

Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting

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Abstract

Objective

To analyze the rate and baseline prognostic factors of clinical remission in a series of patients with early rheumatoid arthritis (RA) after 2 years of therapy based on a structured algorithm using disease-modifying anti-rheumatic drugs (DMARDs) in a clinical setting. To determine whether a good therapeutic response at 6 months of therapy is associated with remission at 2 years.

Methods

One hundred and five patients (81% female) with early RA (disease duration < 2 years) treated with the same therapeutic protocol using gold salts and methotrexate in a step-up strategy, together with methylprednisolone (4 mg/day), were followed up for 2 years. The outcome variable was clinical remission after 2 years of DMARD therapy using the 28-joint disease activity score (DAS28 < 2.6). Clinical, biological, immunogenetic and radiographic data (Larsen score) were analyzed at study entry and after 6, 12, 18 and 24 months of follow-up. Therapeutic response was analyzed using the ACR and EULAR criteria.

Results

Remission was observed in 34 patients (32.4%) after 2 years of follow-up. A baseline DAS28 score < 5.1 ($p = 0.004$), hemoglobin ($p = 0.04$) and male gender ($p = 0.02$) were associated with remission in the univariate analysis. In the multivariate logistic regression analysis, only a DAS28 < 5.1 was associated with remission at 2 years (OR 4.1, 95% CI: 1.56;10.77, $p = 0.004$). The percentage of ACR50 responses after 6 months was significantly higher in patients with remission at 2 years than in those without (66.7% vs 43.3%; $p = 0.04$). Similar results were obtained when analyzing the good EULAR response (50% vs 20.9%; $p = 0.003$). Furthermore, when the therapeutic response at 6 months was included in the logistic regression model, only an ACR50 response (OR 3.9, 95% CI 1.14;13.38, $p = 0.03$) and a good EULAR response (OR 6.23, 95% CI 1.61; 24.04, $p = 0.008$), but not an ACR20 response or a whole EULAR response were significantly associated with remission.

Conclusion

In a series of early RA patients treated using a structured algorithm with DMARDs and very low doses of glucocorticoids, clinical remission was observed in one-third of patients after 2 years. Low or moderate disease activity (DAS28 < 5.1) at baseline and a good therapeutic response during the first months of therapy predicts clinical remission at 2 years.

Result

Rheumatoid arthritis, early, prognosis, remission, DMARD.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the synovial joints that produces progressive joint destruction, significant disability and a long-term reduction in the quality of life (1). Since there is no cure for this disease at present, the goal of treatment is suppression of the inflammatory process to achieve clinical remission. However, persistent remission is uncommon in RA after therapy with traditional disease-modifying anti-rheumatic drugs (DMARDs) (2), although in recent years high rates of remission have been achieved in early RA patients using intensive combination therapy with DMARDs (3, 4).

Remission in RA is not clearly defined and remains controversial. The preliminary criteria of Pinals *et al.* (5), which were adopted by the ACR, have been widely used since 1981, but in recent years the definition of remission by the disease activity score has been gaining acceptance, both the score based on the original DAS (6) and that based on the simplified 28-joint score (DAS28) (7), although the cut-off points that define true disease remission have been subject to criticism (8-10). Other useful composite indices have been developed in recent years to define disease activity and remission (11).

Few studies have analysed the prognostic factors of clinical remission in patients with early RA (12-15). To our knowledge, no such studies have been published on patients with early RA after the application of a structured therapeutic algorithm with DMARDs in a clinical setting. The present study analysed the prognostic value of clinical, biological, immunogenetic and radiographic parameters for 2 years of remission in a series of patients with early RA after the introduction of a structured treatment strategy with DMARDs and low doses of glucocorticoids. We also determined whether an early therapeutic response during the first 6 months of therapy was associated with remission after 2 years of follow-up.

Patients and methods

Patients

Patients fulfilling the American College

of Rheumatology (ACR: formerly the American Rheumatism Association) criteria for the classification of RA, with symptoms for < 24 months were enrolled in the study. All were outpatients attending the rheumatology units of the Hospital Clinic of Barcelona or the Hospital Parc Tauli of Sabadell between 1998 and 2003 and were followed for 2 years. Patients who had been treated previously with DMARDs or prednisone or equivalent at a dose > 10 mg/day were excluded. Hospital Clinic ethics committee approval was obtained.

