



A Survey of Barriers to Treatment Access in Rheumatoid Arthritis

in

France, Germany, Italy, Spain and the UK

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Executive summary

The objective of this report was to evaluate factors that influence the diagnosis and treatment of rheumatoid arthritis (RA) in five countries (France, Italy, Spain, Germany and the United Kingdom) in order to identify potential barriers to treatment access in Europe. Structured desk research was consolidated by semi-structured, qualitative telephone interviews with senior treating physicians and patient representatives in each country to examine how closely each phase of the treatment pathway – diagnosis, treatment and monitoring – followed best-practice recommendations by the European League against Rheumatism (EULAR).

The burden of rheumatoid arthritis: RA is generally, though not exclusively, an adult-onset disease of early middle age (40–50 years) which predominantly affects women. Prevalence across Europe is reported to range from 0.2% to 3% of the population depending on study and region. RA is a chronic disease with a high burden of pain, fatigue, reduced function and lowered quality of life. At the societal level it also comes with a loss of production in that studies indicate that one third to one half of those affected have been forced to quit the workplace within ten years of onset.

Goals of treatment: In addition to symptomatic alleviation with corticosteroids and non-steroidal anti-inflammatories, disease-modifying anti-rheumatism drugs (DMARDs) have revolutionized therapy from their first introduction in the 1980s by allowing the disease process itself to be targeted. These agents comprise both “conventional” small molecule DMARDs and biologic agents that were first introduced in the 1990s. The availability today of multiple drugs and drug classes has rendered disease remission to be the goal of treatment, as explicitly defined by EULAR and accepted internationally.

Disease diagnosis: Both desk research and interviews established that delays in RA diagnosis are the most significant barrier to initial treatment access. EULAR recommends that those presenting with RA be seen by a rheumatology specialist within 6 weeks of symptomatic onset, but only France appears to come close to meeting this criterion according to interview data. Delays are attributable to national (Germany, UK) or local (Italy, Spain) shortages in available rheumatologists; to low GP expertise in RA that results in referral delays, and, anecdotally, to low societal disease awareness in at least some countries that results in late presentation. The methodology of diagnosis also varies considerably between countries and in its compliance with EULAR recommendations; and there is some suggestion of deficiencies in diagnosing patients with poor prognoses, due to restrictions in the availability or funding of recommended tests (such as magnetic resonance imaging) that are particularly suited to identify this type of patient.

Treatment: All countries follow the EULAR recommendation to initiate DMARD treatment with methotrexate, and all reserve biologics for second or – more commonly – later lines of treatment after insufficient response on one or more small-molecule DMARDs. Treatments are changed for lack of response typically 6-9 months after initiation. In each country the first biologic used is almost always a TNF- α antagonist, based on the length of clinical experience with this class. There is no consistency in the choice of second or subsequent biologic, however, and substitution of a second anti-TNF after failure of a first is not uncommon. Between 7% and 16% of RA patients are estimated to be treated with biologic agents across the five countries, with uptake highest in France and Spain and lowest in Italy. Significant restrictions exist on access to biologic agents in most of the countries studied, relating to budgetary caps and funding restrictions at the national and/or local levels, restrictive national guidelines, and inter-regional differences in either the availability of authorised prescribing centres or in the procedures and processes involved in their prescription.

Treatment monitoring: Treatment monitoring varied considerably in its alignment with EULAR recommendations. Both France and Spain have national guidelines that stipulate monitoring of disease activity and structural damage according to EULAR-recommended intervals. However, longer-than-recommended intervals between structural damage assessments were reported by interviewees in Germany, where national guidelines are not explicit about monitoring, and in Italy, where there are no national RA guidelines. In the UK, where guidelines recommend only an annual review of disease activity, interviews identified typically longer intervals between disease evaluations and no regular assessment of damage.

Conclusions: Of the five countries studied, France presented very few barriers to access and uptake of RA treatments, facilitated by a liberal reimbursement process, non-restrictive treatment guidelines, consistent medical infrastructure and an efficient referrals process – although regional differences persist. Despite a high uptake of biologic treatments and a high overall number of rheumatology specialists, Spain suffers from inter-regional differences in specialist numbers and prescribing processes which may delay or restrict treatment in some situations. Germany, Italy and the UK all presented relatively high barriers to treatment based on limited specialist availability, restricted access to or funding of biologics and/or restrictive guidelines for RA practice.

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1 Glossary and Abbreviations

Abatacept (Orencia®)

Manufactured and marketed by Bristol–Myers Squibb. Orencia is a T-cell co-stimulation modulator, which inhibits T-cell activation by blocking interactions with CD28. It is administered by intravenous infusion.

Adalimumab (Humira®)

Manufactured and marketed by Abbott. Humira is an anti-TNF administered via subcutaneous injection twice a month.

Anakinra (Kineret®)

Manufactured by Amgen. Marketed by Biovitrum and Amgen for the rheumatology indication. Kineret is an IL-1 receptor antagonist administered via daily subcutaneous injection.

Anti-TNFs

Biologic anti-rheumatic drugs which target tumour necrosis factor (TNF, see below).

AS

Ankylosing spondylitis.

Biologics

In this monograph, 'biologics' refers to a group of DMARDs that are derived from biologic molecules such as antibodies or receptors. They modulate the disease process by directly targeting signalling pathways, cytokines, receptors and other mediators contributing to the pathogenesis of RA. Current biologics include anti-TNFs (adalimumab, etanercept, infliximab, golimumab, certolizumab), B-cell targeted therapies (rituximab), a T-lymphocyte co-stimulation modulator (abatacept), an anti-IL6R (tocilizumab) and an IL-1 inhibitor (anakinra).

