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Review Article

Factors Associated With Sustained Remission in Patients With Rheumatoid Arthritis☆

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ABSTRACT

Objective: To find out the factors that are associated with sustained remission measured by DAS28 and *Boolean* ACR EULAR 2011 criteria at the time of diagnosis of rheumatoid arthritis.
Materials and methods: Medical records of patients with rheumatoid arthritis in sustained remission according to DAS28 were reviewed. They were compared with patients who did not achieved values of DAS28 < 2.6 in any visit during the first 3 years after diagnosis. We also evaluated if patients achieved the *boolean* ACR/EULAR criteria. Variables analyzed: sex, age, smoking, comorbidities, rheumatoid factor, anti-CCP, ESR, CRP, erosions, HAQ, DAS28, extra-articular manifestations, time to initiation of treatment, involvement of large joints, number of tender joints, number of swollen joints, pharmacological treatment.
Results: Forty-five patients that achieved sustained remission were compared with 44 controls. The variables present at diagnosis that significantly were associated with remission by DAS28 were: lower values of DAS28, HAQ, ESR, NTJ, NSJ, negative CRP, absence of erosions, male sex and absence of involvement of large joints. Only 24.71% achieved the *boolean* criteria. The variables associated with sustained remission by these criteria were: lower values of DAS28, HAQ, ESR, number of tender joints and number of swollen joints, negative CRP and absence of erosions.
Conclusion: The factors associated with sustained remission were the lower baseline disease activity, the low degree of functional disability and lower joint involvement. We consider it important to recognize these factors to optimize treatment.

Factores asociados a remisión sostenida en pacientes con artritis reumatoide

Palabras clave:
Artritis
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RESUMEN

Objetivo: Hallar factores presentes en el momento del diagnóstico de artritis reumatoide, que se asocian a remisión sostenida medida por DAS28 y criterios *booleanos* ACR EULAR.
Materiales y métodos: Se revisaron historias clínicas de pacientes con artritis reumatoide en remisión sostenida según DAS28. Se compararon con pacientes que no alcanzaron valores de DAS 28 < 2,6 en ninguna visita durante los 3 primeros años desde el diagnóstico. También fueron evaluados si cumplían los criterios ACR/EULAR *booleanos*. Variables analizadas: sexo, edad al inicio de los síntomas, tabaquismo, comorbilidades, factor reumatoide, anti-CCP, VSG, PCR, erosiones, HAQ, DAS28, manifestaciones extraarticulares, tiempo en iniciar el tratamiento, compromiso de grandes articulaciones, número de articulaciones dolorosas, número de articulaciones tumefactas, tratamiento farmacológico.

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Resultados: Cuarenta y cinco pacientes que habían alcanzado la remisión sostenida se compararon con 44 controles. Las variables que se asociaron de manera significativa con remisión sostenida por DAS28 fueron: menores valores de DAS28, HAQ, VSG, número de articulaciones dolorosas y número de articulaciones tumefactas, PCR negativa, ausencia de erosiones, sexo masculino y ausencia de compromiso de grandes articulaciones. Solo un 24,71% de los pacientes alcanzaron los criterios *booleanos*. Las variables que se asociaron a remisión sostenida por estos criterios fueron: menores valores de DAS28, HAQ, VSG, número de articulaciones dolorosas y número de articulaciones tumefactas, PCR negativa y ausencia de erosiones.
Conclusión: Los factores asociados a remisión sostenida fueron la menor actividad inflamatoria basal, el bajo grado de discapacidad funcional y el menor compromiso articular. Consideramos relevante reconocer estos factores para optimizar el tratamiento.

