Patterns of Disease Modifing Antirheumatic Drug Use in a Spanish Cohort of Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine the adequacy of disease modifying antirheumatic drug (DMARD) prescription to disease activity in patients with rheumatoid arthritis (RA) and to assess whether the reasons for DMARD discontinuation agree with published evidence.

Methods. Cross-sectional analysis of the baseline year of a RA cohort (n = 788) randomly selected from the clinical registries of 34 centers. Data about current and previous DMARD use was collected from medical records and confirmed by the patient. Disease activity score (DAS), Health Assessment Questionnaire (HAQ) and Larsen scores, and other clinical data were obtained during the study visit.

Results. At baseline visit, 607 patients (77%) were receiving one or more DMARD. Mean DAS, HAQ, and Larsen scores (± SD) were: 3.40 ± 1.22, 1.6 ± 0.4, and 54.68 ± 26.37, respectively. Methotrexate (MTX) was the most frequently prescribed DMARD and parenteral gold salts (GS) showed the highest rate of discontinuation. MTX was used as single therapy in a significantly higher proportion (64.3%) than other DMARD (< 50%) and treatment discontinuation due to inefficacy was significantly less frequent (25.5%) than with other DMARD (> 40%). However, the DAS28 was significantly worse in the group treated with MTX in single therapy than in the group treated with GS alone (4.13 vs 3.43; p = 0.032).

Conclusion. Despite the high use of DMARD among Spanish patients with RA, a significant number of them still have poor control of the disease. In addition, our data show a different perception of ineffectiveness depending on the DMARD used. A non-systematic use of objective quantitative tools for assessment of RA activity and some non-evidence based decisions on the management of DMARD may account for these findings. (J Rheumatol 2003;30:697–704)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — DISEASE MODIFYING ANTIRHEUMATIC DRUGS
COHORT STUDY — TREATMENT DISCONTINUATION

The number of well conducted clinical trials on the efficacy of treatments in rheumatoid arthritis (RA) is increasing. Efficacy studies provide evidence that many traditional and new disease modifying antirheumatic drugs (DMARD) reduce pain and disability and slow the rate of joint destruction in RA[1]. However, longterm outcome in RA with traditional DMARD has been reported as disappointing[2]. This reflects the controversial issues that arise when efficacy data on DMARD are translated into clinical practice.

Evidence from clinical trials shows no clear superiority of any of these drugs in the treatment of RA, mainly due to the few studies formally comparing them[3-11]. Some meta-analyses have tried to investigate this problem, but they have also failed to establish a well defined hierarchy among DMARD[12-14].

In addition, there are clear differences between the populations studied in clinical trials and those in observational studies. Patients included in clinical trials are usually younger, have fewer comorbidities, and show greater disease activity. Moreover, drugs are prescribed according to strict protocols. By contrast, observational studies capture the point of view of physicians attending non-selected patients; thus drug and dose prescription are based, not only on characteristics of the patients, but also on physician preferences[2,15-17].

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Promoted and supported by the Spanish Society of Rheumatology. The medical department of Aventis Pharma, S.A. provided the funding for the project.

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Submitted June 14, 2002; revision accepted September 19, 2002.

We describe the patterns of DMARD prescription compared to disease activity level in a Spanish cohort of patients with prevalent RA. The purpose of the study was to determine the adequacy of the DMARD prescription to control disease activity of the cohort and to assess whether the reasons for DMARD withdrawal were in agreement with published evidence.