CCP

Cyclic citrullinated peptide. Anti-CCP antibodies can suggest a diagnosis of RA.

Certolizumab (Cimzia®)

Manufactured by UCB. Cimzia is an anti-TNF administered by subcutaneous injection once a month.

COX2

Cyclooxygenase 2. A key enzyme in the biosynthesis of complex fatty acids (prostanoids) involved in the development of inflammation.

CRP

C-reactive protein. A serum marker of systemic inflammation.

DAS

Disease activity score. The following parameters are included in the calculation: number of tender joints, number of swollen joints, erythrocyte sedimentation rate (ESR) and patient assessment of disease activity. The DAS provides a number between 0 and 10, indicating how active the rheumatoid arthritis is at any given time

DAS28

A version of the DAS based on a 28 joints which is commonly used to measure disease activity in RA. A DAS28 of <2.6 is typically used to define clinical disease remission, though other clinical definitions exist.

DMARD

Disease-modifying anti-rheumatic drug. Any of a class of therapeutic agents of widely variable structures and mechanisms of action that act on one or more of the underlying causes of RA to slow disease progression. There are two basic categories of DMARD: synthetic or traditional agents, and biologic agents. DMARDs are distinct from symptomatic RA treatments such as NSAIDs or COX2 inhibitors, which treat pain and inflammation without altering disease progression. In this monograph, the term DMARD refers to traditional small-molecule agents; biologic DMARDs are referred to as biologics.

EMEA

European Medicines Agency.

Etanercept (Enbrel®)

Manufactured by Amgen. Marketed by Amgen/Wyeth. Enbrel is an anti-TNF administered subcutaneously, once or twice weekly.

ESR

Erythrocyte sedimentation rate. The rate, in mm/hour, at which red blood cells precipitate in uncoagulated blood. The ESR is a common haematological test used as a non-specific measure of inflammation.

EULAR

European League Against Rheumatism.

EULAR response criteria

Criteria developed by EULAR that combine the DAS28 at the time of evaluation with the change in DAS28 between two time points, and enable the user to define improvement or response to treatment. Response categories include good, moderate and no response.

Golimumab (Simponi®)

Manufactured by Centocor Ortho Biotech. Marketed by Centocor/Schering-Plough. Simponi is an anti-TNF administered via monthly subcutaneous injection.

GP

General practitioner.

HAQ

Health assessment questionnaire.

IL-6R

Interleukin-6 receptor.

IMI

Innovative Medicines Initiative.

Infliximab (Remicade®)

Manufactured and co-marketed by Centocor and Schering-Plough. Remicade is an anti-TNF administered by intravenous infusion.

INSERM

Institut National de la Santé Et de la Recherche Médicale (National Institute of Health and Medical Research).

Joint erosion

Localised loss of bone substance within a joint, due to joint-related osteoporosis or growth of inflammation-associated fibrous tissue.

MTX

Methotrexate. A synthetic DMARD that acts as an inhibitor of folic acid and of purine metabolism.

MRI

Magnetic resonance imaging.

NICE

National Institute for Health and Clinical Excellence.

NHS

National Health Service.

NSAID

Non-steroidal anti-inflammatory drug.

PPI

Proton pump inhibitor.

RA

Rheumatoid arthritis.

RF

Rheumatoid factor. An autoantibody directed against immunoglobulin G. About 80% of patients with RA are seropositive for RF, and its presence predicts a more aggressive, destructive course.

Rituximab (MabThera®)

Manufactured by Genentech and Biogen Idec. Marketed by Genentech and Roche. MabThera, called Rituxan® in the US, is a B-cell modulator administered by intravenous infusion.

Swollen joint

A joint that is swollen on physical examination.

Tender joint

An inflamed joint that is painful when pressed.

TNF

Tumour necrosis factor. A cytokine involved in the inflammatory reaction of the immune system.

Tocilizumab (RoActemra® / Actemra®)

Manufactured and marketed by Roche and Chugai Pharmaceuticals. Tocilizumab is a humanized monoclonal antibody to IL-6R administered by intravenous infusion.

2 Introduction and rationale

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that can affect virtually all joints, but most commonly involves the hands and feet. Other frequently affected joints include the wrist, knee and other large joints of the extremities. Onset can be gradual or acute, but in the majority of patients the course is progressive, leading to destruction of joints, functional disability and reduced quality of life. RA is also associated with a range of extra-articular manifestations, and patients with RA have increased morbidity and mortality compared with the general population, mostly due to the cardiovascular consequences of chronic inflammation and an increased frequency of lymphomas in relation to the severity of the disease [1].

RA predominantly affects women (70–80% of cases) and disease onset is most common between the ages of 40 and 50 years, although RA can affect younger populations including children and adolescents [2]. Patients often cope for many years with the effects of the disease, in terms of restricted function, chronic pain and fatigue, but many (35–50%) are unable to work within 10 years of disease onset [3,4].

The prevalence of RA is generally estimated at 0.5–1.0% of the adult population in Europe [5], but ranges from 0.2% to 3.0% in published studies, with differences reported between and within countries. Differences may be due to a number of factors, including: changes in diagnostic criteria in 1987, which have led to a reduction in the number of patients with confirmed RA [6]; the size of the reported studies and the selected study populations; and the presence or absence of corrections for different prevalence rates within different age groups.

This makes it difficult to precisely estimate the overall number of patients with RA and the proportion of patients that would qualify for treatments in the five countries included in this report – France, Germany, Italy, Spain and the United Kingdom (UK). A recent report by the Innovative Medicines Initiative [7] estimates that the total number of patients with RA in these five key European markets is around 1.67 million. Similar numbers were estimated in a comparative study on access to biologics [8]. More recently, the number of adult patients (over 19 years of age) diagnosed with RA in these countries has been estimated at around 1.25 million [9].

