

Original article

Influence of gender on treatment response in a cohort of patients with early rheumatoid arthritis in the area 2 of Madrid

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ABSTRACT

Objective: To evaluate the differences between the responses to treatment using DAS28 based on erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in male and female patients. We then analyzed the individual behaviour of each component in a cohort of early arthritis patients in zone 2 of Madrid.

Patients and methods: We studied a total of 134 patients (77.6% women) who met the American College of Rheumatology (ACR) criteria for the diagnosis of rheumatoid arthritis (RA) belonging to an early arthritis register of the Hospital de La Princesa. We performed 4 visits following a standardized protocol which included necessary variables to calculate the DAS28 with ESR and CRP as well as determining the treatment received by the patients. We analyzed the differences in responses to treatment in males and females using both indexes, as well as their component and the assessment of the disease by the physician.

Results: Women had higher disease activity and disability at baseline. Although they received more intensive treatment, their average value of DAS28 remained significantly higher compared to men during the follow-up. By contrast, the global disease assessment evaluated by the patient and by the physician remained similar in both gender. When we analyze the DAS28 components separately, it was observed that this discrepancy was due mainly to the tender joints count and the ESR.

Conclusions: Women with early RA have higher DAS28ESR scores as a result of higher tender joint counts and ESR. This may represent bias when assessing the response to treatment using the DAS28ESR.

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Influencia del género en la respuesta al tratamiento en una cohorte de pacientes con artritis reumatoide precoz del área 2 de la Comunidad de Madrid

RESUMEN

Palabras clave:

Artritis reumatoide

Género

Índices de actividad

DAS28

Velocidad de sedimentación globular

Proteína C reactiva

Objetivo: Valorar las diferencias de respuesta al tratamiento mediante DAS28 calculado mediante velocidad de sedimentación globular (VSG) y proteína C reactiva teniendo en cuenta el género del paciente y analizar el comportamiento individual de cada uno de sus componentes en una cohorte de pacientes de artritis precoz en el área 2 de la Comunidad de Madrid.

Pacientes y métodos: Se estudiaron un total de 134 pacientes (77,6% mujeres) que cumplían criterios del Colegio Americano de Reumatología para el diagnóstico de artritis reumatoide del registro de artritis precoz del Hospital de La Princesa. En dicho registro se realizaron 4 visitas protocolizadas en las que se recogen de forma sistemática los datos necesarios para calcular el DAS28 con VSG y proteína C reactiva, así como el tratamiento prescrito a los pacientes. Se analizaron las diferencias por género en la respuesta al tratamiento mediante ambos índices compuestos, así como de las variables que los componen y la valoración de la enfermedad por el médico.

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Resultados: Las mujeres presentaron mayor actividad de la enfermedad y discapacidad al inicio del seguimiento. A pesar de que éstas recibieron un tratamiento más intenso, su valor promedio de DAS28 no llegó a igualarse con el de los hombres a lo largo del seguimiento. Por el contrario, la valoración de la enfermedad por parte del paciente y del médico sí llegó a igualarse. Al analizar los componentes del DAS28 por separado, se observó que esta discordancia era debida principalmente a las variables VSG y recuento de articulaciones dolorosas.

Conclusiones: La VSG y el recuento de articulaciones dolorosas causan un sesgo en la evaluación de la actividad de la artritis reumatoide con el DAS28 que puede afectar a la evaluación de la respuesta al tratamiento.

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Introduction

The management of rheumatoid arthritis (RA) has improved considerably in recent years. In addition to the development of new drugs, an important part of this improvement could be due to better management of classic disease-modifying drugs (FAME), including methotrexate, as well as a result of the use of composite indexes which assess the activity of disease and help us optimize treatment decisions.^{1,2}

Currently, the DAS28 is probably the most widely used composite index in daily clinical practice. This index includes a weighted number of tender and swollen joints on a 28 joint count, evaluation of disease activity by the patient and the erythrocyte sedimentation rate (ESR) and acute-phase reactants.³ However, during the past decade some limitations of this index have been demonstrated. Overall, women score higher and are therefore classified as in remission less frequently than men.⁴ This is due, in part, to the fact that women have a higher ESR.⁵ On the other hand, using the remission definition of the American College of Rheumatology criteria,⁶ no gender differences are seen because it gives a uses a different cutpoint for the ESR (women <30 and men <20).

