Descriptive study of the use of DMARD in patients with Rheumatoid arthritis or persistent arthritis who start drug treatment in Spain (FIRST)

Francisco Javier Blanco, Javier Ballina, Jordi Carbonell, Emilio Martín-Mola, Jesús Tornero, Esteban Ramírez, Jordi Galván

Introduction: Rheumatoid arthritis is clinically very heterogeneous and variable in its progression, and no one treatment works the same for all patients, as this will depend on the clinical course and specific situations.

Objective: To describe the treatment with DMARDs established for the first time in patients with rheumatoid arthritis (RA) or persistent arthritis (PA) in routine clinical practice in Spain.

Material and methods: Epidemiological, cross-sectional, uncontrolled, multicenter study in 15 regions of Spain during a period of five months (July to November 2006). We included patients of both genders, aged 18 years and diagnosed with RA according to ACR criteria or PA defined as any arthritis (oligoarthritis or polyarthritis) lasting ≥12 weeks, which would be given DMARD to treat their disease.

Results: 1079 patients were recruited, 915 analyzed (33% of 67%) meeting all the criteria required to be evaluated in the study. Mean age of patients was 54.6 (SD=15.4) years. The mean time from onset of symptoms until the 1st visit with the rheumatologist was 6.3 (11.3) months and the time from the 1st visit with the rheumatologist and the start of treatment was 4 (13.5) months. Of the patients tested, 96.7% was treated with at least one DMARD, 62.1% were given NSAIDs, corticosteroids to 59.2% and 3.8% biological therapy. In patients who received DMARDs, 90.3% received treatment with a single DMARD, 9.5% with 2 DMARDs and 0.2% with three DMARDs. In polytherapy, the DMARDs that are most often administered together were MTX + hydroxychloroquine (4.8%), MTX + leflunomide (2.0%) and MTX + sulfasalazine (1.5%). The most frequently used DMARD in monotherapy was MTX (81.3%), followed by leflunomide (4.1%) and hydroxychloroquine (3.2%). In 89.6%, the treatment of first choice was adequate according to the SER.

Conclusion: The most common pattern of initial treatment of RA is MTX monotherapy. Treatment of RA by rheumatologists has been homogenized in recent years.

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**Estudio descriptivo de la utilización de los FAMES en los pacientes con artritis reumatoide o artritis persistente que inician tratamiento farmacológico en España. (ESTUDIO FIRST)**

**Resumen**

Introducción: La artritis reumatoide es clínicamente muy heterogénea y variable en su evolución, lo que ocasiona que no se pueda detallar un mismo tratamiento para todos los pacientes, ya que éste va a depender del curso clínico y de situaciones concretas que se van a presentar a lo largo del mismo. Objetivo: Realizar una descripción del tratamiento con fármacos modificadores de la enfermedad (FAME) que se instauran por primera vez en pacientes con artritis reumatoide (AR) o artritis persistente (AP) en la práctica clínica habitual en España. Material y métodos: Estudio epidemiológico, transversal, no controlado, multicéntrico realizado en 15 comunidades autónomas de España durante un período de 5 meses (julio a noviembre del 2006). Se incluyeron pacientes de ambos sexos, mayores de 18 años y diagnosticados de AR según los criterios de la ACR o bien de AP definida como toda artritis (oligoartritis o poliartritis) ≥ 12 semanas de duración, a los que se les iba a administrar el primer FAME para tratar su enfermedad. Resultados: Se reclutaron 1.079 pacientes, pero finalmente, 915 (33% ♂/67% ♀) cumplieron todos los criterios exigidos para ser evaluados en el estudio. La edad media de los pacientes fue de 54,6 (DE = 15,4) años. El tiempo medio desde la aparición de los síntomas hasta la 1a visita con el reumatólogo fue de 6,3 (11,3) meses y el tiempo desde la 1a visita con el reumatólogo y el inicio del tratamiento fue de 4 (13,5) meses. Del total de pacientes evaluados, al 96,7% se les instauró tratamiento con al menos un FAME, al 62,1% se les administraron AINE, al 59,2% corticosteroides y al 3,8% una terapia biológica. En los pacientes que recibieron FAME, el 90,3% recibió tratamiento con un solo FAME, el 9,5% con 2 FAME y el 0,2% con 3 FAME. En politerapia, los FAME que más a menudo se administraron conjuntamente fueron MTX + hidroxicloroquina (4,8%), MTX + leflunomida (2,0%) y MTX + sulfasalazina (1,5%). El FAME más frecuentemente utilizado en monoterapia fue el MTX (81,3%), seguido de la leflunomida (4,1%) y la hidroxicloroquina (3,2%). En el 89,6%, el tratamiento de primera elección fue el adecuado según las recomendaciones de la SER. Conclusión: La pauta de tratamiento de inicio de la AR más frecuente es el MTX en monoterapia. El tratamiento de la AR por los reumatólogos se ha homogeneizado en los últimos años.