Study design

This was an open-label study, where all patients were treated according to a therapeutic protocol with the early introduction of DMARDs, using a step-up approach. In all cases, intramuscular sodium aurothiomalate at a dose of 50 mg/week was prescribed as the first-choice DMARD together with methylprednisolone 4 mg/day. Non-steroidal anti-inflammatory drugs and intra-articular steroid therapy were used according to clinical judgment. Methotrexate, at an increasing dose of 7.5 to 20 mg, was instituted if adverse effects without clinical improvement or no ACR20 response were observed at month 6. However, if patients showed high disease activity during the first 6 months despite this treatment strategy, methotrexate was added. If an ACR50 response at 6 months was achieved, gold salts were scheduled every 2-3 weeks, but if a patient had an ACR20 response but no ACR50 response, combination therapy with sodium aurothiomalate and methotrexate was initiated. Oral steroid therapy was tapered according to clinical judgment. After the first year of therapy, patients were treated according to the criteria of the attending physician, but using an aggressive approach with the initiation of other DMARDs in cases of poor response to previous DMARDs. Biological therapy was instituted in a few patients who showed a poor response to DMARD therapy.

At study entry, the patients' demographic characteristics, disease duration, serum rheumatoid factor meas-

Table I. Baseline characteristics of the 105 patients with early RA.

Women (%)	81
Age (yr), mean $\pm$ S.D.	55 $\pm$ 14.9
Disease duration (months), mean $\pm$ S.D.	10 $\pm$ 6.7
VAS pain (mm), mean $\pm$ S.D.	51.3 $\pm$ 21.6
Patients global assessment (mm), mean $\pm$ S.D.	57.8 $\pm$ 15.1
Physician global assessment (mm), mean $\pm$ S.D.	55.8 $\pm$ 13.9
28 tender joint count, mean $\pm$ S.D.	10.1 $\pm$ 5.9
28 swollen joint count, mean $\pm$ S.D.	8.3 $\pm$ 4.1
DAS 28, mean $\pm$ S.D.	5.7 $\pm$ 0.9
DAS28 > 5.1 (%)	75.7
mHAQ, mean $\pm$ S.D.	1 $\pm$ 0.6
ESR (mm/h), mean $\pm$ S.D.	39.6 $\pm$ 24.5
CRP (mg/dL), mean $\pm$ S.D.	2.8 $\pm$ 2.9
Hemoglobin (mg/dL), mean $\pm$ S.D.	12.7 $\pm$ 1.4
Rheumatoid factor-positive (%)	74.3
Anti-CCP positive (%)	70.4
Shared epitope (%)	70.6
Shared epitope homozygosity (%)	20.6
HLA-DRB1-04 (%)	44.1
Larsen score, mean $\pm$ S.D.	1.2 $\pm$ 2.7

S.D.: standard deviation.

ured by nephelometry (NV < 25 UI/L), anti-cyclic citrullinated peptide antibodies (CCP) measured by a second-generation ELISA test (Immunoscan, Eurodiagnostica) (NV < 50 UI/L) and DRB1 genotype determined by direct DNA sequencing, were analysed. At baseline and at 6, 12, 18 and 24

months the following parameters were recorded: pain using a visual analogue scale (VAS), the 28 tender and swollen joints count, patient and physician assessment of disease status on a Likert scale, the 28-joint disease activity score (DAS28), functional status using the modified Health Assessment Ques-

tionnaire (mHAQ), and the erythrocyte sedimentation rate and C reactive protein measured by nephelometry. The therapeutic response was analysed according to both ACR (16) and EULAR (17) criteria.

Remission criteria

Clinical remission was defined according to the DAS28 score. A cut-off point of 2.6 was considered as indicative of remission (DAS28 < 2.6).

Radiographic evaluation

Radiographs of the hands and feet were obtained at months 0, 12 and 24. The modified Larsen method was used to evaluate radiographic damage, as previously described (18). The minimal clinically important difference was used as the measure of radiographic progression (19), defined as an increase of 4 or more units in the Larsen score between baseline and 24 months.

Statistical analysis

The outcome measure was remission after 2 years of follow-up. The univariate analysis of categorical variables used the chi-square test or Fisher's exact test, and continuous variables were

Table II. Clinical, biological and radiological parameters and therapeutic response after 6, 12, 18 and 24 months of follow-up.

