Original Articles

Reduction in Time Until First Treatment With Disease Modifying Treatment in Patients With Rheumatoid Arthritis

Daniel Clemente,[a] César Hernández-García,[a] Lydia Abásolo,[a] Virginia Villaverde,[b] Cristina Lajas,[a] Estíbaliz Loza,[a] Ruth López-González,[a] Cristina Vadillo,[a] Benjamín Fernández-Gutiérrez,[a] Inmaculada Morado,[a] Juan Ángel Jover,[a] and the emAR Study Group*

[a]Servicio de Reumatología, Hospital Clínico San Carlos, Madrid, Spain
[b]Servicio de Reumatología, Hospital General de Móstoles, Móstoles, Madrid, Spain

Objective: To analyze changes in the lag time to first disease modifying antirheumatic drug (DMARD) prescription since onset of symptoms of rheumatoid arthritis (RA) over the last 2 decades in Spain.
Patients and method: Review of medical records of 865 patients diagnosed with RA living in Spain and attended in specialty care settings of the National Health System. The principal variable was the lag time between the onset of symptoms of RA and the date of first DMARD therapy prescription. Analyses were performed by year and 5-year periods and differences between groups were assessed by χ^2 test, Student t test, and analysis of variance.
Results: Sociodemographic and clinical characteristics corresponded to a typical cross-sectional population of patients diagnosed with RA. The median lag time between symptom onset and first DMARD therapy was 14 months (6-36) for the whole group. However, a significant shortening of time to first DMARD was observed over the last 2 decades (−4.59 [0.2] months by year; $P<.001$). Shortening of time to first DMARD was mainly due to a shortening of time to first visit with specialists since onset of symptoms with a smaller decrease in time from first visit to first prescription of a DMARD agent.
Conclusions: A significant shortening in the lag time to first DMARD therapy was observed over the last 2 decades in Spain, being a significant reduction in the time to first visit with a specialists its major cause.

Key words: Rheumatoid arthritis. Disease modifying antirheumatic drugs. Time to first DMARD.

Disminución del tiempo hasta el primer tratamiento con fármacos modificadores de la enfermedad en pacientes con artritis reumatoide

Objetivo: Analizar el cambio en el tiempo hasta el primer tratamiento con fármacos modificadores de la enfermedad (FAME) desde el inicio de los síntomas en pacientes diagnosticados de artritis reumatoide (AR) a lo largo de dos décadas en España.
Pacientes y método: Revisión de historias clínicas de 865 pacientes diagnosticados de AR atendidos en centros de atención especializada del Sistema Nacional de Salud en España. La variable principal fue el tiempo desde el inicio de los síntomas de la AR hasta la fecha del inicio del primer tratamiento con algún FAME. Las diferencias por año desde el inicio de los síntomas o agrupaciones de 5 años se compararon mediante la prueba de la χ^2, la t de Student y el análisis de la variancia.
Resultados: Las características clínicas y sociodemográficas se correspondieron con las típicas de una muestra de corte transversal de pacientes diagnosticados de AR. La mediana del tiempo desde el inicio de los síntomas y el primer tratamiento con FAME fue de 14 (6-36) meses para el conjunto de la muestra. Se observó, sin embargo, una reducción significativa del tiempo hasta el primer FAME en las últimas dos décadas (−4,59 ± 0,2 meses por año entre 1980 y 2000; p < 0,0001). Esta disminución se debió principalmente a una reducción en el tiempo hasta la primera visita con un especialista desde el inicio de los síntomas, con una reducción comparativamente menor en el tiempo entre la primera visita y la primera prescripción del FAME.
Conclusiones: Entre los años 1980 y 2000 se ha producido en España una disminución muy significativa en el tiempo que tardan los pacientes con AR en recibir

su primer FAME, motivada principalmente por una reducción en el tiempo de acceso al especialista que prescribe estos tratamientos.