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**Polígrafas clave:**
FAME
Artritis reumatoide
Artritis persistente
Metotrexato

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**Introduction**

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown origin, characterised by a symmetrical polyarthritis affecting small and large joints, with a tendency to chronicity and evolution towards joint deformation and destruction. Its aetiology is multifactorial and requires an interaction between genetic and antigenic stimuli, probably exogenous, which are as yet unknown. Its distribution is universal and its worldwide prevalence is estimated at about 0.8%, with an incidence of approximately 0.5/1,000 inhabitants per year.\(^2\)\(^3\)

Clinically, RA is very heterogeneous, with significant differences not only between patients but also in a single patient at different stages of evolution. This phenomenon illustrates the difficulty of describing the natural course of the disease and, therefore, the difficulty in predicting its evolution a priori, an aspect of great importance in effectively altering the course of the disease.\(^4\) In recent years, the information obtained from studies with cohorts of patients who were included in newly created clinics for early detection of rheumatoid arthritis (recent onset arthritis) has greatly improved our knowledge about the course of the disease, and has also led to the definition of persistent arthritis.\(^5\)

The purpose of RA treatment is to achieve a complete remission or a cure. However, this objective is not yet possible and the therapeutic approach consequently focuses on reducing disease activity, to minimise the possibility of joint damage, to relieve pain and to maintain the best possible functional level and quality of life.\(^6\)\(^7\) Unfortunately, this last goal is rarely achieved, because, RA currently has no cure. Like other chronic diseases, RA requires regular and comprehensive assessment of the patients, so as to establish their clinical condition at each moment during the evolution. These periodic reviews enable physicians to assess the progress of the disease, predict a prognosis and therefore indicate the most appropriate treatment program; in addition, the reviews help to assess the degree of compliance with treatment and its effectiveness as well as any possible adverse effects.\(^8\)\(^9\)

Given the heterogeneity and variability of RA evolution, it is not possible to prescribe the same treatment for all patients, as this will depend on their clinical course and on specific situations appearing during evolution. Until about 20 years ago, the treatment of RA was based on a “pyramidal” model, which involved the initial use of nonsteroidal anti-inflammatory drugs (NSAIDs), the judicious use of corticosteroids and, after a year of observation of disease progression, the inclusion of a disease-modifying antirheumatic drug (DMARD), which was kept until its efficacy or adverse reaction and substitution could be judged.\(^9\)\(^3\) This attitude has changed in recent years in the light of evidence proving that RA is not a benign disease and that radiological lesions can be observed in the first two years of evolution. Hence, DMARDs (methotrexate, leflunomide, sulfasalazine and hydroxychloroquine, or drugs called “biological therapy”) that modify the course of the disease are employed earlier and their use in more aggressive combination therapies is advocated, in an attempt to achieve disease remission or its minimum possible activity, the latter being the current goal of RA treatment.\(^10\)

However, the use of these drugs is empirical and, although all have proved effective in RA treatment, there is no unanimous view on what treatment regime to use or which drug or drug combination to select. When prescribing a drug of this type, the physician should also take into account the degree of disease activity, the possible results expected and any potential toxic effects. Guidelines and protocols aimed at standardising and/or establishing a formal protocol for the treatment of RA patients...
have been and are still being developed. In this sense, the Spanish Society of Rheumatology (SER) has developed GUIPCAR, the most comprehensive practical guide on the management of rheumatoid arthritis in Spain.