	Baseline	6 months	12 months	18 months	24 months
28 tender joint count, mean $\pm$ S.D.	10.1 $\pm$ 5.9	4.3 $\pm$ 5.6	3.5 $\pm$ 4.7	2.9 $\pm$ 4.1	2.7 $\pm$ 4.1
28 swollen joint count, mean $\pm$ S.D.	8.3 $\pm$ 4.1	3.4 $\pm$ 4.4	2.6 $\pm$ 3.3	2.3 $\pm$ 3.3	2.1 $\pm$ 3.5
Patient's global assessment (mm), mean $\pm$ S.D.	57.8 $\pm$ 15.1	41.3 $\pm$ 19.2	40.5 $\pm$ 17.4	39.1 $\pm$ 18	37.2 $\pm$ 18.3
Physician's global assessment (mm), mean $\pm$ S.D.	55.8 $\pm$ 13.9	38.3 $\pm$ 19.8	36.9 $\pm$ 18.9	33.6 $\pm$ 19.5	32.8 $\pm$ 18.1
VAS pain, mean $\pm$ S.D.	51.3 $\pm$ 21.6	31 $\pm$ 24.5	31.9 $\pm$ 23.9	29.8 $\pm$ 24.1	28.8 $\pm$ 21.1
ESR (mm/h), mean $\pm$ S.D.	39.6 $\pm$ 24.5	27.1 $\pm$ 21.2	25.5 $\pm$ 18.9	23 $\pm$ 14.1	22.9 $\pm$ 15.8
CRP (mg/dL), mean $\pm$ S.D.	2.8 $\pm$ 2.9	1.6 $\pm$ 3.2	1.3 $\pm$ 1.6	1.2 $\pm$ 1.4	1.2 $\pm$ 1.5
Hemoglobin (mg/dL)	12.7 $\pm$ 1.4	12.8 $\pm$ 1.4	13 $\pm$ 1.4	13 $\pm$ 1.4	13 $\pm$ 1.3
mHAQ, mean $\pm$ S.D.	1 $\pm$ 0.6	0.5 $\pm$ 0.6	0.5 $\pm$ 0.5	0.5 $\pm$ 0.5	0.5 $\pm$ 0.5
DAS28, mean $\pm$ S.D.	5.7 $\pm$ 1	4 $\pm$ 1.4	3.8 $\pm$ 1.3	3.6 $\pm$ 1.3	3.5 $\pm$ 1.3
DAS28 < 2.6 (%)	0	16.8	23.5	28.4	32.4
DAS28 > 2.6 $\leq$ 3.2 (%)	0	16.8	12.7	13.6	17.1
DAS28 > 3.2 $\leq$ 5.1 (%)	24	48.4	44.1	45.4	34.3
DAS28 > 5.1 (%)	75.7	17.9	19.6	13.6	15.2
ACR20 response (%)		70	73.3	77	73.3
ACR50 response (%)		51	44.8	56.2	55.2
Whole EULAR response (%)		74.2	78	78.2	81.9
Good EULAR response (%)		30.7	35.2	41.4	48.6
Erosive disease (%)	18.3		28.9		44.6
EJC, mean $\pm$ S.D.	0.4 $\pm$ 0.9		0.8 $\pm$ 1.5		1 $\pm$ 1.4
Larsen score, mean $\pm$ S.D.	1.2 $\pm$ 2.7		3.5 $\pm$ 6.7		6.1 $\pm$ 9.3
Patients receiving oral steroids (%)	94.2	77.6	65.7	67	62.5
Dose of oral steroids (methylprednisolone), mean $\pm$ S.D.	4.5 $\pm$ 2.4	3.4 $\pm$ 2.5	2.6 $\pm$ 2.3	2.4 $\pm$ 2.2	2.3 $\pm$ 2.5
Patients receiving methotrexate (%)	0	9.5	36.1	40.9	46.6

Table III. Drug therapy at months 12 and 24 in patients with and without remission at 2 years.