For this reason we have developed a formula for calculating the DAS28 using C-reactive protein (CRP) instead of ESR (<http://www.das-score.nl>). Although there is a good correlation between both indices, different studies have shown that they are not fully equivalent.^{7,8} In this sense, our group has reported that the DAS28 with ESR tends to give higher values, mainly in women and in patients with longer disease progression.⁹

Therefore, the objective of this study is to assess the differences in response to treatment with DAS28 calculated by using ESR and CRP and taking into account the gender of the patient, as well as analyzing the individual behavior of each of its components.

Patients and methods

We used data from patient records belonging to the recent onset arthritis clinic of the Hospital Universitario de La Princesa in area 2 of the Community of Madrid. In this clinic we received patients derived from primary care with two or more swollen joints for at least four weeks and with no more than a year of progression. We excluded patients with microcrystalline arthritis, septic arthritis, spondyloarthropathies or connective tissue diseases. The study protocol was reviewed and approved by the ethics committee and all participating patients signed an informed consent.

Registration began in September 2001 and the cutoff date for data analysis was July 2008. 484 visits of 134 patients were studied (mean=3.6 visits per patient with a range of 2 to 4 visits per patient). Patients included fulfilled the American College of Rheumatology criteria for the classification of RA at the end of follow-up.¹⁰ Seventy-seven point six percent were women with an age at onset of 66 years for men and 51 years for women, and this difference was statistically significant (Table 1). Four visits were conducted according to protocol in a follow-up period of two years, consisting of a baseline visit, a visit at 6 months, one year and two years. In each visit, clinical and demographic data were collected and included in a database, such as the 28 tender and swollen joint counts, global assessment of disease by the physician (VGEM) and by the patient (VGEP) on a visual analog scale and blood tests were conducted, including ESR, CRP, rheumatoid factor, anti-CCP antibodies (ACCP) and others. Acute Phase reactants were measured by routine laboratory techniques (ESR by Westergren and CRP by nephelometry), RF by nephelometry (positive>20 IU/ml) and ACCP was determined by ELISA (Immunoscan CCPlus,® Euro-Diagnostica. Arnhem, Netherlands).

DAS28 were calculated both with CRP and ESR as previously described:

Table 1

Patient demographic and baseline characteristics (n=134)

	Male	Female	P	Total
Gender n (%)	30 (22%)	104 (78%)		134
Age at onset of disease, median (RI), years	66.4 (50.8–71)	51.2 (42.7–63.2)	<.01 ^a	54.08 (42.9–67.3)
Time since onset of disease in months (1st visit), median (RI)	5.35 (3.8–7)	6.4 (4.2–8.8)	.14	5.7 (4.2–8.5)
Positive RF, No. (%)	16 (53%)	56 (54%)	.96	72 (54%)
Positive ACCP, No. (%)	11 (39%)	54 (52%)	.22	65 (49%)
Median DAS28 (RI)	3.8 (3.3–4.9)	5 (3.9–6)	<.01 ^a	4.9 (3.8–5.9)
Median HAQ (RI)	0.675 (0–1.375)	1.375 (0.75–1.085)	<.01 ^a	1.125 (0.05–1.75)
Median ESR (RI), mm first hour	22 (11–38)	28 (18–46)	.11	24.5 (17–45)
Median CRP (RI), mg/dl	1 (0.6–1.67)	0.8 (0.3–1.8)	.30	0.8 (0.3–1.8)
Median PJC (RI)	2 (0–6)	6 (2–12)	<.01 ^a	5.5 (2–11)
Median SJC (RI)	4 (2–6)	5 (2–10)	.11	5 (2–9)
Median VGEP (RI)	38.5 (24–49.5)	47 (30–60)	.04 ^a	45 (26.5–57)
Median VGEM (RI)	31 (25–50)	47.5 (25–66)	.03 ^a	40.5 (25–65)

