of 1.2.

The 2005 BSR guidelines made no changes. However, in 2010 the BSR and BHPR (British Health Professionals in Rheumatology) published a new set of recommendations (Deighton et al. 2010). These made a key change to the recommended eligibility criteria.

Thus biological therapies were recommended for adults who meet the following criteria:

- active RA as measured by DAS-28 > 3.2 with at least three or more tender and three or more swollen joints; and,
- have undergone trials of two DMARDs one of which is methotrexate (unless contra-indicated) where a trial is defined as at least two DMARDs usually given concurrently over a six-month period, with two months at standard doses unless significant toxicity has limited the dose or duration of treatment.

Treatment should be continued only if there is evidence of an adequate response following the first six months of continuous treatment where an adequate response is defined as a good or moderate EULAR response. Moreover after initial response, anti-TNF therapy should be monitored with assessment of DAS-28 no less frequently than six-monthly and should be withdrawn if an inadequate response is seen despite six months of continuous therapy.

Why the change to DAS-28 > 3.2?

DAS-28 has become the accepted measure of disease activity in looking at patients with RA. There are alternatives eg Clinical Disease Activity Index, simplified Disease Activity Index, but the BSR has decided to continue with DAS-28. Current NICE guidelines only allow the use of biologics for patients where DAS-28 > 5.1 ie patients with high disease activity. However DAS-28 < 3.2 is regarded as the threshold for good disease control. Thus there are a group of patients whose disease is not well-controlled but who remain ineligible for biologics, those with a DAS-28 between 3.2 and 5.1.
Deighton et al. (2010) quote several studies that show conventional DMARD treatment strategies do not suppress disease progression in patients with DAS-28 < 5.1 but > 3.2, and conclude that such patients would benefit from a more aggressive therapy regime. Moreover they claim greater efficacy for biologics in patients with moderate compared with severe baseline disease activity – in terms of decreased disease activity and radiological outcomes. Finally they note that EULAR consensus guidelines, Swedish, Dutch and Spanish guidelines all use a threshold of 3.2 (Deighton et al. 2010).

As one leading rheumatologist said,

*England and Wales stand outside the recommendations of all other RA societies and individual countries concerning which patients should be able to start on biologics.*

The BSR guidelines also modify those of NICE in that they state patients should have undergone trials of two DMARDs one of which is methotrexate (unless contra-indicated) where a trial is defined as at least two DMARDs *usually* given concurrently over a six-month period, as opposed to insisting on a combination therapy. This is intended to allow patients who have been on sequential DMARD monotherapies access to biologics (Deighton et al. 2010).

The BSR guidelines note that the American College of Rheumatology 2008 guidelines argue that patients with poor prognostic RA should be offered access to anti-TNF therapy as a first-line DMARD. However the BSR reject this on the grounds that it is not supported by cost-effectiveness data stating that (Deighton et al. 2010),

*Until reliable biomarkers are identified that predict patients with a poor prognosis, who will do badly on conventional DMARDs but well on anti-TNF therapies, the BSRBG [British Society of Rheumatology Biological Group] felt that an argument cannot be made for the use of anti-TNF therapy prior to a trial of conventional DMARDs.*

The BSR discuss the extra usage of biological therapies that would result from the changes in criteria suggested. These are outlined in section 7 of this paper.

The BSR has stated its intention to review these guidelines every three years or prior to the next round of NICE multiple and single TAs, whichever is sooner, unless substantial new evidence becomes available before this.

### 6.2 Professional views

More recently, an article in Rheumatology by Kiely et al. (2012) has also stressed the need to change the NICE guidelines. Kiely and colleagues make two main points:

First they argue there is,
a common consensus that a biologic should be started in patients who fail to achieve a 28-joint DAS (DAS-28) <3.2 after treatment with traditional DMARDs.

They point to the fact that the use of a threshold of 5.1 for use of biologics sets England and Wales at odds with many published guidelines and standards in the EU and the US.

Second they argue that the current NICE guidelines restrict the choices of biologics available especially for methotrexate-intolerant patients who are confined only to anti-TNF drugs and for serial DMARD-IR (DMARD inadequate responders) where no switching is allowed between anti-TNF drugs, and the use of abatacept is not allowed.

Thus, for example, Kiely et al. (2012) argue that tocilizumab should be allowed as a choice of first-line biologic for patients who are methotrexate-intolerant. They also argue that alternative biologics eg abatacept, tocilizumab should be allowed where a patient is anti-TNF intolerant. In the current situation, if a patient has not responded to conventional DMARDs, then the only biological drugs that can be offered are anti-TNFs. And they argue that rituximab should be made more readily available as a biologic agent.

7 Patient access to therapies

Most DMARDS and all biological therapies can only be prescribed by specialists (NAO 2009). Hence early referral to specialist services is very important if people with RA are to be able to access appropriate treatments.

Patient access to biologics is largely determined by NICE guidelines and TAs. Thus, the NAO found that in 2007/08, 97% of patients who qualified for biologics according to the NICE TA criteria were treated with those drugs. No figures were provided in the NAO’s report for patients who did not qualify yet gained access. However it was reported that although NICE does not recommend treatment with further biologics if the patient does not respond to a first biological therapy, many PCTs fund further biologics in such cases (NAO 2009).

The NAO estimates that the NHS spends £560 million on RA each year (of which £160 million is spent on biologics), and that the wider cost to society in terms of sick leave and work-related disability is £1.8 billion a year. The approximate NHS cost per annum per patient for conventional DMARDs is £300 compared with £10,000 for biologics (rituximab is less) (NAO 2009).

More recent data from the NHS Information Centre reveals that in 2010, hospital prescribing expenditure on the four key RA biologics came to £557 million – total expenditure on hospital prescribing was £4.1 billion (see Table 7.1). Expenditure on these four drugs was among the top six, and grew at an annual rate of between 13-19%. The cost of prescribing these drugs anywhere (community, primary care) was £575 million. However biological drugs are not prescribed just for RA but for a range of other diseases, eg inflammatory bowel disease, other auto-immune diseases (NHS Information Centre 2011). No further breakdown was available in the figures quoted.

Table 7.1: NHS expenditure on biological drugs, England, 2010
<table>
<thead>
<tr>
<th>Biologic</th>
<th>Hospital</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>£180.5 million</td>
<td>£189.3 million</td>
</tr>
<tr>
<td>Etanercept</td>
<td>£179.6 million</td>
<td>£188.6 million</td>
</tr>
<tr>
<td>Infliximab</td>
<td>£103.4 million</td>
<td>£103.4 million</td>
</tr>
<tr>
<td>Rituximab</td>
<td>£93.7 million</td>
<td>£93.7 million</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>£557.2 million</strong></td>
<td><strong>£575 million</strong></td>
</tr>
</tbody>
</table>

Source: NHS Information Centre 2011

As discussed earlier, the BSR has produced new guidelines suggesting that the DAS-28 criteria be reduced to > 3.2 (as it is in some other countries eg Spain, Sweden and Holland). They suggest that this has the potential to increase usage from the currently estimated 6% of RA patients on anti-TNF to between 8-12%; however, this increase may be reduced if specialists adhere more closely to NICE guidelines in treating active disease with combinations of conventional DMARDs and steroids closer to onset (Deighton et al., 2010).

8 Future drug therapies

There are two significant factors that may impact on the use of biological drugs in the NHS in England in the future:

- tocilizumab is likely to be allowed soon by NICE as an alternative biologic to anti-TNF therapies. This has in part been facilitated by a reduction in the unit cost to the NHS of this drug (see NICE 2011b).
- a new drug – tofacitinib – has been developed that can be delivered in tablet form (not infusion) and which will act as an JAK3 inhibitor. It was suggested by one leading rheumatologist that this form of biological therapy could be much cheaper and so it may be possible to use it immediately once it is licensed as its cost will not be so prohibitive as to require a NICE TA.

9 Concluding remarks

This paper has identified the guidelines (actually technology appraisals) that impact on the use of biological therapies for the treatment of RA in England, and has indicated how these guidelines are reviewed. The views of professional bodies, patient bodies and leading practitioners are also discussed. Finally some indication of the impact of guidelines on patient access to biological therapies is provided.

The use of biological therapies in England (and Wales) is determined by a set of NICE TAs. NICE also issued a set of guidelines for the treatment of RA (in 2009). These were reviewed in 2011 with a conclusion that no changes are required as there is insufficient new data to justify any changes (NCCP 2012). The next review is in July 2014.

However, although there was substantial consensus in the past between the views of the BSR and those of NICE, the latest BSR guidelines (2010) suggest that the use of
biological drugs should be extended to include patients with moderate disease activity ie \( > 3.2 \) and \( < 5.1 \). Moreover there is a substantial body of professional opinion that believes the NICE guidelines, and in particular the TAs on biological drugs, are overly restrictive in their sequencing of biological drugs following the failure of conventional regimes.

**Bibliography**


http://rheumatology.oxfordjournals.org/content/49/6/1197.full
accessed 15 February 2012


http://rheumatology.oxfordjournals.org/content/51/1/24.full
accessed 15 February 2012

accessed 15 February 2012


http://guidance.nice.org.uk/CG79/Guidance/pdf/English
accessed 15 February 2012


accessed 15 February 2012


http://guidance.nice.org.uk/TA27
accessed 15 February 2012

http://guidance.nice.org.uk/TA36

accessed 15 February 2012


accessed 15 February 2012


http://www.nice.org.uk/guidance/CG79/NICEGuidance

accessed 15 February 2012


accessed 15 February 2012

NICE 2010b. *Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (NICE technology appraisal guidance 195)*. London: NICE.


accessed 15 February 2012


accessed 15 February 2012


accessed 15 February 2012


http://guidance.nice.org.uk/TA/Wave18/63/FAD/FinalAppraisalDetermination/pdf/English

accessed 15 February 2012


http://www.nice.org.uk/guidance/index.jsp?action=download&o=57054

accessed 15 February 2012


http://guidance.nice.org.uk/CG79/ReviewDecision/pdf/English

accessed 15 February 2012
France

Lada Leyens

1. French health system

Health system coverage

The French Social Insurance System offers universal coverage to the French population. 80% of the population is covered by the main health insurance scheme (Régime General), which has the largest health insurance fund at national level (Caisse Nationale de l’Assurance Maladie des Travaillleurs Salariés, CNAMTS). Other important health insurance funds are those for self-employed (Caisse Nationale d’Assurance Maladie des Professions Indépendantes, CANAM) and for farmers (Mutualité Sociale Agricole, MSA). As will be described later the level of co-payments is high, therefore 85% of the population has supplementary health insurance with the "Mutuelles" (supplementary sickness funds) (Österreichisches Bundesinstitut für Gesundheitswesen, ÖBIG Health Economics, 2006).

Stakeholders in the French Health system (Österreichisches Bundesinstitut für Gesundheitswesen, ÖBIG Health Economics, 2006):

- The French Ministry of Health (Ministère de la Santé et Solidarités), in charge of the Medicines Agency and which hosts the Medicinal Products’ Pricing Committee (Comité Economique des Produits de Santé, CEPS).
- The Medicines Agency (Agence Française de Sécurité Sanitaire des Produits de Santé, AFSSAPS) which is the market authorization authority and is responsible for pharmacovigilance.
- The High Authority for Health (Haute Autorité de Santé, HAS), which was newly established in January 2005, responsible for evaluating the medical benefit of pharmaceuticals, medical practices and in charge of the Transparency Committee (Commission de la Transparence).
- The National Union of Health Insurers (Union Nationale des Caisse d'Assurance Maladie, UNCAM), formed in 2005 by grouping the three main health insurers (CNAMTS, CANAM, MSA), in charge of reimbursement.

Pharmaceutical system and pricing

After market authorization, drugs are rated by the transparency commission (Commission de la Transparence) on their clinical benefit (‘Service Medical Rendu’, SMR) and on the improvement in medical services associated with it (‘Amélioration du Service Médical Rendu’, ASMR) (i3 Innovus, 2009). Prices are determined by the Comité Economique (CEPS), based on the SMR and ASMR rating, the expected sales of the pharmaceutical as well as the prices in other EU Member State (Österreichisches Bundesinstitut für Gesundheitswesen, ÖBIG Health Economics, 2006). The reimbursement rates are decided by the national union or health insurers (UNCAM).

In addition, cost-effectiveness information is used as additional information for pricing and reimbursement decisions, although not as formally as in other European countries (European Health Economics and i3 Innovus, 2009).

The ASMR rating is as follows:

- ASMR 1: significant therapeutic value
- ASMR 2: significant improvement in terms of efficacy, and/or reduction of adverse effects
- ASMR 3: modest improvement in terms of efficacy, and/or reduction of adverse effects, as compared with existing products
• ASMR 4: minor improvement of benefit (e.g. user-friendliness, smaller interaction risk), as compared with existing products
• ASMR 5: no therapeutic improvement of benefit, as compared with existing products (still recommended for reimbursement)
• ASMR 6: negative opinion regarding inclusion into reimbursement

Figure 2 French Pharmaceutical system from (Österreichisches Bundesinstitut für Gesundheitswesen, ÖBIG Health Economics, 2006)

Market access
France is seen as a very liberal market in terms of approved drugs, they put more weight on the added therapeutic benefit than on the prices of pharmaceuticals. A decision was made in the early 2000s to fund novel biologics that provided a significant additional medical benefit at the ‘asking’ price. However, there is often an associated obligation to perform post-launch observational studies. The consequence of this, in combination with free access to GPs and specialists, has led to France being one of the countries with
best access to biologics, not only in RA but also in other areas such as oncology and multiple sclerosis.

Even though traditional volume controls still apply to biologics, i.e. companies must still negotiate price volume contracts with the government, the government is particularly generous in the case of biologics (i3 Innovus, 2009).

**Co-payment and Reimbursement**

France has positive reimbursement drug lists. In 2004 the French government published the updated list of reimbursed pharmaceuticals under the law number 2004-810 (Loi n° 2004-810 du 13 août 2004 relative à l’assurance maladie (Legi France, 2004)).

Drugs are classified under reimbursable and not reimbursable pharmaceuticals. Reimbursable pharmaceuticals are further divided in 4 categories defined by the color of the prescription label (white crossed, white, blue and orange). Non-Reimbursable pharmaceuticals have to be fully paid by patients. Reimbursable pharmaceuticals however are either reimbursed at 100% (white crossed, i.e. no co-payment), 65% (white, 35% co-payment), 30% (blue 70% co-payment) or 15% (orange, 85% co-payment). As already mentioned, the majority of the population (approx. 85%) has supplementary health insurance funds (Mutuelles) that cover the co-payments.

**Table 7 French reimbursement categories and maximum prices to be paid by patients, modified from (Ameli, 2011; cprsncf, 2012)**

<table>
<thead>
<tr>
<th>Category (by color of the prescription label)</th>
<th>Type of pharmaceutical</th>
<th>Patient fee if prescribed by a normal physician (outpatients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White crossed</td>
<td>Pharmaceuticals for life-threatening conditions</td>
<td>No patient fee</td>
</tr>
<tr>
<td>White</td>
<td>Pharmaceuticals for serious diseases</td>
<td>35%</td>
</tr>
<tr>
<td>Blue</td>
<td>Pharmaceuticals for acute illnesses and &quot;comfort&quot; medicines</td>
<td>70%</td>
</tr>
<tr>
<td>Orange</td>
<td>Pharmaceuticals for low medical treatment</td>
<td>85%</td>
</tr>
<tr>
<td>Non-reimbursed pharmaceuticals</td>
<td>Usually OTC</td>
<td>100% - no reimbursement and unlimited</td>
</tr>
</tbody>
</table>

French patients do not have to pay a prescription fee. Nevertheless, since the reference price system was introduced in 2003, patients are obliged to pay the difference between the reference price (reimbursed) and the retail price of the pharmaceutical dispensed.

Patients with long-term illnesses (Affections de longue durée, ALD) are exempt from co-payments. The ALD scheme includes around 5,000 medical conditions grouped in 30 serious diseases; it covers around 7 million people (11% of the population). The list of 30 diseases includes (as number 22) severe Rheumatoid Arthritis (HAS, 2012). As for the end of 2009 it was estimated that 171,486 patients with severe RA were classified under the ALD scheme: 26,3% men, 73,7% female with an average age of 61,7 years (LEEM, 2009).
Reimbursement of RA biologics
RA has been recognized as a serious chronic illness for a long time in France, and currently around 60–70% of all RA patients are classified under the ALD scheme. For these patients all RA-related healthcare costs (including biologic DMARDs) are reimbursed 100% (i3 Innovus, 2009).

To get a more general picture, it has been estimated that around 80% of the total cost of RA treatment (€9,200 from the total annual cost of €11,700 (Kobelt, et al., 2008)) is covered by the national health insurance, with the remaining 20% generally picked up by the complimentary insurance organizations (Mutuelles) (i3 Innovus, 2009).

Treatment guidelines
The national guidelines, specifically those regarding the use of biologics, are issued by the national health authority (Haute Autorité de Santé; HAS) which intrinsically links guidelines adherence to funding (European Health Economics and i3 Innovus, 2009). They cover an extent number of conditions and can be found in their website. Additionally treatment guidelines for all ALD conditions have been issued, these can also be found in their website.

Prescription of biological DMARDs
Due to the high level of experience and understanding required, all DMARDs are preferably prescribed by specialists. Biologic DMARDs have to be prescribed by rheumatologists.

The interviewee reported that usually a specialists committee comes together to discuss the details of treatment for a patient that has been considered for biologic treatment. This committee will decide the medicine, dose and timelines of biologic treatment, considering side effects, experience with DMARDs and patients characteristics (interview).

Referral to specialists.
France does not have the gatekeeper function for GPs in its full definition. However, in 2006 a family doctor system (médecin traitant) with gate-keeping function was enforced, with higher co-payments for patients addressing specialists directly instead of being referred through the family doctor (Österreichisches Bundesinstitut für Gesundheitswesen, ÖBIG Health Economics, 2006).

In the case of RA, the French treatment guidelines recommend (as in the EULAR guidelines) early referral to a rheumatologist, within six weeks of primary onset. France seems to be an exception in the EU in that the referral process appears to shorten rather than lengthen the time to specialist consultation and diagnosis: waiting times to see a rheumatologist directly (up to 2–3 months) are longer than when appointments are directly taken by a GP (1–2 weeks) (European Health Economics and i3 Innovus, 2009).

2. French Demographics and stakeholders

General prevalence and access to specialists
France has an adult population (>19 years of age) of 47.4 million. With a prevalence of 0.48% of RA in the population, the approximate number of RA patients (>19 years of age) is 226,750. The age structure of the disease is as follows: 11% of patients are between 20 and 44, 42% are between 45 and 64, and the remaining 47% if over 64 (European Health Economics and i3 Innovus, 2009).

The estimated number of patients per rheumatologist is 80 (calculated with data prior to 2007), which is one of the lowest number of patients per rheumatology specialist in Europe (with only Hungary, Iceland, Slovenia and Switzerland below that figure). This access to a big pool of specialists is very beneficial for the patients and may be one of the
reasons for the high use of biologics (13% of RA patients) (European Health Economics and i3 Innovus, 2009).

Table 8 Prevalence of RA in France and number of patients. Inferred from (European Health Economics and i3 Innovus, 2009). The data from prevalence and number of patients with RA has to be interpreted carefully since different studies show very different results as it can be seen at the end of the table

<table>
<thead>
<tr>
<th>Population &gt;19 (m)</th>
<th>47.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients &gt;19</td>
<td>226,750</td>
</tr>
<tr>
<td>Aged 20-44 (%)</td>
<td>11</td>
</tr>
<tr>
<td>Aged 45-64 (%)</td>
<td>42</td>
</tr>
<tr>
<td>Aged &gt;64 (%)</td>
<td>47</td>
</tr>
<tr>
<td>Prevalence &gt;19 (%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Different prevalence figures from other previous studies

| Prevalence by Saraux et al 1999 | 0.50% (18 years and over) |
| Prevalence by Guillemin et al 2005 | 0.31% (18 years and over) |
| Prevalence by Roux et al 2007   | 0.31% |

Table 9 Total number of rheumatologists and number of patients per rheumatologist from (European Health Economics and i3 Innovus, 2009)

<table>
<thead>
<tr>
<th>Adult population</th>
<th>50m (18+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number rheumatologists</td>
<td>1,800</td>
</tr>
<tr>
<td>Adult pop/rheumatologists</td>
<td>28,000</td>
</tr>
<tr>
<td>Patient/rheumatologists</td>
<td>80</td>
</tr>
<tr>
<td>Number Patients &gt;19</td>
<td>226,759</td>
</tr>
<tr>
<td>Prevalence % &gt;19</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Use of biologics for the treatment of RA

With approximately 28,000 patients treated with biologic DMARDs, France has the largest market for biologics in Europe as it was reported comparing to Germany, Italy, Spain and the UK (European Health Economics and i3 Innovus, 2009). However, in percentage of RA patients treated with biologics from the total number of RA patient (13% in France), the clear front-runner is Norway, followed by Belgium, Switzerland, Spain, Sweden, Denmark, Finland, France and Netherlands; while Austria, Italy, Germany and the UK provide access below average to their patients.

In annual sales of biologics per patient, France is closely followed by Spain (due to the fact that the biologics dosage per prevalent patient in Spain is higher than in France).
Table 10 Uptake from biologics. Inferred from (European Health Economics and i3 Innovus, 2009)

<table>
<thead>
<tr>
<th>Sales biologics/100000 pop (€, m)</th>
<th>0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number patients treated with biologics (2008)</td>
<td>28,000 (13%)</td>
</tr>
</tbody>
</table>

Costs
The total costs of RA for France in 2008 have been estimated to be 4,653,453,492€ (European Health Economics and i3 Innovus, 2009). A report by Kobelt and colleagues in 2008 reported a total annual cost per patient to the French health system of 11,658€, while the annual costs per RA patient to the French society was estimated to be 21,690€. The report by European Health Economics and i3 innovus revised these figures and reported 20,522€ annual cost per patient (including direct costs –excl. biologics- of 10,252€, informal care costs of 1,284€ and indirect costs of 7'512), the same report estimated the costs of biologics per patient to be 1,475€ (European Health Economics and i3 Innovus, 2009).

Table 11 Total costs of RA in France and annual costs per patient in €

<table>
<thead>
<tr>
<th>From (OECD, 2011). Data for 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health expenditure per capita ($USD)</td>
</tr>
<tr>
<td>Total health expenditure (% GDP)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From (European Health Economics and i3 Innovus, 2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost of RA (2008)</td>
</tr>
<tr>
<td>Total costs/ patient</td>
</tr>
<tr>
<td>Direct costs (excl biologics)</td>
</tr>
<tr>
<td>Biologics cost/ patient</td>
</tr>
<tr>
<td>Informal care</td>
</tr>
<tr>
<td>Indirect cost</td>
</tr>
<tr>
<td>Total cost/ patient per age group</td>
</tr>
<tr>
<td>20-44</td>
</tr>
<tr>
<td>45-64</td>
</tr>
<tr>
<td>&gt;65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From (Kobelt, et al., 2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public payers. Mean (SD)</td>
</tr>
<tr>
<td>Societal. Mean (SD)</td>
</tr>
</tbody>
</table>
### List of associations

- AFLAR (Association Française de Lutte Anti-Rhumatismale) French association for the fight against rheumatism [www.aflar.org](http://www.aflar.org)
- HAS (Haute Autorité de Santé) French High Authority for Health [http://www.has-sante.fr/](http://www.has-sante.fr/)

### 3. Treatment guidelines affecting patient access to biologics for RA

**History (i3 Innovus, 2009)**

2002 First national guidelines for the treatment of RA, published by the national health insurance company. Indirectly linked to reimbursement.

2005 Further elaboration on the previous guidelines, to provide guidance on the use of biologics, published by the scientific society SFR.

2007 Guidelines on overall care of RA published by the government (HAS). Reimbursement of costs of treatment that is outside of the guidelines can be refused. These guidelines are very similar to the EULAR guidelines. Three guidelines were produced:

- RA: diagnostic and early treatment (HAS, Sept 2007)
- RA: treatment in advanced stage (HAS, Sept 2007)
- DMARD treatment (product characteristics)

2008 Guideline on the treatment of severe cases of RA, for patients under the ALD scheme (HAS, April 2008).

2011 Suspension of RA guidelines due to issues of transparency and conflict of interests. The three guidelines published in 2007 were affected. However, physicians may continue to use them until the new guidelines are issued.

**Actual stand**
The guidelines published in 2007 have been suspended due to transparency and conflict of interest issues. The letter published by HAS in September 2011 (HAS, 19 September 2011) reports the suspension of these and other 4 guidelines. Until the actualized treatment guidelines are published, physicians can continue to use the suspended guidelines weighted by the available knowledge and experience.

No information has been found on the date when the reviewed guidelines will be published. The interviewed specialist report they were not informed with when the new guidelines were expected, nor with whether the guidelines will be newly written or the existing guidelines will simply be revised and corrected.

**Diagnosis**

Due to the indirect link with reimbursement for biologics, the guidelines panel settled on a definition of severe RA that appears extremely open compared with other countries – i.e. a Health Assessment Questionnaire (HAQ) score of >0.5. Although not in line with the European consensus, the purpose of this is to give specialists the freedom to initiate biologic treatment in patients who have a low HAQ but evidence of active erosive disease (i3 Innovus, 2009).

Diagnosis is supported by a range of procedures outlined in the EULAR recommendations, i.e. physical examination, blood tests (ESR, CRP, RF, anti-CCP); however, MRI, ultrasound and X-ray are rarely used. (i3 Innovus, 2009).

The 2008 guidelines give an additional definition of severe RA:

- Patients with an active not severe form of RA must have a DAS score between 3.2 and 5.1, be non-dependent on corticoids and not have structural lesions
- Patients with active severe form of RA must have a DAS 28 score >5.1, or >3.2 despite corticoids, with the addition of structural lesions

**Monitoring**

Monthly disease monitoring is recommended until remission is achieved. Thereafter, revision is carried out every 3 months, the following tests are done in these visits: DAS28, global patient assessment (visual analogue scale), morning stiffness, pain, painful joints and swollen joints, CRP, ESR.

Every 6 to 12 months, structural damage is assessed by X-ray. In addition, functional assessment is used to complement disease activity and structural damage.

**Access to biologic DMARDs**

As already mentioned, France has had a very progressive policy for access to innovative treatments, with almost no restrictions. Novel biologic agents of high added medical benefit have been funded under the French healthcare system at the asking price. This availability combined with unlimited access to a large physician pool, a relatively high proportion of rheumatology specialists and a generally efficient system of GP referrals, results in high levels of biologics use which is estimated in 13% of RA patients (European Health Economics and i3 Innovus, 2009).

Access is restricted by the treatment guidelines, which also affect reimbursement. But as we already insisted on, their guidelines are very liberal, with a very broad definition of the conditions to qualify as severe RA form, leaving it to the judgement of the specialist when it is best for the patients to be initiated on biologic DMARDs.