Palabras clave: Artritis reumatoide. Fármacos modificadores de la enfermedad. Tiempo hasta el primer FAME.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a prevalence of about 0.5% of the general population,[1] of a partially unknown etiology and associated to high degrees of pain, functional incapacity, psychological stress, job-loss, and a reduction in the life expectancy.[2] The treatment of RA has for years been centered on the control of symptoms.[3] However, the traditional conservative therapeutic plans have been largely rejected due to unacceptably high degrees of incapacity and radiologic progression associated to the delay in the start of therapy with disease modifying antirheumatic drugs (DMARD).[4] The fact is that, currently, in most cases, the consequences of the delay in the start of DMARD therapy is much more important to the patient that the potential toxicity of treatment.[5] In addition, patients with RA who start treatment with any DMARD in the early stages of their disease, have a larger probability or reaching a significant clinical response than patients who are receiving the same drugs but in latter stages of their disease,[6] something that has led to the definition of a "therapeutic window of opportunity" in RA. Therefore, the correct treatment during this initial phase would have a larger probability of being successful than the same treatment started after this period had started.[7]

Even though the early treatment of RA with DMARD has become a paradigm for all rheumatologists,[8] what remains unclear is whether a simple change in attitude is enough to guarantee that the majority or totality of patients with RA receive treatment with DMARD in the first 3 to 6 months since the onset of disease, as is being currently recommended. The objective of this study is to study the time lapse from the onset of symptoms to the start of treatment with the first DMARD in a large sample of patients with RA treated in Spain between 1980 and 2000.

Patients and Methods

Study design, patient ample, and data acquisition. The study on management of rheumatoid arthritis in Spain (emAR) was a national study, with transversal cut-points, designed to evaluate the variability in the management of RA in Spain.[9] In summary, it contained a probabilistic sample of clinical histories (CH) of individuals who were over 16 years of age, diagnosed with RA, and who attended specialized health care units in Spain. With the objective of insuring a representative sample of the general population, the CH was randomly selected through a stratified sampling of autonomous communities and hospitals. In first place, each autonomous community was assigned a number of CH to be reviewed, proportional to its population. Communities with less than 25 reviewable CH, according to their population, a minimum number of 25 CH was assigned. Then, a list of the hospitals of each community was obtained through the National Hospital Index; those who did not have a rheumatology or internal medicine department were excluded. After that, hospitals in each autonomous community were randomly selected, adjusting their probability of being chosen to the size of the population each one of them tended to. The number of hospitals selected in each autonomous community was estimated in order to insure a sample size per community that was 5 times higher than the assigned one. Hospitals that refused to participate in the study were replaced by the one next on the randomization list of each autonomous community. Each hospital was then asked to submit a list of patients with RA who were attended in the past 2 years, independently of the number of contacts with the hospital or if these contacts had involved outpatient visits or hospitalization. After that, a systematic sampling of all of the patients residing in each autonomous community was performed. CH that did not correspond to RA patients were substituted with the next one on the randomization list of the same hospital, while lost or incomplete CH were not replaced. All of the objective data of the patients in the study (including the date of RA diagnosis which was based on the moment they fulfilled the American College of Rheumatology 1987 criteria for RA) were obtained by the researchers in each of the hospitals through the CH. For incomplete or lost CH, a group of minimal data was obtained, in order to insure that no significant differences existed with the population included in the study. All of the data was collected in standardized questionnaires.

A total 9299 CH of RA patients in selected hospitals were obtained and from them, 1550 were selected for review; 53 CH from 3 autonomous communities were not reviewed because none of the hospitals in these communities agreed to participate in the study and 188 more were lost or incomplete. Therefore, the final sample of the emAR study reunited 1379 CH of RA patients distributed in 16 of the 19 Spanish communities. Lost or incomplete CH were homogeneously distributed in all of the communities without overrepresentation of any of them. For the purpose of the present analysis, we specifically studied 865 patients included in the emAR

database whose symptoms started between 1980 and 1999 and who had received at least one DMARD in the course of their disease.