ACCP indicates anti-citrullinated peptide antibody; CRP, C reactive protein; DAS28, Disease Activity Score 28 (DAS28); ESR, erythrocyte sedimentation rate; PJC, painful joint count; RF, rheumatoid factor; RI, interquartile range; SJC, swollen joint counts; VGEM, global assesment on the part of the physician; VGEP, global evaluation on the part of the patient. ^aStatistically significant differences.

$$\text{DAS28ESR} = 0.56 \cdot \ddot{\text{O}}(\text{TJC28}) + 0.28 \cdot \ddot{\text{O}}(\text{SJC28}) + 0.70 \cdot \ln(\text{ESR}) + 0.014 \cdot (\text{GDAP})^3$$

$$\text{DAS28CRP} = 0.56 \cdot \ddot{\text{O}}(\text{TJC28}) + 0.28 \cdot \ddot{\text{O}}(\text{SJC28}) + 0.36 \cdot \ln(\text{C-RP} + 1) + 0.014 \cdot (\text{GDAP}) + 0.96$$

(<http://www.das-score.nl>)

In the arthritis of recent onset clinic (ARC) the following data is also systematically collected: the date of start and end of each DMARD and the maximum and minimum dose reached throughout the follow up. This allowed us to determine which DMARD was prescribed at each visit to the patient but not the dose prescribed at each visit. The database does not contemplate a treatment protocol, with decisions being made by the rheumatologist following each patient.

Statistical analysis was performed with Stata 9.2[®] for Windows (StataCorp LP College Station, TX, USA). We calculated the median and interquartile range of each variable, in some cases the data is shown as mean and deviation. To evaluate differences between groups, we employed the Mann Whitney U test for continuous independent variables. For qualitative variables we used the chi-square test. A $P < .05$ was considered statistically significant.

Results

Patient characteristics at first visit

Baseline data of patients is reflected in Table 1. Before initiating treatment, women showed greater activity of the disease and greater disability, as reflected by higher values of DAS28 and HAQ. The ESR showed a tendency to be higher in women. However, there was no gender difference in the percentage of patients with severity markers such as rheumatoid factor and ACCP, or duration of disease at first visit (Table 1).

Treatments

As a result of their greater degree of disease activity, women received more aggressive treatment. So the percentage of women who did not receive DMARDs during follow up was reduced with respect to that of men, while the percentage of women treated with combination therapy was higher, and these differences were statistically significant (Table 2). With regard to steroids, there were no significant differences by gender in the subsequent visits (data not shown).

Regarding the type of DMARD used in men and women, the most frequently used were methotrexate and antimalarials with similar usage rates in both genders, but women received significantly higher doses of methotrexate than men. Furthermore, the percentage of women to which leflunomide was prescribed was twice as many as men in the number of total visits and this difference was statistically significant ($P = .026$, Table 3). Also, TNF-blocking agents were used more often in women, although this difference was not statistically significant (Table 3).

Disease activity

Although women received more aggressive treatment since the onset of follow up, the activity level measured by DAS28 with ESR never matched that of men (Figure 1A). When we analyzed the behavior of DAS28 calculated with CRP, differences with men, once treatment was established, were not as striking, but persisted during follow-up and were not statistically significant except at the 1-year visit when it was close to being statistically significant (Figure 1B). One possibility is that despite treatment, women had responded less and maintain a higher activity of the disease and, therefore, maintain higher values on the indices. To test this possibility we analyzed the VGEM VGEP throughout follow up in both sexes. As shown in

Table 2
Number of patients without treatment, in monotherapy or as combined therapy in visits 2, 3, and 4

Treatment	Visit 2 n=108		Visit 3 n=118		Visit 4 n=124	
	Male	Female	Male	Female	Male	Female
No treatment	4 (17%)	8 (9%)	4 (15%)	1 (1%)	4 (15%)	6 (6%)
Monotherapy	17 (74%)	56 (66%)	20 (77%)	59 (64%)	19 (70%)	49 (51%)
Combined	2 (9%)	21 (25%)	2 (8%)	32 (35%)	4 (15%)	42 (43%)
P	.18		<.001 ^a		.018 ^a	

^aStatistically significant.