**Use of biologics** (i3 Innovus, 2009)

Biologics are used in less than 5% of patients as a first-line strategy. They are considered second and third-line treatments for most patients. Anti-TNFαs are the first treatment option giving priority to drugs with few side effects and longer experience.
Typically, biologics are used in patients with severe RA or those who fail to sufficiently respond to DMARDs – which is 40–60% of patients initially treated with MTX. According to HAS guidelines all patients with severe disease should be treated with MTX within 3 months of diagnosis and should be switched to biologics if there is no adequate response within 6 months (after a minimum of 3 months on MTX or the first synthetic DMARD applied).

First-line biologics, etanercept (Enbrel) and adalimumab (Humira) are the most frequently used biologics, in 80% of cases used in combination with MTX and as monotherapy for the rest. Safety and tolerability are important criteria for this choice of drugs.

Subsequent biologic use: infliximab (Remicade) is usually reserved as second line biologic treatment due to the higher incidence of side effects observed, infliximab is not recommended as monotherapy. Cycling of etanercept and adalimumab also occurs. Additionally, rituximab (MabThera) and abatacept (Orencia) are also used as a strategy after unsuccessful treatment with adalimumab or etanercept (or infliximab), with a preference for rituximab due to its less frequent administration requirements.

**Best practice** *(i3 Innovus, 2009)*
A high level of compliance with the 2007 guidelines was reported *(i3 Innovus, 2009).* Some reasons for that may be:

- The guidelines of 2007 did, to a large extent, simply reflect existing treatment practices.
- In terms of early referral the HAS guidelines are in concordance with the 2008 EULAR recommendations, and also followed existing practices.
- Physicians are encouraged to adhere to the official HAS guidelines since they are indirectly linked to reimbursement, particularly for more expensive treatment options such as biologics.
- The SFR started a nationwide campaign to educate GPs and office-based rheumatologists about the early diagnosis of patients with active and potentially erosive RA.

**Table 12 Summary of national Guideline recommendations. Modified from** *(i3 Innovus, 2009; HAS, Sept 2007; HAS, Sept 2007; HAS, April 2008)*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Suspicion of RA:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Morning stiffness longer than 30 min</td>
</tr>
<tr>
<td></td>
<td>• symptoms for more than 6 weeks</td>
</tr>
<tr>
<td></td>
<td>• arthritis in at least three joints (of the wrist and hand)</td>
</tr>
<tr>
<td></td>
<td>• pain on pressure (hand and finger joints)</td>
</tr>
<tr>
<td></td>
<td>• symmetric symptoms</td>
</tr>
</tbody>
</table>

Factors measured in patients with early RA:

- radiographic test (X-rays) for number of swollen and tender joints
- lab tests: ESR of CRP, level of RF and anti-CCP antibodies
- radiographic erosion bodies
if specialist not sure on: further tests are ultrasound and MRI

Severe RA defined as: (View comment on broad definition (above, in diagnosis point))

- structural lesions
- systemic symptoms
- HAQ>0.5

Severe RA more specific definition (HAS, April 2008):

- Active not evolutive RA
  - 3.2< DAS 28 >5.1
  - without corticoids
  - without structural lesions
- Active and evolutive RA
  - DAS 28 >5.1
  - DAS 28 >3.2 despite corticoids
  - structural lesions

Referral

Patient presenting with arthritis is referred to and seen by a rheumatologist ideally within 6 weeks of symptomatic onset.

Goal of treatment

The main goal of DMARD treatment is to:

- obtain stable low disease activity (Das 28 <3.2) and if possible stable remission (Das 28 <2.6)
- control and prevention from structural lesions
- pain and disability control
- limitation of adverse reactions to treatments
- limit psychosocial consequences
- increase quality of life

Treatment

Early treatment initiation is advised:

- at first or second visit to specialist, within 3 months
- patients developing persistent/erosive arthritis should initiate DMARDs as early as possible (on first specialist visit if symptoms are confirmed)
1st DMARD

Mild/moderate RA:
- MTX, starting with 10 mg (max dose 25 mg).
- If MTX contraindicated or unsuccessful as 1st treatment:
  - leflunomide (20 mg/day) monotherapy
  - sulphazalazine (2 g/day) monotherapy
- + local cortisone infiltrations if required

Severe RA at start:
- MTX + sulphazalazine/ hydroxychloroquine/ cortisone
- Anti-TNFα (+ MTX) first–line treatment
- + local cortisone infiltrations if required

First line treatment for patients with severe RA if considered necessary

Otherwise, as 2nd and 3rd line treatment, given the conditions:
- unsuccessful treatment with at least 1 synthetic DMARD
- minimum time on previous DMARD treatment of 3 months

1st biologic
- Anti-TNFα Adalimumab or etanercept (+MTX)

2nd and 3rd biologic
- Cycling of anti-TNFs (including infliximab) or Abatacept or Rituximab (+MTX)

Monotherapy possible for anti-TNFs adalimumab and etanercept, not recommended for infliximab

Monitoring

Monthly disease monitoring until remission is achieved.

Thereafter, revision every 3 months:
- DAS28
- global patient assessment (visual analogue scale)
- morning stiffness
- pain
- painful joints and swollen joints
- CRP
Structural damage is assessed by X-ray every 6–12 months. Functional assessment is used to complement disease activity and structural damage.

**Treatment failure**

Defined by:

- Intolerance
- Lack of efficacy assessed over 12–24 weeks using EULAR criteria
  - No effect:
    - DAS >5.1 and change <1.2
    - DAS <5.1 and change <0.6
  - Moderate effect:
    - DAS 3.2–5.1 and change >0.6
    - DAS 3.2–5.1 and change 0.6–1.2 but judged insufficient by patient and physician
- Continuous reduction in response
- Unable to stop corticosteroids

4. **Differences with other countries**

As already specified, France has one of the most liberal guidelines for the treatment of RA. Early treatment with MTX is advised for all patients. Furthermore, patients can access biologic DMARDs as second line treatment after unsuccessful treatment with only one previous synthetic DMARD for at least three months; while other countries such as the UK and Belgium require patients to have received two previous synthetic DMARD treatments.

Also differently to other countries, French patients with the severe form of RA (taking into account that the definition of severe RA is very broad and flexible) have the possibility to access biologic DMARD treatment as first line treatment if their specialists considers it necessary.

Both conditions make France the largest market for biological in Europe. The percentage of RA patients receiving biologic DMARDs is estimated to be 13%. Very few countries exceed this figure, Belgium between them with a 20% of patients receiving biologic DMARDs.

The guidelines and reimbursement conditions published by NICE seem very far away from the current practice in France. Compared to French patients, UK patients suffer a very strict policy and have very much restricted access to biologic DMARDs.

5. **Clinical expert interview extracts**
“We look at NICE for the good scientific references. However their (NICE’s) guidelines are too stringent, too severe”

Synthesis of main points:

- The guidelines were suspended in 2011 due to conflict of interest issues with the papers they were based upon. Specialists are advice to continue using the old guidelines. Specialists have not been warned as to when the new guidelines will be issued, neither whether the guidelines will be reviewed or newly written.
- The suspended guidelines were usable because they reflected current practice. France has the right attitude toward biologic treatment and allows early access to biologics if it is deemed necessary by the specialist. Thus the guidelines are seen as open, flexible and pragmatic.
- The only part of the guidelines that may not be very practicable is the early use of biologics as first line treatment. The treatment of patients with biologics is discussed by a committee of specialists in the clinic and until a consensus is reached, in terms of the appropriate drug and dose, patients are treated with MTX.
- The guidelines issued by NICE provide good scientific references, but in terms of treatment they are too severe, they do not allow proper treatment of patients and may miss good chances of disease remission by forbidding access to biologics until later stages of treatment, when it might be too late.
- The only change that could be included in the new guidelines is a more thorough explanation on the inclusion of GC in the treatment of RA patients, and a better insight into when and how to reduce or discontinue biologic DMARD treatment once the remission is observed.

Specifics on French guidelines

Rheumatologists in France are still using the suspended guidelines, as recommended by HAS. The interviewee was not informed as to when the new guidelines will be issued, what revision process they are carrying out and whether the guidelines will be newly written or simply corrected.

Specialists consider the French guidelines very open; they give flexibility to apply biologics as soon as rheumatologists consider it necessary, allowing early appropriate treatment of patients with severe RA to facilitate the treatment goal of early remission. The only improvements the interviewee would do to the treatment guidelines are to include more information on the treatment of patients with GC and on the appropriate strategies to reduce or discontinue treatment with biologic DMARDs once disease remission is achieved.

On treatment strategies

“biologic DMARDs give the possibility to obtain early disease remission and early disease prevention”. However, the interviewee did not feel the need to always use biologics as first line treatment. In the treatment planning process, once a specialist has decided to treat a patient with biologic DMARDs, an expert committee gets together to discuss the treatment details. Patients are treated with MTX until the committee reaches a conclusion regarding the most suitable treatment and dose of biologic DMARD.
on international guidelines

French specialists consider NICE’s documents and guidelines for their scientific references. However, the interviewee considers their guidelines for the treatment of RA "too stringent, too severe, even unacceptable facing patients"(...) "access to biologic DMARD treatment (in the UK) is too delayed, missing good opportunities of achieving early disease remission and early disease prevention". The fact that patients cannot access biologic DMARD treatment earlier may affect their disease progression and worsen their health state.

5. Comments from stakeholders

Concerns from the patient’s associations in France are: (i3 Innovus, 2009)

- Peer influence: Care is clearly best in the areas near large university hospitals (CHU, centre hospitalier universitaire) with a particular research interest in RA (Montpellier, Toulouse, Paris, Strasbourg and Lyon). Access to care is better, both because the density of specialists is higher and their knowledge is better.
- Geographical distribution: In general, urban areas have better access to treatment than very rural areas, where care can be highly variable with few specialists. Therefore, care in these rural areas is dependent on the individual GP’s knowledge.
- Education: Knowledge at the level of the GP, particularly the older generation of GPs and those in rural areas, still needs to be improved. In particular, patients with moderate or not easily diagnosed disease can still, according to a 2003 survey of the AFP, have to wait 2–10 years for a proper diagnosis [9].

From the high adherence to the guidelines found (i3 Innovus, 2009), and from the interview we could infer that physicians are content with the existing guidelines. The interviewee reported that they would like to have more specific information on the use of GC and additional information on how to diminish or stop biologic DMARD treatment.

6. Summary

What guidelines affect the use of biologic therapies for the treatment of RA?

The two suspended 2007 treatment guidelines published by HAS, which were suspended in 2011 but can still be used until new guidelines are issued.

For patient with the severe RA form, considered under the ALD scheme a treatment guideline published in 2008 is still in force.

How do these affect patients’ access to these therapies?

France has very flexible guidelines that allow early access to biologic DMARDs. Biologic DMARDs can be used as second line treatment after the use of a synthetic DMARD for at least three months. Patients diagnosed with the severe form of the disease can receive biologic DMARDs as first line treatment, if the specialist considers it appropriate.

How are the guidelines reviewed?
The French RA treatment guidelines are in the process of review since September 2011 due to problems with conflict of interests in the previous guidelines. A definition of the review process has not been published and it is not known when the new guidelines will be issued.

What comments have the guidelines provoked (from patients, clinicians, and other opinion leaders)?

Due to the fact that biologic DMARDs are rather accessible, concerns in France are more linked to the access of RA patients to specialists and access to adequate treatment rather than to the access to biologic DMARD treatment.

Abreviations
AFSSAPS: Agence Francaise de Sécurité Sanitaire des Produits de Santé (Medicines Agency)
ALD: Affections de longue durée (long-term illness)
ASMR: Amélioration du Service Médical Rendu (improvement in medical services)
CEPS: Comité Économique des Produits de Santé (Medicinal Products’ Pricing Committee)
CRP: protéine C reactive test
DMARD: Disease-modifying antirheumatic drugs.
ESR: erythrocyte sedimentation rate blood test
EULAR: European League Against Rheumatism
GC: Glucocorticoid
MTX: methotrexate
OTC: Over The Counter drugs
RA: Rheumatoid Arthritis
SFR: Scientific society
SMR: Service Medical Rendu (clinical benefit)
UNCAM: Union Nationale des Caisses d’Assurance Maladie (National Union of Health Insurers)

References


Available at: http://www.cbip.be/Folia/index.cfm?FoliaWelk=F38F09B&keyword=polyarthrite%20r


FPS Social Security, Jan 2011. Social Security. Everything you have always wanted to know, s.l.: s.n.


HAS, April 2008. GUIDE – AFFECTION DE LONGUE DURÉE: Polyarthrite rhumatoïde évolutive grave, s.l.: HAS.

HAS, Sept 2007. Polyarthrite rhumatoïde (PR): diagnostic et prise en charge initiale, s.l.: HAS.


OECD, 2011. OECD Health Data, s.l.: OECD.


**Germany**

*Max Schlueter*

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACPA</td>
<td>Anti-citrullinated protein antibodies</td>
</tr>
<tr>
<td>ACR</td>
<td>American College for Rheumatology</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AMSTAR</td>
<td>Assessment of multiple systematic reviews</td>
</tr>
<tr>
<td>AP</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td>AWMF</td>
<td>Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Working Group of the Scientific Medical Associations)</td>
</tr>
<tr>
<td>bDMARD</td>
<td>biologic Disease Modifying Anti Rheumatic Drugs</td>
</tr>
<tr>
<td>BMG</td>
<td>Bundesministerium für Gesundheit (German Federal Ministry of Health)</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>DAHTA</td>
<td>Deutsche Agentur für Health Technology Assessment (German Agency of Health Technology Assessment)</td>
</tr>
<tr>
<td>DAS</td>
<td>Disease Activity Score</td>
</tr>
<tr>
<td>DGRh</td>
<td>Deutsche Gesellschaft für Rheumatologie e.V. (German Society for Rheumatology)</td>
</tr>
<tr>
<td>DIMDI</td>
<td>Deutsches Institut für Medizinische Dokumentation und Information (German Institute of Medical Documentation and Information)</td>
</tr>
<tr>
<td>DMARD</td>
<td>Disease Modifying Anti Rheumatic Drugs</td>
</tr>
<tr>
<td>DRFZ</td>
<td>Deutsches Rheuma-Forschungszentrum (German Rheumatism Research Centre)</td>
</tr>
<tr>
<td>ERA</td>
<td>Early Rheumatoid Arthritis</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>EULAR</td>
<td>The European League Against Rheumatism</td>
</tr>
<tr>
<td>FFbH</td>
<td>Funktions-Fragebogen Hannover (Function Questionnaire Hannover)</td>
</tr>
<tr>
<td>G-BA</td>
<td>Gemeinsamer Bundesausschuss (Federal Joint Committee)</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma-glutamyl transpeptidase</td>
</tr>
<tr>
<td>GPT</td>
<td>Glutamate pyruvate transaminase</td>
</tr>
<tr>
<td>GOT</td>
<td>Glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>HAQ</td>
<td>Health Assessment Questionnaire</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>IQWIG</td>
<td>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (German Institute for Quality and Efficiency in Health Care)</td>
</tr>
<tr>
<td>MTX</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
</tbody>
</table>
Clinical Guidelines

German clinical guidelines on Rheumatoid Arthritis (RA) are summarised in an interdisciplinary guideline published by the German Society for Rheumatology (DGfR), titled "Management of Early Rheumatoid Arthritis".

Guideline objective and target groups

The guideline objective is to provide all affected people in Germany with a realistic potential for early diagnosis and introduction of a disease modifying and, wherever necessary, multidisciplinary therapy (p. 3). Early Rheumatoid Arthritis (ERA) is defined as the timeframe of 2 years after onset of the symptomatology, and operationalised as a medium disease duration of ≤ 2 years in the respective study population. It refers to patients in ambulatory care and is aimed primarily at primary care physicians, internists and orthopaedists, and to a lesser degree at all other professionals involved in the coordinated and problem-oriented care of patients affected by RA. In terms of the latter, the guideline aims at process optimisation, for example a quicker treatment of patients with suspected RA.

Scope and methodology

The guideline is structured into 9 chapters (introduction, diagnosis and prognosis of ERA, treatment pathways, principles of therapy, medicinal therapy, non-medicinal interventions in multidisciplinary therapy, complementary measures, patient information, guideline report) plus annexes.

The guideline authors and technical experts discussed a number of issues for the last revision published in August 2011, including whether the guideline should be extended to the entire RA, and whether economic recommendations should be included. It was agreed that an extension of the subject scope would not be feasible and sensible or desirable, and that economic considerations may be included where appropriate, but not to (de-) legitimise value based decisions (p. 71). We understand from interviews with experts that the emphasis on ERA is the result of deficiencies in Germany in timely initiating therapies, i.e. within 12 weeks.

The guideline draws on evidence extracted through a two-pronged systematic research. First, research was undertaken on RCTs (limited to 2002 and after, and limited to Leflunomid and the biologics Abatacept, Adalimumab, Anakinra, Etanercept, Infliximab, Rituximab, Certolizumab and Tocilizumab) in the databases MEDLINE/PubMed and Cochrane CENTRAL. Hits were assessed using the Cochrane risk of bias tool. Second, research was undertaken on systematic reviews (SR) and HTA reports in the databases MEDLINE/PubMed, Cochrane DARE and CDR HTA, followed by a quality assessment.
using the AMSTAR instrument. The UK national guideline on RA published by NICE in 2009 was used as an additional source due to its timeliness and high methodological quality (p. 74-82).

**Therapy initiation**

The guideline recommends starting a DMARD therapy as early as possible since evidence suggests this positively influences the prognosis of RA, including therapies initiated before confirmation of an RA diagnosis. It is further advised to maintain the therapy continually, to perform regular checks to monitor responsiveness to the therapy, and to provide for modification through escalation or de-escalation, if applicable (p. 23-24). The guideline explicitly states in its preface that the aim is to provide all new cases of RA in Germany with specialised care within 12 weeks – a goal that is currently only achieved in less than 25% of all new RA cases in Germany.

Overall, the guideline strongly emphasises the importance of early diagnosis and treatment, which is said to offer the biggest potential for optimisation. This is underlined by the new classification criteria jointly published by the American College for Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010, which facilitate early diagnosis.

The clinically critical findings for an estimated diagnosis of RA are: More than 2 affected joints since ≥ 6 weeks, symmetric polyarticular distribution pattern, and morning stiffness ≥ 60 minutes (p. 9). Critical laboratory findings for RA are: Increased erythrocyte sedimentation rate (ESR), increased C-reactive protein levels, detection of rheumatoid factors and/or detection of antibodies against cyclic citrullinated peptides/proteins (ACPA).

The guideline does not make any specific provisions in terms of duration of therapy (this applies both to mono therapy as well as combination regimens using biologics), noting only that the average length of a particular medication with biologics and DMARDs is 3 to 6 years (p. 24).

**Mono and combination therapies**

The guideline makes a general distinction between DMARD mono therapies and combination therapies. For mono therapy, Methotrexate is favoured in terms of effectiveness and tolerability, followed by Sulfasalazine and Cyclosporine A. Methotrexate – usually in combination with a glucocorticoid – is recommended as first line therapy for Early Rheumatoid Arthritis (ERA).

Compared to mono therapies, combination therapies using biologics together with Methotrexate are regarded clinically and radiologically superior in terms of effectiveness and tolerability for patients with ERA (Abatacept + Methotrexate; Infliximab + Methotrexate; Etanercept + Methotrexate; Sulfasalazine + Hydrocholoquine + Methotrexate). Little published evidence exists on other biologics tested in clinical studies on patients with ERA. The guideline draws on evidence from a meta-review of the Cochrane Collaboration (Singh et al 2009), which found all biologics to have good effectiveness except for Anakinra, and Adalimumab, Rituximab and Etanercept to have higher tolerability than other biologics. It further refers to a large-scale systematic overview by Donahue (2008), which found a superiority of combination therapies wherever mono therapies had failed, without determining a specific combination as superior.
Access to biologics

The guideline does not make universally binding recommendations about access to treatment with biologics, or contain any provisions about whether these may only be used for second-line or subsequent treatment. As mentioned above, the guideline generally recommends initiating an ERA therapy with Methotrexat, which can achieve remission in 20-30% of cases. Biologics are said to be monotherapeutically not superior to Methotrexat in cases of ERA, but in line with other RA guidelines they are recommended in cases of failure of a classic DMARD mono therapy with Methotrexate or similar as they are deemed far more effective in combination with Methotrexate than classic DMARDs (p.31, 40). This stance remains unchanged despite recent findings of the OPTIMA study, which used an induction/maintenance model for a 78-week RCT with a combined Adalimumab and Methotrexate regimen and achieved a higher proportion of patients with a DAS28-CRP score below 3.2 compared to the control group treated with a Methotrexate mono therapy (Zoler 2011).

The chapter 'Medicinal Therapy' also includes evidence tables on combination regimens. These have been omitted here but could be included upon request.

DMARD therapy strategies

In terms of therapy strategies, the guideline recommends an early combination therapy as it is clinically superior and inhibits radiological progression compared to mono therapies or sequential therapies. Methotrexate is recommended for therapy initiation as combination partner or mono therapeutic due to its fast effect. This effect is strengthened through a step-down therapy with corticosteroids. In general, close monitoring and control of the disease activity with a specific therapy target (e.g. DAS28 remission) is advised, followed by therapy escalation if the target is missed.

The guideline remarks that in contrast to other countries, Germany has not yet developed a system for multidisciplinary therapy coordinated by clinical nurse specialists, which has been found to yield a higher cost-effectiveness in terms of quality of life and a favourable cost-utility ratio in the overall patient group (Van den Hout et al 2003), although elderly RA patients continue to prefer traditional ambulatory or stationary care by a multidisciplinary team.

Safety

The guideline points out that there is little published evidence on possible adverse drug reactions (ADR) for Leflunomid and other biologics. This applies especially to long-term therapies and effects, and is to be taken into account when making a decision on which therapy to adopt. Therapies with TNF inhibitors usually entail a higher infection risk and a dose-dependent higher rate of malignomas, for which reason the European and American licensing authorities have ordered safety information for biologics. Patients shall be informed about adverse drug reactions and handed out written information materials, and therapies be monitored by means of therapy monitoring sheets (see Annex 4.2).

Documentation and evaluation

In line with modern therapy strategies of RA, the guideline recommends regular recording and documentation of disease activity and course of disease. Subject to the reaction time of the various DMARDs, such documentation is to be carried out every 3
As a standard instrument, the guidelines suggest using the Disease Activity Score (DAS28), or optionally the ACR remission criteria of ACR50. Values < 2.6 reflect a well-controlled disease activity, while values > 3.2 mean insufficient control. Besides disease activity, other outcome parameters listed in the guidelines for assessment of the effectiveness of DMARD therapies mainly include functionality (by means of the Function-Questionnaire Hannover (FFbH) or the Health Assessment Questionnaire (HAQ)), quality of life (SF-36, patient self-assessment, fatigue), and radiological progression (to be assessed annually) (p. 20, 23).

**Guideline review, dissemination and enforcement**

First published in 2005, the guideline was revised in 2007 and in August 2011. The next revision is planned for 2015. The guideline director will commission a revision research and activate the guideline group. The guideline authors will notify the guideline director in case any significant findings emerge in the meantime. Further, the guideline director shall contact all guideline authors every 2 years to enquire whether a revision is necessary ahead of schedule.

In terms of dissemination, the guideline is published with an initial circulation of 2,500 copies and provided to interested doctors. Besides the document is available online for download on the DGRh and AWMF websites. The guideline contents are presented in quality circles of doctors in private practice and made available as downloadable slide-kit for training purposes. Finally, the guideline is supported by a patient version (chapter 8 of the guideline) and integrated therapy monitoring sheets (with patient and doctor versions).

No provisions are included about guideline enforcement. This issue was followed up in the interview with the guideline coordinator, Prof. Markus Schneider (see chapter 3.1).

**Health Technology Assessment**

**DIMDI**

Research was undertaken to ascertain the existence of any German HTA reports on RA. Consulted databases included the German Cochrane Centre and the German Institute of Medical Documentation and Information (DIMDI), which houses the German Agency of Health Technology Assessment (DAHTA). Upon written request to the director of DIMDI it was confirmed that up to date there are no German HTA reports on biologic therapies for the treatment of Rheumatoid Arthritis.

**IQWIG**

The German Institute for Quality and Efficiency in Health Care (IQWIG) published a preliminary report plan in May 2011, titled “Biotechnologically produced pharmaceuticals in second line therapy for Rheumatoid Arthritis. Report plan”. Commissioned by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany, the objective of the report is to assess the following bDMARDs for second line therapy of Rheumatoid Arthritis:

- Abatacept (Orencia®)
- Adalimumab (Humira®)
- Anakinra (Kineret®)
- Certolizumab Pegol (Cimzia®)
- Etanercept (Enbrel®)
• Golimumab (Simponi®)
• Infliximab (Remicade®)
• Rituximab (MabThera®)
• Tocilizumab (RoActemra®)

Comparator interventions will be the treatment with another bDMARD, non-biotechnologically produced pharmaceuticals, or treatment without therapy expansion.

Patient relevant endpoints used for the study will be: Remission; pathology of RA; structural joint deformity; bodily functional status, including daily activities; social functional level (participation in professional and social life); health related quality of life; overall mortality; adverse drug reactions (ADR).

Methodologically, the IQWIG study will collect data through systematic literature research on primary RCT studies in the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and BIOSIS Previews databases. In addition, relevant secondary publications from systematic overviews and HTAs will be included. Finally, the study will also draw on available data from pharmaceutical companies, publicly accessible study registers, publicly accessible documents of licensing authorities, and information from selected authors as well as feedback provided on the hearing and preliminary report.

In a comment on the IQWIG report plan, the DGRh has criticised the choice of clinical endpoints and requested a review of selected criteria (Braun et al. 2011). More specifically, by drawing solely on randomised clinical trials the sample sizes and follow-up periods will be insufficient to validly measure endpoints such as overall mortality and structural joint deformity. Other selected endpoints such as pain, fatigue and morning stiffness are said to lack sufficient specificity, for which reason DGRh rather advises use of response criteria such as ACR50 or DAS28. Finally, the authors criticise a lack of patient relevant endpoints and a formulation of statistical methods for evaluation of results, which increases the risk of misinterpretations.

Interview Comments

A total of 4 interviews were conducted with representatives of relevant organisations and patient groups to gather comments on the above guidelines and their implications for the access to biologic therapies for the treatment of RA. The interviews further served the aim of verifying the accuracy of data on current guidelines and future reviews, and to obtain views on how Germany compares with other European countries in terms of access to, and treatment with biologics. Three of the interviews are reported below. The fourth was excluded in order to protect the anonymity of the interviewee, who would have been identifiable from the data.

Interview 1

With regard to the guideline contents and recommendations, there have been no changes since its last revision in August 2011. In terms of enforcement the guideline is widely accepted and used among rheumatologists in Germany, not least since "physicians realised that the guideline is accepted and endorsed by payers". Acceptance among GPs was more difficult to measure, but by now 5,000 copies of the guideline have been disseminated at congresses, further training courses and other events.