Treatment of RA is both symptomatic (corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs]) and targeted at the disease process (disease-modifying anti-rheumatic drugs [DMARDs]). Conventional (non-biologic) small-molecule DMARDs (hereafter referred to as DMARDs) have been available since the 1980s. One of these, methotrexate (MTX), became the mainstay of RA treatment in the 1990s, with increasing use earlier within the disease course.

The late 1990s saw a revolution in the management of RA with the introduction of biological DMARDs (hereafter referred to as biologics). These agents have

demonstrated good efficacy in RA, effectively reducing inflammation, disease activity and the progression of joint erosion.

The first clinical trials of biologics involved patients with severe, long-standing disease who were unresponsive to treatment with DMARDs, including MTX. This, combined with the adverse event profile of these agents, led to their use being restricted to the severe RA patient segment by licensing and reimbursement authorities, as well as in clinical guidelines. However, recent trials have highlighted the benefit of biologic treatment in early RA. When used within 6–12 months of symptomatic onset, before joint damage has occurred, total or temporary remission can be achieved in a proportion of patients.

Thus, the window of opportunity to use biologics at their fullest potential is early in the disease course. The cost of biologics, however, is a concern to policy makers and payers, given the size of the potential patient population to be treated. Earlier introduction of biologic treatment will increase costs in the short term. It is therefore important to identify those patients who have a poor prognosis, who would therefore incur high costs in the medium and long term and whose quality of life would be severely reduced in the absence of effective treatment.

There are currently six biologics that are widely available in Europe (etanercept/Etanercept[®], infliximab/Remicade[®], adalimumab/Humira[®], anakinra/Kineret[®], rituximab/MabThera[®] and abatacept/Orencia[®]). Three more biologics – tocilizumab/RoActemra[®], certolizumab/Cimzia[®] and golimumab/Simponi[®] – were recently granted European marketing authorization in 2009.

Usage of these drugs has been shown to vary considerably across Europe, as well as between the five major markets [10]. The most recent estimates suggest that between 7% and 16% of the diagnosed adult patient population are being treated with biologics [9].

A range of factors may contribute to these observed differences, including:

- ◆ reimbursement restrictions
- ◆ budget restrictions
- ◆ administrative restrictions (limited prescribers, referral processes, need for a second opinion, regional differences in access to rheumatologists)
- ◆ clinical guidelines for diagnostic work-up and initiation of biologic treatment
- ◆ limitations in diagnostic procedures (availability and reimbursement)
- ◆ limitations in infusion capacity.

Clinical guidelines are likely to exert a strong influence on the use of biologics, but administrative and reimbursement restrictions will also have an impact. National

guidelines, generated by both health technology assessment (HTA) agencies and medical organisations, exist in all countries covered by this report except Italy. At the European level, recommendations are developed and published by the European League Against Rheumatism (EULAR) [11,12]. The EULAR recommendations, which encompass diagnostic work-up, treatment initiation and patient follow-up, are formulated by a panel that includes specialists from all five countries covered by this report, and can be considered a benchmark among RA treatment guidelines, with strong peer influence.

This report describes some of the barriers to RA treatment access mentioned above, and summarises levels of adherence to national and international clinical guidelines.

3 Objectives

In order to expand on previous reports [10,13] on access to treatment in RA, the objective of the current study was to identify the typical RA patient pathway and factors that influence access to treatment in RA by investigating how clinical guidelines are followed in practice.

4 Methods

In each of the five countries included in the study initial desk research on RA and its treatment was followed by qualitative interviews.

- ◆ Desk research was conducted using a structured guide and covered topics such as treatment guidelines, regulatory or clinical restrictions on prescribing biologics, time to diagnosis, treatment strategy, and the use of biologics.
- ◆ Interviews followed a semi-structured guide to allow adaptation to the background of the participants and inclusion of additional relevant information. Five to six telephone interviews per country with hospital- and office-based specialists, general practitioners (GPs) and representatives from patient organisations were conducted. No interviews were conducted with representatives of authorities or payers.

The information that was gathered is organised along the patient management pathway, from diagnosis to treatment initiation and follow-up, and findings are compared with the recommendations published by EULAR.

5 Results

5.1 General findings

Overall, desk research yielded valuable information on reimbursement conditions, clinical guidelines, physician density, and published cohort and registry studies. However, information regarding current treatment patterns was not only scarce, but also generally outdated. The most obvious example of this is time to diagnosis and treatment initiation, which, in view of the importance of early treatment, was one of the key variables to be investigated in this report. Desk research yielded data that were generally at least 5 years old; even if reported recently, they referred to diagnosis and treatment patterns in the late 1990s or early 2000s. As a consequence, most of the information we report on the patient pathway comes from the interviews, which, in view of their limited number, may constitute a weakness. Further substantiation of this aspect of the report may therefore be warranted.

National and regional guidelines were generally found to be in accordance the EULAR recommendations (and were often authored by specialists who had participated in the development of the EULAR recommendations) but with notable differences. In particular, guidelines originating from individual countries stipulated more specific treatment algorithms in terms of drug selection and use than the EULAR recommendations; and recommendations for diagnosis and monitoring practiced also differed significantly between countries.