Table 3
Use of DMARD in men and women in the total number of visits. The second column reflects the duration of treatment in days and the third column reflects the maximum dose reached for each one of the treatments

Treatment	Number of visits with DMARD during follow up n (%)			Time of treatment, days Mean±SD			Maximum dose, mg Median (RI)		
	Female	Male	P	Female	Male	P	Female	Male	P
Methotrexate	218 (76)	58 (71)	n.s.	569±29	487±65	n.s.	17.5 (15-20)	15 (10-17.5)	<.001
Antimalarials	69 (25)	15 (19)	n.s.	211±35	87±42	.03	400 (200-400)	300 (200-400)	n.s.
Leflunomide	62 (22)	8 (11)	.026	150±24	47±30	.02	14.5 (10-20)	20 (10-20)	n.s.
Sulphasalazine	13 (5)	3 (4)	n.s.	29±11	30±30	n.s.	1,500 (1,500-1,500)	1,500 (1,500-1,500)	n.s.
Gold salts	4 (1)	4 (4)	n.s.	10±7	37±27	n.s.	200 (200-200)	125 (50-200)	n.s.
Anti-TNF	11 (4)	0 (0)	.079	27±9	0	.07	n.d.	n.d.	-

SD indicates standard deviation.

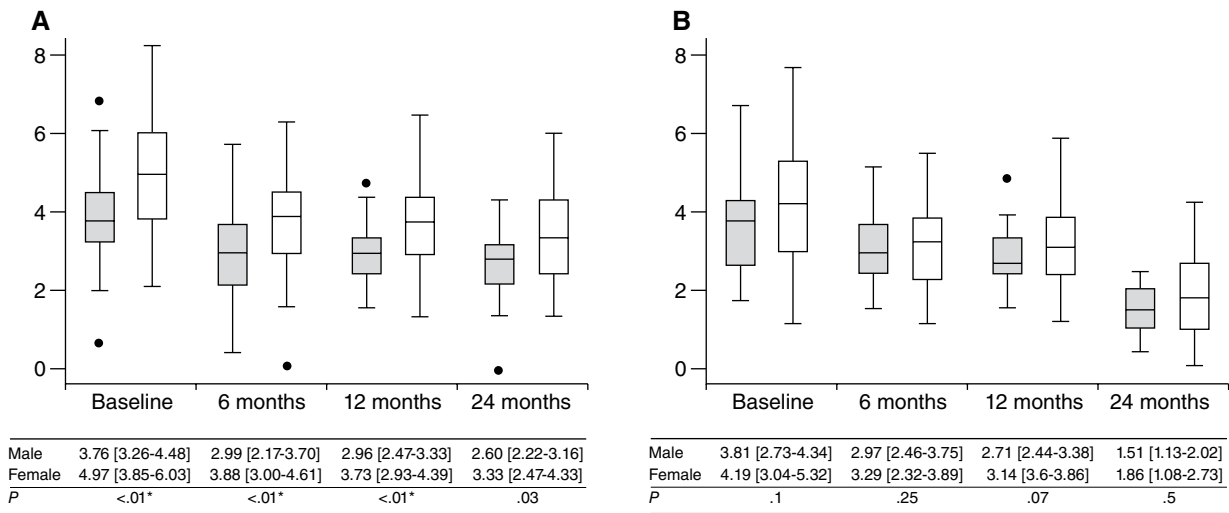


Figure 1. DAS28 values in a population of recent onset Rheumatoid Arthritis calculated with: 1A) ESR and 1B) CRP. Data is presented as median (line within the box, 75 and 25 percentiles [superior and inferior limits of the box, respectively], as well as percentiles 95 and 5 [superior and inferior lines outside the box]). Data from males is presented in gray and women in white. Data from tables are presented as median and the interquartile range. *Statistically significant differences with the Mann Whitney U test.