Variables. The main variable was the time between onset of RA symptoms and the date the first DMARD was started. The following variables were also recorded: *a)* socio-demographic variables, such as the age at symptom onset, gender, and place of residence (same as the patients hospitals location or different city); *b)* date of RA symptoms onset; *c)* date of the first visit related to RA treatment in a specialized care setting (rheumatology or internal medicine); *d)* date on start of first DMARD treatment; and *e)* first DMARD prescribed.

Analysis. The results are shown as a median (percentiles 25-75) or a mean (standard deviation). The date of symptoms onset and the date of the first DMARD were categorized according by years and 5-year periods (1980-1984, 1985-1989, 1990-1994, and 1995-1999). In order to analyze differences between groups we employed the χ^2, Student *t,* and variance analysis; significance was considered as $P<.05$. All of the analyses were done using the Stata 7.0 software package(Stata Corporation, Colleague Station, TX).

Results

The socio-demographic and clinical characteristics of the sample included in the emAR study have been published,[9] and correspond to those which are typical of a transversal cohort of patients with RA, with 72.1% women and a man age at the onset of symptoms of 52 (42-62) years. The 54.4% of the patients lived in the same city where the hospital they attended was and the rheumatologist was the main physician of 89.4% of patients. No differences in the clinical variables were observed between the patients stratified according to year since RA symptoms onset. Parenteral gold salts (32.9%), methotrexate (31.5%), and antimalarials were the DMARDs employed as first treatment with a greater frequency. However, there were great differences when the date of the first DMARD was categorized in 5-year periods (Table). While parenteral gold salts were the first therapy chosen during the first years analyzed, methotrexate became the treatment of choice in the past decade. Antimalarials showed a slight increase throughout the whole study period, while other DMARDs, such as gold salts or azathioprine, have practically disappeared from the treatment of RA. It is notable that sulphasalazine is scarcely employed as a first treatment of RA in Spain.

The median time between the onset of symptoms and the first DMARD was 14 (6-36) months. However, a significant tendency towards the reduction of this period was seen when analyzed according to the number of years

of onset of symptoms (Figure 1) or in 5-year periods (Figure 2). The magnitude of this fall was −4.59 (0.2) months per year that passed from 1980 to 1999 ($P<.0001$) after adjusting for gender, age at onset of symptoms, and place of residence. The median time to the first DMARD was 62 (25-124) months in patients whose symptoms started in the period between 1980-1984 in comparison to 24 (10-45) months in 1985-1989, 14 (6-29) months in 1990-1994, and 8 (3-13) months in 1995-1999 ($P<.0001$). This reduction in time to the first DMARD during these 2 decades was mainly owed to the reduction of the time from the onset of symptoms to the first visit to a specialist (−4.18 [0.2] months per year that passed from 1980 to 1999; $P<.0001$), with a smaller reduction in the time which passed from the first visit to the specialist and the first prescription of a DMARD (−1 [0.1] months per year from 1980 to 1999; $P<.02$) after adjusting for gender, age at the onset of symptoms, and place of residence with respect to the hospital in which the patients were attended. Lastly, it must be pointed out that the median time that passed from the diagnosis to the beginning of the first DMARD was 2 (0-15) months.

Discussion

The current guidelines on the treatment of RA recommend an early star of DMARD therapy in the course of the disease and notable efforts have been made to make the rheumatologists, the primary care physicians, and the general population aware of the importance of the fact that patients with RA need the earliest possible access to DMARD therapy. In this article we showed that there has been an important reduction in the time until treatment is started with the RA patients' first

Percentage of Patients Who Started Treatment With Each DMARD in Period of 5 Years Between 1980 and 1999[a]

	1980-1984	1985-1989	1990-1994	1995-1999
Parenteral gold	44.74	43.72	33.75	16.88
Methotrexate	16.67	14.07	31.25	53.59
Antimalarial[b]	12.28	14.07	17.81	24.05
Auranophin	18.42	20.10	9.69	1.69
Sulphasalazine	0.88	4.02	5.63	3.38
Azathioprine	2.63	1.51	0.31	0.42
D-penicillamine	3.51	2.51	1.25	0
Others[c]	0.88	0	0.31	0