- ◆ The French and Spanish guidelines have the broadest scope for biologic usage, acknowledging the role of early biologic treatment with few limitations [14]. The consequence of this was highlighted in an earlier report that found that usage of biologics, in particular anti-tumour necrosis factors (anti-TNFs), among the five countries included in this report was highest in France and Spain [10]. This finding has been reconfirmed in a more recent analysis [9].
- ◆ In the UK, as might be expected, the rather restrictive guidance from the National Institute for Health and Clinical Excellence (NICE) influences usage more than EULAR or other clinical guidelines; both the reports mentioned above found that access to innovative drugs was limited in the UK.
- ◆ National guidelines in Germany are comparable to the EULAR recommendations, as are regional guidelines in Italy (which has no national guidelines). In both countries, however, access to biologics appears to be strongly influenced by budget restrictions (practice budgets in Germany and drug budgets in Italy) and by limited access to rheumatologists (lack of specialists in Germany and a limited number of prescribing centres in Italy). Both the reports mentioned above found that, among the five countries included in this report, usage of anti-TNFs was lowest in Germany and Italy.

The interviews also highlighted the issue of regional differences within each country. As would be expected, the density of specialists, and even GPs, varies between rural and urban areas and between regions with different economic conditions. This translates into variable access to innovative treatments and differing overall treatment patterns. Not surprisingly, areas around academic research hospitals seemed to benefit from the best treatment. Also, both desk research and interviews indicated that access to treatment was better for cases with severe and active disease, but often delayed for moderate and difficult to diagnose cases.

At the policy and healthcare system level, RA does not appear to have particularly high priority, and no national education programmes to enhance disease knowledge in the general population or in RA patients were identified. However, all RA patient associations typically had a goal to increase the general public's knowledge of RA, in addition to providing information to association members.

When comparing the EULAR recommendations for diagnosis, treatment initiation and monitoring with the information received through interviews, it appears that the main obstacles to compliance with recommended practice arise at the point of diagnostic work-up, and also in the way patients are monitored. Differences were found in the use of sophisticated diagnostic procedures to aid early identification of patients with active erosive disease, as well as in the time to diagnosis that is achievable within the system. Furthermore, in some countries both the frequency of monitoring and the parameters assessed differed from the EULAR recommendations. Overall, the findings indicate that the diagnostic work-up and treatment of RA patients in France are closest to what EULAR considers best practice, with Spain the next closest.

In the following sections, we discuss these issues in more detail, and summarise our interpretation of whether current clinical practice in each country is consistent with the EULAR recommendations. It should be remembered that most of this information comes from a limited number of interviews per country, and is therefore qualitative, not quantitative.

5.2 Diagnosis

Across the five countries, the majority of patients suffering from RA (80%) are diagnosed by rheumatologists, followed by GPs or other specialists accounting for the other 20%. Time to diagnosis is shortest in France (6 months) and longest in Germany, Italy and Spain, where it takes on average 12 months or more from symptom onset to consultation with an RA specialist. One reason for this is limited access to rheumatologists. It is a commonly accepted benchmark in Rheumatology that one specialist per 50,000 members of the population is required for effective diagnosis and treatment [15]. If we compare the number of rheumatologists per adults in the population – since RA is predominantly an adult-onset disease – substantial differences between countries are

seen (Table 1). This has implications for the time to diagnosis and access to treatment for the UK and, especially, Germany, which have fewer available rheumatologists than the rest. In addition, Spain and Italy reported large regional variations in the numbers of specialists, and therefore overall longer times to diagnosis. Reported numbers of specialists should, however, be considered with caution, as not all rheumatologists treat RA, while specialists other than rheumatologists may also treat RA.

Table 1. Availability of rheumatologists

| | FRA | GER | ITA | SPA | UK |
|--|--------|---------|--------|--------|--------|
| Adult population (million) | 50 | 68 | 50 | 37 | 45 |
| Number of rheumatologists | 1,800 | 600 | 1,200 | 1,300 | 584 |
| Adult population per rheumatologist | 28,000 | 114,000 | 41,000 | 28,000 | 77,000 |

- ◆ A second factor that can lengthen time to diagnosis is the referral process. In all countries other than the UK, patients can theoretically consult a rheumatologist directly. However, in practice initial consultations with a GP are commonplace, which often results in delays of six months or more from the initial GP consultation and testing through referral to a rheumatologist and the establishment of a definitive diagnosis. However, France is an exception to this 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).
- ◆ Finally, several interviewees from Italy and Spain spontaneously highlighted what they perceived to be a low level of public awareness of RA in these countries, which would lead to later clinical presentation and diagnosis and hence to a delay in treatment access.

According to the EULAR recommendations, clinical examination is the method of choice for detecting arthritis, with subsequent confirmation by a minimum set of laboratory tests. For patients presenting with possible RA, it is recommended that (in addition to standard blood, transaminase and urinary analysis) the following factors, predictive of persistent and erosive disease, should be measured:

- ◆ numbers of swollen and tender joints
- ◆ erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
- ◆ levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies

- ◆ radiographic erosions.

In doubtful cases, ultrasound, power Doppler and magnetic resonance imaging (MRI) should be used to detect synovitis.

Considerable differences between these recommendations and actual practice were apparent (Table 2).