MATERIALS AND METHODS

Patient sample, selection, and characteristics. The EMECAR cohort (Estudio de la Morbilidad y Expresión Clínica de la Artritis Reumatoide) comprises a random sample of patients with RA, selected from 34 participating centers. It is a countrywide representative sample of patients referred to hospital-based rheumatology clinics. Participants sent a list of all patients ever registered at their clinics with a diagnosis of RA. Patients were then randomly selected from these registries by an independent investigator (LC) at a central facility after checking for duplicates between centers. The selection complied with the Spanish regulations for data protection. Participating rheumatologists confirmed that the patients selected fulfilled the American College of Rheumatology 1987 criteria for the classification of RA[18]. Second, rheumatologists followed a rigorous contact protocol to optimize recruitment of patients (27.3% of them could not be contacted). If a contacted patient declined to enter the study, he was asked to complete a short questionnaire on the reason for refusal and basic sociodemographic and clinical characteristics, including the Modified Health Assessment Questionnaire (MHAQ). Patients who refused to participate (6% of the eligible and successfully contacted patients) were older on average and showed a slightly better functional status using the MHAQ. The main reason for not participating was dependence on other persons to attend the study visits. All patients who entered the cohort signed a written consent form after being informed about the details of the study. Data are available on 788 patients from a total eligible population of 13,260 (all RA patients registered in the 34 centers). In all, 72.1% of the patients were female and 73.7% had a positive rheumatoid factor. The average age at the time of the diagnosis was 48 ± 15 (mean ± standard deviation, SD). The mean disease duration at cohort baseline was 10 ± 8 years (mean ± SD), with 14.4% of the patients having less than 2 years of disease duration (early arthritis).

Design. The data presented here were obtained from the cross-sectional analysis of the baseline year (November 1999 to November 2000) of the EMECAR cohort. Rheumatologists were instructed to collect the data following standard definitions and procedures, and trained in the performance of joint counts and other measurements. All patients were examined and had radiographs taken of hands and wrists, as well as laboratory tests. Data about current and previous treatments with DMARD were collected from the medical records and confirmed by the patient during the study visit. Due to the complexity of the collection of retrospective treatment data, information about dosing was not obtained. Corticosteroids are often used intermittently at times of disease flares and then gradually tapered, which makes precise assessment of their use difficult. Thus, in EMECAR, data on corticosteroid use were categorized at this initial visit as: never, less than 1 year, 1 to 5 years, 5 to 10 years, or more than 10 years of cumulative corticosteroid treatment.

Remission was defined as by Pinals and colleagues[19]. The Disease Activity Score (DAS) was obtained from 28-joint counts as described by Prevoo, *et al*[20]. A trained radiologist read hand radiographs centrally, and the radiological damage was assessed using the Larsen score with the Scott modification[21]. All patients were given the Spanish version of the HAQ[22] to assess functional disability.

Statistical analysis. Absolute and relative frequencies of previous and current DMARD use were obtained. To assess whether patient characteristics or measures of disease activity or progression were associated with a specific current pattern of DMARD use [no DMARD use, MTX, antimalarial drugs (AM), parenteral gold salts (GS), sulfasalazine (SSZ), cyclosporine (CSA), and combined therapy], contingency tables and one-way analysis of variance were used. If the distribution of a variable was statistically different between groups, a post hoc analysis was carried out to assess which groups were different from the others by collapsing cells for chi-square analysis and by Student-Newman-Keul's test for analysis of variance. To examine qualitatively the reason for withdrawal among DMARD, analysis of correspondence with symmetric normalization was performed, comparing 2 dimensions: DMARD and reason for discontinuation.

RESULTS

Current patterns of DMARD prescription. Only 33 patients (4.2%) had never received a DMARD during their RA evolution. At baseline, 607 patients (77%) were currently receiving treatment with one or more DMARD.

Figure 1A shows the frequency of current prescription of each drug, both as monotherapy and in combination. MTX