The GUIPCAR guide is divided into chapters that address various aspects, from the suspicion and detection of the disease to diagnosis, evaluation, comorbidity in RA, pharmacological treatment, treatment of the disease in special situations, monitoring, safety and recommendations of disease-modifying drugs or non-pharmacological treatment of RA. The degree to which Spanish rheumatologists use this guide is not known.

The current popularity of clinics aimed towards addressing recent onset arthritis has provided important information on the prognosis of RA. For example, today we now know that some more aggressive treatment strategies improve the prognosis of RA when used at an early stage in patients at high risk for serious illness, understood in terms of functional disability, structural damage and/or mortality. Several studies, such as that by Houssien et al., have shown that referring patients to a rheumatology clinic during the first year after symptom onset improves their functional capacity (as measured by the Nottingham Health Profile [NHP] questionnaire), compared with that of patients treated at a later stage.

Based on all this information, we decided to develop a study whose main objective was to provide a description of DMARD therapy established for the first time in patients with rheumatoid arthritis (RA) or persistent arthritis (PA) in routine clinical practice in Spain. The secondary objectives were: 1) to evaluate the time elapsed from the onset of symptoms until the establishment of drug treatment; 2) to describe the clinical characteristics of patients with active RA or PA; and 3) to evaluate the appropriateness of drug treatment prescribed according to SER recommendations (GUIPCAR-2001).

Patients and methods

This was an epidemiological, observational, non-controlled, multicentre study carried out in Spain for a period of 5 months (July-November 2006). It included a total of 127 physicians specialising in rheumatology from specialist centres or hospitals in 15 Spanish regions (Figure 1). It included patients of both genders, aged over 18 years and diagnosed with RA according to ACR criteria or with PA defined as any arthritis (oligoarthritis or polyarthritis) ≥12 weeks duration, who were about to be administered a DMARD for the first time as treatment for their disease. In addition to demographic and anthropometric data (age, gender, height and weight), the data registry collected background information on arthritis: date of onset of symptoms, date of diagnosis, time from onset of symptoms until being seen by a physician and time from start of treatment. Variables collected on clinical and radiological assessment of the patient were the number of swollen and painful joints, duration of morning stiffness, global health assessment completed by the patient and the physician on a visual analogue scale, pain as assessed by the patient and the presence of radiological erosions. In addition, data on drug use, dosage and time elapsed from symptom onset to the start of the first drug treatment were also collected. The GUIPCAR guide from 2001 was used to assess the consistency of treatments with the SER recommendations.

We used the 2-sample t-test to compare the number of swollen and painful joints, duration of morning stiffness and DAS28 index among those patients treated with methotrexate injection and those treated with oral methotrexate. The chi-square test was used to compare radiological erosions. The results were considered significant for values of P ≤ .05.

The study protocol was approved by the corresponding local ethics committees and followed the guidelines of the Declaration of Helsinki.
Table 1
Demographic data and clinical history

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female/male) (%)</td>
<td>67/33</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>54.6±15.4</td>
</tr>
<tr>
<td>Weight, kg (mean ± SD)</td>
<td>70.3±12.1</td>
</tr>
<tr>
<td>Height, cm (mean ± SD)</td>
<td>163.9±8.7</td>
</tr>
<tr>
<td>BMI, kg/m² (mean ± SD)</td>
<td>26.2±4.0</td>
</tr>
<tr>
<td>Number of swollen joints (mean ± SD)</td>
<td>8.3±6.1</td>
</tr>
<tr>
<td>Number of painful joints (mean ± SD)</td>
<td>6.4±4.9</td>
</tr>
</tbody>
</table>

aAltered PCR values are defined as >1 mg/dL.
bNormal ESR values <20 mm/h.