Table 2. Diagnostic work-up compared with EULAR recommendations

| EULAR guidance (recommendation number) | National practice consistent with EULAR recommendation? | | | | |
|--|---|-----|-----|-----|----|
| | FRA | GER | ITA | SPA | UK |
| Patient presenting with arthritis should be referred to and seen by a rheumatologist ideally within 6 weeks of symptom onset (#1) | ✓ | ● | ✗ | ● | ● |
| Clinical examination for detecting arthritis may include ultrasound, power Doppler and MRI for detecting synovitis in doubtful cases (#2) | ● | ✗ | ● | ● | ✗ |
| Diagnosis requires at least the following laboratory tests: complete blood cell count, urinary analysis, transaminases and antinuclear antibodies (#3) | ✓ | ✓ | ✓ | ✓ | ✗ |
| Patient presenting with early arthritis should have the following factors measured: number of swollen and tender joints, ESR or CRP, level of RF and anti-CCP antibodies, and radiographic erosions (#4) | ✓ | ● | ● | ✓ | ✗ |

✓ = Yes; ✗ = No; ● = Mixed responses

Source: Desk research and interviews

In general, interviewees reported more significant deviations from the recommendations than published sources – particularly shortfalls in the use of imaging techniques (MRI) and laboratory tests (anti-CCP) to identify patients with active erosive disease, and a poor prognosis at symptom onset. The main reasons given for these shortfalls were funding restrictions (Germany, Spain, UK), availability of imaging facilities (in the UK there are just 3.2 MRI scanners per million head of population vs. Italy which has 9.8) and lack of staff trained to interpret imaging results (Spain). The use of imaging and the anti-CCP test has not conventionally been part of the diagnostic work-up in RA, and it appears that in some countries their funding on public national insurance is still limited (Germany, UK). Ultrasound and, more extensively, X-ray are typically used instead.

5.3 Treatment

According to all interviewees, the current goal of RA treatment is disease remission and regular monitoring of disease activity is required to adapt treatment as needed to achieve this.

The information on treatment patterns presented in this report is mainly focused on patients with active erosive disease, who are most at risk if treatment is suboptimal. Information regarding patients with difficult-to-diagnose or mild disease is more limited.

5.3.1 DMARDs

The EULAR recommendations (recommendation number 5) state that treatment with DMARDs should be started as early as possible in patients with active disease, reflecting the change in patient management that came about in the 1990s. Previously, most patients were initially treated with NSAIDs. Although this recommendation does not explicitly specify that initiation be with a small-molecule DMARD, the presence of an additional recommendation (number 9) that MTX be considered the anchor drug for initial use, positions the small molecule DMARDs as first-line agents.

In all countries, both recommendations are followed (Table 3). Treatment with DMARDs is essentially initiated at diagnosis for patients with active erosive disease, mainly by the RA specialist. In more than 90% of such patients the initial treatment choice is MTX. Other DMARDs, such as hydroxychloroquine, D-penicillamine and sulphasalazine, are typically used in milder forms of RA. In active disease, NSAIDs and low-dose continuous corticosteroids are often used in addition to MTX. More rarely, MTX is combined with leflunomide, azathioprine or cyclosporine.

Corticosteroids are frequently used as a bridging therapy while waiting for confirmation of diagnosis. Once DMARD treatment is initiated, steroids are tapered off to low-dose or are discontinued. Although some interviewees expressed a preference for DMARDs other than MTX, it can be concluded that initial treatment with DMARDs is similar across the five countries.

The EULAR recommendations however do not specify a strategy or timescale for changing an initial therapy. In practice, if after 6–9 months, a patient has shown an insufficient response to initial DMARD therapy, treatment is adjusted (increased dose, switch to another DMARD or treat with a DMARD combination). In France and Spain, treatment with a biologic is considered.

According to the interviews, as discussed earlier, the current time to treatment initiation typically ranges from 6 to 12 months for patients with active erosive disease. Published studies as well as interviewees report longer delays in some patients, particularly in those for whom the diagnosis is more uncertain [16,17]. Thus, first-line treatment in

clinical practice in all countries reflects overall EULAR recommendations (Table 3). The fact that national guidelines in all countries except Italy clearly recommend MTX as the anchor drug in first-line treatment obviously contributes to this consistent treatment pattern.

Table 3. Treatment initiation compared with EULAR recommendations

| EULAR guidance (recommendation number) | National practice consistent with EULAR recommendation? | | | | |
|--|---|-----|-----|-----|----|
| | FRA | GER | ITA | SPA | UK |
| Patients developing persistent/erosive arthritis should be started with DMARDs as early as possible (#5) | ✓ | ✓ | ✓ | ✓ | ✓ |
| The main goal of treatment is to achieve remission. Regular monitoring of disease activity and adverse events should guide decisions on choice and changes in treatment (DMARDs and biologics) (#10) | ✓* | ✓* | ✓* | ✓* | ✓* |
| NSAIDs should be considered in symptomatic patients (#7) | ✓ | ✓ | ✓ | ✓ | ✓ |
| Among DMARDs, MTX is considered the anchor drug and should be used first in patients at risk of developing persistent disease (#9) | ✓ | ✓ | ✓ | ✓ | ✓ |
| Systematic glucocorticoids reduce pain and swelling and should be considered as a (mainly temporary) adjunct to the DMARD strategy (#8) | ✓ | ● | ✓ | ✓ | ✓ |

✓ = Yes; ✖ = No; ● = Mixed responses;
 ✓* = Yes but with wide variations in the implementation and timing of monitoring

Source: Desk research and interviews

5.3.2 Biologics

Biologics are prescribed for patients with severe RA who fail to sufficiently respond to one or two DMARDs, including MTX. Interestingly, there are no specific recommendations on use of biologics in the EULAR guidelines. Data highlighting their potential clinical benefit, both in established and early RA, are included in the sections of text supporting general treatment recommendation number 9 (specifying MTX as the anchor drug for first-line therapy) and recommendation number 10 (specifying remission to be the goal of treatment and regular monitoring to guide therapy changes).