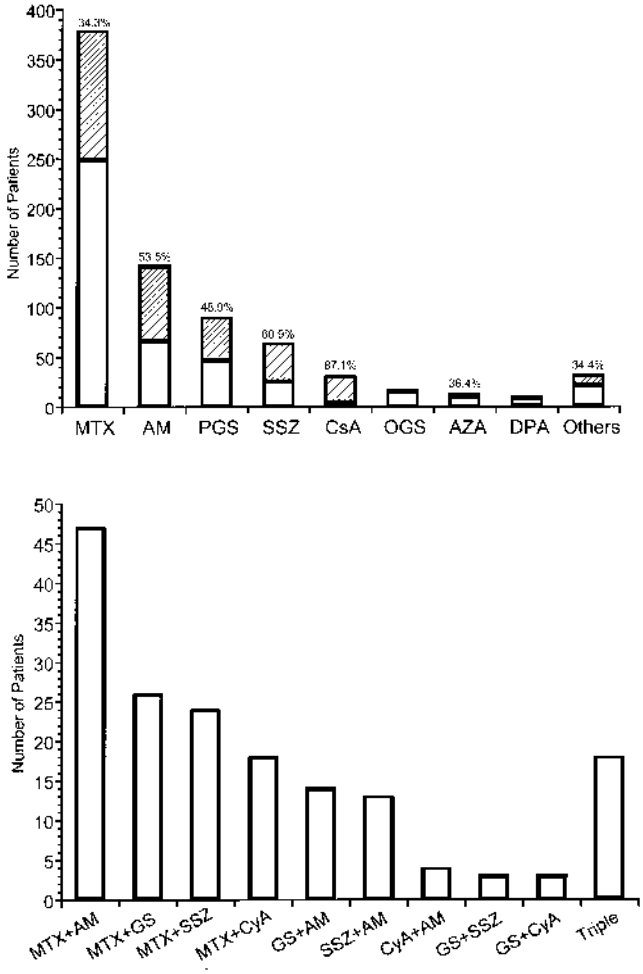

Figure 1. A. Current use of DMARD in EMECAR study. The blank section of the bars represents the number of patients receiving monotherapy, while the shaded section represents patients using each drug in combination with other DMARD. The number at the top of the bars corresponds to the proportion of patients receiving combination therapy for each drug. B. Current use of combination therapy. See the text for extended description of other DMARD and triple therapy. MTX: methotrexate; AM: antimalarials; PGS: parenteral gold salts; SSZ: sulfasalazine; CSA: cyclosporin A; OGS: oral gold salts; AZA: azathioprine; DPA: D-penicillamine.

was the most frequently prescribed drug, and was mainly used as single therapy (50.3% with folic acid supplementations), in contrast to the pattern of use of the next 4 most frequently prescribed drugs: AM (mainly chloroquine, but also hydroxychloroquine), GS, SSZ, and especially CSA. Other drugs with a limited frequency of prescription at first visit were oral gold salts, azathioprine, cyclophosphamide, clorambucil, D-penicillamine, etanercept (5 patients), infliximab (3), leflunomide (7) and mycophenolate mofetil (1).

Combination therapy (CT) was used in 164 patients (20.8%). The most frequently prescribed combination of DMARD was MTX + AM, followed by MTX + GS, MTX + SSZ, and MTX + CSA, although a heterogeneous group of combinations was also used in the cohort as shown in Figure 1B. This figure illustrates that more than 75% of combinations were based on MTX, and then on AM. Eighteen patients were taking triple therapy: MTX + SSZ + AM (7 patients), MTX + GS + AM (5), MTX + CSA + AM (2), MTX + GS + CSA (1), GS + CSA + AM (1), GS + SSZ + AM (1), and SSZ + AM + cyclophosphamide (1).

Patient characteristics by DMARD use. Table 1 shows the characteristics of the patients by current treatment. Only the 6 most frequent treatments are shown: (1) single drug therapy with MTX, AM, GS, or SSZ; (2) a group including all kinds of combined therapy; and (3) patients taking no DMARD. No significant association of current treatment was seen with rheumatoid factor (RF) positivity or early disease. However, patients treated with combined therapy or GS were significantly younger than patients taking no DMARD ($p < 0.001$ and $p = 0.011$, respectively). Patients receiving combined therapy were also significantly younger than patients treated with MTX or AM alone ($p < 0.001$). In addition, patients treated with combined therapy or GS had a shorter disease duration than those taking no DMARD ($p = 0.006$ and 0.023, respectively).

The number of previous DMARD differed depending on current DMARD used in monotherapy (Table 1). The majority of patients currently taking GS had not received a previous DMARD. Interestingly, patients with no current treatment or those currently taking MTX had received significantly more DMARD than patients receiving GS treatment ($p < 0.01$).

Regarding combined therapy, no significant associations of demographic factors were observed with any of the 4 main combinations, probably due to the low number of patients in these groups (Table 2).

Patients who had never been treated with a DMARD during RA evolution were significantly older than the rest of the patients (74.2 ± 10.8 vs 60.9 ± 12.9 yrs; $p < 0.001$), had seronegative disease more frequently (42.4% vs 25.6%; $p = 0.052$), and more of them were early RA cases (39.4% vs 13.3%; $p < 0.001$).