Introduction

Rheumatoid arthritis (RA) is a chronic disease with serious consequences such as work disability and high mortality. Predictive factors (PF) are sociodemographic, clinical, laboratory and/or radiological data that provide information about the possible evolution of the patient. This is useful to guide therapeutic decisions.[1] Currently, one of the main goals of treatment is to get the patient to achieve remission. This is defined as the absence of disease activity and is measured with different sets of criteria, the most commonly used being DAS28. In recent years this measurement tool has been criticized because patients below certain values still present swollen joints. Due to this, lower threshold values and new measurement instruments have been proposed.[2] EULAR and ACR along with OMERACT have proposed using more stringent criteria such as the Simplified Disease Activity Index, the Clinical Disease Activity Index and the ACR EULAR *Boolean* criteria.[3] Despite advances in the treatment of this disease there are subgroups of patients who do not achieve values currently assigned to remission.[4]

The objective of this study was to evaluate which factors, at the time of diagnosis of RA, are associated with sustained remission as measured by DAS28 and the new ACR EULAR *Boolean* criteria.

Materials and Methods

This was a retrospective, observational, case–control study, developed during the period May 2012 to May 2013. Patients older than 18 years were included, with a diagnosis of RA according to ACR/EULAR 2010 criteria. This study was performed on the patient database of the Rheumatology Service, Hospital Bernardino Rivadavia of the City of Buenos Aires. Medical records of patients who achieved sustained remission as measured by DAS28 were reviewed. Sustained remission was considered as the presence of DAS28 scores <2.6 for six months in three consecutive quarterly measurements, at baseline, at three months and again at six months, in the first three years of diagnosis. Then, patient records during the same period of those that achieved DAS28 values <2.6 were selected. Patients who met the new ACR/EULAR *Boolean* criteria were also evaluated. Patients included were those who came spontaneously to the Bernardino Rivadavia Hospital clinic, where they were evaluated by a general practitioner. The treatment strategy used was, once symmetric polyarthritis was detected, to start prednisone 5 mg per day and non steroidal antiinflammatory drugs at maximum doses in all patients. During the same visit, routine laboratory tests, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anti-CCP antibodies were measured. One month after this visit and with these laboratory findings, the patient was referred to the Department of Rheumatology of the hospital and, if the patient met ACR EULAR 2010 criteria for RA, the baseline DAS28 was performed, as well as the baseline HAQ, tender joint count (TJC) and swollen joint count (SJC), considering gender, age, smoking, comorbidities, erosions, extraarticular manifestations, time to onset of treatment, involvement of large joints, and the treatment strategy decided by the physician once the diagnosis of RA was made, as baseline variables for evaluating the association with sustained remission. During this first visit, all patients start methotrexate 15 mg weekly associated with folic acid 5 mg week.

We excluded patients with other connective tissue diseases such as systemic lupus erythematosus, scleroderma, inflammatory myopathies, systemic vasculitis and spondylitis and patients treated with corticosteroids over 5 mg of prednisone or equivalent doses.

The study was approved by the Ethics Committee of the Hospital Bernardino Rivadavia and was conducted in accordance with the Declaration of Helsinki.

The variables listed below were evaluated and compared between the group of patients who had achieved sustained remission and the control group. The same analysis comparing patients who had achieved sustained remission was performed for the *Boolean* criteria with those who had failed to achieve them.

The following data were analyzed at diagnosis (first visit to the Rheumatology Service): demographics (gender and age); Clinical data: TJC, SJC, involvement of large joints (arthritis confirmed by the physician of at least one large joint such as the knee, hip, shoulder or ankle), DAS28; immunological profile: RF and anticyclic citrullinated peptide antibodies (anti-CCP); ESR and CRP, extra-articular manifestations (rheumatoid nodules, rheumatoid vasculitis, pleural effusion, pulmonary nodules or isolated Caplan's syndrome, interstitial lung disease, episcleritis, scleritis and sicca syndrome); duration of arthritis at baseline: number of months from the onset of symptoms to the start of the administration of the first disease modifying drug (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide); radiographic erosions (presence of at least one erosion evaluated by ultrasound, X-ray or MRI of hands and feet); degree of disability assessed by HAQ, presence of comorbidities (present or past smoking, hypothyroidism, hypertension, asthma); treatment established at diagnosis: use of corticosteroids, disease modifying drugs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine) and use of biological drugs (etanercept, adalimumab, abatacept, tocilizumab, golimumab, certolizumab pegol, rituximab) in the three months prior to achieving remission.