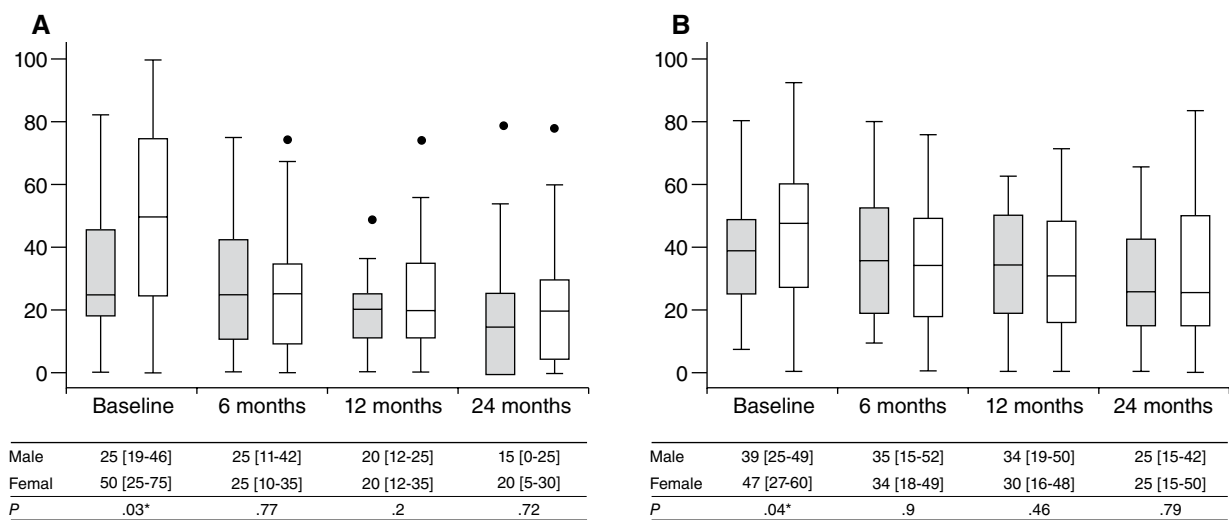


Figure 2. Global evaluation of the disease: A) performed by the physician and B) performed by the patient in a population of recent onset arthritis during the first four follow up visits. At the beginning of follow up, both the evaluation of the disease by the physician as well as by the patient is greater in women but in both cases tend to equalize during follow up. Data is presented as a median (line within the box), percentiles 75 and 25 (superior and inferior limits of the box, respectively), as well as percentiles 95 and 5 (superior and inferior line outside the box). Data belonging to males is shown in gray and females in white. Data of the tables are presented as median and interquartile range. *Statistically significant differences with the Mann Whitney U test.

Figure 2, although both VGEM and VGEP were higher in women before treatment, these evaluations were similar in both genders in subsequent visits.

Given this discrepancy, we analyzed the behavior of the various components of DAS28, noting that women have significantly higher tender joint counts over follow up (Figure 3A). By contrast, even at the start of follow up, the swollen joint count was higher in women, this variable matched that of men after the start of treatment (Figure 3B). Moreover, as is well known, women had higher ESR values throughout the follow-up, while CRP showed no statistically significant differences (Figure 4A and B, respectively).

Discussion

The main finding of our study is that there is a gender difference in treatment response as assessed by DAS28, as well in the assessment of the disease by the doctor and the patient. The main differences responsible for this are the ESR in the classical DAS28, and the tender joint count in the classic-DAS28 and the one calculated using CRP.

These differences in the DAS28 due to gender have been described by other authors. Several studies have been seen in which women tended to score higher than men in this index,¹¹ mainly because