cResults

Population description

A total of 1,079 patients were recruited for the study, of which 164 were excluded because they did not meet one or more of the selection criteria, such as not presenting a diagnosis of RA or not meeting the definition of PA (1 patient), patients who did not start their first treatment with DMARDs (161 patients) or because informed consent was not available (79 patients). In the end, 915 patients (33% of recruited) were included in the study (Table 1). Of these, 621% were treated with NSAIDs, 59.2% with corticosteroids, 47.1% with deflazacort and 41.7% with prednisone) and 3.8% received a biological therapy (Figure 2). In patients who received DMARDs, 90.3% received treatment with a single DMARD, 9.5% with 2 DMARDs and 0.2% with 3 DMARDs. In combination therapy, the DMARDs administered most often in combination were MTX + hydroxychloroquine (4.8%), MTX + leflunomide (2.0%) and MTX + sulfasalazine (1.5%) (Figure 3).

The most frequently used DMARD in monotherapy was MTX (81.3%), followed by leflunomide (4.1%) and hydroxychloroquine (3.2%) (Figure 2). The mean MTX dose was 11.27 (3.5) mg/week. In this study, pre-filled syringes for injection were the main method of administration of MTX (77.1%), followed by oral administration with tablets (21.6%). Out of all patients taking MTX, 19.5% combined it with NSAIDs, 15.2% with corticosteroids and 34.7% with corticosteroids + NSAIDs. Of the adjuvant therapies, the most frequent were folic acid (77.2% of patients with MTX) and antilucer (55.2% in combination with MTX) treatments.

At the time of establishing the first-line pharmacological treatment, patients whom the doctor decided to treat with MTX injection showed a longer period of morning stiffness (72.1 (53.5) vs 7.5 (5.3), P=.025) and a higher percentage of radiographic erosions (35.7% vs 23.1%, P=.003), a greater number of swollen joints (8.7 (6.2) vs 7.5 (5.3), P=.025) and painful joints (6.6 (4.8) vs 5.7 (4.8), P=.022) and a higher DAS28 index (5.4 (1.4) vs 5.2 (1.3), P=.047) than those who were treated with oral MTX (Table 2).

Patients who received biologic therapy (3.8% of the total) had a median time from diagnosis of 5 years, 81.8% were RF positive, 66.7% had more than 6 painful joints, 72.7% had more than 6 swollen joints and 51.5% had radiographic erosions.

A total of 83.6% of the patients reported morning stiffness with a mean duration of 69.0 (51.6) min. At that time, the assessment of the disease by the patient and the physician, using a visual analogue scale (VAS), was similar, with values of 58.3 (23.6) and 53.7 (22.1) mm respectively. The mean ESR was 38.1 (23.7) mm/h and CRP was 15.8 (53.4) mg/dL. A total of 60.1% of the patients were rheumatoid factor (RF) positive and 31.0% presented radiographic erosions. The mean DAS28 at the time of starting treatment was 5.3.14

Description of the therapy employed

Of all the patients evaluated, 96.7% received treatment with at least one DMARD. Of these, 62.1% were treated with NSAIDs, 59.2% with corticosteroids (47.1% with deflazacort and 41.7% with prednisone) and 3.8% received a biological therapy (Figure 2). In patients who received DMARDs, 90.3% received treatment with a single DMARD, 9.5% with 2 DMARDs and 0.2% with 3 DMARDs. In combination therapy, the DMARDs administered most often in combination were MTX + hydroxychloroquine (4.8%), MTX + leflunomide (2.0%) and MTX + sulfasalazine (1.5%) (Figure 3).

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Figure 2. Description of the use of treatments in RA and PA.