The interviewee pointed out a number of differences between the DGRh guidelines and those of other EULAR member countries: "The biggest difference is that our guideline is marked by interdisciplinarity – all relevant stakeholders are involved [in the
development of the guideline. With regard to the classic EULAR recommendations, the difference is that we are not only medically oriented but cover all other treatment options and aspects as well. Undoubtedly there is demand for complex therapies, and in this regard the EULAR recommendations do not go far enough in our view. The only comparable guideline I am aware of is that of SIGN (Scottish Intercollegiate Guidelines Network). The problem I see with the SIGN guideline is that it needs to be updated. In comparison to the UK, in Germany we focus on Early Rheumatoid Arthritis."

The DGRh is currently developing an algorithm guideline for RA therapy stratification that will allow a hierarchisation of medicinal treatment options. The corresponding publication is planned for autumn 2012.

Interview 2

With regard to the DGRh decision to focus on ERA, the interviewee pointed out that the SIGN guideline with its emphasis on ERA was used as the starting point for the development of the German guideline and that it was in ERA that Germany faced the biggest deficiencies. He also added that the current evidence-based algorithm guideline project will incorporate EULAR recommendations and close the gap to provide medicinal recommendations for the entire RA.

Asked about the guideline recommendations on access to biologic therapies, he stressed that they were “intentionally formulated in more general terms” so as to allow more flexibility in treatment options for individual cases, subject to individual treatment responsiveness. Generally speaking, however, it is advised to apply two DMARD therapies (first MTX, then a combination therapy) before switching to biologics: “According to economic considerations as well as available evidence it is right and sensible to start a therapy with Methotrexate and a corticoid.”

In this context, he highlighted differences with other countries applying “more restrictive regimes, such as the UK, which demand a particular DAS to be achieved or dictate Rituximab as second biologic”.

Interview 3 – Patient Representative

The interviewee generally endorsed the guideline. Asked about access to treatment with biologics, they responded that the primary concern was not the therapy itself (which is regarded as excellent), but rather the high figures of delayed therapy commencement, saying that only about 20% of RA patients are seen to by a rheumatologist within three months and that the therapy is not initiated early enough. The waiting time for the initial visit to the rheumatologist is too long, and this causes the entire treatment process of MTX, combination therapy and biologics to start too late. The interviewee emphasised the importance of improving close disease monitoring and performing continuous treatment adjustments.

A further point of criticism was not about the guideline per se but about its implementation, supply inequalities due to an insufficient number of rheumatologists. There is also a degree of gender inequality, with elderly women less likely to receive biologic treatment than men.

The weak point of guidelines generally is that we have too few comparative clinical trials on combination therapy vs. biologic therapy and their relative effectiveness, and too few comparative trials among the various biologics. In this sense, there still is a lack of evidence as to when which biologic should be used.
### Annexes

**List of Disease Modifying Drugs licensed in Germany**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Medicinal Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept</td>
<td>Orencia®</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira®</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Kineret®</td>
</tr>
<tr>
<td>Hydroxychloroquin</td>
<td>Quensyl®</td>
</tr>
<tr>
<td>Chloroquin</td>
<td>Resochin®, Weimer quin®</td>
</tr>
<tr>
<td>Azathioprin</td>
<td>Azafalk®, Azaimun®, Azamedac®, Aza-Q®, Azathioprin®, Colinsan®, Imurek®, Zytrim®</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Cimzia®</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Ciclooral®, Ciclosporin®, Immunosporin®, Sandimmun®</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel®</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Simponi®</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade®</td>
</tr>
<tr>
<td>Leflunomid</td>
<td>Arava®, Leflunomid®</td>
</tr>
<tr>
<td>Mehtotraxat</td>
<td>Lantarel®, Metex®, Methotrexat®, Mtx®</td>
</tr>
<tr>
<td>Parenteral Gold</td>
<td>Tauredon®</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Mabthera®</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Azulfidine®, Colo-Pleon®, Pleon.®, Sulfasalazin®</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Ro-Actemra®</td>
</tr>
</tbody>
</table>

### Therapy monitoring sheets for biologics

The table below lists abridged versions of therapy monitoring sheets (doctor version) for selected biologics licensed in Germany. Some indicators such as contraindication, contraception / pregnancy and interactions with other pharmaceuticals are omitted from the overview table. Monitoring sheets are foreseen for all biologics licensed in Germany; although there may be delays in finalising some of the sheets and publishing them on the DGRh website (including, for example, Golimumab).

#### Abatacet

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Continuous long-term therapy; 10mg/kg body weight as intravenous infusion at beginning, after 2 and 4 weeks, every 4 weeks thereafter; patients to be monitored for 1 hour after infusion for ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>Expected 3 months after therapy initiation; reconsider treatment if</td>
</tr>
<tr>
<td><strong>No sufficient response after 6 months</strong></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

**Monitoring prior to therapy**
- Ruling out of clinically active infections; determination of disease activity via validated activity and function scores; up-to-date radiographs; screening for active or latent tuberculosis

**Monitoring during therapy**
- Clinical rheumatologic documentation with validated activity scores (infections, abscesses, fever, cough, weight loss, lymph node status, B symptomatology) after 3, 6 and 12 months and every 6 months thereafter; annual radiography of relevant joints; laboratory safety and activity parameters (ESR, CRP, complete blood count, SGOT, AP, creatinine) after 2 and 4 weeks, every 3 months thereafter

**Indicators for therapy interruption**
- No data on infection risks for surgical interventions during Abatacept therapy, therefore interruption 4 weeks prior to surgery and reuptake after ≥ 14 days

**Documentation**
- No specification

### **Adalimumab**

**Dosage**
- Continuous long-term therapy; 40mg (hypodermic) every 14 days

**Onset of action**
- Expected after 2-3 weeks; reconsider treatment if no sufficient response after 8-12 weeks or dosage increase to 40mg per week

**Monitoring prior to therapy**
- Ruling out of cardiac insufficiency (NYHA III/IV); screening for active or latent TB; up-to-date radiography of thorax, complete blood count; SGOT; AP and creatinine

**Monitoring during therapy**
- Check for infections, abscesses, fever, cough, weight loss, lymph node status, B symptomatology; laboratory assessments for ESR, CRP, complete blood count, GOT, AP creatinine after 2 and 4 weeks, after 2 and 3 months, and according to clinical discretion thereafter

**Indicators for therapy interruption**
- Severe infections (e.g. sepsis, opportunistic infections, active TB); lupus like syndrome; new or deteriorating symptoms of decomposing cardiac insufficiency; No data on infection risks for surgical interventions during Adalimumab therapy, therefore interruption 14 days prior to surgery and reuptake after ≥ 14 days

**Documentation**
- No specification

### **Anakinra**

**Dosage**
- 100mg/day (hypodermic)

**Onset of action**
- Expected after 2 weeks; reconsider treatment if no sufficient response after 8-12 weeks

**Monitoring prior to therapy**
- Ruling out of clinically active infections; laboratory assessment for severe renal dysfunction and neutropenia; up-to-date radiography of thorax

**Monitoring during therapy**
- Questioning and clinical assessment (reactions at injection site, infections, abscesses, fever, cough, lymph node status); laboratory assessment via monthly haemogram during the first 6 months and every 3 months thereafter; creatinine every 3 months; annual radiography
<table>
<thead>
<tr>
<th>Indicators for therapy interruption</th>
<th>Severe allergic reactions; severe infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation</td>
<td>Standardised long-term documentation using the DRFZ tool “Rabbit”</td>
</tr>
</tbody>
</table>

**Etanercept**

<table>
<thead>
<tr>
<th>Dosage</th>
<th>No specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>Expected 3 months after therapy initiation; reconsider treatment if no sufficient response after 6 months</td>
</tr>
<tr>
<td>Monitoring prior to therapy</td>
<td>Ruling out of clinically active infections; up-to-date radiograph of thorax; tuberculin test where applicable</td>
</tr>
<tr>
<td>Monitoring during therapy</td>
<td>Questioning and clinical assessment (infections, abscesses, fever, cough, dyspnea, lymph node status, B symptomatology); laboratory assessment via haemograms every 14 days during the first 3 months of therapy, every 4 weeks from months 4-6, every 3 months thereafter</td>
</tr>
<tr>
<td>Indicators for therapy interruption</td>
<td>In cases of localised or generalised infections (both acute and chronic); lupus like disease or multiple sclerosis; active TB; No data on infection risks for surgical interventions during Etanercept therapy, therefore interruption 1 week prior to surgery</td>
</tr>
<tr>
<td>Documentation</td>
<td>Standardised long-term documentation using the DRFZ tool “Rabbit”</td>
</tr>
</tbody>
</table>

**Infliximab**

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Continuous long-term therapy, indication dependent 3-5mg/kg body weight as intravenous infusion at start, after 2 and 6 weeks, every 8 weeks thereafter; patients to be monitored for 1-2 hours after infusion for ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>Expected after 2-3 weeks; reconsider treatment if no sufficient response after 8-12 weeks or dosage increase up to 7.5mg/kg</td>
</tr>
<tr>
<td>Monitoring prior to therapy</td>
<td>Ruling out of clinically active infections and cardiac insufficiency (NYHA III/IV); screening for active or latent TB; up-to-date radiography of thorax; laboratory assessment via complete blood count, GOT, AP and creatinine</td>
</tr>
<tr>
<td>Monitoring during therapy</td>
<td>Check for infections, abscesses, fever, cough, weight loss, lymph node status, B symptomatology; laboratory assessments for (ESR, CRP, complete blood count, GOT, AP creatinine) after 2 and 4 weeks, after 2 and 3 months, and according to clinical discretion thereafter</td>
</tr>
<tr>
<td>Indicators for therapy interruption</td>
<td>Severe infections (e.g. sepsis, opportunistic infections, active TB); lupus like syndrome; new or deteriorating symptoms of decomposing cardiac insufficiency; No data on infection risks for surgical interventions during Infliximab therapy, therefore surgery preferably only after end of infusion interval and reuptake after ≥ 14 days</td>
</tr>
<tr>
<td>Documentation</td>
<td>No specification</td>
</tr>
<tr>
<td><strong>Leflunomid</strong></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>No specification</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>Expected after 4-6 weeks; reconsider treatment if no sufficient response after 4 months</td>
</tr>
<tr>
<td><strong>Monitoring prior to therapy</strong></td>
<td>No specification</td>
</tr>
<tr>
<td><strong>Monitoring during therapy</strong></td>
<td>Questioning and clinical assessment (blood pressure, herpetiform skin lesions, gastro-intestinal indication, weight loss); laboratory assessment via differential haemogram, GOT, AP, creatinine, GPT, GGT</td>
</tr>
<tr>
<td><strong>Indicators for therapy interruption</strong></td>
<td>Haematology (leucopenia, lymphocytopenia, thrombopenia), gastroenterology (transaminases)</td>
</tr>
<tr>
<td><strong>Documentation</strong></td>
<td>No specification</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Rituximab</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>Two-time infusion therapy with 1,000mg in 14-day intervals, possibly further treatment cycles after 6 and 12 months</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td>Expected after 2-8 weeks; reconsider treatment if no sufficient response after 16-24 weeks</td>
</tr>
<tr>
<td><strong>Monitoring prior to therapy</strong></td>
<td>Ruling out of clinically active infections, Hepatitis B, cardiac insufficiency (NYHA III/IV)</td>
</tr>
<tr>
<td><strong>Monitoring during therapy</strong></td>
<td>Clinical assessment (infusion reactions such as urticaria, pruritus, exanthema, dyspnea, angina pectoris, blood pressure, fever, myalgia and arthralgia</td>
</tr>
<tr>
<td><strong>Indicators for therapy interruption</strong></td>
<td>Severe infections, cardiac insufficiency</td>
</tr>
<tr>
<td><strong>Documentation</strong></td>
<td>Monitoring using MTX-specific controls if used in combination with methotrexate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Sulfasalazine</strong></th>
<th></th>
</tr>
</thead>
</table>
| **Dosage** | Continuous long-term therapy:  
1. Week: 0 - 0 - 1 tablets/day  
2. Week: 1 - 0 - 1 tablets/day  
3. Week: 1 - 0 - 2 tablets/day  
4. Week: 2 - 0 - 2 tablets/day |
| **Onset of action** | Expected after 4-12 weeks; reconsider increase of dosage if no sufficient response after 3 months to 2 / 2-2 tablets/day; discontinue treatment if no effect after 6 months |
| **Monitoring prior to therapy** | No specification |
| **Monitoring** | Every 14 days during first 3 months, every 4 weeks during months 4-6, every 3 months thereafter: Questioning and clinical assessment |
during therapy (exanthema, gastro-intestinal symptoms, fever); laboratory assessment via differential haemogram including thrombocytes, alkaline phosphatase, GPT, creatinine, urine status

Indicators for therapy interruption Exanthema, stomatitis, severe gastro-intestinal disorders, hepatitis, leucopenia, thrombopenia, proteinuria, pulmonary infiltrate, neurological disorders, allergic symptoms

Documentation No specification

References


Greece

Sotiris Vandoros

Introduction

Following the need to reduce pharmaceutical expenditure in Greece (which was the highest per capita in the EU in 2009), the Ministry of Health has reduced costs significantly by a) directly targeting pharmaceutical prices and 2) increasing generic market shares, although there is still room for improvement in the very inefficient pharmaceutical market.

However, access to medicines has not been affected, and co-payments have not changed. As mentioned in the interview, medicines for RA are fully reimbursed.

The authorities state that access to medicines is guaranteed, but in a country in financial crisis nothing can be taken for granted.

Translation of the Official Guidelines produced by the National Organisation for Medicines (EOF)

Basic principles of treatment

- Objective of the treatment must be to put the patient into remission or into low disease activity as soon as possible (3-6 months).

If this goal is not achieved, the treatment should be modified following strict and regular monitoring follow up (modification of current treatment every 1-3 months)

- Treatment with Disease-Modifying Anti-Rheumatic Drugs (DMARDs) should begin upon diagnosis of RA.

- If the therapy objectives are not met following the use of the first DMARD and if adverse prognostic factors* exist, biologic factors should then be added. If adverse prognostic factors do not exist, treatment could involve another DMARD or a combination of disease-modifying drugs (leflunomide, cyclosporine, sulphazalazine, injectable gold, D-penicillamine)

- Depression of the disease achievement requires drug treatment for life and regular medical assessment.

* Adverse prognostic factors are the following:

  a. Presence of RF or/and anti-cyclic citrullinated peptide (CCP) antibodies (especially at high levels).

  b. Radiological abnormal findings in hands or/and feet.

  c. High levels of achievement of the disease (based on indicators of achievement of the disease, the number of inflamed joints, or the presence of acute phase proteins).

1st choice

- glucorticoids 7.5 mg/day
- methotrexate (7.5-15 mg) and
- In case of intolerance the following could be used: Leflunomide, cyclosporine, sulphazalazine, injectable gold, D-penicillamine

The duration of the treatment should be at least 3-6 months so that the effectiveness could be appraised. If the effectiveness is satisfactory the treatment should be continued.

**2nd choice**

(added in cases of failure of drugs of the 1st choice + presence of adverse prognostic factors)

- Anti-TNF factors (infliximab, adalimumab, etanercept, certolizumab, golimumab)

**3rd choice**

If treatment with the first inhibitor of the TNF fails, another inhibitor of TNF or abatacept or rituximab or tocilizumab should be provided.

**Note 1:** Abatacept and tocilizumab have indication for first line treatment with biological factors but the long time experience of the international academic community as well as ours with regards to anti-TNF factors, tends to propose starting treatment with anti-TNF.

Also, approval has been given to anakinra but we belive that its effectiveness is not equivalent to others and we do not suggest it as treatment for RA

**Note 2** The coexistence of other diseases is always crucial for the selection of a biological factor eg. Suffering from HbSAg should be seriously taken into account with regards to the administration of rituximad. The same holds for a personal history of tumor neoplasia with the administration of TNF factors.

**Note 3** Treatment with biological factors in RA should be continued only if there is evidence of satisfactory response of the disease after 6 months of continuous treatment.

If the response is not satisfactory, treatment should be ceased and substituted by another biological factor or any other treatment that is considered necessary.

**Note 4** The cost of the treatment should always considered in relation to the result for the patient.

**Notes on the Unofficial Guidelines produced by the Hellenic Society for Rheumatology (ERE-the organization of Greek Rheumatologists), Greece**

As stated on the website of the Hellenic Society for Rheumatology (ERE-the organization of Greek Rheumatologists) the therapeutic prescribing guidelines for rheumatoid diseases were developed by the Scientific Committee of the National Organisation for Medicines (EOF) with the comments of the Hellenic Society for Rheumatology and adopted unanimously by the Central Health Council on 26-09-2011.
The guidelines that are currently presented on the website of the Hellenic Society for Rheumatology are exactly the guidelines adopted by the National Organisation for Medicines (EOF) in 2011.

However, these guidelines are rather vague. As requested, I present the guidelines presented by the Hellenic Society for Rheumatology in 2008, which were more detailed, as they refer to DAS28. In particular, below please find the additional features and specific information included in these guidelines that are not mentioned in the National Organisation for Medicines (EOF) guidelines in 2011.

The Guidelines of the Hellenic Society for Rheumatology (issued in 2008) mention the following (in addition to what is included in the National Organisation for Medicines (EOF) guidelines in 2011):

**Anti-TNFα factors**

Anti-TNFα factors are recommended for the treatment of rheumatoid arthritis for the patients who have an established disease, as long as treatment with ≥1 traditional DMARDs or combinations of DMARDs has failed. The first phase of treatment with DMARDs must certainly include methotrexate or leflunomide, unless there are indications against their use.

- Sufficient therapeutic treatment of DMARDs is considered the administration of the following for at least 3 months:
  
  Methotrexate ≥ 15mg/week
  
  Leflunomide 20mg/day
  
  Sulphazalazine 3gr/day
  
  Hydroxychloroquine 400mg/day
  
  Azathioprine 2mg/kg/day
  
  Cyclosporine 3mg/kg/day

- **Early Rheumatoid Arthritis** (duration of symptoms <6-9 months). Patients with early RA who begin treatment for the first time should take traditional DMARDs (methotrexate, leflunomide, sulphazalazine, hydroxychloroquine, cyclosporine).

  Treatment can involve anti-TNFα factors (in combination with methotrexate) in cases that we observe:

  a) High achievement of the disease (DAS28>5.1 or >6 joints with edema and >6 sensitivity

  AND

  b) presence of 2/5 adverse prognostic factors

  - It is recommended that anti-TNFα factors be combined with DMARDs.
  
  - The efficacy of anti-TNFα factors is higher than that of anakinra.
- Recommended criteria for interruption of treatment with biologic factors due to lack of effectiveness are the following:

a) improvement of DAS28 < 1.2 and current DAS28 > 5.1

OR

b) ≤ 30% decrease in the number of active joints and active joints > 6 with edema and sensitivity.

- In cases of failure of the first anti-TNFα factor, it is acceptable to switch to another anti-TNFα factor or to administrate abatacept or rituximab.

- Adalimumab, etanercept and infliximab have been approved for use individually or in combination with other DMARDs (MTX, SSA) for the treatment of serious, established RA.

- A value of BASDAI > 4 (together with an expert’s advice) is suggested as a criterion of the achievement of serious, established RA and the beginning of treatment with anti-TNFα factors.

- There are differences between anti-TNFα factors with regards to efficacy, safety and way of administration, which must be taken into account when deciding upon the appropriate treatment.

- Recommended doses:

  Adalimumab: 40mg/2 weeks

  Etanercept: 25mg/twice/week or 50mg/week

  Infliximab: 5mg/kg

There are no studies on the efficacy of increased doses

- Response to treatment is expected after 16-24 weeks, which is when this must be quantified with objective indexes (BASDAI, pain index etc). Improvement of BASDAI by less than 50% or less than 2 on a 0-10 scale indicates ineffective response.

- Prior to treatment with anti-TNFα factors, every patient must be screened by having their medical history studied, with a chest x-ray and a Mantoux test (positive: >=5mm). Similar preventative measures must be taken for all three anti-TNFα factors.

**Rituximab**

- Rituximab is recommended in combination with MTX if the disease is resistant to methotrexate and at least one anti-TNFα factor.

- Rituximab can be used as the first biologic treatment (before the use of anti-TNFα factors), when there are indications against the use of anti-TNFα factors, in the following cases:

  a) Patient history of lemphohyperplastic disease
b) Chronic/relapsing infection with intracellular pathogen (HSV, HZV, listeria)
c) Demyelinating disease, optic neuritis

**Abatacept**

Abatacept is recommended in combination with MTX if the disease is resistant to methotrexate and at least one anti-TNFα factor.

**Anakinra**

According to clinical trials, the effectiveness of Anakinra is lower compared to anti-TNFα factors.

**Interview with a Greek expert in rheumatology**

1. **Do guidelines affect the use of biologic therapies for the treatment of R.A?**

Although there is no formal evaluation of the exact impact of existing guidelines on daily clinical practice, they certainly affect the way that rheumatologists prescribe different biologics in patients with RA.

2. **How do these guidelines affect patients’ access to medicines?**

In general there are no obstacles in patients’ access to biologic therapies as long as these are officially indicated for RA.

3. **How often are the guidelines reviewed?**

In 2011, therapeutic protocols were published by the authorities (EOF-National Organisation for Medicines). These include the newest biologics for rheumatoid arthritis. Apart from the guidelines from the National Organisation for Medicines, there are also the guidelines from the Hellenic Society for Rheumatology (ERE-the organization of Greek Rheumatologists), which have been updated twice since 2004 (2004 and 2009 and a new update is scheduled for this year). However, the latter is not a government agency.

4. **Are new biologics being introduced frequently?**

New biologics are introduced fairly quickly as soon as they receive approval from the EU (EMEA) and National (EOF - National Organisation for Medicines) regulatory agencies.
5. What comments have the guidelines provoked (from patients, clinicians and other opinion leaders)?

In general, although there are some arguments in favour of or against these guidelines, they are widely accepted by rheumatologists and opinion leaders. It is important to note that these Guidelines are in close agreement with European Guidelines/recommendations issued by the European League against Rheumatism (EULAR), which is the official organization of European Rheumatologists.

6. How are guidelines applied in practice in Greece?

To date, these Guidelines are not binding for practicing clinicians and there is no formal way for evaluating clinician practices. Recently, with the publication of the therapeutic protocols from EOF, medications prescribed off label or for compassionate use (not officially indicated for a particular disease) and need EOF authorization, must conform to these protocols, otherwise they are not usually authorized for use.

7. Are there variations in access to new medicines? Are there variations in different geographical regions in the use of medicines for RA?

In general there is no significant variation in access to these medications all over Greece. There could be some difficulties in accessing intravenous biologics in rural areas where there are no hospitals for administration of these medications.

8. What is the reimbursement situation?

These medications are 100% reimbursable.

9. Is there a scoring system (DAS28)?

For patients with rheumatoid arthritis, the existing Guidelines for implementation of biologic therapies (start, continuation, switching) are based on the DAS28 score (a marker of clinical and laboratory activity of the disease).

10. Are there restrictions on the use of funds with regards to the use of medicines for RA?

To date there are no restrictions in the number of prescriptions of biologics for patients with rheumatic diseases.
11. Are physicians up-to-date with developments with regards to new medicines and interventions?

Greek rheumatologists are in general up to date with the new developments for the treatment of rheumatic diseases with biologics through National and International Meetings that they frequently attend.
Ireland

Sean Boyle

Rheumatoid arthritis in adults: review of the guidelines in Ireland

This paper is intended to provide material relating to health care in Ireland for a comparative review of guidelines across several European countries on the use of biological therapies in the treatment of rheumatoid arthritis (RA) in adults.

There are no statutory guidelines in place in Ireland. There is a reference to an expectation that guidelines would be introduced (Kee et al. 2005), but so far there is no declared intention to publish statutory guidelines. However, the Irish Society for Rheumatology (ISR) published guidelines in 2005 (ISR 2005). These are discussed below.

There follows some discussion of the practical impact on access to these therapies, mostly based on the Kee et al. paper mentioned above.

Juvenile RA is not discussed in this paper.

1 Background

Rheumatoid arthritis (RA) is an ‘auto‐immune’ disease that affects the joints of the body. It is a long‐term disease – there is no cure – that causes inflammation, swelling and stiffness and resultant pain. Treatments are designed to ease the pain and slow down the development of the disease. Early initiation of treatment may help to minimise damage to joints (NICE 2009). Usually a distinction is made between RA patients who are ‘recent onset’ defined as disease duration of up to two years, and ‘established’, defined as disease duration longer than two years.

In Ireland, around 75% of people with RA are women. The onset of RA is most common between the ages of 30 and 50 years, but it can occur at any age (http://www.arthritisireland.ie/go/publications/information_booklets/living_with_rheumatoid_arthritis accessed 16 February 2012).

No information is available at a national level on the overall costs of RA to the Irish health care system. There is also no nationally available information on the use of biological drugs within the Irish health care system.

2 The care pathway for adults with RA

The care pathway for adults with RA consists of four key elements:

5. early identification of the problem;
6. pharmacological management;
7. ongoing monitoring of the patient; and,
8. timing and referral for surgery.
Although ongoing monitoring and surgery are important aspects of the care pathway, they are not discussed in this paper. In addition other key aspects of care include good communication with and appropriate education of the patient, the use of a multi-disciplinary team, good symptom control, and the use of diet and complementary therapies where considered appropriate.

2.1 Early identification

It is important that recent-onset RA is identified as soon as possible and that the patient is referred for specialist opinion. Key to identification is to establish the existence of synovitis (inflammation of the membrane lining the inside of synovial joints which is revealed in pain, swelling, heat, loss of function and stiffness). Early recognition of RA is important as left untreated it can result in substantial damage to the joints which may otherwise be avoided.

2.2 Pharmacological management

The key intervention for people with RA is the use of DMARDs (disease-modifying anti-rheumatic drugs). There is a consensus that DMARD therapy should be started as soon as possible. However, the key questions are which DMARD to use, and whether one drug or a combination should be used.

A key distinction is made between ‘conventional’ DMARDs and biological therapies. It is to the latter group that this paper is directed. The full NICE guidelines (NCCCC 2009) define biological drugs as,

*a type of DMARD which targets pro-inflammatory cytokines that are involved in joint destruction (particularly TNF-α and IL-1).*

All DMARDs can be helpful in slowing down the damaging component of the disease process although it is widely recognised that biologics can act more quickly and be more successful.

Conventional DMARDs include six main drugs: methotrexate, sulphasalazine, hydroxychloroquine, leflunomide, ciclosporin and gold injections.

The development of biological therapies over the last ten years has seen their increasing use in the treatment of RA. This group of drugs consist of monoclonal antibodies and soluble receptors that specifically modify the disease process by blocking key protein messenger molecules (such as cytokines) or cells (such as B-lymphocytes). The development of biological drugs has been based on an increasing understanding of the disease pathology. The key drivers of RA include cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) (NCCCC 2009, p6).