The inclusion of biologics however differs in national guidelines. In France and Spain, national guidelines indicate that biologic treatment should be started after failure of initial

MTX treatment, or, in severe cases, as first-line treatment. In the other countries, biologics are only recommended after failure of MTX and at least one other DMARD [14]. In general, clinical practice seemed to be consistent with national guidelines, particularly where these are indirectly linked to reimbursement, such as in France and the UK.

There is no clear picture of the specific sequence in which the different biologics are used. However, the data indicates that in all countries, the first biologics which are prescribed are anti-TNFs (etanercept, infliximab, adalimumab). Reasons attributed to this may be that prescribers have more experience with these agents and they have been in the market for a longer period of time. The newer agents with different mechanisms of action (rituximab, abatacept, toclizumab) are prescribed in patients who fail to achieve a satisfactory response to anti-TNFs, in accordance with their approved treatment indication.

The anti-TNFs are considered to have similar efficacy, and the choice of which drug is prescribed first appears to be generally related to physician and patient preference. In France, preference is given to etanercept and adalimumab as a consequence of a national safety study that indicated that adverse events with infliximab were more frequent. A similar preference is seen in Italy, although the rationale is less obvious. In the other three countries, all three anti-TNFs are used as first biologics.

Cycling of anti-TNFs has until recently been standard practice in all countries if the initial anti-TNF shows insufficient efficacy or is not well tolerated. Increasingly, however, rituximab and abatacept are used as the second biologic. These two agents are therefore used both as second and third biologics. Based on our data, it is not possible to define the sequence more precisely, except for the observation that in third-line treatment there is greater use of biologics with a different mechanism of action to anti-TNFs, including investigational agents in clinical trials. Most physicians interviewed expect to establish a sufficient and durable response with the first two biologics.

In general, interviewees did not report issues with current infusion capacity, although there was some indication that in France infliximab was also used as the second anti-TNF choice due to the need for infusion, and rituximab was preferred over abatacept because of the need for less frequent infusions. It may therefore be that infusion capacity was not identified as an issue simply because of the current relatively limited use of infused drugs.

Interviewees were also asked to estimate the proportion of patients treated with biologics in their country (Table 4). Except for Germany, these estimates were relatively close to estimates of current usage based on 2008 IMS data (13% for France, 8% for Germany, 7% for Italy, 16% for Spain, 10% for the UK;[9]. It is possible that the German responses referred to treatment in specialised centres (Rheuma-Netzwerk) rather than at the national level.

When biologics were first introduced in the 1990s, most countries established biologic registries, with the primary objective of monitoring safety. Most of these registries also

monitor the efficacy of biologics in clinical practice and, as a result, a considerable number of research papers are being published on various aspects of biologic treatment, including safety, efficacy, mortality, discontinuation rates, anti-TNF cycling, work capacity and quality of life. These research findings are likely to have a considerable influence on usage, as biologic treatment choices in the current clinical setting are mainly driven by the degree of accumulated experience with each agent and the level of supporting safety and efficacy data.

Table 4. Treatment with biologics

| | FRA | GER | ITA | SPA | UK |
|--|---|--|---|--|--|
| Interviewee estimates of the proportion of patients treated with a biologic (%) | 10–20 | 10–30 | 7 | 10–13 | 10–20 |
| Proportion of patients treated with a biologic – IMS 2008 data (%) | 13 | 8 | 7 | 16 | 10 |
| First biologic* | Adalimumab Etanercept | Adalimumab Etanercept Infliximab | Adalimumab Etanercept | Adalimumab Etanercept Infliximab | Adalimumab Etanercept Infliximab |
| Subsequent biologics* | Cycling of anti-TNFs (including infliximab) Abatacept Rituximab | Cycling of anti-TNFs (including infliximab) Abatacept Rituximab Tocilizumab | Cycling of anti-TNFs (including infliximab) Abatacept Anakinra Rituximab | Cycling of anti-TNFs Abatacept Rituximab Experimental drugs | Etanercept Rituximab |

* Agents are not listed in any priority order

5.3.3 Non-pharmacological interventions

Countries differ in their adherence to the EULAR recommendations on non-pharmacological interventions and patient education programmes (Table 5). For both these topics, EULAR provides less specific guidance than in other areas, as there is less robust evidence on the effectiveness of either intervention. The use of these supportive

interventions is thus more driven by the preferences of individual physicians and patients.

Table 5. Non-pharmacological treatments compared with EULAR recommendations

| EULAR guidance (recommendation number) | National practice consistent with EULAR recommendation? | | | | |
|---|---|-----|-----|-----|----|
| | FRA | GER | ITA | SPA | UK |
| Education programmes to inform patients on coping with pain disability and maintenance of work may be employed (#6) | ● | ✓ | ✘ | ✓ | ✓ |
| Non-pharmaceutical interventions, such as dynamic exercises, occupational therapy and hydrotherapy, can be applied as treatment adjunct to pharmaceutical interventions (#11) | ✓ | ● | ● | ● | ✓ |

✓ = Yes; ✘ = No; ● = Mixed responses

Source: Desk research and interviews

5.3.4 Treatment monitoring

EULAR recommends that disease activity is assessed at 1–3-month intervals and that structural damage is assessed every 6–12 months. These assessments include clinical examination, determination of inflammatory markers and, for structural damage, radiographs of the hands and feet.

French and Spanish national guidelines follow this approach to monitoring, but Italy does not have national guidelines and the German guidelines are not explicit about this aspect of RA management. In the UK, the NICE clinical guidelines recommend an ‘annual review to assess disease activity’.