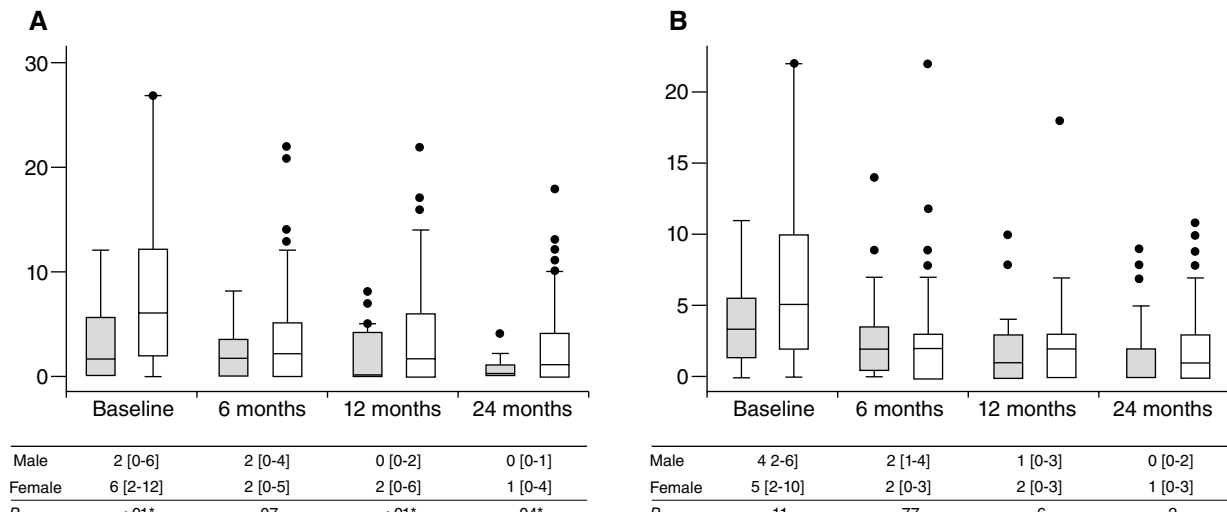


Figure 3. A) tender joint count B) swollen joint counts in subsequent visits in a recent onset arthritis cohort. The painful joint count is higher during practically all of the follow up, while the swollen joint count is higher in women during their first visit (not statistically significant) but tends to equalize once treatment was started. Data are presented as median (line within the box, percentiles 75 and 25 [superior and inferior limits of the box, respectively], as well as percentiles 95 and 5 [superior e inferior lines outside the box]). Data from males is shown in gray and females in white. Data from the tables is presented as median and interquartile range.
*Statistically significant differences with the Mann Whitney U Test.

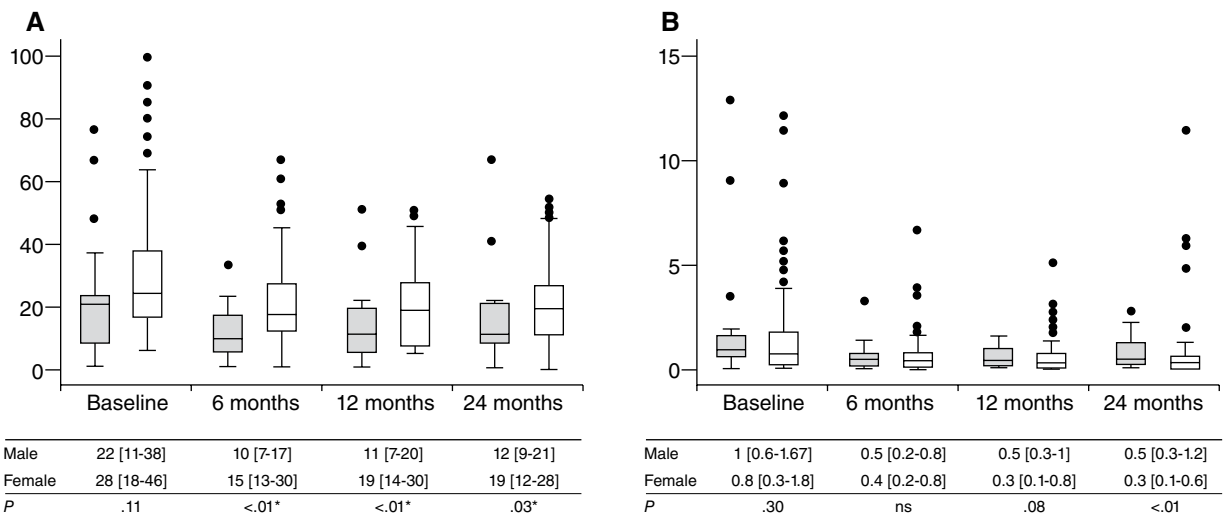


Figure 4. A) ESR and B) CRp values during follow up. ESR has higher values in women in all of the visits while CRP showed this only at the beginning of follow up. Data is presented as median (line within the box, percentile 75 and 25 [superior and inferior limits if the box, respectively], as well as percentiles 95 and 5 [superior and inferior line outside the box]). Data from males is shown in gray and women in white. Data from tables is presented as males and interquartile range.
*Statistically significant differences with the Mann Whitney U test.

women have higher levels of ESR. But even if the ESR is a clear cause for this difference, the use of CRP does not fully solve the differences by gender, and therefore other factors of the DAS28 should contribute to these differences.