Biologic drugs include the five TNF-α inhibitors (also known as anti-TNF (tumour necrosis factor)): etanercept, adalimumab, infliximab, certolizumab pelog, and golimumab. Additional
biological drugs that are licensed for use include: rituximab, a chimeric monoclonal antibody that depletes B-cells; abatacept, a selective T-cell co-stimulation modulator that blocks a key co-stimulatory signal required for T-cell activation; and tocilizumab which is a humanised monoclonal antibody that inhibits cytokine interleukin-6 (IL-6).

The optimal sequencing of DMARDs remains a source of debate; whether patients should be started on combinations of therapies or single DMARDs is also contentious. Biological drugs are substantially more expensive than conventional DMARDs and so the distinction is crucial.

3 Guidelines for biological therapies

There are no formal or statutory guidelines in Ireland relating to the use of biological drugs for treatment of RA in adults. Five anti-TNF drugs are licensed for use in Ireland for the treatment of RA: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab (Adams et al. 2011). In Ireland the Health Service Executive (HSE) is the body responsible for the delivery of health and social services. The HSE provides some information about the treatment of RA on its website but at a fairly basic level (accessed 16 February 2012: http://www.hse.ie/eng/services/swineflu/A-Z/R/Rheumatoid-arthritis/Rheumatoid-arthritis-Treatment.html).

Thus, the HSE states there are many conventional DMARDs available for use including methotrexate, gold injections, leflunomide, hydroxychloroquine and sulphasalazine. Methotrexate is often the first drug given for RA, and may be taken in combination with other DMARDs. The HSE describes biological therapies eg TNF-α inhibitors (etanercept, infliximab, adalimumab and certolizumab pelog), rituximab and tocilizumab as a newer form of treatment for RA – although they are not that new – and states that these are usually taken in combination with methotrexate or sometimes with another DMARD.

The HSE also mentions that rituximab and tocilizumab are recommended by NICE in combination with methotrexate for severe RA but only if a patient has been on a DMARD and one of the TNF inhibitors, and still has ‘quite active’ RA.

Arthritis Ireland is the Irish patient organisation (arthritisireland.ie) and the ISR is the organisation for rheumatologists (isr.ie). In addition there is the Irish Rheumatology Health Professionals Society (irhps.ie).

3.1 ISR guidelines for biological therapies

In 2005 the ISR produced a set of guidelines for prescribing TNF-α blockers in adults with RA (ISR 2005). These guidelines are referred to in several published articles but are not longer available on the ISR website. The guidelines were not formally published although according to one Irish rheumatologist, there was a high degree of acceptance by the profession. A hard copy was obtained from a UK rheumatologist.

These guidelines were said to be based on the British Society of Rheumatology (BSR) guidelines that were published in 2004. The guidelines relate to just three biologics: adalimumab, etanercept, and infliximab.
The ISR states that the guidelines are: not prescriptive and need to be tailored to the individual patient, clinic, institution and jurisdiction.

The ISR guidelines state that to be eligible for treatment with biological therapies, most patients should meet the following criteria:

- fulfil the 1987 criteria of the American College of Rheumatology classification criteria for a diagnosis of RA;
- have persistent, active RA with a DAS > 5.1; and,
- have failed standard therapy.


We assume that by DAS the ISR intends DAS‐28 as this as the one in use by the BSR. The original DAS measure would give slightly different results, and also has a different range. The ISR goes on to indicate that lesser DAS values may also indicate disease activity, and also suggests physician global assessment, progressive erosive change, acute phase elevation as alternative disease activity measures. It is also suggested that measurement should take place on two occasions separated by a minimum of four weeks, although this is not mandatory.

Failure to respond to standard therapy is defined in the guidelines by failure to respond or tolerate an adequate therapeutic trial of standard DMARD. Adequate therapeutic trial is defined as at least three months, with at least two months at a standard target dose unless significant toxicity limited the dose tolerated. Treatment may be less than three months where it was withdrawn due to drug intolerance or toxicity.

In most cases the standard therapy will be methotrexate at a target dose of up to 25mg per week. Poor prognosis patients may be considered for anti-TNF therapy after a single agent failure where markers for poor prognosis may be: rheumatoid factor seropositivity, erosive disease, rheumatoid nodules and / or elevation of acute phase response.

In cases where standard DMARDs are contraindicated, anti-TNF therapy may be considered early in the course of the disease, even where methotrexate has not been used. Although adalimumab and etanercept are licensed for use as monotherapies, the evidence suggests that in the absence of contraindication, most patients are best managed by co-prescription with methotrexate.

The ISR recommends that biological therapy should be withdrawn if it is inefficacious. The guidelines encourage the use of composite scoring systems for this purpose eg DAS-28 but ultimately suggest that efficacy must be determined by the supervising clinician and the patient. However, if one anti-TNF therapy does not work, then an alternative anti-TNF therapy can be tried.

With respect to reduction in dosage, The ISR notes,
Some patients who have responded well to anti-TNF therapy may be able to remain in remission with a reduced dose or reduced frequency of treatment...[but]...each patient needs to have their regime tailored individually.

3.2 Information from Arthritis Ireland

Information for patients on the Arthritis Ireland website suggests that etanercept, infliximab and adalimumab are the biologics that are widely used in Ireland but only for people with severe RA who have not been helped by conventional DMARDs. Rituximab and abatacept are also available but only if other DMARDs including anti-TNFs have not been successful. Rituximab is given with methotrexate; abatacept can be given as a monotherapy. Finally, tocilizumab is described as a new biological drug that is prescribed for treatment of moderate to severe RA that has not responded to other treatments. It can be given as a monotherapy or in conjunction with methotrexate (accessed 16 February 2012: http://www.arthritisireland.ie/go/publications/information_booklets/living_with_rheumatoid_arthritis).

4 Review of guidelines

There have not been any guidelines published subsequently by the ISR, nor is there any stated intention to review these guidelines. Professional bodies and academics throughout the world continue a process of research and development and critique of existing guidelines. In the next section there is a brief discussion of access to biological drugs before a comparison of behaviours in Ireland and Northern Ireland is discussed, in the context of patient access to therapies.

5 Patient access to therapies

Most expenditure on pharmaceuticals in Ireland is incurred through the Community Drug Schemes (CDS). There are four main categories:

1. General medical services (GMS) scheme: drugs were provided free to those who are means tested as unable to afford to pay but a small charge per item (€0.50) was introduced in October 2010;
2. Long-term illness (LTI) scheme: people with certain chronic conditions are entitled to free drugs regardless of income (RA is not included);
3. High-tech drugs (HTD) scheme: intended to cover the supply by community pharmacies of certain high-cost drugs; and,
4. Drug payment (DP) scheme: limited payments by those who do not qualify through one of the other schemes.

In 2007 total expenditure on pharmaceuticals in Ireland under the CDS was €1.74 billion (this amounts to around 85% of total drug expenditure). Of this, the HTD scheme accounted for €250 million in 2007 (Barry et al. 2008) – CDS had increased to €1.9 billion and HTD to €290 million in 2008 (Barry and Tilson 2010). Biologics are prescribed through the high-tech drug (HTD) scheme. In 2007 the anti-TNF drugs etanercept and adalimumab accounted for 25% of
total spend under the HTD scheme, although not all of this relates to treatment of RA (Barry et al. 2008).

The National Centre for Pharmoeconomics (NCPE), set up in 1998, is responsible for health technology assessment (HTA) of drugs on behalf of the HSE (see http://www.ncpe.ie/index.php accessed 28 February 2012). Since 2009 the NCPE has considered the cost effectiveness of all new drugs entering the Irish CDS; the Corporate Pharmaceutical Unit of the HSE formally refers products for economic evaluation to the HSE. All drugs are considered under a rapid review process but only high-cost or those with high budget impact are subjected to formal economic evaluation. Existing drugs may also be reviewed if there is a query regarding value for money (for example from the Minster of Health or the Department of Health and Children).

The NCPE has not published any formal reviews of biological drugs for RA but there is a paper awaiting publication. Using incremental cost effectiveness ratio (ICER) analysis, each anti-TNF was compared to methotrexate. Infliximab was dominated in all scenarios, being more costly and less effective. Etanercept and adalimumab proved to be the most effective options but also most costly. Golimumab was less effective and less costly, while etanercept and adalimumab were more costly than certolizumab pegol (Adams et al. 2011).

5.1 Comparing access

All patients have access to biologics through the HTD scheme. Drugs provided through subcutaneous injections ie under the skin (mainly etanercept and adalimumab) are available relatively freely, whereas IV (intravenous) biologics eg infliximab are not available as widely due to HSE budget constraints. Patients accessing biologics through private insurance may find it easier to access IV biologics although there is an increasing tendency for insurance companies to query use in terms of costs and indications. Unfortunately as far as we are aware, there are no national data available at a detailed level on usage of individual drugs by source of payment.

In 2005, in Northern Ireland biological therapies were prescribed according to NICE / BSR guidelines whereas rheumatologists in Ireland were not restricted in how they might prescribe – other than by drug licensing requirements. In a paper in Rheumatology, Kee et al. (2005) showed that the clinical judgement policies of practitioners in Ireland were similar to those in Northern Ireland, although the adoption of NICE / BSR guidelines in Northern Ireland may have improved the uniformity of practice. So, the paper suggests that specialists from Ireland and those from Northern Ireland would maintain similar groups of patients on biological therapies.

Kee and colleagues (2005) also reported that funding restrictions in Northern Ireland resulted in waiting lists of RA patients for treatment with biologics resulting in unacceptable levels of patient discomfort, and contributing to long-term joint damage and disability.

Kee et al. (2005) reported that it was estimated that 2000 patients were receiving biological therapies in Ireland, and that the number of new patients each year that would be offered this treatment was 660. This represents approximately 2-3 times the availability of treatment in Northern Ireland.
6  Future drug therapies

The HSE has set up a committee to look at the use of biologics for RA. No material has been made publically available from this committee so far.

One leading rheumatologist suggested that it has become more difficult for new drugs to gain approval through the NCPE process as the economic evaluation has become more rigorous.

A new drug – tofacitinib – has been developed that can be delivered in tablet form (not infusion) and which will act as an JAK3 inhibitor. It was suggested by one leading rheumatologist in the UK that this form of biological therapy could be much cheaper and so it may be possible to use it immediately once it is licensed as its cost will not be prohibitive. However as of early 2012, it is not licensed.

7  Concluding remarks

This paper has identified that there are no statutory guidelines in place in Ireland. The ISR published a set of guidelines in 2005 relating to the prescribing of anti-TNF-α therapies; however, it is clear that this is not intended to be prescriptive but merely to act as guidance for the professional decision-makers. Moreover there has not been a subsequent update of this guidance although there have since been considerable developments in biologics for use with adults with RA.

Bibliography


ITALY

Cecilia Minelli & Aureliano Finch

The health system framework in Italy
Italy has a publicly funded national health system providing universal coverage free at the point of use for all citizens. Each region (20 regions in total) is allocated a budget, which is funded through general and local taxation, and is responsible for purchasing health services and providing these locally; in doing so they are free to choose what services to purchase and how to organize the delivery \(^1\). Since 2007 patients have been increasingly required to contribute to the cost of health care by paying a *ticket* when using hospital services. The size of the ticket varies geographically with some regions charging a flat fee of €25 such as in Trento, Valle D'Aosta, and Umbria, while in others patients are charged according to the diagnostics services they use such as in Liguria and Friuli-Venezia Giulia. Many exemptions exist for patients with specific conditions, disabilities, or according to age, income or regional legislations \(^2\). The delivery of health care occurs at the community level, through GPs and outpatient settings, usually providing specialist care; and through a mixture of public and private, often accredited, hospitals. At all levels, except for emergencies, patients are free to choose their provider. Access to specialists occurs either by referral from a GP or by patients directly booking an appointment with one of them: in this latter case however patients are required to pay a user fee and they usually have to wait for a long period. In regards to waiting time it is important to notice that there is substantial variation between the North and the South, with much longer waiting lists in the Southern regions \(^1\).

Rheumatoid Arthritis in Italy
The prevalence of rheumatoid arthritis (RA) in Italy is estimated to be between 0.33%-0.46%, affecting women in particular. This is consistent with the experience of other European countries which shows a prevalence of 0.54%-0.8% \(^3,4\). Before the introduction of biologics, patients were treated with a combination of non-steroidal anti-inflammatory drugs and DMARDs (disease modifying anti-rheumatic drugs). Nonetheless, most patients affected by RA do not respond effectively to this combination therapy, mostly due to the loss of efficacy of the DMARDs \(^5,7\). In the following section we are presenting the current guidelines regarding the use of biologics and anti-TNF in Italy.
Diagnosis and measures of disease activity
The process of diagnosing RA requires looking at the disease symptoms, as described by the patients, and looking at the presence of clinical signs. The presence of at least 4 out of the 7 classification criteria of the American College of Rheumatology (ACR) allows obtaining a diagnosis of RA. A diagnosis has to be made by a physician with extensive experience in managing RA. Following the national guidelines, once RA is diagnosed, treatment ought to start immediately

Treatment choice depends on the presence of negative or positive prognostic factors. The treatment of RA includes non-pharmacological measures, non-steroidal anti-inflammatory drugs and glucocorticoids. Traditionally the main strategy to achieve disease control has been the use of DMARDs. Over the last years however there have been important changes in the treatment strategies and there has been a move towards early referral and early DMARD use as the most important strategy in order to maximize response and to reduce long-term disability. It has also been demonstrated that tight control of disease activity, using composite measures, and the use of appropriate combination and switching of drug treatment is highly effective.

Current national guidelines thus recommend the use of different drugs depending on the state of the disease, which is defined by taking into account both activity grade and diagnostic factors.

Activity grade and clinical improvements are evaluated through the Disease Activity Score (DAS). This is an internationally recognized system introduced following the recommendations of the EULAR (European League Against Rheumatism). It is calculated taking into account diseases variables such as the number of swollen joints and tender joints, the Erythrocyte Sedimentation Rate and the Global Disease Activity measured through the Rating Scale instrument. Using these data, DAS28 can be calculated through the formula:

\[\text{DAS28} = 0.56 \times \sqrt{\text{tender28}} + 0.28 \times \sqrt{\text{swollen28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}\]

The DAS28 criterion is effective in the majority of cases of RA, but the DAS44 is considered a better mean of evaluation when the disease is aggressive particularly on inferior arts. The DAS28 benchmark values as recommended by EULAR are listed as follows:

- Remission for DAS28 < 2.6
- Low disease activity DAS28 ≤ 3.2
- Moderate activity 3.2 > DAS28 ≤ 5.1
- High activity DAS28 > 5.1

As recommended by the American College of Rheumatology (ACR) and the European League guidelines, the choice of treatment is heavily influenced by the presence of high number of tendon or swollen joints, radiological progression, anti-CCP, anti-citrullinate cyclical antibodies,
rheumatoid factor, Health Assessment Questionnaire (HAQ) and extra-articular manifestations.

**Recommendation for drugs administration to patients with RA**

During the time of preparation of the latest guidelines the following biologics were licensed and available in Italy: one inhibitor of IL-1 (Anakinra), one B-cell depleting drug (Rituximab) and one inhibitor of T-cell costimulation (Abatacept). With these also three anti-TNF drugs: Infliximab, Etanercept and Adalimumab. Rituximab and Abatacept can be used after the failure of first-line treatment with other biologic drugs and prior to the publication of the 2011 guidelines Abatacept was also approved as a first-line drug after DMARDs failure by the EMA- the European regulatory agency. Anakinra and anti-TNF drugs are recommended after the failure of DMARDs. In respect to Anakinra, clinical practice has indicated little efficacy for the treatment of RA while it has been used successfully in the treatment of other inflammatory diseases. 

Prior to the publication of the guidelines three more biologics came on the market: an inhibitor of IL6 receptor (Tocilizumab) and 2 other anti-TNF (golimumab and certolizumab). Tocilizumab has been licensed for treatment of RA in the occurrence of DMARDs or biologics failure. Table 1 summarises the biological drugs currently available in Italy.

**Table 1. Biological drugs approved for treating RA.**

<table>
<thead>
<tr>
<th>Biological DMARD</th>
<th>Target</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>TNF-a</td>
<td>Human TNF-a receptor p75Fc fusion protein</td>
</tr>
<tr>
<td>Infliximab</td>
<td>TNF-a</td>
<td>Chimeric human-murine anti-TNF-a</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>TNF-a</td>
<td>Recombinant human anti-TNF-a monoclonal antibody</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>TNF-a</td>
<td>Fab pegylated anti-TNFα</td>
</tr>
<tr>
<td>Golimumab</td>
<td>TNF-a</td>
<td>mAb anti-TNFα</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IL-6</td>
<td>Humanised anti-IL-6R monoclonal antibody</td>
</tr>
<tr>
<td>Anakinra</td>
<td>IL-1</td>
<td>Recombinant human IL-1 receptor antagonist</td>
</tr>
<tr>
<td>Rituximab</td>
<td>B cell</td>
<td>Chimeric human-murine anti-CD20</td>
</tr>
<tr>
<td>Abatacept</td>
<td>T cell</td>
<td>Human fusion protein (CTLA4-Ig)</td>
</tr>
</tbody>
</table>

However, after a diagnosis has been obtained, it is recommended to begin the administration of Methotrexate (MTX) within three months from the first clinical manifestations. After three months a first assessment takes place by looking at DAS28. If the prognostic factors are negative then it is possible to start a therapy with anti-TNF agents. For those patients that are intolerant to MTX then an alternative DMARDs or biologic treatments can be used. If MTX is not being efficacious then an alternative DMARD or a combination therapy with MTX and a TNF

---

2. Tocilizumab has also been approved for monotherapy use and therefore it can be used as a first line treatment. Nonetheless, in some regions Tocilizumab is considered a second-line treatment.

3. Currently in Italy Rituximab is the only drug approved as second-line of treatment.
antagonist can be used. The administration of the drugs, as recommended by the Italian Society of Rheumatology (SIR), has to occur in centers with consolidated experience with the use of biological treatments. However, the provision of anti-rheumatic drugs is organized regionally. This creates a heterogeneous context with some regions authorizing tertiary centers only to administer the biologics (e.g. Lombardy) while others authorizing ambulatory units to administer the drugs too (e.g. Piedmont).

**Guidelines for the use of anti-TNF**
The Italian Society of Rheumatology (SIR) is the national body for the creation and adaptation of the European guidelines (EULAR) to the national needs. The creation of the guidelines involves multiple steps. First of all a selected group of rheumatologists and research fellows undertake an international systematic literature review to investigate whether new developments have been documented in order to update the current guidelines. The outcome of the systematic literature review is then presented at a national congress organized by the SIR where rheumatologists can express their opinions on the new developments. To reach a consensus the Oxford scale is used. The proposed guidelines are then voted by a committee and once approved they are implemented nationally. The frequency of such meetings, organized specifically to review the current guidelines, depends on the quantity of literature published, on the improvements in the field and on the national needs. Regions on the national territory have to implement the aforementioned recommendations, but all of them can include additional criteria.

Since the 2011 congress that took place in Rimini, the SIR has adopted the following guidelines.

In order to be eligible for TNF antagonist treatment patients should:

- Having been treated for at least 3 months with MTX at the highest possible dosage (20mg/week) without registering significant reduction in the DAS28;
- Patients intolerant to MTX or patients with contraindications to MTX.

In this latter case TNF antagonists should be taken only after the use of a different drug, administrated for at least three months at the optimal dosage e.g. leflunomide 20 mg/day, sulfasalazine 2 g/day, cyclosporin A 3 mg/Kg/day.

In case of MTX failure the Italian Society of Rheumatology recommends the use of anti-TNF, when:

- High disease activity defined by DAS28>5.1 for at least one month;
- DAS28 registers a moderate disease activity (DAS28 >3.2 and ≤5.1) in concomitance with unfavorable prognostic factors e.g. immunological and serological factors, clinical markers, imaging markers, joint damage progression.
- The presence of the progression of joints damage (occurrence of new erosions),
regardless of disease activity, is documented by plain radiographs;

Physicians always have to justify the switch between drugs. A system based on periodical checks has therefore been implemented. The DAS28 is controlled every 3 months, health assessment questionnaires (HAQ) every 6 and structural damage every 6-12 months.

Biological drugs can also be used in combination therapy with DMARDs. In fact the combination MTX and biologics is more efficacious than monotherapy and show fewer adverse events. It is worth mentioning that Infliximab should only be used in combination with methotrexate and Rituximab and Adalimumab should also be used in combination with MTX. A combination therapy is recommended in those cases when the DAS28 indicates moderate diagnostic factors yet unfavorable diagnostic factors remain absent. If patients are intolerant or refuse to take MTX or in case of toxicity of MTX then the combination therapy can be with an anti-TNF alpha drug and another DMARDs such as leflunomide, azathioprine, sulphasalazine and cyclosporine.

Which anti-TNF should be used first?

Rheumatologists can choose freely which anti-TNF to administer among the five anti-TNF drugs currently available on the Italian market. Such a choice largely depends on physician's opinion and it should be shared with the patients taking into account factors such as the different way of administration (subcutaneous or intravenous) or the frequency of administration. When patients present co-morbidities the choice is the also affected by the level of efficacy demonstrated by the different anti-TNF in respect to the given co-morbidity.

The recommended regimens for the main anti-TNF are:

- Infliximab: 3mg/kg intravenously at week 0,2,6 and every 8 weeks afterwards.
- Etanercept: 50mg subcutaneously twice a week or 50mg once a week.
- Adalimumab: 40mg subcutaneously every 2 weeks.
- Golimumab: 50mg subcutaneously every 4 weeks.
- Certolizumab pegol: 200mg subcutaneously every 15 days.

Adalimumab and Etanercept can be used in monotherapy while Infliximab should only be used in combination therapy with MTX.

When not to use Anti TNF

In the following cases the use of anti-TNF biological is not recommended:

- In the presence of acute infections caused by bacteria, fungus and virus such as HIV.

---

4 This drug has not been included in the 2011 recommendations but is currently being used in clinical practice routinely.
5 This drug has not been included in the 2011 recommendations but is currently being used in clinical practice routinely.
tuberculosis and hepatitis;
- In case of tumors diagnosed within 5 years with possible progression;
- In the presence of heart failure of grade III or IV;

Furthermore, the use of anti-TNF drugs is also not recommended for women in fertile age.

Recent trend in discontinuation of anti-TNF therapies

Clinical experience suggests that a lot of patients do not sustain a response to anti-TNF therapy: as a response clinicians often switch to a different drug or escalate the dose. Drug discontinuations are particularly important and usually arise because of poor or absent tolerability. A recent observational retrospective study carried out in 23 centres (9 in the North, 4 in the South, 10 in the centre) has highlighted a high rate of discontinuation and dose adjustment over a 36-month period. This is particularly true for therapies based on Infliximab for which there is an elevated occurrence of the adverse events: in fact the discontinuation rate of Infliximab is 14.5% compared to 7.7% for Etanercept and 11.2% Adalimumab. It was also noticed that a lot of patients either switched from Infliximab to Etanercept or Adalimumab or otherwise they required dose-escalations: so from a cost-effective perspective even if in principle Infliximab is the least expensive between the three drugs, Infliximab-based therapies have the highest incremental cost.

Recommendations in case of biologics failure

Patients’ failure to respond to biologic therapy is determined through the EULAR criteria using DAS28. A patient is said to fail if there is no response after 12 weeks of treatment with biologics. At the time of preparation of the 2011 guidelines a large number of patients, up to 50%, failed to respond to the three anti-TNF drugs available in Italy- Infliximab, Etanercept and Adalimumab. Many patients also developed adverse events, which caused treatment discontinuation. For patients who experience a first failure to anti-TNF therapy, there are different treatment options: the first one is to add conventional DMARD such as MTX. For patients using Infliximab it may be effective to increase dosage or to reduce the administration intervals. For patients that fail to respond to the first anti-TNF agent or patients that develop adverse events it is recommended to switch to an alternative anti-TNF agent. In case of failure of a second anti-TNF agent then it is recommended to switch other biologics with a different mechanism of action.

Patients’ accessibility to biologic therapies

The level of accessibility to biologic therapies in Italy varies substantially across regions depending on various factors such as the length of time required to complete a diagnosis and the availability of rheumatologic services. Typically, the time between the onset of the first symptoms and the actual diagnosis varies substantially depending on the type of provider that
actually makes the diagnosis. In a recent study conducted across the whole country the researchers have found that it takes on average 11.7 months to make a diagnosis. However this figure varies from 7.7 months for a GP, compared to 12.6 months for a rheumatologist and 18.1 months for a different specialist.

A study by Salaffi et al. (2009) evaluating the accessibility to pharmacological therapies for the treatment of RA in Italy confirmed that in the Northern regions there is a tendency to rely more on the GP for a diagnosis while in the South and in the Centre it is more common to visit a specialist. Among the people interviewed, in the North-East it was common practice to visit a rheumatologic centre for 18.1% of respondents, while in the North West it was common only for 3.6%. Such a variation concerning the choice of provider is heavily influenced by the availability of services, a point that has also been stressed by our interviewee. In fact they confirmed the existence of a lack of rheumatologists and of rheumatologic centres in some areas in Italy. For example, some Southern regions are particularly affected by such a shortage of rheumatologic services and with relatively low mobility of patients the accessibility to biologics therapies remain low (Interview). A further finding of the study conducted by Salaffi et al. (2009) is the existence of significant structural differences between the patients who rely on rheumatologic centres as their point of reference compared to those who do not: among the group of people sampled the users of rheumatologic centres were in fact more educated and younger patients. The study also highlighted that distance from a rheumatologic center was an important obstacle to access to treatment for rheumatoid arthritis in general: 41.7% of respondents reported to have been unable to visit a rheumatologic center because of the distance.

Even if cost was not directly mentioned one should consider that especially for patients living on the islands, Sicily and Sardinia, the cost of traveling to another region to get treatment. This can be very high due to the necessary sea or air transportation costs. Nevertheless there has been some improvement in this regard over time. Finally, low information and long waiting lists represent other crucial obstacles; overall, 77.6% of respondents have visited a rheumatologic after having been referred by a GP: this implies that if the GP does not make a referral or fail to diagnose the disease promptly then patients are less likely to visit a rheumatologic center and thus access to therapies.

In conclusion, the picture that emerges seems to be the following: access to biologic therapies depends on two main factors: the ability of providers to complete a diagnosis promptly and thus to refer patients to specialized centers as soon as possible; and the availability of rheumatologic service locally. Because of a shortage of such services in some areas, some patients have to travel long distances to see a specialist as well as having to wait for a long time before obtaining a
Finally an important point of difference between Italy and the UK, which affects patients’ accessibility to biologics, is the role played by the providers in deciding whether to put a patient on biologic therapies or not. According to our interviewee, such a decision is made following the guidelines while simultaneously considering important factors such as age. Put differently, there seems to be more flexibility in the way the guidelines are implemented in Italy compared to the UK, in that the eligibility criterion established through the DAS28 is a crucial component of the decision to move a patient to biologics, but not the only one.

**Bibliography**


The Netherlands

Bernard van den Berg

1. The Dutch healthcare system

In January 2006, the Dutch government introduced a new health insurance act based on the principles of managed competition (Enthoven & Van de Ven, 2007). Before 2006, inhabitants had either compulsory social (sickness fund, 62%) or voluntarily private (36%) health insurance depending among others on income (below a gross annual income of €33,000 people were socially-insured). This combined system of social and private health insurance was replaced by a compulsory single universal basic health insurance covering a legally defined package of basic benefits excluding long-term care (see for details on the Dutch long term care system Schut and Van den Berg).