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Figure 2. Description of the use of treatments in RA and PA.
Data of patients treated with MTX injection and oral MTX

<table>
<thead>
<tr>
<th>MTX administration methods</th>
<th>Oral (mean ± SD)</th>
<th>Injection (mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness, minutes</td>
<td>59.8±38.0</td>
<td>72.1±53.5</td>
<td>.012</td>
</tr>
<tr>
<td>Number of swollen joints</td>
<td>7.5±5.3</td>
<td>8.7±6.2</td>
<td>.025</td>
</tr>
<tr>
<td>Number of painful joints</td>
<td>5.7±4.8</td>
<td>6.6±4.8</td>
<td>.022</td>
</tr>
<tr>
<td>Radiological erosions, %</td>
<td>23.1</td>
<td>35.7</td>
<td>.003</td>
</tr>
<tr>
<td>DAS28 (mean ± SD)</td>
<td>5.2±1.3</td>
<td>5.4±1.4</td>
<td>.047</td>
</tr>
</tbody>
</table>

In 89.6%, the first choice of treatment was adequate according to the SER recommendations. Comparing patients with erosive and non-erosive arthritis, it was possible to appreciate a higher percentage of non-agreement with the recommendations in non-erosive arthritis (12.5%) than in patients with erosive arthritis (4.7%) (P=0.0009).

Discussion

This descriptive study of RA included approximately 1,000 patients with RA or PA from the entire Spanish territory. This sample represents a group of patients with typical and serological clinical features of inflammatory joint disease: more common in women, with an average age of approximately 50 years, 60% of patients were RF positive, with acute phase reactants such as elevated ESR and CRP and with 6-8 swollen and painful joints.

It is noteworthy that patients with RA and PA are seen by rheumatologists in their clinics after an average period of about 6 months from the onset of symptoms. This period represents a short length of time and it seems logical to think that various elements influence on this reduced time in which the patient is attended by a rheumatologist. Such elements include the existence of clinics for the early detection of RA that have been promoted by SER during recent years. However, it is important to mention that the design of this study ruled out the inclusion of patients who had been referred to these clinics. The reason was that, in general, these clinics often use established action protocols and they are usually part of research projects. On the other hand, the aim of this study was to describe, as objectively as possible, the situation of RA in everyday clinical practice. Other factors that may have influenced this reduction in time to be treated by a rheumatologist are the multiple outreach and awareness campaigns that have conveyed the idea that rheumatic diseases should be dealt with as soon as possible by a rheumatologist.

Another interesting finding of this study is that treatment with DMARDs is established early. This therapeutic decision is justified by the current knowledge that irreversible joint damage takes place in the early stages of the disease, and it is estimated that the optimal time to initiate treatment is about 3 months after the symptoms are first perceived. Thus, if RA is treated appropriately and early, it may be possible to avoid the disability that rheumatoid arthritis leads to with the passage of time.

Almost all the patients in this study (96.7%) received DMARDs as a first line treatment for their RA/PA. This change in the use of DMARDs from the onset of the disease has definitely led to the outdating of the famous RA treatment pyramid. DMARD monotherapy represents the most frequently used treatment option and clearly MTX is the drug chosen by almost all rheumatologists to initiate treatment. The study shows that MTX injection in pre-filled syringes was the most widely used DMARD. However, this data should be analysed carefully since the study design facilitated their use. Another interesting fact observed is that, at the time of starting treatment, patients treated with MTX injection presented worse disease conditions, with increased inflammatory activity and radiographic erosions, than those who were treated with oral MTX. This therapeutic practice is in line with the EULAR recommendations for the use of MTX in RA. The same approach was employed by rheumatologists when prescribing biological therapies.

Lastly, the study shows that the vast majority of Spanish rheumatologists used the recommendations from SER to initiate RA or PA treatment. This shows that clinical practice in Spanish rheumatology is achieving a high degree of homogeneity in the treatment of RA. These results are also consistent with those obtained in the EMECAR study (Study of Morbidity and Clinical Expression of Rheumatoid Arthritis), which confirmed the existence of a significant change in the treatment of RA in the past 5 years.

Conflict of interest

Jordi Galván is the Medical Director of Gebro Pharma, S.A., Barcelona, Spain; this company financed the project.

References