[a]DMARD indicates disease-modifying anti-rheumatic drug.
[b]Includes cloroquine or hydroxicloroquine.
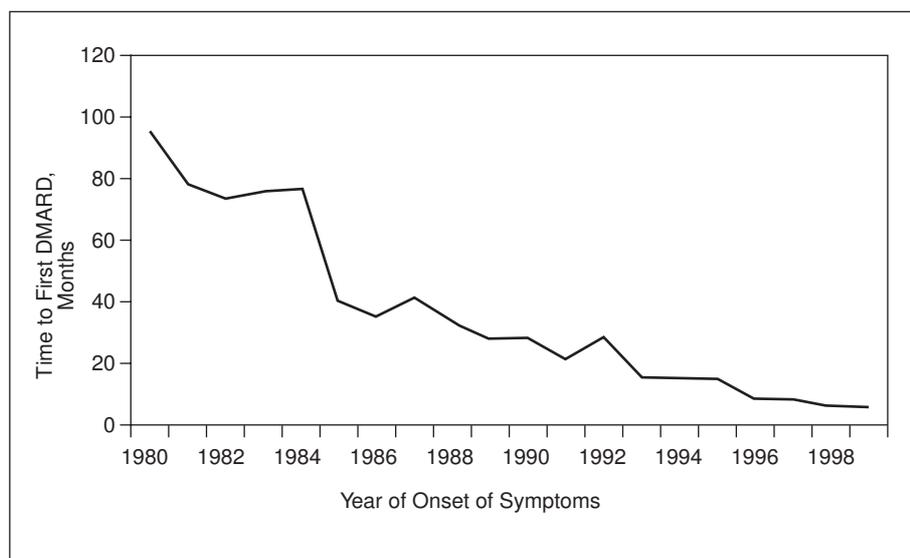[c]Includes leflunomide, alkylating agents (cyclophosphamide, chlorambucil), and cyclosporine A.

Figure 1. Mean time (months) from the onset of symptoms of rheumatoid arthritis to the first treatment with disease modifying drugs (DMARD) per year since the start of symptoms.
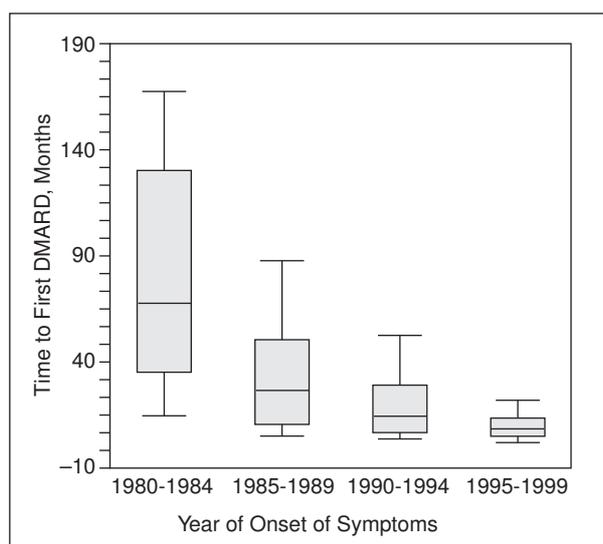

Figure 2. Mean time (months) since the onset of symptoms of rheumatoid arthritis to the start of treatment with disease modifying drugs (DMARD) per 5-year periods since the onset of symptoms.

treatment options and the attitudes and/or interest of the specialists in the medical management of RA, and the pharmacologic options which are available. The results observed in this study can be due to changes in all or some of these factors.