The introduction of the Health Insurance Act is arguably the most significant health policy reform in Europe in decades (Van den Berg et al. 2008). The Dutch system of managed competition involves quite a few unique features. Under the new Dutch Health Insurance Act, all citizens are required to purchase a basic health insurance policy. They can choose any insurer they like. Competing health insurance companies are required to accept all applicants during a yearly open enrolment period (Enthoven and Van den Ven, 2007).

The government determines the content of the basic health insurance package (medical care except long term care) insurers have to offer. The minister of health will make the final decisions on the content of the basic health insurance package health insurers have to offer on a yearly base. She/he will make use of guidance offered by health technology assessment studies as summarized by the Dutch Health Insurance Board. It is however crucial to note that the basic benefits are not defined in terms of providers but in functions of care (Enthoven and Van den Ven, 2007). This offers flexibility to health insurers to design their products and contracts with care providers to better appeal to the preferences of the consumers (Van den Berg et al. 2008). Health insurers are allowed to selectively contract care providers, which could lead to more competition between care providers. With respect to medicines “the Netherlands has operated a reference pricing system since 1991, based on therapeutic equivalence. In addition, health technology assessments are undertaken for drugs that are, a priori, considered to be sufficiently innovative to justify a premium price (Drummond et al., 2011).” The minister of health will make a decision within 90 days.
This might also hold for medicines as insurers have quite a lot of flexibility with respect to what they finance within the legal context of the basic health insurance package. This should encourage them for instance to think in terms of total costs per patient and not in costs per healthcare provider and costs for medicines. This because the central idea of the new system is that provider competition has either a downward pressure on prices/costs given a certain level of healthcare quality or has better incentives to improve or differentiate healthcare quality, potentially at higher prices/costs, as long as consumers and patients are willing to pay for better quality or diversification (Van den Berg et al. 2008). Typical for the Dutch healthcare system is also that general practitioners (GPs) act as gatekeepers not only for medical specialists but also for physiotherapists partly to avoid unnecessary use and/or to avoid unnecessary use of relatively expensive care (Delnoij et al., 2000). In practice, a GPs’ gatekeeper function implies that it is necessary for citizens to get a referral from their GP to visit a medical specialist, a hospital or a pharmacist. Please note that it is not necessary for the system of managed competition to work that GPs act as gatekeepers.

A necessary condition for the system of managed competition to work is that quality information about care providers and health insurers is available. Without quality information, health insurers can only negotiate with care providers on prices and without this information consumers can neither choose between insurers’ quality of contracted care nor on the quality of their service provision. A complementary requirement is that insurers use this information to purchase healthcare and consumers and patients use this information to choose a health insurer and a care provider when they need care. If consumers and patients do not use quality information in making decisions, it is likely that managed competition just becomes a price competition involving a race to the bottom, but if they do use this information, a system of managed competition involves incentives for care providers to become conscious about the costs and the quality of the services they provide.

In Dutch healthcare, different sources provide healthcare quality information, for instance the government, health insurers and the media. The government only sets the minimum level of healthcare quality via the Healthcare Inspectorate. Clinical guidelines are developed by the professionals but not by the government or health insurers. The clinical guidelines do not have a legal status, although the professionals have to carry them out. They can only decide not to
follow the clinical guidelines if they consult the patient and if they document the reasoning not to follow the guidelines. Further details on the clinical guidelines will be provided in section 3.

2. Dutch demographics

The Netherlands has 16 million insured inhabitants. In 2003 approximately 57,100 males and 90,400 females had RA (prevalence: 7.1 per 1,000 males and 11.0 per 1,000 females per year) (RIVM, 2012). RA incidence was: 0.7 per 1,000 males and 1.4 per 1,000 females). In 2005 32 males and 98 females died because of RA (0.4 per 100,000 males and 1.2 per 100,000 females). This was defined as RA is primary cause of death (RIVM, 2012a). The total costs of RA were in 2003 estimated as approximately 103 million euro (RIVM, 2012a).

3. The Dutch RA guidelines

3.1 The general guideline on diagnosis and treatment

The Dutch RA medical professionals developed in 2009 the Dutch clinical guidelines for treatment of RA patients. As mentioned the clinical guidelines do not have a legal status, although the professionals have to carry them out. They can only decide not to follow the clinical guidelines if they consult the patient and if they document the reasoning not to follow the guidelines.

This clinical guideline distinguishes between diagnosis and treatment. It states what the GPs should do and when they should refer patients to the rheumatology medical specialist. According to a few criteria the GP should refer the patients to the medical specialist because the DMARD treatment is very important for patient. With regard to this treatment there is a section on prescription of medicines in the guidelines. This section stresses the importance of prescribing DMARD as soon as possible which is defined as suspicion of RA, in other words likely RA.

The prescription of medicines section in the guidelines includes also guidance on prescription of NSAIDS. Basically the guidelines suggest that NSAIDS are effective to relief pain for RA patients. Moreover, according to the guidelines there seems no difference in clinical effects between various types of NSAIDS, although the COX-2 inhibitors are safer for the stomach. It seems that both conventional NSAIDS and COX-2 are associated with higher risks on cardiovascular diseases.
With respect to the influence of guidelines on patients’ access to care it is important to understand that all Dutch citizens have a GP and GP care is covered by basic health insurance. It is therefore fair to say that in the broad sense of the concept, patients have access to basic RA care. Moreover, medical professionals can only decide not to follow the clinical guidelines if they consult the patient. At first glance this seems not a potential limitation of access. However, the guidelines also has a section on wider considerations which might include economics which is kind of narrowly defined in terms of cost considerations. This seems to involve some degrees of freedom for the medical professionals to take other considerations into account. On the other hand, as was emphasized in the description of the Dutch healthcare system, the basic benefits are not defined in terms of providers but in functions of care (Enthoven and Van den Ven, 2007). This offers flexibility to health insurers to design their products and contracts with care providers to better appeal to the preferences of the consumers (Van den Berg et al. 2008). The guidelines surprisingly do not mention this at all, but it is very clear that there is potential for health insurers to not reimburse everything. Obviously the more flexibility in the clinical guidelines, for instance with respect to available substitutes, the more degrees of freedom involved for health insurers. However, as long as there is heterogeneity between competing insurers, people with RA could change insurer every year as insurers are obliged to accept all applicants. They might also be willing to purchase supplementary insurance if that would cover additional RA related benefits although insurers are allowed to refuse applicants for supplementary insurance. But obviously there is potential for health insurers no longer to reimburse all substitutes. As the guidelines state there seems no difference in clinical effects between various types of NSAIDS in principle a health insurer could decide only to reimburse the cheapest.

This general guideline on diagnosis and treatment might be updated in 5 years time or something like that as was elaborated on in the interview (section 4).

3.2 The guidelines on biologics version January 2011

This guideline is mainly about the responsible prescription of biological emphasizing potential side effects and what to do in case of com-morbidities (Nederlandse Vereniging voor Reumatologie, 2011a).
3.3 The guidelines on biologics version July 2011

This updated guideline recommends:

1) Patients with active RA should be treated with a traditional DMARD, preferably methotrexate, (whether or not with glucocorticoiden), for a period of minimum 3 months using the adequate dose.

2) In case of insufficient effect, there are 2 options:

a) For patients with a bad prognosis a biological will be considered, in principle a TNF-blocker combined with methotrexate or leflunomide.

b) For patients without a bad prognosis another conventional DMARD will be considered first.

The choice for the first biological is mainly determined based on experience. For a period of 10 years only three TNF-blockers were available if patients failed for the conventional DMARD therapy: infliximab, etanercept and adalimumab. This makes that information is available on these three TNF-blockers. The guidelines state that it is to be expected that one in the future can exploit information on the patient’s immune system and/or biomarkers more targeted choice can be made (personalized medicine). However, the following TNF-blockers are available (being reimbursed) in the Netherlands: infliximab, etanercept, adalimumab, certolizumab or golimumab. Alternatively one can opt for either abatacept or tocilizumab. According to the guideline there is lack of evidence to support choice between a TNF-blocker, abatacept or tocilizumab, as “first choice biological”. Because of this lack of evidence choice will mainly based on patient preferences regarding route of administration, estimated risks of side effects or co-morbidities.

Frequent monitoring for treatment with biologics is crucial. Monthly monitoring is recommended till response DAS28<3.2 or drop of at least 1.2 points. After a three monthly monitoring is required. Without required response within 3-6 months it is recommended to stop with the biological. In case of secondary non-response defined as loose effectiveness it is recommended to stop with biological. One could start with another biological but so far the guideline does not recommend another one. The guidelines state that using a biological of the same class not necessarily involves similar side-effects. Another TNF-blocker could be effective
and a direct switch to another mechanism (B cell depletion) might be effective for RF and/or CCP positive patients.

If a patient is treated for more than 6 months with a biological and disease activity is low (DAS28<3.2) or in remission (DAS28<2.6) one could consider to reduce or even stop. Frequent monitoring 1-3 monthly is required and in case of increase DAS28 with 1.2 points a restart should be considered.

The specific guidelines on biologics will be reviewed on a regular base as was elaborated on in the interview (section 4).

4. Extracts from an Expert Interview

How and when are the guidelines reviewed?

Regarding the general RA guidelines our interviewee was unsure but guessed that it might be reviewed in 5 years or so. As the first steps were made early 2000 and the extensive guidelines were published in 2009 the next 5 years or so seems to make sense.

The specific guidelines on the prescription of biologics were published in January 2011 and updated in July 2011 and will be updated on a regular basis implying much shorter time interval compared with the general guidelines.

Adherence to the guidelines

The guidelines have a section on adherence stating that adherence is beyond the responsibility of writing the guidelines. GP’s are gatekeepers in the Dutch system, who behave according to the guidelines and refer patients on time. “I believe we do not see patients anymore, as happened 10 or 20 years ago, in a later stage of RA.” He believes however there is substantial room for improvement in terms of monitoring the effects of use of medicines. Moreover, he states “although there is quite a lot of talking about personalised medicine and patient centred medicine, we do not have the necessary tools to be that specific.”

Would there be economic incentives in the Dutch system preventing patients getting the best possible treatment?
The interviewee could not answer questions about potential differences in co-payments between various products but refers to a perverse incentive (which is also mentioned in Drummond et al., 2011) that in the case of infliximab health insurers reimburse 80 percent of the costs leaving 20 percent to be paid from the hospital budget. This might result in variation between hospitals in prescription based on economic arguments. In general, however, things have changed over time as previously health insurers had to explicitly grant permission to prescribe biologics but nowadays this is no longer necessary as it seems health insurers trust the physicians as they were previously worried they would put everybody on the expensive biologics, with price differences of 500 versus 15,000 euro. The clinical guidance to determine when to start prescribing biologics works in practice and is standardised across Europe.

Comparison with other European countries

Our interviewee does not get the impression there are very substantial differences although in the UK GP’s might do slightly more compared with other countries. He also has the impression that France and Ireland might be slightly less strict in prescribing biologics compared with other including the Netherlands.

5. Comments from stakeholders

The RA patient organisation seems quite positive about the guidelines and is working on translating the guidelines in so-called patient terminology. This would help patients to better understand the guidelines and help them to empower. It should help them to better communicate with the medical professionals about the received care. Strictly speaking it could also benefit them to consider changing health insurer but I got the impression that the RA patient organisation is not that involved in the new insurance system as for instance is the diabetes patient organisation.

6. Key features

- Competing health insurers
- Basic package
- Content off basic health insurance determined by minister of health advised by the health insurance board based on evidence from health technology assessment
- Competing health insurers sell supplementary insurance for things that are not (fully) covered by basic health insurance like physiotherapy
• Patient organisations might recommend one or more health insurers as they might be specialized in certain disease areas (also via complementary insurance)
• GP gatekeeper to secondary care
• Government (Healthcare Inspectorate) set minimum standards for quality and patient safety
• Clinical guidelines are determined by the professionals
• Recently a new clinical guideline for treating patients with RA was developed
• Note that thinking in terms of guidelines not necessarily consistent with the new health insurance system which explicitly allows heterogeneity and therefore involves a whole of opportunity to diversification within the context of the governmental regulation (no free market) (e.g. able to top up if health insurers’ wishes).
• General guidelines state that treatment early in the course of the disease, along with early diagnosis, has a positive influence on clinical outcome in patients with RA.

7. References


Poland

Anna Sagan

I. Context

Around 70% of health expenditure comes from public sources. Over 83.5% of this expenditure can be attributed to the universal health insurance. The second most important source of public funds is the State budget, followed by the budgets of the territorial self-governments. Private health care financing plays a larger role in Poland than in most other EU Member States and comes mainly from out-of-pocket spending (about 22% of total health expenditure in 2009). Informal payments are widespread but their extent has been decreasing following substantial anti-corruption measures.

Cost-sharing is limited, with the exception of medicines, medicinal products and auxiliary medical devices, health resort treatments and certain dental procedures and materials. Positive reimbursement lists have been in place since end-2009 and are issued periodically by the Ministry of Health (Sagan A, 2011). Special reimbursement privileges also apply to certain population groups. Drugs administered during inpatient treatment are free of charge. They are financed by the NFZ through various schemes, including the DRG system, health programmes and standard chemotherapy schemes. The most expensive (innovative) drugs, including biologics for RA treatment, are sometimes reimbursed through health programmes, which cover only a limited number of patients fulfilling strict criteria. Chemotherapy and drug programmes for rare diseases have been one of the most rapidly growing parts of NFZ drug expenditure in recent years.

According to a recent W.A.I.T. (Waiting to Access Innovative Therapies) analysis prepared by the European Federation of Pharmaceutical Industry Representatives and Associations, between 2003 and 2007 the number of newly introduced medicinal substances in the Czech Republic and Slovakia was 8 times higher than in Poland. Although the report noted that more new drugs were included in the reimbursement lists in 2007 and 2008, it concluded that the share of innovative drugs in the reimbursement lists is very low. At the same time, the share of private expenditure on drugs is quite significant, implying that access to drugs may be difficult in Poland. Indeed, a 2008 CSIOZ survey (CSIOZ, 2008) confirmed that 8% of respondents could not afford to purchase any of the prescribed drugs and 26% of respondents could not afford to purchase some of prescribed medications (Sagan A, 2011).

1. Health policy in the area of rheumatology

Treatment of rheumatic diseases is considered as one of the health priorities both in the EU and in Poland. At the EU level, importance of this problem was confirmed in the recent statement of the European Parliament (2009/C285/E11) issued on November 26, 2009, which recognized the need to develop national and Community-wide strategies to improve diagnosis, accessibility, quality of treatment and information on rheumatic diseases. Given that musculoskeletal disorders affect more than a third of Europe’s population, these activities were identified as a priority.

In Poland, current national health policy has been formulated in the National Health Programme for 2007–2015 (Narodowy Program Zdrowia, NPZ). Improvement of the diagnosis and care for rheumatic patients was included as one of the strategic objectives of the NPZ (Grabowska-Woźniak E, 2011). The specific measures recommended in this document include: increasing access and improving equity in access to rehabilitation services, monitoring the share of patients receiving disability benefits, improving public awareness about the risks associated
with rheumatic diseases, reducing the number of people suffering from disabilities caused by rheumatic diseases, reducing inequalities in access to specialist medical care.\textsuperscript{6}

2. RA incidence

According to estimates, approximately 400,000 people suffer from RA in Poland and every year there are between 8,000 and 16,000 new cases.\textsuperscript{7}

II. Access to RA therapies

1. Clinical guidelines

Recommendations on the diagnosis and treatment of RA patients were published in 2008 by a team of experts appointed by the National Consultant for Rheumatology, Prof. Witold Tłustochowicz MD, PhD (W. Tłustochowicz, Brzosko, M, Filipowicz-Sosnowska, A, Głąszko, P, Kucharz, E J, Maśliński, W, Samborski, W, Szechiński, J, Wiland, P, 2008). They followed publication of the American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis.\textsuperscript{8} However, principles of the use of certain biologics were published earlier, for example, principles of the use of anti-TNFs were published in 2002 (Filipowicz-Sosnowska A, 2002) and on the use of rituximab in 2007 (Szechiński J, 2007).

However, these recommendations do not establish a clear pattern of care and therefore cannot be recognized as standards of care. Application of these recommendations in clinical practice depends on several factors, including doctor’s knowledge about modern therapies, availability of medicines, and features of the health system organisation (e.g. whether a timely access to a specialist is assured) (W. Tłustochowicz, Filipowicz-Sosnowska, A, Kucharz, E J, Maśliński, W, Wiland, P, 2008).

Recommendations on the treatment of RA patients are summarised in Figure 1.

\textsuperscript{6} Adapted from the Annex to the 2007 Resolution of the Council of Ministers (No. 90/2007).
\textsuperscript{7} Mentioned in explanatory notes to recommendations published by AOTM (see Tables 1 and 2).
\textsuperscript{8} The position of the team of experts appointed by the National Consultant for Rheumatology is very close to the preliminary recommendations developed by the European League Against Rheumatism (EULAR) (W Tłustochowicz, 2010).
In each case of diagnosed arthritis (except infective arthritis) treatment with glucocorticoids should be employed, at a dose that allows to suppress symptoms. Depending on the established diagnosis, this treatment should be accompanied by a first-line medication, not later than from the 4th month. Preferred first-line medication is methotrexate at a weekly dose of 15–25 mg. In case of intolerance to methotrexate, treatment with leflunomide should be applied. If monotherapy with either of the above mentioned medications is ineffective, combined treatment with several drugs modifying the course of disease should be administered. If this is inefficient, anticytokine drugs (such as infliximab, etanercept, adalimumab, etc.) should be used in combination with full doses of methotrexate or, in exceptional cases, with another first-line drug. Treatment with rituximab and abatacept is reserved for patients in whom the combined therapy involving anticytokine drugs is ineffective. Nonsteroid anti-inflammatory drugs (NSAIDs) can be used as an adjuvant therapy only during exacerbations. Drug therapy should be accompanied by a properly planned and systematic physiotherapy. Treatment should aim at achieving and maintaining low activity of the disease, evaluated according to DAS28 criteria (W).
3. Clinical practice

Clinical practice in the area of RA was assessed in a 2008 survey of 116 rheumatologists and 54 internists employed in (mainly larger) rheumatology wards and clinics across the country (all eligible to administer biological treatment) (W. Tłustochowicz, Filipowicz-Sosnowska, A, Kucharz, E J, Maśliński, W, Samborski, W, Szechiniński, J, Wiland, P, 2008).

The majority of surveyed physicians use well-established rules of RA diagnosis and treatment in everyday practice. However, interpretation of examination results and disease activity index differ among doctors, indicating that there may be a need for further education and dissemination of guidelines. In a large group of patients undergoing treatment, no remission is reached, or the high disease activity persists. According to 75% of physicians, high disease activity persists in 10-30% of patients, regardless of the applied treatment. Seventy-nine percent of physicians confirm remission in less than 40% of patients.

Methotrexate in a dose of 15-20 mg per week is the most frequently administered non-biological disease-modifying anti-rheumatic drug, both in monotherapy and in combined therapy (this is consistent with the recommended clinical guidelines described earlier). After methotrexate, sulfasalazine, cyclosporine and leflunomide (which according to the recommended clinical guidelines should be used as a second choice therapy in case of intolerance to methotrexate) are, respectively, second, third and fourth DMARDs most frequently used as first-line treatment. Combined therapy including at least 2 non-biological disease-modifying anti-rheumatic drugs is used in 15-45% of patients.

Biological agents are considered to be effective in RA treatment. The most commonly used biologics are: adalimumab (47% of doctors participating in the survey use it in their patients), etanercept (99%), inflixymab (81%) and rituximab (64%). Abatacept and anakinra are used the least frequently (12 and 1% respectively). Biological treatment is initiated within less than 5 years after the diagnosis (answer provided by 44% of physicians participating in the survey), and often after even less than 3 years (29%) but in some patients biological treatment is applied as late 5-10 years after diagnosis (24%). There are also cases of early initiation - less than one year after diagnosis (3%). Biological treatment is used in the following cases: high disease activity (according to 94% of doctors surveyed), both seronegative and seropositive form of RA (82%), young age (76%), ineffectiveness of treatment with at least two DMARDs (62%).

According to the survey, biological treatment should be used in approximately 10-20% of the patients (32% of respondents) or even in as much as 20-30% patients (36% of respondents). However, only about 5% of the patients obtain such treatment (according to 70% of respondents).

The average duration of a biological therapy is from 12 months (44% of respondents) to 24 months (18%) or longer (25%). Some doctors continue to administer biological therapy after remission since discontinuation of the therapy may lead to disease exacerbation (if the biological therapy has to be restarted, the risk of side effects may be higher) and a new application has to be made with the NFZ. Moreover, according to the respondents, continuation of the biological therapy after achieving remission helps prevent joint destruction, improve quality of life and reduce the risk of disability. The respondents also indicated that remission should last sufficiently long before treatment is discontinued (treatment is not discontinued when remission is achieved in clinical trials and continuation of treatment is also recommended in the clinical guidelines). Some doctors choose to discontinue biological treatment after remission has been achieved. This is because continuation of treatment in remission is not refunded, it is not consistent with the requirements of the NFZ, it is very costly and a prolonged therapy increases
the risk of side effects. Moreover, some doctors believe that only methotrexate should be administered during remission. Also, discontinuation of biological treatment after achieving remission gives new patients the opportunity to try out such treatment.

According to the findings, the main obstacles to the administration of biological treatment are: lack of availability, high price, medical contraindications, and time consuming administrative procedures associated with application of biological therapies.

4. HTA guidelines

The Agency for Health Technology Assessment (AOTM) is a state financed agency that serves as an advisory body to the Minister of Health to inform decisions on public funding of health technologies, especially those which are included in the basic benefits package. Before the agency was created in 2005, there was no public entity in the Polish health care system whose main activity was the assessment of technologies financed by public means. However, some activities related to health technology assessment were undertaken by the NFZ and by the Centre for Quality Monitoring in Health Care (Centrum Monitorowania Jakości w Ochronie Zdrowia, CMJ), established in 1994.

The most important tasks of AOTM are:

- Issuing recommendation on health care services, determining:
  - Their inclusion in the list of guaranteed services;
  - The level or method of financing, or the conditions for provision of services (or changes in these);
  - The removal of a service from the list of guaranteed services;
- Issuing recommendation on the inclusion of medicines or medical devices in the reimbursement lists;
- Issuing appraisals of health programmes.

The Agency’s main activity is drug appraisal (see Figure 2). To have a drug included in the reimbursement list a pharmaceutical company must submit an application to the Ministry of Health, which instructs AOTM to conduct an HTA assessment, and underlying data and analysis to AOTM. This application must contain a full health technology assessment (HTA) report analysing clinical effectiveness, cost effectiveness and budget impact. The report is then critically assessed by an analytical team of the Agency, according to a set of HTA guidelines elaborated by a team of experts under the auspices of the AOTM. The review procedure includes a review of submitted evidence, a search for new available evidence, a review of the economic analysis, a recalculation of costs and economic modeling as well as a budget impact analysis. Key clinical experts and the NFZ are also consulted by the Agency. The outcome of the Agency’s assessment can be commented on by the applicant during a special procedure implemented since January 1st, 2010. Both the assessment and the comments are then presented to the Consultative Council of AOTM (to the Transparency Council from January 1, 2012), which formulates the final opinion. This opinion then provides the basis for the recommendation submitted to the Ministry of Health by the President of the Agency. The number of HTAs has increased rapidly since the Consultative Council was established in 2007. Recommendations of AOTM are not legally binding and the final decision always belongs to the Minister of Health. Deadlines in the application process are in line with Council Directive 89/105 EEC of 21 December 1988 (also called the Transparency Directive), which stipulates that a decision on the application is made within 90 days of submission (AOTM also assesses products containing active substances that are not yet qualified for reimbursement – in such cases, HTA assessment takes longer (up to 180 days?)).
A limited number of guidelines has so far been issued in the area of RA. All published guidelines have been summarised in Table 1 (recommendations issued on the basis of Minister of Health Regulation of 10 September 2009) and Table 2 (recommendations issued on the basis of Law on health care benefits financed from public sources and on prices (Ustawa o świadczeniach opieki zdrowotnej finansowanych ze środków publicznych oraz o cenach))