Statistical Analysis

T tests or Mann Whitney tests according to distribution and sample size were used for continuous variables. The Chi square or Fisher exact test was used as expected according to frequency distribution tables for categorical variables. Because this was a case–control study, the OR and the 95% confidence interval was calculated. Significance was considered as $P<.05$. To assess the independent

association of variables, a multivariate logistic regression analysis was performed, taking the sustained remission as the dependent variable. All variables were included in stages in which a *P*<.2 was obtained in the univariate analysis.

Results

89 medical records of patients with RA, of which 45 had achieved sustained remission and 44 patients who in the first three years of monitoring had not reached, at any time, scores of DAS28<2.6 were analyzed.80.90% of the patients evaluated were female and 19.10% male. The median age at onset of arthritis of all patients included in the study was 41 (IQR 30–52) and the median age at achieving remission of the cases was 47 (IQR: 33–54).

When comparing the groups, the variables significantly associated with sustained remission as measured by DAS28 were lower baseline DAS28, HAQ, ESR, negative CRP, absence of erosions, male gender, lower TJC, SJC and absence of the involvement of large joints (Table 1). Multivariate analysis there was a significant and independent association found with the following variables: DAS28<3.2 (OR 12.2, CI 3.65 and 41.17, *P*>.001); negative CRP (OR 4.35, CI 1.22–15.42, *P* 0.023); absence of erosions (OR 4.34, CI 1.32–14.21, *P* 0.015); and male gender (OR 0.16, CI 0.03–0 .79, *P* 0.025).

Of the 89 patients evaluated, only 24.71% achieved *the Boolean* remission criteria (n=22). The variables at the time of diagnosis, which was significantly associated with sustained remission values, were a lower DAS28, HAQ, ESR, negative CRP, absence of erosions: lower TJC and SJC (Table 2).

Discussion

Different studies have searched for patient characteristics that may determine a better or worse prognosis in the progression of disease as well as factors that work as predictors of remission.[5] The clinical significance of these variables is that they identify patients with poor prognostic factors who would be candidates for more aggressive treatment in order to achieve remission of the disease and prevent irreversible damage and disability. There are also differences in the literature on the minimal time the patient must remain in such a state to be considered as being in remission. In this study we chose to use the definition of sustained remission that was agreed upon in the most recent EULAR guidelines for the treatment of RA. This is defined as a minimum of six months with DAS scores <2.6 in three consecutive measurements.[6] The decision to select patients with sustained remission over time has its advantages and disadvantages. On the one hand, as a limitation, the number of patients achieving remission in this time period is lower, which leads to fewer patients in the sample. However, the fact of evaluating patients who achieved sustained remission for more than one evaluation would give greater prominence to the results obtained, especially when considering the decision of a reduction in the treatment strategy.

With respect to remission PF, we can divide them into two groups. On the one hand there is those modifiable features, such as levels of acute phase reactants, DAS28 scores, HAQ and treatment.[1]

On the other, the non-modifiable factors, such as gender and age of the patient, RF positivity, anti-CCP and shared epitope stand out.

With regard to sociodemographic factors, in our study, male gender was associated independently of sustained remission as assessed by DAS28 but not by the *Boolean* criteria. In some studies, this association was not as clear,[7] although it was in the TEMPO study in patients treated with Etanercept[8] as well as in the ReAct study in patients treated with adalimumab.[9]

Other factors that were not significant in our work were in other studies, such as advanced patient age and smoking.[10,11]

As shown by our results, the functional status measured by HAQ at the time of diagnosis was inversely proportional to the possibility of achieving persistent[9] clinical remission. A recent study also found that higher levels of disability were directly related to the impossibility of achieving remission by *Boolean* criteria in patients treated with tocilizumab.[12]

The absence of anti-CCP and RF was not associated with sustained DAS28 remission nor with *Boolean criteria* in our evaluation. Instead, it was associated with markers of inflammation. CRP negativity in both univariate and multivariate analysis was significantly associated to sustained remission as measured by DAS28 and in the univariate analysis for the *Boolean* criteria. Previous studies have shown that these levels also had significance as patients with CRP levels greater than or equal to 20 mg/l are less likely to achieve remission 9.