Given these individual guideline recommendations, it is perhaps not surprising that considerable country-specific differences exist in monitoring practices. France and Spain appear to follow the EULAR-recommended monitoring schedule according to both desk research and interviewee responses. Italian interviewees report disease activity monitoring is consistent with EULAR recommendations but were divided on structural damage monitoring, with the initial assessment reported to occur within the first 6–12 months as recommended but subsequent assessments at longer (typically 24 month) intervals. German interviewees also report EULAR-compliant disease activity monitoring but longer (12–24 month) intervals between structural damage assessments. Finally, the UK interviewees confirmed typically longer (6–12 month) intervals between assessments of disease activity and highlighted that regular structural damage monitoring is not routinely undertaken.

Overall across the five countries, patients are monitored for response to treatment at intervals of 3–6 months and treatment is changed (higher dosing or a new therapy) after 6–9 months in the case of insufficient clinical response, or changed immediately in the case of severe side effects.

Table 6. Monitoring compared to EULAR recommendations

| EULAR guidance (recommendation number) | National practice consistent with EULAR recommendation? | | | | |
|---|---|-----|-----|-----|----|
| | FRA | GER | ITA | SPA | UK |
| Monitoring disease activity should include tender and swollen joint count, ESR and CRP assessment, at 1–3-month intervals (#12) | ✓ | ● | ● | ✓ | ● |
| Structural damage should be assessed by X-ray every 6– 12 months; functional assessment can be used to complement disease activity and structural damage monitoring (#12) | ✓ | ● | ● | ✓ | ✗ |

✓ = Yes; ✗ = No; ● = Mixed responses

Source: Desk research and interviews

Note: The specific wording of the recommendations has been shortened in some instances for editorial reasons

5.3.5 Factors influencing treatment choice

According to interviewee responses, access barriers to the uptake of biologics varied significantly between countries, but grouped into difficulties with funding, problems with referral patterns or prescription rights and/or issues with recommendations for use.

- ◆ Based on our data, France and Spain have the greatest access to biologics and thus the highest use. Since the early 2000s, 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”, often with the obligation attached to perform post-launch observational studies. 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. In addition to these considerations, 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. In Spain, although differences between the autonomous regions exist in terms of the procedures for the provision of biologics, their availability combined with a relatively high proportion of rheumatology specialists also helps drive uptake. In addition, access to RA treatments including

biologics is likely to be elevated in Spain by a greater awareness of the importance of early diagnosis and referral in the light of an initiative by the Spanish Society for Rheumatology to provide a protocol for early diagnosis in the hospital setting.

- ◆ In Italy, the biggest barrier to biologic treatment is the budget cap for hospital drugs, which is fixed nationally and then regionally, and cannot exceed 2.4% of global healthcare costs. As biologics are essentially hospital drugs, they compete for funds with drugs used in areas such as oncology and multiple sclerosis, and so this cap has a significant impact on the extent to which biologics are used. In addition, the prescription of biologics is restricted to a limited number of centres (n=196), which are not equally distributed across regions, and this constitutes another considerable barrier to access. This uneven distribution is not the result of specific healthcare planning but likely reflects multi-factorial local influences, which may include such facets as the presence of key opinion leaders and existing centres of excellence, population distribution and local population demographics, and the presence of large cities. The result of this restriction and uneven distribution is clearly reflected in the low proportion of patients treated in Italy (Table 4).
- ◆ In Germany, private practice physicians work within defined office budgets, which drive cautious and cost-conscious behaviour for two main reasons: uncertainty about actual payment, as budgets are retrospectively calculated; and personal liability for exceeding the budget.
- ◆ In the UK, the restrictive clinical guidelines issued by NICE present a significant barrier to biologics access within the National Health Service (NHS). Adalimumab, etanercept and infliximab are recommended with restrictions, rituximab is recommended only for patients with severe RA after inadequate response to an anti-TNF, and abatacept is not recommended.

6 Discussion

Overall, we observed that, in the five countries included in the study, management of RA varies considerably in its adherence to the 12 EULAR recommendations commonly taken as a benchmark for desirable practice. Differences in diagnostic procedures and patient monitoring are particularly marked, and appear to result in part from national guidelines or established practices at variance with the EULAR consensus.

Other barriers that hinder full adherence to these recommendations were found at the level of the healthcare systems, such as:

- ◆ funding restrictions at the diagnosis level
- ◆ budget restrictions for biologics

- ◆ lengthy referral processes and delayed access to specialists
- ◆ limitations of prescribers
- ◆ limitations of resources.

Most countries, with the possible exception of France, were found to suffer from one or several of these limitations, and it is difficult to combine the findings into one overall picture. Rather, countries have to be considered individually, with specific issues for each described in the detailed country reports included as annexes to this monograph.

By contrast, the following observations were made for the other four countries.

- ◆ Germany has an apparent lack of specialists and a potentially long referral process; has national guidelines that are less liberal regarding the initiation of biologic treatment and are not specific about monitoring; and there are considerable budget and funding restrictions.
- ◆ Italy lacks specific national guidelines for RA; has limitations in the number of specialists that can prescribe biologics; has national and regional budget caps on hospital drugs; and there are regional differences in the availability of appropriate medical personnel and technical resources.
- ◆ Spain has guidelines that closely resemble the French guidelines, and thus allow for faster access to biologics than suggested by EULAR recommendations. Spanish use of biologics is relatively high; however, there are funding restrictions for specific diagnostic tests aimed at identifying patients with a poor diagnosis, a slow referral process and, in some regions, a shortfall in the number of specialists.
- ◆ The UK has an apparent lack of specialists and the referral process can be lengthy; funding restrictions exist at the level of specific diagnostic tests aimed at identifying patients with a poor prognosis; and the NICE guidelines on biologics are considerably more restrictive than the French, Spanish and EULAR recommendations, leading to biologic use late in the disease course.