---

<table>
<thead>
<tr>
<th>Drug</th>
<th>Product name</th>
<th>Drug application considered in the recommendation</th>
<th>Position of AOTM's Consultative Council</th>
<th>Rec. type*</th>
<th>Decision</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam (NSAIDS)</td>
<td>Mova/is</td>
<td>Symptomatic treatment of RA, osteoarthritis, ankylosing spondylitis</td>
<td>44/13/2010</td>
<td>DR No</td>
<td></td>
<td>High risk of side effects and high costs</td>
</tr>
<tr>
<td>Leflunomid (DMARDS)</td>
<td>Arava</td>
<td>Second line treatment of RA (before the use of biologics)</td>
<td>50/15/2009</td>
<td>DR Yes</td>
<td></td>
<td>So far financed within therapeutic programmes; increase in the number of patients treated with leflunomid could potentially reduce demand for (expensive) biological therapies</td>
</tr>
<tr>
<td>Deksibuprofen (NSAIDS)</td>
<td>Seractil</td>
<td>Symptomatic treatment of RA, osteoarthritis, muscoskeletal pain</td>
<td>60/17/2008</td>
<td>DR Yes</td>
<td></td>
<td>But provided that the cost of therapy is brought down to the level of therapy with ibuprofen</td>
</tr>
<tr>
<td>Etanercept (Biologics: Anti-TNFα)</td>
<td>Enbrel</td>
<td>First line of biologic treatment of RA</td>
<td>52/15/2008 **</td>
<td>TP Yes</td>
<td>***</td>
<td>In the initiating therapy the cheapest drug should be used (at the time of publication of the recommendation it was Infliksimab; now it is etanercept (see below))</td>
</tr>
<tr>
<td>Infliksimab (Biologics: Anti-TNFα)</td>
<td>Remica de</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (Biologics: Anti-TNFα)</td>
<td>Humira</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abatacept (Biologics: T cell costimulation blocker)</td>
<td>Orenicia</td>
<td>To be used in case of insufficient response to DMARDS and to at least one anti-TNF</td>
<td>31/09/2008 **</td>
<td>DR No</td>
<td></td>
<td>Insufficient evidence on the drug application in patients; risk of side effects; costs higher than those of rituximab</td>
</tr>
<tr>
<td>Leflunomid (DMARDS)</td>
<td>Arava</td>
<td>Second line treatment of RA (before the use of biologics)</td>
<td>26/08/2008 **</td>
<td>DR No</td>
<td></td>
<td>Leflunomid is available within a drug programme, which allows proper</td>
</tr>
</tbody>
</table>
Source: (AOTM, undated-b)
Notes:
*DR – Drug Reimbursement, TP – Therapeutic Programme for treatment of RA
** Resolution of AOTM’s Consultative Council
*** The programme is called ‘Treatment of aggressive RA and JIA’
Guidelines on biological drugs are highlighted in grey.
<table>
<thead>
<tr>
<th>Rec no</th>
<th>Rec subject</th>
<th>Decision</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>109/2011</td>
<td>Whether to qualify „Treatment of aggressive RA and JIA with biologics“ as a guaranteed benefit</td>
<td>Yes, if the cost of tocilizumab (RoActerma) treatment is reduced to the level of other biologics</td>
<td>Main change: addition of tocilizumab (RoActerma) to the therapeutic programme (as second-line RA therapy (combined with methotrexate or, if application of methotrexate is not possible, as a standalone therapy)</td>
</tr>
<tr>
<td>93/2011</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>108/2011</td>
<td>Whether to remove „Treatment of aggressive RA and JIA with biologics“ (in the existing wording) from the list of guaranteed benefits</td>
<td>Yes (i.e. remove)</td>
<td>Programme in the existing wording had to be removed from the list of guaranteed benefits in order to include new version of the programme (with tocilizumab) in the list of guaranteed benefits (see CC 109/2011 and Rec 93/2011 above)</td>
</tr>
<tr>
<td>92/2011</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>94/2011</td>
<td>Wether to remove from the list of guaranteed benefits / change type or level of financing of „Treatment of RA with rituximab (Mabthera)”</td>
<td>No (i.e. do not remove from the list of guaranteed benefits) if its price is significantly reduced</td>
<td>Rituximab (Mabthera) is a biologic drug (other than anti-TNF) recommended as third-line of RA treatment (after DMARDs (first-line) and anti-TNF (second-line))</td>
</tr>
<tr>
<td>79/2011</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>13/4/2011</td>
<td>Whether to include „Treatment of RA with tocilizumab (RoActerma) within a therapeutic programme of the NFZ“ in the list of guaranteed benefits</td>
<td>Yes, if the cost of treatment with tocilizumab will not exceed the cost of initiating therapy for RA (for 2 years, after which the responsible entity will provide data on the product’s safety)</td>
<td>- - -</td>
</tr>
<tr>
<td>Date</td>
<td>Details</td>
<td>Acceptance</td>
<td>Notes</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>9/2010 (Rec)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>20/10/26/2009 (CC)</td>
<td>Changes in 21 therapeutic programmes proposed by the Ministry of Health (including changes to „Treatment of aggressive RA and JIA”)</td>
<td>Yes (i.e. accept changes)</td>
<td>?</td>
</tr>
<tr>
<td>25/2009 (Rec)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>36/12/2010 (CC)</td>
<td>Change in the level and method of financing and in the terms of provision of the benefit „Treatment of aggressive RA and JIA”</td>
<td>Yes (i.e. accept changes)</td>
<td>?</td>
</tr>
<tr>
<td>17/2010 (Rec)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>84/26/2010 (CC)</td>
<td>Whether to include lornoksykam (Xefo) in the symptomatic treatment of pain and inflammatory changes in RA patients (and in two other indications) in the list of guaranteed benefits</td>
<td>No</td>
<td>Other NSAIDS achieve similar therapeutic effects at much lower costs</td>
</tr>
<tr>
<td>35/12/2010 (CC)</td>
<td>Change in the terms of provision of the benefit „Treatment of RA and JIA with disease modifying drugs with high and moderate activity of the disease in</td>
<td>Yes (i.e. accept change)</td>
<td>Changes in the qualification criteria</td>
</tr>
<tr>
<td>Date</td>
<td>Decision 1</td>
<td>Decision 2</td>
<td>Decision 3</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>15/2010 (Rec)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>12/4/2010 (CC)</td>
<td>Whether to include „Treatment of RA with abatacept (Orencia) within a therapeutic programme of the NFZ” in the list of guaranteed benefits</td>
<td>No</td>
<td>Not enough compelling evidence on that treatment with abatacept is equivalent to treatment with rituximab, lack of complete safety assessment, supplied analysis does not meet all criteria of the Polish HTA agency</td>
</tr>
<tr>
<td>8/2010 (Rec)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>19/10/26/2009 (CC)</td>
<td>Whether to qualify 5 therapeutic programmes (including „Treatment of RA and JIA with disease modifying drugs with high and moderate activity of the disease in ambulatory settings”</td>
<td>Yes</td>
<td>The programme covers treatment with methotrexate (subcutaneous application)</td>
</tr>
<tr>
<td>12/2009 (Rec)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
</tbody>
</table>

Source: (AOTM, undated-a)

Notes:
CC – position of AOTM’s Consultative Council
Rec - Recommendation of AOTM’s President
JIA - juvenile idiopathic arthritis
Guidelines on biological drugs are highlighted in grey.

5. Financing of and access to RA therapies: until 30 June 2012

The following RA therapies are financed from public sources:

**DMARDS**
Methotrexate (first line)

Treatment with methotrexate (subcutaneous application) is covered within two health programmes:
- Since 2011, within the Programme for treatment of highly and moderately active RA and JIA in ambulatory settings (Leczenie reumatoidalnego zapalenia stawów i młodościowego idiopatycznego zapalenia stawów lekami modyfikującymi o dużej i umiarkowanej aktywności choroby w warunkach ambulatoryjnych); and
- Since 2009, within the Programme for treatment of aggressive RA and JIA (Leczenie reumatoidalnego zapalenia stawów i młodościowego idiopatycznego zapalenia stawów o przebiegu agresywnym) (see Table 1).

Leflunomide (second line)

In 2004, a drug programme for treatment with leflunomide was established. Later, in 2006, a drug programme for treatment of RA with leflunomide was created and, in 2009, thanks to the efforts of the National Consultant for Rheumatology, the Polish Rheumatological Society and the Ministry of Health, a therapeutic programme for treatment of RA was created, providing leflunomide free of charge to patients meeting certain criteria.

To improve accessibility to this drug, patient and doctor groups have been advocating inclusion of leflunomide on the reimbursement list. The condition was that it obtained a positive recommendation from the Polish HTA agency, which it did in 2009.10 On December 22, 2010, the Ministry of Health included leflunomide on the ‘list of drugs that can be prescribed free of charge, at a flat fee or against a partial co‐payment’. From then on, leflunomide can be prescribed by rheumatologists at a flat fee to patients with an active form of RA and free of charge treatment of leflunomide within a therapeutic programme is no longer available (in accordance with a Ministry’s regulation of 22 December 2010 on the guaranteed benefits available within health programmes) (both regulations came into force on 30 December 2010) (Stajszczyk, 2011).

Biological treatment

Use of biologics in RA treatment (and in the treatment of JIA) was introduced in Poland during the system of 17 sickness funds (kasy chorych), i.e. before the establishment of the NFZ in 2004.11 They were introduced within drug programmes, which provided additional public funds to finance expensive and innovative drug therapies. Development of the system of health programmes followed evolution of medical knowledge as well as the organisational and financial capacity of the health care system. Transition from a drug programme (centred around a particular drug) to a therapeutic programme (centred around a particular therapeutic application) in 2006 gave the doctors more flexibility in prescribing and adapting therapy to the needs of the patient (budgets of therapeutic programmes cover the whole programme and not a particular drug) and simplified reporting and programme accounting for the providers (Śliwczyński, 2010).

From 2010, decision to qualify an individual patient for a particular therapy within a therapeutic for the Biological Treatment of Rheumatic Diseases), affiliated with the Rheumatology Institute in Warsaw, which also monitors the therapy. The therapy is terminated in case of remission and resumed in case of disease progression (in which case the patient has to

---

10 Earlier, in 2008, the Polish HTA agency decided against inclusion of leflunomide on the reimbursement list because it was already available within a drug programme and according to the agency, a drug programme was better suited to guarantee a proper administration of the drug.

11 During the system of 17 sickness funds (kasy chorych).
repeat the qualification process) (Śliwczyński, 2010). Programme was entrusted to a team of specialists in the field of rheumatology (Coordinating Group).

Table 3 Financing of therapeutic programmes for treatment of RA* with the use of biologics in Poland, 2004 – 30 June 2012

<table>
<thead>
<tr>
<th>Year introduced</th>
<th>Programme Focus</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Programme of treatment with infliximab and etanercept</td>
<td>Drug</td>
</tr>
<tr>
<td>2006</td>
<td>Programme of RA treatment with etanercept</td>
<td>Disease</td>
</tr>
<tr>
<td>2007</td>
<td>Programme of treatment of RA and JIA with etanercept</td>
<td>Disease</td>
</tr>
<tr>
<td>2008</td>
<td>Programme for treatment of RA with infliximab</td>
<td>Disease</td>
</tr>
<tr>
<td>2009</td>
<td>Programme for treatment of aggressive RA and JIA</td>
<td>Disease</td>
</tr>
<tr>
<td>2011</td>
<td>Programme for treatment of highly and moderately active RA and JIA in ambulatory settings</td>
<td>Disease</td>
</tr>
</tbody>
</table>

Change of financing of the therapy: replacement of the monthly-lum sum accounting to settlement of a single administration of the drug

<table>
<thead>
<tr>
<th>Year introduced</th>
<th>Programme Focus</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Programme of RA treatment with etanercept</td>
<td>Disease</td>
</tr>
<tr>
<td>2007</td>
<td>Programme of treatment of RA and JIA with etanercept</td>
<td>Disease</td>
</tr>
<tr>
<td>2008</td>
<td>Programme for treatment of RA with infliximab</td>
<td>Disease</td>
</tr>
<tr>
<td>2009</td>
<td>Programme for treatment of aggressive RA and JIA</td>
<td>Disease</td>
</tr>
<tr>
<td>2011</td>
<td>Programme for treatment of highly and moderately active RA and JIA in ambulatory settings</td>
<td>Disease</td>
</tr>
</tbody>
</table>

Change of the financing system: introduction of DRGs; administration of the drug is financed within a contract for a therapeutic programme

<table>
<thead>
<tr>
<th>Year introduced</th>
<th>Programme Focus</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Programme for treatment of aggressive RA and JIA</td>
<td>Disease</td>
</tr>
<tr>
<td>2011</td>
<td>Programme for treatment of highly and moderately active RA and JIA in ambulatory settings</td>
<td>Disease</td>
</tr>
</tbody>
</table>

Change of financing of the therapy: replacement of the monthly-lum sum accounting to settlement of a single administration of the drug

Source: (Śliwczyński, 2010)

* Programmes for other rheumatic diseases, such as ankylosing spondylitis (AS), are not included in this table.

The Ministry introduced a so-called initiating biological therapy by prescribing the least expensive first-line therapy (the following factors are considered: the cost of administration, number of applications, required dose, cost of a single dose and the cost of disposal of unused drug). The Ministry prescribes the initiating therapy every 6 months, following negotiations with the responsible entities (Jakubiak, 2011). Currently (from 1 January 2012 until 30 June 2012), etanercept is the initiating therapy drug in the programme for treatment of aggressive RA and JIA (for adults and children above 13 years old). Rituximab was chosen as the second-line therapy in this programme (Ministry of Health, 2011).

Providers were usually indifferent to the Ministry's choice of initiating therapy, except for when it chose infliximab. Infliximab was available in large packs that did not match patients'
needs and as a result sometimes up to 80% of the (very expensive) dose had to be thrown away. With the NFZ paying only for the portion used, this generated significant financial losses to hospitals participating in the programme (Jakubiak, 2011).

According to the data gathered by the Systems of Therapeutic Programmes Monitoring (Systemy Monitorowania Programów Terapeutycznych, SMPT), as of 20 December 2011 (since the beginning of the year), 3281 patients were actively treated with biological therapies (at 88 providers), 455 were in remission (287 RA patients), 526 finished their treatment (350 RA patients), 95 applications were rejected (60 RA patients).12

Table 4 Number of new patients qualified for therapeutical programmes, second half of 2011

<table>
<thead>
<tr>
<th>Month</th>
<th>Jul</th>
<th>Aug</th>
<th>Sep</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of new patients</td>
<td>32</td>
<td>50</td>
<td>37</td>
<td>26</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>No of patients qualified to change drug within programme</td>
<td>16</td>
<td>26</td>
<td>33</td>
<td>9</td>
<td>23</td>
<td>15</td>
</tr>
</tbody>
</table>

Source: Annexes to the Minutes from the meetings of the Coordinating Team for the Biological Treatment of Rheumatic Diseases, from July to December 2011

Detailed information on the number of patients (RA, JIA and AS) treated within therapeutic programmes is available for April 201113:
- treatment with methotrexate: 611 patients (41 providers);
- treatment with biologics: 3061 patients (87 providers);
- treatment with adalimumab: 969 patients;
- treatment with etanercept: 1452 patients;
- treatment with infliximab: 205 patients;
- treatment with rituximab: 437 patients.

6. Financing of RA therapies: from 1 July 2012

Substantial changes to the Polish drug reimbursement system were introduced by the 2011 Law on the Reimbursement of Medicines, Foodstuffs Intended for Particular Nutritional Purposes and Medical Devices of 12 May 2011 (Ustawa z dnia 12 maja 2011 r. o refundacji leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych). Some of the provisions of this Law came into force on January 1, 2012 and the remaining ones will come into force on 1 July 2012. Some of these changes (see (4) and (5) below) may have implications to RA patients and the use of biological therapies. Key changes include:

1) Introduction of fixed, official prices and margins for reimbursed medicines – with reimbursed drugs to cost the same in every pharmacy – and a ban on pharmacies to offer price promotions on reimbursed drugs (which were often used by chains to attract clients);

2) Introduction of a ceiling on reimbursement expenditure as a proportion of overall annual healthcare expenditure by the NFZ (it cannot exceed 17% of total planned expenditure).

12 Minutes No 35 from the meeting of the Coordinating Team for the Biological Treatment of Rheumatic Diseases of 21 December 2011.
13 Annexe to the Minutes from the 27th meeting of the Coordinating Team for the Biological Treatment of Rheumatic Diseases, 27 April 2011.
This means a reduction of available funds in real terms since the financial plan does not take into account the so-called 'drug donations' (negotiated every 6 months between the pharmaceutical companies and the Ministry of health), which allowed to cover more patients;

3) A clawback system, under which pharma companies will pay back a certain amount of the overspend above the 17% limit, based on the structure and dynamics of the increase in the reimbursement amount. Pharma companies will have the option to negotiate individual risk sharing agreements with the NFZ, which may be based on drug's effectiveness, turnover or discounts;

4) Limiting drug reimbursement to registered indications. From 1 January 2012, doctors cannot prescribe drugs against a partial copayment (lump sum, 30% or 50%) to patients who suffer from a disease, which is not listed among the drug’s registered indications;\(^\text{14}\)

5) Abolition of the system of therapeutic programmes and their replacement with drug programmes, with each drug subject to individual reimbursement decisions (to come in force on 1 July 2012).

To ensure a prompt and regular publication of reimbursement lists (incl. proposals for new drug programmes and changes to the existing programmes), the Ministry of Health will utilise announcements. However, announcements (unlike regulations used so far) do not need to be subjected to public consultations before they are published and hence significantly increase the Ministry of Health's power over the content of the reimbursement lists. According to the 2011 Law, only pharma companies will have the right to submit applications for inclusion of a drug/drug programme in the reimbursement lists (or propose changes to the level or method of reimbursement). The National Consultant will no longer have this right.\(^\text{15}\)

7. **Reactions to the 2011 Law**

On 9 January 2012, the Polish Society of Rheumatology (*Polskie Towarzystwo Reumatologiczne*, PTR) issued a message for physicians and patients with rheumatic diseases, presenting its opinion on the 2011 Law and the potential threats to access to biologic RA therapies that stem from it (*PTR*, 2012a). Although it recognized that the introduction of statutory prices for the reimbursed drugs and possibility of concluding risk-sharing contracts between the Ministry of Health and pharma companies could help reduce the cost of innovative treatment, it criticized the replacement of therapeutic programmes (centered on a particular clinical indication) with drug programmes (centered on a particular drug). According to PTR this will cause problems for patients suffering from diseases, which are treated with several drugs (including sequential treatment), since instead of being covered by a single therapeutic programme, they will need to be covered by several drug programmes – these may be inconsistent with one another and difficult to manage in practice since health care providers wanting to provide biological treatment will have to obtain a separate reimbursement decision for each drug, each clinical indication and for each of the available dose size (some drugs need to be applied in different dose sizes, depending on the patient’s body weight) and predict the corresponding number of patients.

In another message issued on 2 January 2012 (*PTR*, 2012b), the PTR criticized limiting drug reimbursement to registered indications, since this is likely to lead to increases in patient cost sharing. This problem may affect a large number of RA patients, since most drugs used in the

---

\(^\text{14}\) The Law also foresaw financial penalties for doctors, issuing prescription with incorrect copayment levels, but the relevant paragraph was ultimately removed by the amendment to this Law passed on 13 January 2012, following country wide protests of doctors. However, pharmacists are still financially accountable for disbursing incorrectly prescribed medications.

\(^\text{15}\) Polish scientific societies do not and never had such right.
treatment of rheumatoid diseases are not registered for all clinical indications in which they are applied and some do not have any registered indication in the area of rheumatology.

In particular, this will affect children suffering from JIA, who are treated with methotrexate, chloroquine, sulphasalazine and cyclosporin A, patients with certain rheumatic diseases such as psoriatic arthritis, reactive arthritis and arthritis associated with spondyloarthropathy, and patients treated with cyclophosphamide because this drug does not have a registered indication for any rheumatic disease.

Table 5 List of reimbursable drugs, their registered indications and reimbursement levels

<table>
<thead>
<tr>
<th>Drug type</th>
<th>Product name</th>
<th>Reimbursement level</th>
<th>Registered indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Trexan</td>
<td>Flat rate</td>
<td>RA and psoriatic arthritis</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Equoral and Sandimmun Neoral</td>
<td>Flat rate</td>
<td>RA and uveitis</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Arechina</td>
<td>30%</td>
<td>RA and systemic lupus erythematosus</td>
</tr>
<tr>
<td>Sulfasalazine EN</td>
<td>Salazopyrin EN and sulfasalazine EN Krka</td>
<td>30%</td>
<td>RA</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Arava</td>
<td>Flat rate</td>
<td>RA</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>VIS azathioprine and Imuran</td>
<td>Flat rate</td>
<td>RA</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Prednisone</td>
<td>Encorton</td>
<td>Flat rare</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>Metypred and Medrol</td>
<td>Flat rate</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>Depo-Medrol</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Azathioprine has the broadest range of registered indications in rheumatology, but even in this case not all clinical indications are registered.

Source: Based on (PTR, 2012b)

NSAIDs have registered indications for symptomatic, analgesic and anti-inflammatory treatment of rheumatic diseases. They are prescribed against a "50% copayment (with the exception of ibuprofen – which is prescribed against a lump sum" R ").

8. Access to RA therapies – other considerations

At the end of 2009, 1,531 rheumatologists were registered at the Polish Chamber of Physicians: 583 (38%) were at the age of 51-60, 384 at the age of 41-50 (25%), 186 at the age of 61-65 (12%) and 312 were older than 65 (20%). In total, 1,007 rheumatologists were less than 60 years old. Only around 50 rheumatologists qualify each year, which means that in the long term it will not be possible to replace the retiring specialists and access to specialist care may become more difficult.
There is on average 2.6 rheumatologist in the pre-retirement age (less than 60 years old) per 100,000 inhabitants in Poland, which is quite high compared to other European countries (according to Eurostat data, the number of rheumatologists in Europe ranges from 0.5 per 100,000 inhabitants in Ireland to 4.2 in France\textsuperscript{16}) and meets the criteria of the British Society for Rheumatology (one rheumatologist per 85,000 inhabitants), even if one assumes that 50\% of rheumatologists work outside rheumatology clinics (i.e. in hospitals).\textsuperscript{17} The fact that it takes on average only 4 months to start an RA therapy, which is one of the shortest in Europe, further confirms that access to rheumatologists is good.\textsuperscript{18}

Unfortunately, effectiveness of care does not seem to be very high compared with the rest of Europe. Polish RA patients have high disease activity of, on average, DAS28 of 5.3 (DAS28 $>$ 5.1 is considered as very high activity). In countries where care is at a relatively good level DAS28 values range between 3.2 and 3.5 (low levels of activity). This may be caused by the overuse of sulfasalazine (many doctors use it instead of methotrexate, which they consider more risky)\textsuperscript{19} and to some extent because the NFZ does not have sufficient funds to reimburse modern RA therapies (W Thustochowicz, 2011).

According to the PTR, existing therapeutic programs in rheumatology do not meet the current recommendations of the scientific societies. Although a number of changes to these programmes have been proposed during the public consultation process, no significant changes have been made. Programmes are often ambiguous, which makes them difficult to implement. For example, no aim of treatment has been specified for JIA, which means that the computer application, which is used to monitor the efficacy of the therapy, often requires ending a therapy that may in fact be efficacious (PTR, 2012a).

Bibliography


Filipowicz-Sosnowska A, K. E., Maśliński W et al. (2002). Rekomendacje stosowania blokerów TNF-alfa u chorych na reumatoidalne zapalenie stawów. Reumatologia(40), 216-221.


\textsuperscript{16} As of 2005 or 2007.

\textsuperscript{17} It is not known how many rheumatologists work in hospitals and how many work in rheumatology clinics.

\textsuperscript{18} It takes from from 5 months (the Netherlands) to 15 months (Germany) to implement RA treatment in a patients.

\textsuperscript{19} This may be more pronounced among older doctors.


Appendix A

Extracts from the comments of a clinical leader in rheumatology in Poland (email correspondence, January 2012)
I think that the recommendations of the European League Against Rheumatism (EULAR) should be made binding in Poland. These recommendations should be well known, since we have full access to the original publications and they were also translated into Polish. A set of recommendations based on these are ready to be published. However, these give HTA agencies significant decision power.\textsuperscript{20}

Application of biological therapies is regulated by therapeutic programmes. They were created several years ago and reflect old and at the time still imprecise regulations. I hope that new programmes will be established this year in the area of rheumatology, which will fully reflect EULAR 2010 recommendations for RA and 2012 recommendations for psoriatic arthritis. However, in my opinion, because of administrative hurdles implementation of changes takes too long.

Unfortunately, the European guidelines severely restrict access to biological treatment, because different rules are applied in Poland in practice. The main precondition to the use of biological treatment is ineffectiveness of methotrexate (applied in recommended therapeutic doses of 20-30 mg/week). Methotrexate is the most effective and the safest drug currently available, and it improves the efficacy of biologics by 100%. In Poland, methotrexate is applied in much smaller doses (10-12.5 mg/week). We cannot allow that such a good drug is replaced by less effective and less safe drugs only because it is cheap and not well advertised. I don’t know who is to blame for this, but according to my observations, it’s mainly the patients, who are at fault: they are convinced that methotrexate is lethally toxic and do not accept rational arguments that prove otherwise. Moreover, Polish patients regard treatment in sanatoria as panacea for all diseases that can replace pharmacotherapy. Disease activity in RA patients in Poland is one of the highest in Europe.

Another problem is the high price of biologics in Poland. Biologics may cost much more in Poland than, for example, in England - up to 40% higher, depending on the exchange rate. For this reason some drugs are not available in Poland (and even in England, they were qualified for reimbursement as late as last year, after their price had been reduced).

Total outlays on biological treatment, which benefits approx. 3,000 patients, amounted to PLN120 million in 2011. Total outlays on treatment in rheumatology wards, in which almost 100 thousand patients were hospitalized (including patients in life threatening conditions), amounted to about PLN200 million. At the same time, total outlays on outpatient clinics, with approx. 650 thousand registered patients, were only PLN76 million.

Administrative hurdles encountered in the process of qualifying patients for biological treatment are also perceived as a problem, although I don’t see it as a problem in my hospital. Treatment with biologics, which are reimbursed by the National Health Fund (Narodowy Fundusz Zdrowia, NFZ), is monitored by the so-called Coordinating Group, and rheumatologists must file online applications in order to have patients qualified for treatment. This is quite time consuming and takes about 20-30 minutes. However, approvals are granted automatically and the number of RA patients approved for biological treatment has doubled since the Coordinating Group was established. I therefore don’t think that existence of this administrative procedure limits accessibility to biological treatment.

\textsuperscript{20} The Polish HTA agency, AOTM (Agencja Oceny Technologii Medycznych – Agency for Health Technology Assessment), models itself on the English NICE.

\textsuperscript{21} Comment: Poland has a long tradition in health resort treatment, which is offered in health resort hospitals and sanatoria.
In my opinion, improvement of clinical results in Poland requires introduction of all European rheumatology standards into the clinical practice and improvement of patients’ awareness [of the European standards]. At the same time, the number of patients treated with biological therapies should be increased.
Slovenia

1. What guidelines affect the use of biologic therapies for the treatment of RA?

In the area of rheumatoid arthritis Slovenia has adopted EULAR recommendations for the management of RA with disease modifying anti-rheumatic drugs (DMARDs). Slovenia has developed a computer protocol for treating patients with biological therapies.

Interview: The EULAR 2011 guidelines are adopted by the Slovenian Society of Rheumatologists, however, cannot be fully implemented in the practice, due to the low number of rheumatologists in Slovenia (in comparison to other EU countries). In Slovenia, there are only 0.8 rheumatologists per 100 thousand inhabitants, while the average 1.7 rheumatologists in Europe the same number of people. Especially in the first period of treatment, when the guidelines recommend every 1-3 months visits from the diagnosis, it is impossible to adhere to the recommendations.

According to our interviewee, there are almost 1000 patients being treated with biologics in Slovenia. However, great variations between the two University clinical centres on the number of patients can be observed, where in 2010 the University Clinical centre in Ljubljana was treating ca 300 patients with biological treatment (10 rheumatologists), while in the University medical centre in Maribor 55 RA patients (5 rheumatologists). As an example, the general hospital of Murska Sobota, with only 1 rheumatologist, was in 2010 treating 35 patients with biological treatment. Moreover, also in the University clinical centre Ljubljana, the numbers of patients with biological treatment varies from 9 to 69 depending on the rheumatologist in the team. There is no official explanation for the differences in number of patients treated with biological therapy.

From the moment, when the patient needs biological treatment, the process is very standardised. The e-protocol serves for guiding the treatment, cancelling the treatment, reporting the adverse effects etc. However, the time from diagnosing to defining the need for the biological treatment is critical, and the biological treatment depends obviously on the decision of the certain physician, although the accessibility to the treatment is the same all over Slovenia.

2. How do these affect patients' access to these therapies?

Although EULAR guidelines are followed, the protocols of defining accessibility to RA therapies depend on system of financing and human resources. EULAR recommendations are incorporated in online e-protocol for management of RA DMARDs.