Other markers which are not used in clinical practice in our environment but were independent predictors of remission in some studies are IL-2[13] and low levels of baseline RANKL.[14]

Regarding radiological compromise, according to Gossec et al., a Sharp score <4 is an independent predictor of remission when adjusted for other variables.[15] In our study we observed that the

Table 1
Results of Patients Evaluated by DAS28.

Variable	Patients who achieved sustained remission (n=45)	Patients who did not achieve remission (n=44)	OR	*P*	CI
Baseline DAS28 *m* (IQR)	2.5 (1.97–3.55)	4.72 (3.8–5.7)	0.44	<.01	0.31–0.63
Baseline HAQ *m* (IQR)	0,37 (0,125–1)	1 (0.5–1.61)	0.21	<.01	0.02–1.19
FR positive n (%)	38 (8444)	41 (93,18)	0.40	.17	0.2–1.92
Anti-CCP positive n (%)	30 (75)	36 (90)	0.33	.07	0.07–1.32
Negative CRP n (%)	23 (51,11)	7 (15,91)	5.53	<.01	1.8–17.53
ESR *m* (IQR)	15 (10–23)	26.5 (20.5–45)	0.97	<.01	0.95–0.99
Absence of erosions n (%)	27 (60)	15 (34,09)	2.9	<.01	1.13–7.54
Time to onset of treatment in months *m* (IQR)	12,5 (6–27)	12 (6–24)	0.99	.46	0.989–1.01
DMARD monotherapy n (%)	40 (88,89)	38 (88,37)	1.05	.94	0.22–4.97
Biological n (%)	7 (15,56)	3 (6,82)	2.52	.19	0.52–16
Age onset of symptoms *m* (IQR)	44 (31–52)	38.5 (26.5–51.5)	1.02	.32	0.99–1.05
Female n (%)	32 (71,11)	40 (90,91)	0.25	.016	0.05–0,91
Smoking n (%)	15 (33,33)	15 (34,88)	0.93	.88	0.35–2.47
Comorbidities n (%)	13 (28,89)	9 (20,45)	1.58	.36	0.54–4.78
Absence of extra-articular manifestations n (%)	35 (77,78)	30 (68,18)	1.63	.31	0.57–4.75
TJC *m* (range)	0 (0–1)	4.5 (2–11)	0.03	<.01	0.005–1.22
SJC *m* (range)	0 (0–1)	4 (2–8)	0.02	<.01	0.002–0.1
Absence of compromise of large joints n (%)	17 (37,78)	7 (16,67)	3.04	.028	1.008–9.82

Anti-CCP: anti-cyclic citrulinated peptide antibody; DMARD: disease modifying anti-rheumatic nonbiological drugs; RF: rheumatoid factor; CI: confidence interval; *m*: median; n: number of observations; TJC: tender joint count; SJC: swollen joint count; OR: odds ratio; CRP: C-reactive protein; IQR, interquartile range; ESR, erythrocyte sedimentation rate.

Table 2
Results of Patients Evaluated by the ACR EULAR *Boolean* Criteria.