Differences in disease activity, functional ability, and joint damage between patterns of DMARD use. We did not observe significant differences in the proportion of patients fulfilling Pinals' remission criteria between the different current treatments (Table 1). However, patients with a DAS28 below 2.6 (considered as no RA activity[23]) were significantly more frequently in the GS group compared to the non-treated ($p = 0.02$), MTX ($p = 0.005$), and combined therapy groups ($p = 0.008$). The proportion of patients with no RA activity was also significantly higher in the AM group versus MTX ($p = 0.016$) and combined therapy groups ($p = 0.025$) (Table 1). Significant differences in mean DAS28 scores were found between AM and combined therapy ($p = 0.001$), and between GS and MTX or combined therapy ($p = 0.032$ and $p < 0.01$, respectively). Figure 2 shows the distribution in quartiles of DAS28 by treatment group. More than 75% of untreated patients and those taking MTX or combined therapy showed moderate to high RA

Table 1. Characteristics of the patients included in the main groups of current treatment in the EMECAR study. Data are shown as percentage or mean ± standard deviation, except for Previous DMARD.

	No Treatment	MTX	AM	GS	SSZ	Combined Therapy	p
Patients, %	181 (23)	249 (31.6)	66 (8.4)	46 (5.8)	25 (3.2)	164 (20.8)	—
Female, %	72.8	76.3	69.7	58.7	68	70.7	NS
RF +, %	68.8	75.9	71.2	71.1	76	77.4	NS
Age, yrs	65.4 ± 12.9	62 ± 12.3	63.7 ± 12.4	58.3 ± 15	60.6 ± 13.1	56.5 ± 12	< 0.001
RA duration, yrs	12 ± 9.5	10.2 ± 7.5	8.7 ± 7.2	7.9 ± 6.2	8.4 ± 6.6	9 ± 6.7	0.001
Early RA (< 2 yrs), %	11	13.7	15.2	19.6	24	17.7	NS
Previous DMARD, median [IQR]	2 [1–3]	1 [1–2]	1 [0–2]	0 [0–1]	1 [0–2]	—	< 0.001
Remission (Pinals), %	4	5.6	3	2.2	4	2.4	NS
DAS28 < 2.6, %	14.1	12.7	25.8	31	25	12.4	0.004
DAS28, mean	4.1 ± 1.33	4.13 ± 1.24	3.63 ± 1.47	3.43 ± 1.26	3.6 ± 1.65	4.46 ± 1.5	< 0.001
HAQ	1.67 ± 0.5	1.63 ± 0.45	1.6 ± 0.5	1.45 ± 0.35	1.44 ± 0.35	1.59 ± 0.38	0.013
Larsen	59.2 ± 31.4	53.1 ± 22.8	51.3 ± 25.2	39.9 ± 22.3	42.1 ± 17.8	57.5 ± 26.5	0.001
Arthroplasty, %	13.8	10.4	19.7	10.9	8	8.8	NS
Corticosteroid, %	90.6	89	84.6	75.6	76	91.1	0.018

IQR: interquartile range.

Table 2. Characteristics of the patients included in the main groups of current combined therapy in the EMECAR study.

	MTX + AM	MTX + GS	MTX + SSZ	MTX + CsA	Triple	p
Patients, n	47	26	24	18	18	—
Female, %	85.1	65.4	79.2	88.9	11.1	NS
RF +, %	87.2	65.4	91.6	100	11.1	NS
Age, yrs	58.7 ± 12.7	58.5 ± 12	53.7 ± 13.4	53.2 ± 10.7	52.4 ± 11.9	NS
RA duration, yrs	9.7 ± 7.9	6.6 ± 5	8.2 ± 5.5	9.9 ± 5.1	6.5 ± 4.8	NS
Early RA (< 2yrs), %	25.5	26.9	16.7	5.6	5.6	NS
Remission (Pinals), %	4.3	0	0	5.6	0	NS
DAS28 < 2.6, %	21.3	15.4	8.3	0	0	NS
DAS28, mean	4.04 ± 1.3	4.21 ± 1.7	5.06 ± 1.6	4.7 ± 1.2	4.49 ± 1.5	NS
HAQ	1.54 ± 0.32	1.48 ± 0.37	1.68 ± 0.45	1.7 ± 0.34	1.63 ± 0.42	NS
Larsen	57.6 ± 24.6	49.4 ± 17.1	53.5 ± 23	70 ± 32.9	46.5 ± 22.9	NS
Arthroplasty, %	10.6	0	16.7	11.1	0	NS