Regarding the accessibility of patients to biologic therapies for RA treatment we can distinguish between two time periods in Slovenia. The first started in 2004 when first biological drugs for treatment of RA were introduced in Slovenia (Remicade) until 2007. During this period the accessibility of patients to biologic treatment was based on the primary criteria of financial means available. Health Insurance Institute of Slovenia which is a national insurance company and the only one providing compulsory health insurance in Slovenia, defined annually budget that was made available for biological therapies for patients with RA. It was up to the rheumatologists to define and determine patients that were most in need of the drugs. In the process of selecting patients the rheumatologists were facing ethical dilemma who among almost equally ill is more eligible to treatment. As it was exposed that the decisions on patients selection could be affected by subjective factors such as level of authority, bonds and
acquaintances and other subjective matters a model was built that was more transparent and objective in the patients selection. At the time there were two committees in Slovenia, one in Ljubljana (for western part of Slovenia) consisting of 16 rheumatologists who developed the model. The second committee was based in Maribor (for eastern part of Slovenia), who chose different ways of patient selection.

The model chose the patients who were according to the set criteria most eligible to treatment – the priority was given to younger patients and those whose responsiveness to other drugs was low. The model was named RA_BTZ_V1 and was in use from August 2004 to September 2007. Each rheumatologist suggested own eligible patients whose current treatment of RA was unsuccessful and illness difficult. For each patient a form needed to be filled out and sent to the commission. According to the criteria each patient was given a certain number of points. According to the financial funds allocated to RA biological drugs the number of patients was defined and later on the limit on the number of the points was set. All patients whose number of points was above the set limit could be included into the process of biological treatment. The chosen patients were treated with one of the biological drugs that were accessible at the time: adalimumab, etanercept or infliksimab.

What is special in Slovenian health care system is that it was specialists in internal medicine who worked as rheumatologists - the specialization in rheumatology started late and first graduates finished the rheumatology study only in 2010. This is why additional education was needed for proper use of the model by the commission if we were to start using the wide spectrum of DMARD drugs as therapies.

A form on the basis of which the patients were selected included the name and family name of the patient, gender, year of birth and region. Further, the year of first diagnosis of RA needed to be specified, last X-ray results, results of the last CCP test and the therapy. The duration of each therapy in the past needed to be marked and if it was discontinued the reasons needed to be stated. Also it needed to be stated whether the patients have been previously treated with biological drugs; if yes, which. Also the contra-indications for anti TNF α therapy needed to be reported. The further contents of the form referred to data on tuberculosis screening (symptoms, present risk factors for reactivation of latent infection, mantoux test, X-ray of lungs). Further data on DAS 28, ESR and VAS had to be filled out.

The Committee decided that of all data collected only age, number of already prescribed monotherapies of imonomodulating drugs for RA treatment and number of combinations of imunomodulating drugs will be taken into account. According to these three categories of data the patients were given a certain number of points. The maximum number of points was 30; the limit that was sufficient for the inclusion of patient into treatment depended on the financial funds available. All patients from 2004-2007 were treated either with etanercept or adalimumab (50:50). Three patients were treated with infliksimab, but those were paid by pharmaceutical company through clinical research. In 2008 rituksimab for treatment of 47 patients was introduced and in 2010 further financial fund for patients with RA for treatment with infliksimab and rituksimab were approved.

The second era of defining accessibility to the therapies started in September 2007 when the basic model RA_BTZ_V1 was upgraded into RA_BTZ_V2 – the model was contextually equal to RA_BTZ_V1. The only difference was that it was web based and the forms were sent also to HIIS. It was in use until February 2008. The treatment of RA according to RA_BTZ_V2 was guaranteed for all patients who fulfilled the following criteria:

- Duration of RA is shorter than 60 months
- Latent tuberculosis infection is not present; the conditions are result of Mantoux test <5mm and normal X-ray. If the conditions are not fulfilled, pulmologist’s opinion that there is no contra-indication for biological drug is sufficient,
- No pregnancy
- DAS 28>4,2 (at least moderately active illness)
- Number of swollen joints>8
- Treatment with the following DMARDs under A) or B):
  - A) two of the therapies, each at least for 4 months:
    - Metotreksat 20 mg/week
    - Leflunomid 10 or 20 mg/day
    - Combination of metotreksat and leflunomid
    - Combination of metotreksat, sulfasalazin and hydroksiklorokin
    - Combination of metotreksat and cyclosporin A
  - B) if treatment with metotreksat was discontinued due to unwanted effects, then at least 2 of the following therapies in duration of 4 months are condition: leflunomid, sulfasalazin, cyclosporin A, hydroksiklorokin, parenteral salts of gold.

The patients who do not fulfil the criteria and had RA present for more than 5 years were subject to RA_BTZ_V1.

The model that is currently in use was developed in February 2008 and is called RA_BTZ_V3. It is an evolution of model RA_BTZ_V2. Among the conditions for treatment the duration of RA was eliminated. Also, the patients who do not fulfil the set criteria are not subject to RA_BTZ_V1, meaning that no need for committee exists. Patients with approved treatment are included in the register called Evidence of patients with RA treated with biological drugs. The treatment with biological drugs is approved for all patients who fulfil the following criteria:

- Latent tuberculosis infection is not present; the conditions are result of Mantoux test <5mm and normal X-ray. If the conditions are not fulfilled, pulomogist's opinion that there is no contra-indication for biological drug is sufficient,
- No pregnancy
- DAS 28>4,2 (at least moderately active illness)
- Number of swollen joints>8
- Treatment with the following DMARDs under A) or B):
  - A) two of the therapies, each at least for 4 months:
    - Metotreksat 20 mg/week
    - Leflunomid 10 or 20 mg/day
    - Combination of metotreksat and leflunomid
    - Combination of metotreksat, sulfasalazin and hydroksiklorokin
    - Combination of metotreksat and cyclosporin A
  - B) if treatment with metotreksat was discontinued due to unwanted effects, then at least 2 of the following therapies in duration of 4 months are condition: leflunomid, sulfasalazin, cyclosporin A, hydroksiklorokin, parenteral salts of gold.

3. How are the guidelines reviewed?

The guidelines are reviewed annually by the Slovenian rheumatology society. The changes in guidelines reflect in the changes in e-protocols.

4. What comments have the guidelines provoked (from patients, clinicians and other opinion leaders)?

There are 20 rheumatologists in Slovenia. EULAR guidelines were well accepted among them. Also, they were well accepted by patients, clinicians and among opinion leaders. Rheumatologists were highly interested in the adoption of guidelines as well as production of e-protocols since those enabled patients equal therapeutic approach to management of RA. Patients were granted more equitable access, based on transparent criteria, to corresponding
appropriate) therapies with biological drugs. Due to higher transparency in the system as well as clearly set limitations also the payer (HIIS) of biological drugs welcomed the guidelines and protocols. Regarding Ministry of Health it has been promoting the production of guidelines and protocols for all diseases.

Until 2010 the decisions for financing biological drugs were taken by the Ministry of Health through a special commission for evaluation of biological drugs. All the other drugs were evaluated by HIIS. In 2010 the evaluation of all drugs (also biological as well as medical devices) was transferred to HIIS, Ministry of Health is only responsible for the evaluation of other health technologies except pharmaceuticals and medical devices.

Sources:

2. Praprotnik S.: Revmatološki priročnik za družinskega zdravnika, elektronska verzija. [http://www.revma.si], access on February 8, 2012
5. HIIS: General Annual Agreement for year 2009. [http://www.zzzs.si], access on February 9, 2012
15. [http://www.rtvslo.si/zdravje/vec‐kot‐leto‐dni‐bolecega‐cakanja‐na‐diagnozo‐revmatizma/268246], accessed on February 10, 2012
Spain

Marta Vilella

1. Introduction

RA is a frequent disease with little variation in prevalence among countries, with a prevalence of 0.5% in Spain (Carmona, 2002). It is estimated that 250,000 persons in Spain are afflicted with RA and that in the next ten years there will be around 36,000 new patients of AR in Spain (Los Reumatismos, Spanish Society of Rheumatology - SER, 2011).

In Mediterranean countries the disease may have a more benign course than in the countries of northern Europe (Ronda, 1994; Drosos, 1992), with fewer extra-articular manifestations and erosions, although the data are not conclusive.

In 2001, the costs due to RA in Spain exceeded 2,250 million euros, and the annual cost per patient was over 10,700 euros. It is estimated that the cost of treating one RA patient in Spain is, as is the case in the US, triple that of an individual of the same age and sex (Lajas, 2003). Moreover, it has been calculated that up to 5% of all permanent work disabilities in Spain are directly due to RA (Carmona, 2001).

1.1 Clinical guidelines

The first version of the guidelines (GUIPCAR) was published in 2001. In 2007 the Spanish Society of Rheumatology (SER) assigned to a panel of 18 experts the actualisation of the guidelines. In 2011 there was another update, which introduced modifications due to new scientific evidence but kept the main structure of the 2007 publication.

1.2 Regional variations

There are Societies of Rheumatology in many Spanish Autonomous Communities: Catalonia (Societat Catalana de Reumatologia), Andalucia (Sociedad Andaluza de Reumatologia), Valencia (Sociedad Valenciana de Reumatologia), La Rioja (Sociedad Riojana de Reumatologia), Canarias (Sociedad Canaria de Reumatologia), Aragon (Sociedad Aragonesa de Reumatologia), Murida (Sociedad Murciana de Reumatologia), Galicia (Sociedade Galega de Reumatoloxia), Madrid (Sociedad de Reumatologia de la Comunidad de Madrid). These societies can occasionally publish recommendations on certain treatments. For RA, there is a recent document from the Catalan Society (March 2011), which includes guidelines for RA and biologic treatments. This will be summarised in Section 3.

There are also health technology agencies at a regional level that can sometimes publish recommendations and economic evaluation of new health technologies. On the issue of biologics, the Catalan agency (Agencia d’Informacio, Avaluacio i Qualitat en Salut) is expected to publish a new report in March 2011 on the efficiency and security of biologic treatment for RA patients which will include a literature review and economic evaluation.

Also the Basque (OSTEBA) and the Andalusian (AETSA) agencies have published over the last two years reports on the issue of biologic treatments for RA. The former on the effectiveness of GOLIMUMAB (Nov 2010) and the latter a literature
review on the efficiency and security of different biologic agents but it does not include recommendations (Mar 2011).

2. Diagnosis and treatment evaluation

The Spanish Society of Rheumatology (SER) has published standards for process times and quality of care in rheumatology. According to these standards, for a patient with inflammatory systemic disease, the maximum wait time between consultation with the primary care physician and access to a specialist in rheumatology should not exceed 2 weeks (SER, 2005).

All cases of arthritis lasting more than 4 weeks should be referred to specialty care, regardless of the suspected diagnosis. Patients with suspected septic arthritis should be referred immediately.

The guidelines raise the question on the debate of whether or not to adopt new RA diagnostic criteria other than the 1987 American College of Rheumatology (ACR). In favour of the change are, on the one hand, the need to have criteria in the initial stages of RA since the ACR criteria are not very useful for this purpose, and, on the other, to be able to divide patients according to prognosis, which would make it possible to suggest different treatment strategies. Nevertheless, against the change of criteria is the fact that not all centers are able to perform the newest and most effective biological tests such as anti-CCP; furthermore, changing the diagnostic criteria would make it difficult to compare patients thus diagnosed with historical series that have used the classic criteria.

For the above reasons, the recommended criteria for diagnosis is to follow the EULAR/ACR 2010 criteria.

3. Pharmacological treatment

Please refer to Table 1, Appendix, for abbreviations used throughout this report on DMARDs (Disease-modifying anti-rheumatic drugs) used in RA treatment.

All RA patients should be treated with a DMARD as soon as the clinical diagnosis of the disease is established, regardless of whether they meet the ACR classification criteria. The time between symptom onset and initiation of treatment with DMARDs is one of the few variables that the physician can modify. Recent recommendations from EULAR (Smolen, 2010) indicate that treatment with DMARDs should begin as soon as diagnostic for RA is confirmed. Early treatment is associated with a higher probability of favourable response.

The initial treatment recommended in all patients who have not been previously treated with a DMARD is MTX, due to its excellent safety and efficacy profile. The advantages of MTX as opposed to other DMARDs with similar short-term efficacy are: an extensively known safety profile, ease of administration, and a lower rate of treatment dropout in the medium to long term. For all these reasons, the Spanish guideline recommends it as the drug of choice.

Given the clinical complexity of RA, the guideline considers that, in some clinical situations, initial DMARD treatment may consist of using other drugs that have also been shown to control signs and symptoms of the disease and to delay radiologic progression.

In early RA with no markers of poor outcome (radiologic erosions, RF, anti-CCP antibodies, absence of extra-articular disease, HAQ over 1 or high inflammatory burden), it is acceptable to begin treatment with other DMARDs that have a lower toxicity profile or are easier to monitor for side effects; typical examples of these are the anti-malarials or SSZ.
In early RA that is expected to be especially incapacitating due to characteristics of the disease initial combination therapy with MTX and an anti-TNF agent may be indicated; the objective of this treatment is to induce rapid remission and try to withdraw the anti-TNF agent and maintain RA remission with MTX in monotherapy.

Figure 1. Summary of recommendations for RA treatment in Spain, 2007 revised in 2011

Regardless of the initial treatment chosen, the patient must be monitored closely. If a satisfactory response is not obtained in 3 months or if DMARD‐related toxicity occurs, the physician should evaluate the possibility of changing treatment by adding a new drug or modifying the dosage. It is essential that a patient with RA who has not responded to a particular DMARD treatment in monotherapy or combination therapy have the option of other treatments of proven efficacy as quickly as possible.

If response to MTX is unsatisfactory after reaching the maximum dosage and assuring the bioavailability of the agent, the panel recommends the use of LEF or SSZ or an anti-TNF agent as the second step in the treatment ladder, either replacing or in addition to MTX. If MTX toxicity is such as to oblige its withdrawal, the panel recommends using LEF or SSZ or an anti-TNF agent as the second step on the treatment ladder.

In patients for whom the previously described guidelines are not useful due to lack of efficacy, toxicity or other reasons, use of any of the DMARDs, combinations or other biologic agents is recommended; if these fail, experimental treatments should be tried.

3.1 Regional variations
In March 2011, the Catalan Society for Rheumatology published the following recommendations on the use of biologics. The document acknowledges the improvement of biologic treatments for patients but also that costs have increased because of them. Due to the current economic situation, the guideline recommends a more efficient and rational use of biologics/anti-TNFs.

The recommendations to use biologics are for situations when other DMARDs have proven ineffective. It is not recommended to start biologic treatment before having tried the use of DMARDs (MTX, LEF, SSF, CLQ).

There is no consensus on the degree of illness at which the biologic treatment should be started. Recommended first options for biologic treatment are TCZ and ABT.

Figure 2. Recommendations for biologic treatment in Catalonia (Catalan Society of Rheumatology), March 2011

4. Clinical practice

Clinical practice varies significantly across regions. In 2011, the results of EMAR II project on the “Variability in RA and spondylarthritis management in Spain” were published. The aim of the study, which followed EMAR I published 10 years earlier, was to assess variability in terms of health resources and use of treatments and methods. The sample of the study includes RA/spondylarthritis patients who have been attended by Rheumatology Units in Spanish hospitals (N=1,410). Here we summarise the main findings for RA patients, particularly those related to the use of biologic agents:

- 1,236 AR patients were treated with DMARDs at some point during the course of their illness – this 97.2% of the total sample.
- Most used DMARD was MTX (59.6%), followed by LEF (22.1%), CLQ/HCQ(12.2%), and SSZ (3.1%).
- Average time of prescription for DMARDs ranged between 0 and 2.9 months.
- 20.7% of patients were prescribed with 2 or more DMARDs simultaneously over the last 2 years.
- DMARDs treatment shows significant variability amongst Autonomous Communities, particularly for MTX, LEF, CLQ/HCQ, with variations such 42%-76%; 17%-48% and 6%-40% for each pharmaceutical.
• 36.9% of patients had received some kind of biologic pharmaceutical during the course of their illness. The average time between the diagnostic and the start of the biologic treatment was 59.8 months.

• Most common drugs and dosages were ADA 40 mg (27.3%); IFX 3 mg/kg (20.5%); ETN 50 mg (19.9%); ETN 25 mg (12.2%); and RTX 1000 mg x 2 infusions (7.6%).

• The most common drug presentation was the IV infusion (37.8%), followed by preloaded syringes (37.2%), self-injector (14.3%) and freeze-dried syringes (5.8%).

• Amongst patients who were treated with biologic agents, only 11.1% had to increase dosage, whilst dosage decrease happened amongst 4% of patients. Also, in 6% of cases there was a shortening of the dosage and a lengthening of the treatment happened in 7.1% of cases.

• Most common reasons for stopping the biologic agents treatment were: inefficiency (47.1%); negative effects (30.1%); doctor’s decision (8.5%); and negative effects and inefficiency (5.6%). Illness remission due to treatment suspension was only shown in 2.6% of patients.

• Biologic agents were used together with other DMARDs in 80.3% of sample patients.

• Average duration of treatment with biologics was 10.3 months.

• Finally, 64 patients were treated with biologics as parts of clinical trials, which represents 5% of the sample. The pharmaceutical most used in these trials were: ADA (38.5%), TCZ (19.2%) and ANK and ETN (both 11.5%). (See Table 2)

The following chart shows the variability in the use of biologic agents during the course of the 2 year study by Autonomous Community. Variability is particularly relevant for ETN (3%-47%), ADA (9%-27%) and IFX (0%-19%).

(Please go to Table 3, Appendix, for a summary on the above clinical practise).

**Chart 1. Variability in use of biologic agents by Autonomous Community (during study period)**
Treatment with biologic agents also showed significant variability during the course of illness amongst Autonomous Communities (AC) as shown in the table below.

(Please refer to Table 4 for more details on AC variability)

Statistical analysis showed that the probability of receiving biologics treatment was affected by the patient’s age and increased by the longer the patient has suffered the illness. Also, type IV, high activity of the illness and the increase of the number of doctors seeing that patient correlated positively with this kind of treatment.

5. Current issues of debate around biologics

The efficiency of pharmacological for RA is a hot topic and currently the Health Ministry is reviewing the case. Research has been commissioned to the Catalan health technology agency as mentioned above. We have contacted Anna Garcia Altes, principal investigator, and the project is expected to be delivered by 15th March, though it is not yet publicly available.

We have also reviewed the official magazine of SER and found news about anti-TNF/biologics in almost every issue over the past year. In particular,

- One article about training on the management of biologic treatments, informing about the contents of the course and why it is important. It acknowledges that biologics have revolutionised the treatment for RA over the last ten years but they have also potential negative effects and have an elevated cost, so it is required to provide training to doctors in this area.
- There is one article reporting on CERTOLIZUMAB PEGOL which reports on its benefits in pain reduction (August 2011).
- Another article shows evidence about the benefits of combined treatment with MTX and ETN (March-April 2011).
- Reporting the Committee for Medicinal Products for Human Use (CHMP) from the European Medicines Agency has adopted a positive view on the use SIMPONI® (golimumab), combined with MTX in patients with serious RA (Jan-Feb 2011).

References


Ronda E, Ruiz MT, Pascual E, Gibson T. Differences between Spanish and British patients in the


APPENDIX

Table 1. Pharmacological agents and abbreviations (biologic agents highlighted in blue)

<table>
<thead>
<tr>
<th>PHARMACOLOGICAL</th>
<th>ABBREVIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABATACEPT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ABT</td>
</tr>
<tr>
<td>ADALIMUMAB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ADA</td>
</tr>
<tr>
<td>ANAKINRA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ANK</td>
</tr>
<tr>
<td>AZATIOPRINA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AZT</td>
</tr>
<tr>
<td>CERTOLIZUMAB PEGOL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CZP</td>
</tr>
<tr>
<td>CICLOFOSFAMIDA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CFA</td>
</tr>
<tr>
<td>CLOROQUINA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CLQ</td>
</tr>
<tr>
<td>CICLOSPORINA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CSA</td>
</tr>
<tr>
<td>D-PENICILAMINA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>DPE</td>
</tr>
<tr>
<td>ETANERCEPT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ETN</td>
</tr>
<tr>
<td>GOLIMUMAB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>GLM</td>
</tr>
<tr>
<td>HIDROXICLOROQUINA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>HCQ</td>
</tr>
<tr>
<td>INFLIXIMAB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IFX</td>
</tr>
<tr>
<td>LEFLUNOMIDA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>LEF</td>
</tr>
<tr>
<td>METOTREXATO&lt;sup&gt;c&lt;/sup&gt;</td>
<td>MTX</td>
</tr>
<tr>
<td>ORO ORAL&lt;sup&gt;d&lt;/sup&gt;</td>
<td>AUR</td>
</tr>
<tr>
<td>ORO INYECTABLE&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ORI</td>
</tr>
<tr>
<td>RITUXIMAB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RTX</td>
</tr>
<tr>
<td>SULFASALAZINA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>SSZ</td>
</tr>
<tr>
<td>TOCILIZUMAB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TCZ</td>
</tr>
</tbody>
</table>

<sup>a</sup> Biologic agents; <sup>b</sup> Chemical agents used occasionally; <sup>c</sup> Chemical agents used frequently; <sup>d</sup> Chemical agents used very infrequently.
Table 2. DMARD'S, recommended does and commercial names
(↑ Highlighted in red the revisions in the 2011 guideline)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE</th>
<th>COMMERCIAL NAMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABATACEPTa</td>
<td>Dosage adjusted to body weight:</td>
<td>ORENCIA_, Lyophilized vials of 250 mg</td>
</tr>
<tr>
<td></td>
<td>&lt;60 kg: 500 mg</td>
<td>to be reconstituted</td>
</tr>
<tr>
<td></td>
<td>from 60 to 100 kg: 750 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;100 kg: 1,000 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravenous infusion during 30 minutes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Additional doses to be administered 2 and 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>weeks after first infusion,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with one dose every 4 weeks thereafter.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be used in monotherapy or in</td>
<td></td>
</tr>
<tr>
<td></td>
<td>combination with another DMARD, except for</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TNF antagonists.</td>
<td></td>
</tr>
<tr>
<td>ADALIMUMABa</td>
<td>40 mg/14 days, in subcutaneous injection</td>
<td>HUMIRA_, Preloaded syringes, 40mg</td>
</tr>
<tr>
<td></td>
<td>In some patients the interval between</td>
<td>HUMiRA Preloaded pen 40 mg</td>
</tr>
<tr>
<td></td>
<td>infusions needs to be shortened to every 7-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 days instead of the recommended 14 days.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The addition of methotrexate may improve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>the therapeutic response in selected</td>
<td></td>
</tr>
<tr>
<td>ANAKINRAa</td>
<td>100 mg/day, in subcutaneous injection</td>
<td>KINERET_, Preloaded syringes, 100 mg</td>
</tr>
<tr>
<td>AZATHIOPRINEb</td>
<td>1.5 – 2.5 mg/kg/day, orally</td>
<td>IMUREL_, Coated tablet, 50 mg</td>
</tr>
<tr>
<td>AZATHIOPRINEb</td>
<td>begin with low doses</td>
<td>IMUREL_, Lyophilized vial, 50 mg</td>
</tr>
<tr>
<td></td>
<td>around 1 mg/kg/day and increase by 4-6 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to maintenance dose of 100-150 mg/day</td>
<td></td>
</tr>
</tbody>
</table>
CERTOLIZUMAB PEGOL 400 mg in weeks 0, 2 and 4, followed by maintenance dose of 200 mg every 2 weeks.

CIMZIA Preloaded syringes, 200mg

CYCLOPHOSPHAMIDEb - 1.5 – 2.5 mg/kg/day, orally
- Begin with 50 mg/day and increase dose every 4-6 weeks until response is obtained, without exceeding 2.5 mg/kg/day.

GENOXAL Amp. IV 1000 mg
GENOXAL Amp. IV 200 mg
GENOXAL Tab. 50 mg

CYCLOSPORINc - 250 mg/day, orally
- Do not exceed 4 mg/kg/day.

RESOCHIN Tab. 250 mg

CHLORO-QUINEc - 2.5 – 5.0 mg/kg/day, orally
- The initial dose can be increased by 0.5 mg/kg/day every 2 weeks up to 5 mg/kg/day.

SANDIMMUN NEORAL 100 mg
SANDIMMUN NEORAL 50 mg
SANDIMMUN NEORAL 25 mg
SANDIMMUN NEORAL Oral sol. 100 mg/ml

D-PENICILLAMINEd - 125 – 500 mg/day, orally
- Begin treatment with 125-250 mg/day and if there is no improvement, increase dose at 8 weeks by 125 mg/day. Dose can be increased gradually every 8 weeks up to 500-750 mg/day. Should be administered 2 hrs before the main meal.

CUPRIPEN Caps .250 mg
CUPRIPEN Caps .125 mg
CUPRIPEN Comp.50 mg
SUFORTANON TAB. 250 MG

ETANERCEPTa - 25 mg in subcutaneous injection twice a week (at intervals of 72-96 hours) or 50 mg once a week.

ENBREL Vial, 25 mg
ENBREL Vial, 50 mg

GOLIMUMAB 50 mg once a month, same day every month
- In combination with MTX

SIMPONI Preloaded siringes, 50 mg
SIMPONI Preloaded pen, 50 mg
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYDROXYCHLOROQUINEc</td>
<td>- 400 mg/day, orally</td>
</tr>
<tr>
<td></td>
<td>- Do not exceed 6.5 mg/kg/day.</td>
</tr>
<tr>
<td>DOLQUINE Tab. 200 mg</td>
<td></td>
</tr>
<tr>
<td>INFLIXIMABa</td>
<td>- 3 mg/kg in intravenous perfusion for 2 hours</td>
</tr>
<tr>
<td></td>
<td>- Then administer additional doses of 3 mg/kg in perfusion at weeks 2 and 6 after the first week, and one dose every 8 weeks thereafter. Dose may be increased to 5 mg/kg if ineffective or in case of relapse. Some patients require a shorter interval of infusion of 4-6 weeks, instead of the 8 weeks recommended for maintenance.</td>
</tr>
<tr>
<td>REMICADE Lyophilized vial, 100 mg</td>
<td></td>
</tr>
<tr>
<td>LEFLUNOMIDEc</td>
<td>- 20 mg/day, orally</td>
</tr>
<tr>
<td></td>
<td>- Begin with 100 mg/day for 3 days and then 20 mg/day continuously.</td>
</tr>
<tr>
<td>ARAVA Tab.100 mg</td>
<td></td>
</tr>
<tr>
<td>ARAVA Tab.20 mg</td>
<td></td>
</tr>
<tr>
<td>ARAVA Tab.10 mg</td>
<td></td>
</tr>
<tr>
<td>METHOTREXATEc</td>
<td>- 7.5-10 mg/week, orally for 4 weeks, 15 mg/week for the following 4 weeks and then increase up to 20-25 mg/week. If ineffective or if there is gastrointestinal toxicity, parenteral administration should be considered.</td>
</tr>
<tr>
<td>ALMIRALL Inj. sol. Vial 50 mg, A.D.1000 mg, 5000 mg, and 500 mg</td>
<td></td>
</tr>
<tr>
<td>METHOTREXATE LEDERLE Tab.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Folic acid should be</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
administered (5-10 mg/week) 24 hours after the administration of methotrexate.