Variable	Patients who achieved sustained remission (n=22)	Patients who did not achieve remission (n=77)	*P*
Baseline DAS28 *m* (IQR)	2.23 (1,91–3,55)	4.08 (2.72–5.25)	<.01
Baseline HAQ *m* (IQR)	0.31 (0,125–1)	0.75 (0.35–1.37)	.047
RF positive n (%)	21 (95,45)	56 (87,50)	.27
Anti-CCP positive n (%)	14 (73,68)	50 (86,21)	.21
CRP negative n (%)	12 (54,55)	18 (28,13)	.03
ESR *m* (IQR)	12,5 (10–22)	23.5 (15–43.5)	<.01
Absence of erosions n (%)	12 (54,55)	29 (43,31)	.045
Time to onset of treatment in months *m* (IQR)	12.5 (10–24)	12 (6–24)	6.64
DMARD monotherapy n (%)	20 (90,91)	56 (87,50)	.5
Biological n (%)	4 (18,18)	6 (9,38)	.23
Age onset of symptoms *m* (IQR)	44 (33–53)	39 (27,5–51)	.18
Female n (%)	16 (72,73)	54 (84,38)	.23
Smoking n (%)	7 (31,82)	23 (36,51)	.69
Comorbidities n (%)	8 (36,36)	13 (20,31)	.13
Absence of extra-articular manifestations n (%)	16 (72,73)	47 (73,44)	.95
TJC *m* (range)	0 (range 0–1)	2 (0–7)	<.01
SJC *m* (range)	0 (range 0–1)	2 (0–6,5)	<.01
Absence of large joint involvement n (%)	8 (36,36)	15 (23,44)	.24

Anti-CCP: anti-cyclic citrullinated peptide antibodies; DMARD: disease modifying antirheumatic non biological drugs; RF: rheumatoid factor; *m*: median; n: number of observations; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; IQR, interquartile range; ESR, erythrocyte sedimentation rate.

absence of erosions at diagnosis was associated significantly and independently with sustained remission as measured by DAS28 and this was also associated in the univariate analysis for the *Boolean* ACR EULAR criteria.

Treatment also plays an important role in the possibility of achieving remission; patients receiving treatment with disease modifying drugs, anti-TNF or combination in an early manner are more likely to achieve remission. The same applies for the delay in starting treatment. The Finnish Rheumatoid Arthritis Combination Therapy trial reported that the combination of disease modifying drugs led to higher remission rates in patients with RA of less than two years of evolution, compared with monotherapy.[16] In the follow up of this study it was found that a delay of four months in the onset of treatment produced a decrease in the frequency of remission when using monotherapy, but this was not observed upon postponing combination therapies.[17] Kristensen et al. sought predictors of remission in patients treated with anti-TNF, and found that the concomitant use of methotrexate was significantly associated with remission as was as a low baseline value of HAQ.[18] In our study, no association was seen with previously received treatment, probably due to the small number of patients and the local economic situation which delayed the implementation of early biological therapies.

We believe it relevant to know these predictors of sustained remission since this strategy has proven cost effective[19] and shown good long-term results, as demonstrated in a recent report of the ESPOIR cohort, which demonstrated that patients with early RA persisting with moderate activity during the first year have worse outcomes in terms of functionality, ability to maintain remission and disability compared to those who achieved sustained remission during the first year.[20] Furthermore, in our study, we decided to determine those factors associated with sustained remission not only using DAS28, but also with the new *Boolean* criteria proposed by ACR EULAR in 2011. Recent studies have shown that patients who achieve these remission criteria have less power Doppler signals in ultrasound[21] and are better in terms of progression, radiology and functionality.[22] However, there are certain limitations, such as the difficulty of achieving them in many patients, with the main limiting factor being global patient assessment.[23]

We believe that this study has limitations, partly related to the sample size, which implies a wide margin of uncertainty for many of the results, especially those obtained in the multivariate analysis. We also believe that documenting the patients first visit to the general practitioner in our database, who performs the first evaluation, would give more weight to our results. But we believe that this is remedied by the low-dose corticosteroids and/or NSAID treatment is established at first contact and the short referral time to the autoimmune disease clinic in our center.

We consider it relevant in clinical practice to know if the patient has factors associated with remission, thereby selecting the most appropriate therapy. In this way we are able to reach our main goal, sustained remission, mainly because it is the one that has shown the best results in terms of functionality, radiological progression and quality of life.

Ethical Responsibilities

Protection of people and animals. The authors declare this research did not perform experiments on humans or animals.

Data confidentiality. The authors declare that they have followed the protocols of their workplace regarding the publication of data from patients, and all patients included in the study have received sufficient information and gave written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the informed consent of patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Conflict of Interest

The authors have no conflict of interest to state.

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