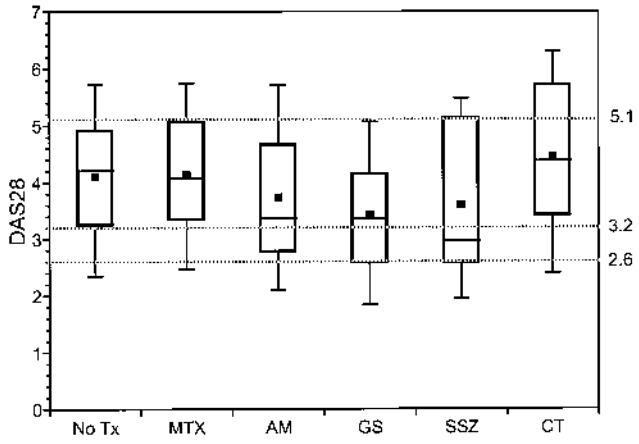

Figure 2. Distribution of DAS28 by DMARD. The mean is represented by the black square and median by the middle line; the edge of the boxes marks the 25 and 75 percentiles and the error bars the 10 and 90 percentiles in each group of patients (No Tx, n = 163; MTX, n = 237; AM, n = 63; GS, n = 42; SSZ, n = 24; CT, n = 153). The limits between high, moderate, low, and no RA activity are represented by broken lines. CT: combination therapy. For other abbreviations see legend to Figure 1.

activity. By contrast, nearly 50% of the patients receiving SSZ and GS had low to no disease activity, with the GS treated group having the lowest proportion of cases with high RA activity.

Another measure of how well the DMARD controls disease is concomitant corticosteroid use. The GS and SSZ groups showed a significantly lower proportion of patients who had ever received corticosteroids (Table 1).

Finally, patients treated with GS had a significantly lower HAQ than patients without DMARD treatment (p = 0.032). A significantly lower Larsen score was observed in the GS group compared to untreated patients (p = 0.004) or patients taking combined therapy (p = 0.012). However, no significant differences between groups were observed in the percentage of patients who had undergone a joint replacement procedure.

No differences in disease activity, functional ability, or joint damage were observed between the 4 groups receiving combined therapy (Table 2).

Reasons for DMARD withdrawal. A total of 1848 treatments with up to 10 different DMARD have ever been prescribed to 755 patients in EMECAR. Until the baseline visit, 1196 treatments had been discontinued. More than 60% of the patients had discontinued 1 to 3 DMARD during the evolution of their RA, while 209 patients (28%) had used the same DMARD continuously. Almost 10% of patients had been treated with 4 or more DMARD, and one patient received up to 9 different DMARD during her disease course.

Figure 3A shows the number of treatment discontinuations and the percentage with respect to the total number of prescriptions of each DMARD. GS was the drug most frequently withdrawn, in relation to the high use of this DMARD in the past.

The reasons for treatment cessation were carefully investigated in the clinical records and further confirmed during the visit with the patient. Reasons were categorized into inefficacy, toxicity, and others (including unexplained patient decision, improvement, unknown reason). The analysis of correspondences is shown in Figure 3B, where the following considerations can be concluded: (1) MTX is suspended almost equally for toxicity and for other reasons; (2) parenteral GS and SSZ are withdrawn for inefficacy and for toxicity; (3) CSA is predominantly suspended due to toxicity; (4) the reasons for withdrawing AM are inefficacy or other; and (5) oral gold salts and D-penicillamine are suspended mostly due to inefficacy.