Lyophilized vial 50 and 500 mg

METHOTREXATE

WASSERMANN

Inj. sol. 25 mg/ml (2 and 20 ml)

EMTHEXATE Vial 50 and 500 mg/2ml

ORALGOLDd

- 6 mg/day, orally

- 2 tablets daily

RIDAURA Tab. 3 mg

CRISINOR Tab. 3 mg

INYECTABLE GOLd

- 50 mg/week in intramuscular injections

- Increasing doses of 10, 25 and 50 mg/week, maintaining the dose (from 6 to 24 months) or adjusting it depending on clinical response or adverse effects

MIOCRIN Inj. sol. IM 10 mg

MIOCRIN Inj. sol. IM 25 mg

MIOCRIN Inj. sol.. IM 50 mg

RITUXIMABa

- Two doses of 1000 mg, in IV infusion, 2 weeks apart, in combination with MTX

- To reduce the incidence and severity of infusion reactions, the administration of 100 mg IV of methylprednisolone (or equivalent) 30 minutes before each infusion is recommended.

MABThERA single-use vials of 100 AND 500 mg

SULFASALAZINEc

- 2-3 g/day, orally

SALAZOPYRIN Tab. 500 mg

TOCILIZUMAB

8 mg/kg of body weight, once every four weeks.

For individuals >100 kg of body weight, do not exceed dosage of 800 mg

ROACTEMRA Vials of 4 ml. (20mg/ml)

ROACTEMRA Vials of 10 ml. (20mg/ml)

ROACTEMRA Vials of 20ml. (20mg/ml)
Table 3. Treatment with biological pharmaceuticals

<table>
<thead>
<tr>
<th>Type of biologic agent</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not stated</td>
<td>7 (0.9%)</td>
</tr>
<tr>
<td>Abatacept (10 mg(k)</td>
<td>16 (2.1%)</td>
</tr>
<tr>
<td>Abatacept (otra dosis)</td>
<td>7 (0.9%)</td>
</tr>
<tr>
<td>Adalimumab (40 mg)</td>
<td>204 (27.3%)</td>
</tr>
<tr>
<td>Adalimumab (otra dosis)</td>
<td>6 (0.8%)</td>
</tr>
<tr>
<td>Anakinra (100 mg)</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td>Anakinra (otra dosis)</td>
<td>-</td>
</tr>
<tr>
<td>Etanercept (25 mg)</td>
<td>91 (12.2%)</td>
</tr>
<tr>
<td>Etanercept (50 mg)</td>
<td>149 (19.9%)</td>
</tr>
<tr>
<td>Etanercept (otra dosis)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Infliximab (3 mg/k)</td>
<td>153 (20.5%)</td>
</tr>
<tr>
<td>Infliximab (5 mg/k)</td>
<td>14 (1.9%)</td>
</tr>
<tr>
<td>Infliximab (otra dosis)</td>
<td>8 (1.1%)</td>
</tr>
<tr>
<td>Rituximab (500 m; 2 infusiones)</td>
<td>8 (1.1%)</td>
</tr>
<tr>
<td>Rituximab (1000 mg; 2 infusiones)</td>
<td>57 (7.6%)</td>
</tr>
<tr>
<td>Rituximab (otra dosis)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Tocilizumab (4 mg)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Tocilizumab (8 mg)</td>
<td>12 (1.6%)</td>
</tr>
<tr>
<td>Tocilizumab (otra dosis)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Presentation</td>
<td>N = 707</td>
</tr>
<tr>
<td>Not stated</td>
<td>35 (4.9%)</td>
</tr>
<tr>
<td>Self-injector</td>
<td>101 (14.3%)</td>
</tr>
<tr>
<td>Infusion IV</td>
<td>267 (37.8%)</td>
</tr>
<tr>
<td>Freeze-dried syringes</td>
<td>41 (5.8%)</td>
</tr>
<tr>
<td>Preloaded syringes</td>
<td>263 (37.2%)</td>
</tr>
<tr>
<td>Category</td>
<td>N</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Dosage increase</td>
<td>746</td>
</tr>
<tr>
<td>No</td>
<td>663</td>
</tr>
<tr>
<td>Yes</td>
<td>83</td>
</tr>
<tr>
<td>Dosage decrease</td>
<td>746</td>
</tr>
<tr>
<td>No</td>
<td>716</td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
</tr>
<tr>
<td>Shortening of treatment</td>
<td>746</td>
</tr>
<tr>
<td>No</td>
<td>701</td>
</tr>
<tr>
<td>Si</td>
<td>45</td>
</tr>
<tr>
<td>Lengthening of treatment</td>
<td>746</td>
</tr>
<tr>
<td>No</td>
<td>693</td>
</tr>
<tr>
<td>Si</td>
<td>53</td>
</tr>
<tr>
<td>Reason for stopping treatment</td>
<td>342</td>
</tr>
<tr>
<td>Not known</td>
<td>9</td>
</tr>
<tr>
<td>Negative effects</td>
<td>103</td>
</tr>
<tr>
<td>Inefficiency</td>
<td>161</td>
</tr>
<tr>
<td>Negative effects and inefficiency</td>
<td>19</td>
</tr>
<tr>
<td>Doctor’s decisión</td>
<td>29</td>
</tr>
<tr>
<td>Other doctor decision</td>
<td>4</td>
</tr>
<tr>
<td>Patient’s decision</td>
<td>8</td>
</tr>
<tr>
<td>Remission</td>
<td>9</td>
</tr>
<tr>
<td>Use with DMARDs</td>
<td>748</td>
</tr>
<tr>
<td>No</td>
<td>147</td>
</tr>
<tr>
<td>Yes</td>
<td>601</td>
</tr>
<tr>
<td>Biologics as part of clinical trial</td>
<td>1.272</td>
</tr>
<tr>
<td>No</td>
<td>1.208</td>
</tr>
<tr>
<td>Yes</td>
<td>64</td>
</tr>
<tr>
<td>Biologics used in clinical trial</td>
<td>52</td>
</tr>
<tr>
<td>Not stated</td>
<td>6</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>20</td>
</tr>
<tr>
<td>Treatment</td>
<td>Count (Percentage)</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Anakinra</td>
<td>6 (11.5%)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>6 (11.5%)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3 (5.8%)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>10 (19.2%)</td>
</tr>
</tbody>
</table>
Table 4. Treatment with biologics, by Autonomous Community (Spain)

<table>
<thead>
<tr>
<th>Autonomous Community</th>
<th>Treatment with biologics</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>AC1</td>
<td>26 (86,7%)</td>
<td>4 (13,3%)</td>
</tr>
<tr>
<td>AC2</td>
<td>33 (84,6%)</td>
<td>6 (15,4%)</td>
</tr>
<tr>
<td>AC3</td>
<td>33 (75%)</td>
<td>11 (25%)</td>
</tr>
<tr>
<td>AC4</td>
<td>112 (74,7%)</td>
<td>38 (25,3%)</td>
</tr>
<tr>
<td>AC5</td>
<td>22 (73,3%)</td>
<td>8 (26,7%)</td>
</tr>
<tr>
<td>AC6</td>
<td>60 (67,4%)</td>
<td>29 (32,6%)</td>
</tr>
<tr>
<td>AC7</td>
<td>60 (66,7%)</td>
<td>30 (33,3%)</td>
</tr>
<tr>
<td>AC8</td>
<td>37 (64,9%)</td>
<td>20 (35,1%)</td>
</tr>
<tr>
<td>AC9</td>
<td>80 (63,5%)</td>
<td>46 (36,5%)</td>
</tr>
<tr>
<td>AC10</td>
<td>18 (62,1%)</td>
<td>11 (37,9%)</td>
</tr>
<tr>
<td>AC11</td>
<td>39 (60,2%)</td>
<td>25 (39,1%)</td>
</tr>
<tr>
<td>AC12</td>
<td>153 (60,2%)</td>
<td>101 (39,8%)</td>
</tr>
<tr>
<td>AC13</td>
<td>33 (55%)</td>
<td>27 (45,0%)</td>
</tr>
<tr>
<td>AC14</td>
<td>87 (48,3%)</td>
<td>93 (51,7%)</td>
</tr>
<tr>
<td>AC15</td>
<td>10 (33,3%)</td>
<td>20 (66,7%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>803 (63,1%)</td>
<td>469 (38,9%)</td>
</tr>
</tbody>
</table>
Sweden

Olivier J. Wouters

Background

Rheumatoid arthritis (RA) affects approximately 0.5% of the Swedish population. In January 1998, the first Swedish RA guidelines were developed jointly by Norwegian and Swedish rheumatology experts for the Norwegian Medicines Control Authority and the Swedish Medical Products Agency. These evidence-based suggestions highlighted the importance of quick referrals to rheumatologists following diagnosis and early prescription of disease-modifying antirheumatic drugs (DMARDs) to curtail disease progression. In addition, the guidelines advocated the use of local steroid injections instead of systemic steroids. Finally, the document encouraged holistic team care for RA patients and careful follow-up after the provision of DMARDs [1]. These suggestions were transformed into official RA clinical guidelines by the Swedish Society for Rheumatology (SSR) in November 1998. The Swedish guidelines are positively formulated (i.e. detail appropriate course of treatment for RA patients) and are non-binding; although the guidelines are reviewed on an annual basis, updated documents were only published online in 2004 and 2011 (see extracts from expert interview for more detailed information on the review process). A number of RA registries exist in Sweden that facilitate the study of adherence to clinical guidelines and permit longitudinal observational studies [2]; these also offer an important source of information to complement the data gathered from randomized, placebo-controlled clinical trials (RCTs) on biological treatment options.

Carli and colleagues (2008) studied the impact of Swedish national guidelines on the management of RA using DMARDs between 1997 and 2001 [3]; the study applied statistical process control methods and regression modelling on data obtained from a Swedish RA register. Based on data from 2,559 patients over the age of 15 and diagnosed with RA, they found a statistically significant (p<0.0001) increase over this time period in the prescription of DMARDs during a patient's first visit to a rheumatologist. The authors determined that a single shift in the data in July 1998 (p=0.0095) was responsible for the observed increase; once the data shift was accounted for, the authors found no trends in the periods before and after July 1998 (p=0.5934 and 0.7497, respectively). These results suggest that the 1998 promulgation of RA treatment recommendations resulted in a positive uptake of clinical evidence and may have improved care for Swedish RA patients.

2004 Guidelines

Emery and colleagues (2009) analyzed similarities and differences across European countries in the clinical guidelines for the prescription of anti-tumour necrosis factor (anti-TNF) therapy, such as etanercept, infliximab, and adalimumab, for RA patients; the authors found that the 2004 Swedish guidelines were less restrictive than those in other countries [4]. The 2004 guidelines first provide general RA information (e.g. definition and symptoms), epidemiologic data (e.g. Swedish incidence and prevalence rates), and details on the usual progression of the disease in the absence of treatment [5]. The guidelines specify that RA should be diagnosed according to patient history (e.g. symptom duration), clinical evaluation, and laboratory findings (e.g. rheumatoid factor [RF] values); the symptoms should conform to the 1987 classification criteria established by the American College of Rheumatology and alternative diagnoses should be excluded. The Swedish guidelines suggest that doctors limit the use of radiographic monitoring (e.g. use only if doctor suspects serious joint deterioration). The guidelines also summarize the clinical evidence about the relative efficacy and effectiveness of various interventions (e.g. DMARDs, including Anti-TNFs, and non-steroidal anti-inflammatory drugs [NSAIDs]).

Disease severity (i.e. inflammation index) is classified according to 28-joint Disease Activity Score (DAS28) with X ≤ 3.2, 3.2 < X ≤ 5.1, and 5.1 < X corresponding to low, moderate, and high-activity RA, respectively. In the case of low-activity RA with no negative prognostic
factors, the guidelines recommend the use of auranofin, chloroquine, methotrexate, or sulfasalazine; it is explained that low-dose methotrexate is usually sufficient. For patients with moderate-activity or worse (or patients with negative prognostic factors), the patients should first try at least two 2-3 month DMARD-treatments; only one treatment round is recommended in the case of rapid disease progression based on certain marker tests (e.g. RF). The first regimen should be methotrexate (or sulfasalazine, leflunomid, or sodium aurothiomalate if contraindication). If methotrexate alone is insufficient in moderate-activity patients, the guidelines also recommend the use of one of two treatment options before the prescription of anti-TNFs (dependent on factors such as drug resistance): (1) methotrexate, sulfasalazine, and chloroquine or (2) methotrexate and cyclosporine. If neither of the drug regimens is successful in curbing disease progression, doctors should then start patients on a combination therapy of anti-TNFs and methotrexate. In the case of methotrexate drug resistance, anti-TNFs (e.g. etanercept or adalimumab) or interleukin-1 (IL-1) inhibitors should be considered as a monotherapy. These recommendations are summarized in Table 1, below.

Table 1. Treatment strategy for newly diagnosed RA patients (adapted from 2004 guidelines).

<table>
<thead>
<tr>
<th>Low-activity RA (in patients with no negative prognostic factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate- and high-activity RA (or patients with negative prognostic factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td><strong>Step 2 (skip if quick disease progression)</strong></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
</tr>
</tbody>
</table>

In addition, the guidelines recommend the supplementary treatment with low doses of prednisolone (5-7.5 mg per day); higher doses can be administered at the discretion of the doctor for high-activity RA patients. NSAIDs may also be prescribed for pain relief. The treatment strategy for previously diagnosed RA patients should follow the aforementioned steps. Patient response to prior drug treatments should be evaluated, however, and the drug regimen should be adjusted accordingly. It is important to note that all decisions are ultimately at the discretion of the physician and the clinical guidelines are non-binding. For example, doctors may decide to administer a biologic treatment at any time if they believe its use is warranted (e.g. even if a patient has low-activity RA according to a DAS28 score).

The 2004 guidelines do not include any explicit restrictions on the prescription of biologic treatments in Sweden (e.g. no economic criteria). The guidelines do not specify which biologic agents should be used or when a switch between agents is advisable, although they mention a few available options at the time (e.g. adalimumab, etanercept, and infliximab); they also do not specify when dosages or prescription frequencies should be adjusted. The treatment response measures are defined on an individual basis and should include evaluation of disease activity (e.g. DAS28 scores and physical examination of joints) and records of side-effects. The patient response should be re-evaluated every 2-3 months. The guidelines discuss the use of surgery in extreme cases where pharmacological treatment is unsuccessful. Finally, the document highlights the importance of holistic care, which includes fostering an environment of patient concordance, and also stresses the impact of lifestyle factors (e.g. smoking) and rehabilitative medicine on successful disease management.

Söderlin and Geborek (2008) studied the conformity of biologic prescription patterns in Southern Sweden to national guidelines based on the data from 1,839 biologically naïve RA patients between 1999 and 2006 [6]; the data was obtained from the Southern Swedish Arthritis...
Treatment Group registry. Overall, the data showed a decreasing trend in disease activity in RA patients between 1999 and 2006 (e.g., falling DAS28 scores and baseline disease duration). The mean DAS28 at the time of biologic treatment initiation was 5.4. In 2006, 16% of patients received biologic agents (etanercept and adalimumab were the preferred biologics) within two years of onset, in comparison with only 3% in 1999 (i.e., possible that patients were treated with biologics earlier after the introduction of the 2004 SSR guidelines); only 15% of patients started biologic treatment within five years in 1999. The study found a decrease in the use of oral corticosteroid treatment, as recommended by the 2004 guidelines. The number of patients prescribed biologics after one round of DMARD increased from 3% in 1999 to 27% in 2006. The data also showed that more patients were switched from one medication to another when compared to 1999, suggesting an increase in the prevalence of treatment-resistant cases. Results from the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) project found that the median delay to start DMARD treatment in Sweden was 12 months [7]; this finding was based on the study of 248 patients between 2005 and 2006 at three treatment sites.

2011 Guidelines

New guidelines were published in 2011 and introduced significant changes [8]. First, the strength of the clinical evidence supporting specific recommendations is evaluated (i.e., scale of very low, low, moderate, or high). The grading system more directly connects clinicians to the ongoing debate over alternative treatment options and highlights more controversial evidence. The guidelines stress the importance of rapid action by physicians to quickly and aggressively counter the serious effects of untreated RA. Prognostic indicators are an important tool to identify patients likely to require biologic treatment. The document also mentions alternate indices to the DAS28 to measure RA activity (e.g., EULAR Disease Activity Score, SR, CRP, or VAS scale); the same DAS28 scale applies as in 2004, but disease remission is now classified as $X < 2.6$. It prioritises the use of certain biologic agents and clarifies the course of action for moderate- and high-activity RA patients. In 2011, the SSR also published separate guidelines on pharmacological treatment for pregnant and breastfeeding women (i.e., impose certain restrictions) and the need for tuberculosis screening prior to the initiation of biological treatment (i.e., to avoid the activation of latent tuberculosis) [9,10]; other guidelines detail the added precautions needed when handling patients with cardiovascular risk factors and patients susceptible to RA-induced osteoporosis.

For low-activity RA, methotrexate remains the primary DMARD intervention according to the 2011 guidelines; intra-articular steroid treatment is favoured to low-dose corticosteroid treatment. For moderate-activity, the first step is to increase the methotrexate dosage to 20-30 mg/week within eight weeks of onset if possible and the patient should be re-evaluated after 2-3 months. The document recommends the use of one or two 5 mg folacin tablets per week to counter methotrexate side-effects and also the use of low-dose corticosteroid (prednisolone). Step two is a methotrexate combination therapy with adalimumab, certolizumab, etanercept, golimumab, or infliximab (all drugs in this guideline are listed alphabetically, not according to priority). In patients with contraindications to the use of anti-TNF treatment or with other pre-existing conditions, doctors should consider the use of abatacept, rituximab, or tocilizumab. If no unfavourable prognostic indicators are present, the combination of methotrexate and other DMARDs can be considered (i.e., the same combinations proposed in the 2004 guidelines). If a patient is intolerant to methotrexate, the use of either (1) sulfasalazine with chloroquine or (2) leflunomid should be considered; patients should be re-evaluated after 3-4 or 2-3 months, respectively. If these are unsuccessful, doctors should switch to monotherapy anti-TNFs (adalimumab, certolizumab, or etanercept). If none of these treatments are effective, step three is the use of alternative anti-TNFs (abatacept, rituximab, or tocilizumab). The treatment strategy for low- and moderate-activity RA patients is summarized in Table 2, below.
Table 2. Treatment strategy for low- and moderate-activity RA patients (adapted from 2011 guidelines).

<table>
<thead>
<tr>
<th>Low-activity RA</th>
<th>Moderate-activity RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td>Chloroquine, methotrexate, or sulfasalazine; low-dose methotrexate is often sufficient in combination with intra-articular steroid treatment.</td>
</tr>
<tr>
<td><strong>Moderate-activity RA</strong></td>
<td>Methotrexate 20-30 mg per week; one or two 5 mg folacin tablets per week to counter methotrexate side-effects and also the use of low-dose corticosteroid (prednisolone).</td>
</tr>
<tr>
<td><strong>Step 2a</strong></td>
<td>Methotrexate combination therapy with adalimumab, certolizumab, etanercept, golimumab, or infliximab (all drugs in the 2011 guideline are listed alphabetically, not according to priority); in patients with contraindications to the use of anti-TNF treatment or with other pre-existing conditions, doctors should consider the use of abatacept, rituximab, or tocilizumab. If no unfavourable prognostic indicators are present, the doctor may instead consider the combination of methotrexate and (1) sulfasalazine and chloroquine or (2) cyclosporine.</td>
</tr>
<tr>
<td><strong>Step 2b</strong></td>
<td>If patient is intolerant to methotrexate, doctors should consider either (1) sulfasalazine with chloroquine or (2) leflunomide. Doctors should also consider the use of monotherapy anti-TNFs (adalimumab, certolizumab, or etanercept).</td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
<td>Abatacept, rituximab, or tocilizumab.</td>
</tr>
</tbody>
</table>

For high-activity RA, the first step is methotrexate alongside low-dose corticosteroids (i.e. identical to step one for moderate-activity). If several indicators of rapid disease progression are present, the use of anti-TNFs (abatacept, rituximab, or tocilizumab) should be initiated alongside methotrexate; the early use of anti-TNFs in these patients is an important factor for the prevention of joint deterioration. Step two is to start all patients on anti-TNFs alongside methotrexate. If a patient is methotrexate-resistant, the exclusive use of adalimumab, certolizumab, or etanercept is recommended (can also couple with second DMARD). Step three is to switch to abatacept, rituximab, or tocilizumab. The guidelines also suggest cyclosporine A, parenteral gold, and anakinra as alternatives at the doctor’s discretion; azathioprine and mycophenolate mofetil are also possibly effective but have not yet been approved for use in RA patients. The treatment strategy for high-activity RA patients is summarized in Table 3, below.

Table 3. Treatment strategy for high-activity RA patients (adapted from 2011 guidelines).

<table>
<thead>
<tr>
<th>High-activity RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td><strong>Step 2a</strong></td>
</tr>
<tr>
<td><strong>Step 2b</strong></td>
</tr>
<tr>
<td><strong>Step 3</strong></td>
</tr>
</tbody>
</table>

The guidelines also review the clinical evidence on the different available Anti-TNFs and detail which have been approved for combination therapy. Adalimumab, etanercept, infliximab, and golimumab have been approved for use with methotrexate, while sulfasalazine, leflunomide, and azathioprine can be used alongside other DMARDs. The guidelines also offer clinical evidence on
the appropriate drugs for use in the case of drug resistance or unsatisfactory patient response to other treatment (batacept, rituximab, or tocilizumab). Dosage-adjustment remains at the doctor's discretion depending on patient response (e.g. remission) and some evidence suggests continued low-doses of adalimumab or infliximab is beneficial. Finally, the document highlights the necessary precautions to ensure patient safety during pharmacological treatment.

Summary

In conclusion, the Swedish RA guidelines support good access to biologic treatment for patients with moderate or severe disease activity. They offer specialists a significant degree of clinical flexibility in their shared decision-making with individual patients and encourage a holistic approach to RA treatment. The emphasis on early detection and treatment with biologic treatment to curb disease progression is central to the Swedish RA management strategy. Continued reliance on RA clinical guidelines will play an important role in the successful treatment of Swedish RA patients.

Extracts from an Expert Interview

(1) When and how are the guidelines reviewed?

The guidelines are updated on an annual basis by the SSR; each year, a small committee of three people is appointed to review any new clinical evidence. The committee then presents a draft of the changes to the professors of rheumatology in Sweden (known as the Professor's Collegium). After this initial review, the draft is sent to all SSR members. The proposed changes are discussed during a January meeting (known as Riktlinjer Dagen - "The Day of the Guidelines"), at which time the committee receives feedback both from members present as well as via email from those absent. This committee reviews the information and prepares a final version. The members of the committee then present this final report to a larger assembly in the spring (a SSR meeting held in March or April) where the changes are formally ratified. The changes are normally incremental, but also incorporate clinical evidence on newly approved medications and other important developments.

The interviewee said that that the online publishing system is not well-coordinated and that much of the information is disseminated via the meetings, emails, and document exchanges rather than official online releases. It may be that only the 2004 and 2011 guidelines are published online because it was determined that these were the only two guidelines with changes significant enough to warrant online publication. The interviewee also explained that the 2004 guidelines are outdated, evidenced by the prominence to "auranofin" which is no longer regularly prescribed due to its perceived ineffectiveness. In 2004, step 2 includes the indirect option to skip directly to step 3 if there is rapid disease progression, which has been a contentious issue in Sweden. It has been heavily debated whether Sweden should encourage quicker access to biologic treatment for RA patients. In 2011, the general consensus was that this should be the case and the guidelines were clearer and more concise on this point; step 2a already includes the possibility for biologic treatments and step 2b discusses the treatment of methotrexate-intolerant patients, which is more consistent with what is done today in Sweden. The Swedish guidelines have improved with time and the writing is today more clear and specific than in previous years.

(2) How are the guidelines disseminated and enforced?

It is important to note that the guidelines are non-binding and are in fact only guiding documents. As a result, Swedish rheumatologists have the option to follow or ignore these recommendations, although most at least review the guidelines. Most rheumatologists in Sweden, however, do not work in solo offices, but instead practice in larger clinics under the supervision of an administrative chief. The chief is bound by a clinical budget and may limit the prescription of expensive biologic medicines because of economic constraints. Although
medication choice is in theory a pure clinical decision, it may in practice therefore also incorporate budgetary considerations. In these cases, if the guidelines specify that a patient with a particular set of clinical symptoms or criteria should be treated with biologics (even if they are expensive), the clinician can use this evidence to approach their administrative chief to explain the necessity of these medicines for the patient. On the other hand, if a physician’s clinical judgment might be that the patient should receive a biologic treatment but the guidelines do not reflect this view (e.g. the particular case may be unusual), it may be difficult to justify prescribing biologics. In other words, the guidelines may have a variable impact depending on the individual case.

Overall the guidelines have been important tool to encourage appropriate access to biologic treatment in Sweden. The access for Swedish patients to biologics was very good to begin with due to complete physician autonomy for many years with regard to prescribing habits; until just a few years ago there were no budget restrictions which impacted the physician’s decision (i.e. everything was reimbursed by the National Health Plan). As a result, the interviewee believes it was hardly possibly to improve Swedish access to biologics when the first guidelines were implemented. In recent years, however, there has been increasing pressure from payers to control escalating health care costs. Therefore, the guidelines may have helped prevent more significant reductions in the prescription of biologic treatments. In other words, the guidelines may have not necessarily improved Anti-TNF consumption, but may have instead prevented a more significant reduction in the access to biologic medicines.

(3) How do the Swedish guidelines compare to others in Europe?

In some other European countries, the RA guidelines are far more restrictive (e.g. clinicians must demonstrate that patients have failed with two DMARDs or combinations with DMARDs). Certain countries even include specific requirements regarding the level of disease activity (DAS28 score) that is required for patients to receive biologic treatment. This is most notably the case in the UK, where NICE does not reimburse the drug unless patients have a high level of activity (i.e. DAS28 of 5.1 or higher). This is a major deviation from the guidelines in Sweden and other countries that do not include these restrictions; about one-third of RA patients in Sweden treated with biologics have moderate activity (DAS28 between 3.2 and 5.1 – usually patients at the higher end of this range, but still classified as moderate activity), which would not be treated in the UK.

Although the Swedish guidelines rely on the DAS28 scores as a general way to classify patients, it is ultimately at the discretion of the clinician whether a patient is treated with biologics. It is noted in the Swedish guidelines that the DAS28 scores have certain limitations. For example, a DAS28 score could be high even if the patient’s symptoms are not as severe as the score would indicate (e.g. reflective of other problems going on at same time). In other cases, a patient with a low score could in fact be very ill (e.g. DAS28 score could be low because inflammation in the feet is not measured in the DAS28 and the test may therefore discriminate against some patients). In other words, a high or low scale of activity in Swedish patients is not necessarily always determined via a DAS28 score, but also from the physician’s general impression of the patient (e.g. the presence of other negative prognostic factors).

(4) What comments have the guidelines provoked from patients, clinicians and other stakeholders?

Clinicians and patient advocacy groups, which have both been involved in the guideline formulation and review processes, have been very supportive of the Swedish guidelines.

References