In this study we have observed that most of the reduction in the time until the first DMARD during these 2 decades is due to an earlier access to specialized care, where it is more likely that the patient will receive DMARD treatment. The time that the patient delays in consulting with a primary care physician —generally a primary care physician—, the time that this physician delays in referring the patient to specialized care and/or the time until the first visit with the specialist once the primary care physician refers the patient can influence access to specialized care. At the same time, the interval until the first visit to the specialist can depend on the availability of this service, the waiting list, or aspects of accessibility derived from the health care system. It has been described that the main cause of diagnostic delay in RA is the physicians' delay in establishing a diagnosis and not the delay in the patient quest for medical attention.[10] We have previously described that some characteristics of the patients (age at onset, degree of family support, or level of education) and the disease (painful and swollen joint counts) are associated to a reduction in the delay of the visit to the rheumatologist.[11] Between 1980 and 1999, the availability of rheumatologists has also increased in the National Health System in Spain, something that reaches the majority of public hospitals.[12] The Spanish Society of Rheumatology has carried out national campaigns on RA and its treatment directed to primary care physicians and the general population. Independently of which factors have had a larger weight, the fact is that the time until the first visit with a specialist has decreased

DMARD between 1980 and 1990 in Spain, although the largest part of this change is attributable to a faster access to the parts of the patient care system in which a DMARD will be prescribed.

The time that passes from the point of onset of RA symptoms in a patient to the point in which the patient received the first DMARD can be influenced by factors such as the characteristics of the patient, the severity of symptoms, the recognition of the disease or the knowledge on the disease by the primary care physicians, the access to a system of specialized care, the availability of different

dramatically in our country between 1980 and 1999 and this seems to have noticeably contributed to a reduction in the delay of the start of DMARD treatment in patient with RA.

Next to this, we have observed a lesser, though consistent, reduction in the time from the first visit to the specialist and the first prescription of a DMARD. It is clear that rheumatologists currently do not continue to consider this disease as "beningn."[13] However, the availability of different options in the treatment of RA could also have impacted on a more decisive attitude among specialists. Our results show significant changes in the physicians' choice of first treatment with a DMARD, something that in some way follows a parallel course to the reduction in time to the first treatment with a DMARD. While methotrexate and antimalarials have steadily turned into the first treatment of choice, other drugs such as parenteral or oral gold salts, D-penicillamine, or cyclophosphamide have disappeared or turned into a marginal choice as first DMARD because of their uncomfortable administration and/or toxicity.[14] The availability and popularization of oral methotrexate since the middle of the eighties as a drug with easy administration, capable of inducing a long term response in the majority of patients, and an acceptable toxicity profile,[15] next to the use of antimalarials in milder forms of the disease, could also have eased a more precocious treatment with DMARDs by rheumatologists in the course of RA.

The final result of all of these changes has been a significant reduction in the time until the first treatment with a DMARD, a result which is consistent with previous studies[10] and which can be considered a success. However, attention must be called upon the fact that at the time the study period ended, one fourth of the patients diagnosed with RA still were starting their treatment with a first DMARD more than 1 year after the onset of symptoms.

In light of the facts demonstrated regarding the early treatment using DMARD and definitely improving the long term prognosis of patients with RA, it must be emphasized once again the need to renew efforts to extend those benefits to all of the population of subjects with RA.

emAR Study Group (in Alphabetical Order)