To further assess how Spanish rheumatologists estimated efficacy and safety in the 4 currently most prescribed DMARD, we compared the current proportion of patients taking single and combined therapy (considered as partial inefficacy) with each DMARD, and the proportion of discontinuations due to inefficacy (Table 3). The patterns are very similar, the only exception being MTX. Current prescription of MTX as monotherapy, in contrast to

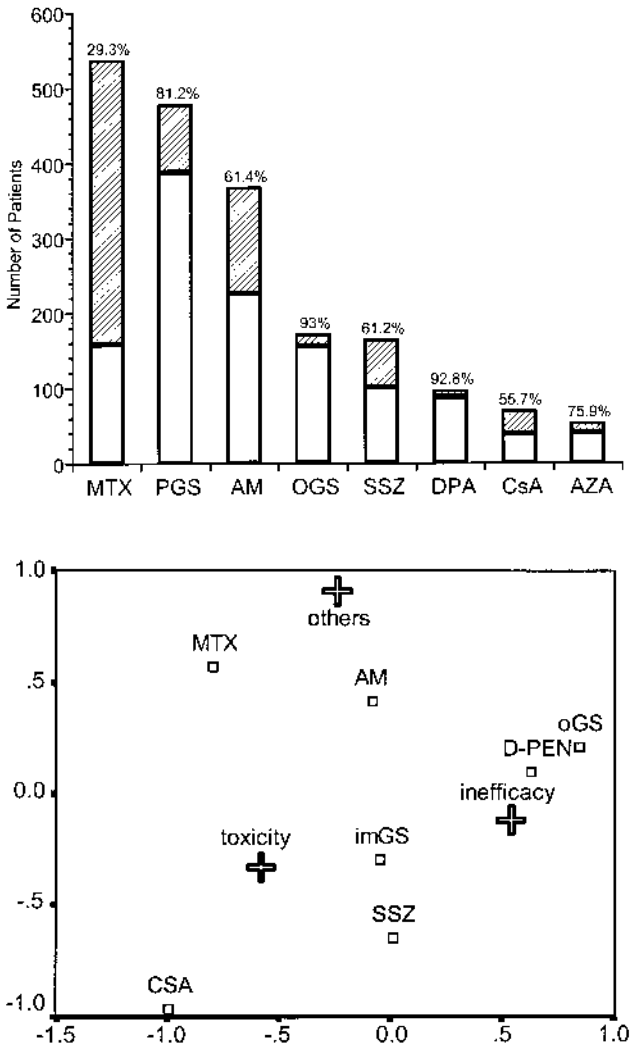

Figure 3. A. Proportion of treatment cessation by DMARD. The blank section of the bars represents the number of withdrawn treatments, while the shaded section represents current treatment. The number at the top of the bars corresponds to the proportion of treatment termination for each drug. B. Map of correspondences of multifactorial analysis of reasons for discontinuation of therapy of the 8 most used DMARD. The geometrical representation should be interpreted as follows: the smaller the space between levels of 2 different variables, the greater the association between them. Thus, the closest levels are inefficacy (variable: reason for withdrawal) and D-penicillamine (variable: DMARD). For abbreviations see legend to Figure 1.

combined therapy, was significantly more frequent compared to other DMARD ($p < 0.001$). In addition, the withdrawal of MTX in the past due to ineffectiveness was significantly less frequent than for the other DMARD ($p < 0.001$).

DISCUSSION

Current recommendations for the treatment of RA encourage use of DMARD and combination therapy[1,24]. In this regard, we observed that patients with RA in Spain are regularly treated with DMARD (77%), a quite large proportion of which are used in combination (21%). DMARD use in our cohort is similar to that from other recent RA cohorts followed up by rheumatologists[15,25-29], and is clearly higher than that of RA patients followed up in the community[30,31].

Regarding the adequacy of DMARD use according to current recommendations, at present there is no firm evidence supporting differences in the efficacy of MTX, parenteral GS, and SSZ[8,11,13]. On the other hand, it is accepted that AM and oral GS are less potent than the other classical DMARD[14], and combined therapy is generally considered valuable for patients who have failed a DMARD as monotherapy[1,32,33]. On these grounds, some findings from EMECAR support the idea that Spanish rheumatologists may prescribe DMARD depending on patient characteristics and RA severity. Seronegative and elderly patients with RA tend to be treated less often with DMARD. If treated, elderly RA patients are prescribed MTX or AM, rather than GS or combination therapy, probably because the former have shown lower toxicity. Similarly, Zink, *et al* reported that German rheumatologists tend to use MTX in severe RA more frequently than AM or SSZ[15].