No clear picture could be gained regarding the issue of infusion capacity, which could potentially impact access to some biologics. There may be two possible explanations for this: interviewees may not be facing restrictions because of the particular situation in their institution, which may have a low use of infused drugs (which could, in turn, be a consequence of lack of infusion capacity); or it could simply be a consequence of the limited number of interviews – findings can only be indicative.

However, two big issues were identified in all countries: regional differences and low disease awareness in the general population. Regional differences were apparent in the

healthcare system and in the availability of specific resources, such as imaging equipment.

7 Conclusions

As distinct from diagnosis and monitoring, both of which show substantial differences between the five countries studied, disease-modifying treatment for active RA shows a notable degree of consensus despite variations in the timing and utilization of specific drugs. All five countries conform to the EULAR recommendations of remission as the goal of therapy and the use of MTX as the first and anchor DMARD. All restrict biologics to second or (more commonly) later lines of treatment and typically change therapies after 6–9 months for insufficient response. All initiate biologic therapy with an anti-TNF.

Across all countries, therefore, access to treatment in the first instance is limited primarily by delays in the diagnosis of RA. These diagnostic restrictions accrue from, variously:

- ◆ Shortages of rheumatologists (UK, Germany, parts of Spain and Italy)
- ◆ Limited RA expertise among GPs resulting in slow referrals
- ◆ Limited RA awareness in the population resulting in late presentation (anecdotal in Italy and Spain)

Barriers to the access of biologic treatments for patients with a pre-existing diagnosis vary considerably between countries, but typically involve budgetary/reimbursement issues and/or variations in national guidelines and practice. Budgetary caps at the national (Italy) and office (Germany) level have a significant influence on the willingness or ability of physicians to prescribe biologics, as do restrictive national guidelines (UK, Germany) and inter-regional differences in the processes for biologic prescription by a physician which may require the approval of third parties (Spain). There is also some suggestion that limitations in several countries in the availability or funding of specific diagnostic tests, such as MRI and anti-CCP antibody testing, may restrict identification of patients with poorer prognoses who may benefit from more aggressive treatments.

The field of RA has changed considerably in the past 20 years, with more aggressive disease-modifying treatment now given earlier in the course of disease and a much broader armamentarium available. However, at time of writing there is no authoritative EULAR guidance on the most appropriate initiation and sequencing of the various different classes of disease-modifying agent available. As a result, and although this will undoubtedly change in future, access and uptake of newer classes of RA treatment such as the biologics will continue to show substantial regional differences across Europe.

8 EMEA Approved Biologics

| Brand name | Generic name | Mode of action | Therapeutic indication RA | Date of EU marketing authorization |
|------------|--------------|--------------------------|---|------------------------------------|
| Remicade | infliximab | TNF- α antagonist | In combination with MTX, indicated for the reduction of signs and symptoms as well as the improvement in physical function in patients with active RA disease when the response to DMARDs, including MTX, has been inadequate. Patients with severe, active and progressive disease not previously treated with MTX or other DMARDs | 13 Aug 1999 |
| Enbrel | etanercept | TNF- α antagonist | Enbrel , in combination with MTX, is indicated for the treatment of moderate to severe active RA in adults when the response to DMARDs, including MTX (unless contraindicated), has been inadequate. Enbrel can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. Enbrel is also indicated in the treatment of severe, active and progressive RA in adults not previously treated with MTX | 03 Feb 2000 |
| Kineret | anakinra | IL-1R antagonist | Kineret, in combination with MTX, is indicated for the treatment of the signs and symptoms of RA in patients with an inadequate response to MTX alone | 08 Mar 2002 |
| Humira | adalimumab | TNF- α antagonist | In combination with MTX, indicated for the treatment of moderate to severe active RA in adult patients when the response to DMARDs including MTX has been inadequate. Humira is also indicated for the treatment of severe, active and progressive RA in adults not previously treated with MTX. Humira can be given as monotherapy in case of intolerance to MTX or when continued MTX treatment is inappropriate | 08 Sep 2003 |

Barriers to RA treatment access across Europe

| Brand name | Generic name | Mode of action | Therapeutic indication RA | Date of EU marketing authorization |
|------------|--------------------|--|--|---|
| MabThera | rituximab | Monoclonal anti-CD20 antibody | MabThera in combination with MTX is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other DMARDs including one or more TNF- α antagonists. | 02 Jun 1998, but indication for RA on 07 Jul 2006 |
| Orencia | abatacept | T-cell costimulation antagonist | In combination with MTX, indicated for the treatment of moderate to severe active RA in adult patients who have had an insufficient response or intolerance to other DMARDs including at least one TNF- α antagonist | 21 May 2007 |
| RoActemra | tocilizumab | Monocolonal IL6-R antibody (humanised) | RoActemra, in combination with MTX, is indicated for the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more DMARDs or TNF- α antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. | 16 Jan 2009 |
| Cimzia | certolizumab pegol | TNF- α antagonist | Cimzia, in combination with MTX, is indicated for the treatment of moderate to severe, active RA in adult patients when the response to DMARDs including MTX, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. | 01 Oct 2009 |
| Simponi | golimumab | TNF- α antagonist | Simponi, in combination with MTX, is indicated for the treatment of moderate to severe, active RA in adult patients when the response to DMARD therapy including MTX has been inadequate. | 01 Oct 2009 |

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Note: The EULAR recommendations for arthritis management (Combe et al, reference 11, below) are available through the EULAR website: <http://www.eular.org/> (accessed 12 Nov 2009)

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