Dr Aragón (Talavera de la Reina), Dr Arboleya (Gijón), Dr Aznar (Tudela), Dr Baixauli Rubio (Valencia), Dr Barbeito (Alcoy), Dr Belmonte (Castelló), Dr Beltrán (Zaragoza), Dr Cabezas (Logroño), Dr Carreño (Madrid), Dr Casado (Badalona), Dr Ciria (Barcelona), Dr Corral (Salamanca), Dr de Agustín (Barcelona), Dr de Paco (Mataró), Dr del Rincón (Cáceres), Dr Doña (Huelva), Dr Espadaler (Palma de Mallorca), Dr Fernández Campillo (Orihuela), Dr Fernández Domínguez (Orense), Dr Fiter (Barcelona), Dr Fraiz (Baracaldo), Dr García Aparicio (Salamanca), Dr García Meijide (Santiago de Compostela), Dr Giménez Ubeda (Zaragoza), Dr Giralt (Barcelona), Dr González (Madrid), Dr González-Álvaro (Madrid), Dr Gracia (Logroño), Dra Grandal (Sevilla), Dr Ibero (Elda), Dr Inxausti (San Sebastián), Dr Iovani (Elda), Dr Jiménez Alfaro (Burgos), Dr Jiménez Zorzo (Zaragoza), Dr Larrosa (Girona), Dr López Longo (Madrid), Dr Macías (Cádiz), Dr Manero (Zaragoza), Dr Martín (Huelva), Dr Mayol (Castelló), Dr Monteagudo (Madrid), Dr Navarro (Elche), Dr Navío (Madrid), Dr Ordás (Oviedo), Dr Pascual (Málaga), Dr Pecondón (Zaragoza), Dr Peiró (Cuenca), Dr Rodríguez de Castro (Mahón), Dr Rodríguez Lozano (Las Palmas), Dr Romero (Córdoba), Dr Rosas (Las Palmas), Dr Rosas (Villajoyosa), Dr Saiz (Torrelavega), Dr Salazar (Badajoz), Dr Sampedro (Toledo), Dr Sandoval (Tudela), Dr Santos (Toledo), Dr Senén (Gijón), Dr Tamarit (Valencia), Dr Tovar (Elche), Dr Ureña (Málaga), Dr Vargas (Huelva), Dr Vargas Castrillón (Madrid), Dr Zubeita (Toledo).

Thank You

References

1. Carmona L, Villaverde V, Hernandez-García C, Ballina J, Gabriel R, Laffon A, the EPISER Study Group. The prevalence of rheumatoid arthritis in the general population of Spain. Rheumatology (Oxford). 2002;41:88-95.
2. Wolfe F, Hawley DJ. The long term outcomes of rheumatoid arthritis: work disability a prospective 18 years study of 823 patients. J Rheumatol. 1998;25:2108-17.
3. Smyth CJ. Therapy of rheumatoid arthritis: a pyramidal plan. Postgrad Med. 1972;51:31-9.
4. Egsmose C, Lund B, Borg G, Petterson H, Berg E, Brodin U, et al. Patients with rheumatoid arthritis benefit from early second line therapy: 5 year follow up of a prospective double blind placebo controlled study. J Rheumatol. 1995;22:2208-13.
5. American College of Rheumatology Subcommittee on Rheumatoid Artritis Guidelines. Guidelines for the management of rheumatoid arthritis:2002 update. Arthritis Rheum. 2002;46:328-46.
6. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the important of disease duration. Arthritis Rheum. 2000;43:22-9.
7. Boers M. Understanding the window opportunity concept in early rheumatoid arthritis. Arthritis Rheum. 2003;48:1771-4.
8. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. N Engl J Med. 2004;350:2591-602.
9. González-Álvaro I, Hernández-García C, Villaverde García V, Vargas E, Ortiz AM. Variabilidad en el tratamiento de la artritis reumatoide en España. Med Clin (Barc). 2002;118:771-6.
10. Irvine S, Munro R, Porter D. Early referral, diagnosis, and treatment of rheumatoid arthritis: evidence for changing medical practice. Ann Rheum Dis. 1999;58:510-3.
11. Hernández-García C, Vargas E, Abásolo L, Lajas C, Bellajdell B, Morado IC, et al. Lag time between onset of symptoms and access to Rheumatology and DMARD therapy in a cohort of patients with rheumatoid arthritis. J Rheumatol. 2000;27:2323-8.

12. Batlle-Gualda E, Jovani Casano V, Ivorra Cortés J, Pascual Gómez E. Las enfermedades del aparato locomotor en España. Magnitud y recursos humanos especializados. Rev Esp Reumatol. 1998;25:91-105.
13. Wolfe F, Hawley DJ, Cathey MA. Clinical and health status measures over time: prognosis and outcome assessment in rheumatoid arthritis. J Rheumatol. 1991;18:1290-7.
14. Mikuls TR, O'Dell J. The changing face of rheumatoid arthritis therapy: results of serial surveys. Arthritis Rheum. 2000;43:464-5.
15. Wolfe F, Hawley DJ, Cathey MA. Termination of a slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol. 1990;17:994-1002.