In spite of the widespread use of DMARD, more than 50% of the Spanish patients show moderate to high disease activity (DAS28 > 3.2). This means that over half the patients would be candidates for treatment modification to control disease activity. Although patients treated with MTX, GS, or SSZ did not significantly differ in risk factors for severe disease (RF positivity, sex, etc.), we observed that compared to the MTX group, patients treated with GS or SSZ seem to follow a more benign evolution, with a higher percentage of patients with no RA activity (DAS28 < 2.6), lower mean DAS28, mean HAQ, and mean Larsen score; moreover, a lower proportion required joint arthroplasty or corticosteroid treatment. Several reasons could account for this finding. Patients treated with MTX were significantly older, with longer disease duration, and many failed one or more previous DMARD; therefore, it is possible that MTX was prescribed in patients with worse disease. All this could explain differences in HAQ, Larsen score, and frequency of joint replacement. In addition, MTX tends to be prescribed in insufficient doses to most patients. This was observed in a study about variability in the management of RA in Spain (1997–98) in which the median maximal dose of MTX was 10 mg/week, and less than 10% of patients received > 15 mg/week as the maximal dose[34]. This is probably so because rheumatologists who prescribe MTX prefer avoiding side effects rather than inducing a strict control of the disease. And finally, it is possible that there were differences in the perception of inefficacy between MTX and the other DMARD by the rheumatologists.

This latter impression is based on the finding that MTX was used in monotherapy more frequently than other DMARD. In addition, MTX was withdrawn due to ineffi-

Table 3. Patterns of past and current management of the 4 main DMARD used in the EMECAR study.

	Current Treatment, n (%)			Reason for Withdrawal, n (%)			
	Single	Combined	Total	Inefficacy	Toxicity	Others	Total
Methotrexate	249 (64.3)*	138 (35.7)	387	35 (25.5)*	63 (46)	39 (28.5)	137
IM gold salts	46 (50)	46 (50)	92	167 (48)	139 (39.9)	42 (12.1)	348
Antimalarials	66 (46.2)	77 (53.8)	143	83 (43.7)	63 (33.2)	44 (23.2)	190
Sulfasalazine	25 (39.1)	39 (60.9)	64	48 (51.1)	40 (42.6)	6 (6.4)	94

* $p < 0.001$ compared to other treatment groups. IM: intramuscular.

cacy less frequently than other DMARD. The low use of formal measures of disease activity in daily practice among Spanish rheumatologists[35] may explain these differences, favoring subjective judgment of effectiveness and personal preferences for DMARD management. Therefore, although it has been published that patients continue taking MTX significantly longer than other DMARD[2,13,36,37], the patients taking MTX may actually be experiencing high disease activity for long periods of time.

Regarding drug discontinuation, although parenteral GS are described as the DMARD with the highest toxicity, and MTX as one of the safest drugs for RA[13], in EMECAR we observed the opposite: the reason stated for withdrawal of MTX was mainly toxicity, while in the case of GS the main reason was inefficacy. Therefore the reasons for withdrawal in these 2 DMARD were not in agreement with the evidence provided by clinical trials[8,11,13,14]. This might be related to changes in drug management at different time periods. GS were frequently used in the past in our cohort, and at that time, partial inefficacy was managed by switching to another DMARD, mainly MTX[15,30]. Nowadays, rheumatologists tend to add on a DMARD when no control of activity is attained[1]; thus when considered inefficacious, MTX is not suspended but combined.

In conclusion, despite the high use of DMARD among Spanish RA patients, a significant number of them still have a substantial level of disease activity. A non-systematic use of objective quantitative tools for assessment of RA activity and some non-evidence based decisions on the management of DMARD may account for this finding.

This cross-sectional, baseline, descriptive study of the EMECAR cohort provides a useful picture of the treatments taken by patients with RA before the widespread use of leflunomide and biological agents in our region. Over the next 5 years planned for this study we hope to obtain sufficient information to analyze the impact of these new agents on control of disease. Nevertheless, we must also be aware of the possibility of the inappropriate use of traditional DMARD, which are less expensive than these new agents and have a better-known longterm toxicity profile.

ACKNOWLEDGMENT

We thank Dr. Armando Laffon for his continuous support, Raquel Ruiz for her impressive work as logistic secretary, and Jesus Maese for his diligent monitoring of the study.

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