Our data provides evidence that another factor contributes to these differences, such as the painful joint count and that, despite more intensive therapy, women on average had higher tender joint counts than men throughout follow-up. Some studies have described how the perception of pain is more pronounced in women than in

men with RA,¹² and this fact has also been confirmed in the general population.¹³ The physiological explanation for this gender difference could be that women have greater activation of nociceptive unmyelinated C type fibers,^{14,15} and have a decreased response to analgesics acting on opioid receptors.¹⁶ Therefore, although some authors consider that tender joint counts should have an important weight in the assessment of disease activity,¹⁷ it is possible that this variable reflects a situation external to RA and, therefore, represent bias in the assessment of disease activity.

One could argue against our results that both VGEP and VGEM are an unsound 'gold standard' and that the highest tender joint counts in women themselves are a manifestation of the increased activity of RA. However, other authors have also found gender-related differences in the DAS28 without it affecting a variable with greater weight such as radiological progression after 5 years of follow-up.¹⁸ This fact, together with our data, suggests that a higher DAS28 does not always necessarily mean a greater aggressiveness and a worse outcome of disease in women.

The impact of this gender difference in the assessment of the disease by DAS28 is very important because of its use in clinical trials to assess response to treatment.¹⁹ On the one hand, by using the DAS28 as an assessment tool, women would reach remission less frequently than men.⁴ On the other hand, since women start with higher DAS28 levels at the onset of follow up, they would have worst rates of treatment response according to the EULAR criteria.²⁰ From a clinical point of view, another problem that arises is that many clinical practice guidelines suggest a DAS28 cutoff point after which biological therapy should be considered.²¹ In this way, it would be easier to start this type of treatment in female patients.

This leads us to consider whether to continue using the classic DAS28 in the evaluation of patients with RA. As demonstrated in this study, DAS28 calculated with CRP has little bias in the assessment of disease activity, although certain gender differences persist due to the high weight of the tender joint count.

With regard to other indices available, SDAI and CDAI also prevent part of the bias that occurs as they include the CRP as an acute phase reactant.^{22,23} However, these indices have some drawbacks; first, they do not ponder the different variables that constitute them and, in addition, CRP is also included as an absolute value despite not having a normal distribution, which can represent a problem. In our population, SDAI also shows differences by gender (Figure 5), with a tendency to be higher in women, although the only statistically significant difference was seen in the visit at one year.

In summary, our study shows that the evaluation of treatment response rates based on currently available indices has a bias related to gender differences. It would be important to develop new

indices to avoid this bias and therefore be more objective when making treatment decisions and evaluating the results in clinical trials.

Conflict of interest

Dr. Isidoro González-Alvaro has received research funding from Abbott Laboratories, Sanofi-Aventis and Bristol-Myers Squibb during the last five years. All these research projects are unrelated to this work.

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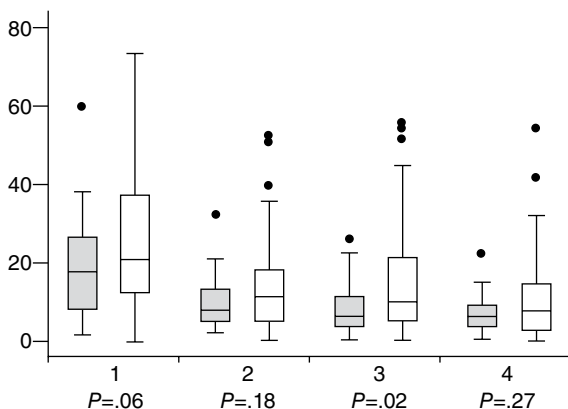


Figure 5. DAI values in male and female patients during follow-up. Data is presented as median (line within the box, percentile 75 and 25 [superior and inferior limitis of the box, respectively], as well as percentiles 95 and 5 [superior and inferior limits outside the box]). Data from males is shown in gray and females in white.

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