	Remission (n = 34)		No remission (n = 71)	
	12 months	24 months	12 months	24 months
Gold salts	23 (67.6%)*	18 (52.9%) τ	30 (42.2%)*	12 (16.9%) τ
Methotrexate	2 (5.9%)**	4 (11.8%) $\tau\tau$	23 (32.4%)**	21 (29.6%) $\tau\tau$
Gold + methotrexate	2 (5.9%)	3 (8.8%)	9 (12.7%)	8 (11.2%)
Other treatments	1 (2.9%)	2 (5.9%)	1 (1.4%)	12 (16.9%)
Anti TNF α treatment	0	0	1 (1.4%)	10 (14.1%)
No DMARD	6 (17.6%)	7 (20.6%)	7 (9.6%)	8 (11.3%)
Glucocorticoids (mean $\pm$ S.D.)	19 (55.9%) (2.2 $\pm$ 2.7)	16 (47%) (1.5 $\pm$ 1.9)	50 (70.4%) (3.1 $\pm$ 2.3)	48 (67.6%) (3.5 $\pm$ 3.3)

*p = 0.02; **p = 0.003; τ p < 0.001; $\tau\tau$ p = 0.05.

assessed using the Student t-test or the Mann-Whitney test as appropriate. For paired samples, the t-test or Wilcoxon test were used. All marginally significant variables ($p < 0.25$) in the univariate analysis were entered into the multivariate analysis (stepwise logistic regression model) as independent variables. For all tests, p values ≤ 0.05 were considered significant. All calculations were carried out using the STATA statistical program, version 8.2.

Results

One hundred and fifteen patients were initially enrolled. Ten patients did not complete the 2-year follow-up for various reasons: transfer out (1 patient), irregular or lost to follow-up (6 patients), death (2 patients), and doubts about the

disease duration (1 patient). The final cohort was 105 patients. Their baseline characteristics are shown in Table I. Most patients had seropositive disease (RF+ 74.3% and anti-CCP+ 70.4%) and 70.6% had the shared epitope. In 73 patients (69.5%), the disease duration was < 1 year. Most patients (75.7%) presented high disease activity (DAS28 > 5.1) at study entry which decreased significantly after one and two years (19.6% and 15.2%, respectively; $p < 0.001$). After one and two years, aurothiomalate as DMARD monotherapy was taken by 50.5% and 28.6% of patients, respectively. The percentage of patients taking methotrexate was 36.1% (23.8% as monotherapy, 10.5% in combination with gold, and 1.9% in combination with other agents) at one

year and 46.6% (21.9% in monotherapy, 10.5% in combination with gold, and 12.4% in combination with other DMARDs) at 2 years. Gold salts were withdrawn due to inefficacy in 28 patients and due to adverse events in 22 patients (mucocutaneous side-effects: 12 patients, proteinuria: 7 patients, and other: 3 patients). No DMARD was being taken by 13 and 15 patients at 1 and 2 years, respectively. After 2 years, 62.5% of patients were still taking oral steroids, with a mean daily dose of methylprednisolone of 2.3 ± 2.5 mg/day. During the follow-up, 18 patients took DMARDs other than gold or methotrexate (leflunomide 11 patients, cyclosporine 5 patients, and hydroxychloroquine 2 patients) while 10 patients were treated with biological therapy (7 patients with infliximab, 2 with etanercept, and one patient with adalimumab); all but one of the patients taking TNF-alpha blockers were included during the second year of follow-up. The evolution of clinical, biological and radiographic parameters in the different time point assessments, together with the rates of ACR and EULAR therapeutic responses, are shown in Table II.

Remission rates

Remission (DAS28 score < 2.6) was observed in 34 patients (32.4%) after 2 years of follow-up. The rates of remission after 6, 12 and 18 months were 16.8%, 23.5%, and 28.1%, respectively. In 32.5% and 51.5% of the patients in remission after 24 months, remission was achieved at months 6 and 12, respectively. Remission was documented in all four evaluation points in only 5 patients. Remission was observed in three of the four time points in 15 patients.

Remission and therapeutic response

The therapeutic regimen used during the follow-up differed significantly in the patients who were or were not in remission after 2 years. As shown in Table III, more patients who were in remission at 2 years remained on gold salts at months 12 and 24 compared with those not in remission. As shown in Table IV, the percentages of ACR

Table IV. Disease activity and response to therapy at 6 and 12 months in patients with and without remission at 2 years.

	Remission (n = 34)	No remission (n = 71)	p value
6 months			
DAS28, mean $\pm$ S.D.	3.2 $\pm$ 1.2	4.4 $\pm$ 1.4	< 0.001
DAS28 < 2.6 (%)	32.6	9.4	0.01
ACR50 (%)	66.7	43.3	0.04
ACR20 (%)	84.8	62.7	0.03
Whole EULAR response (%)	88.2	67.2	0.01
Good EULAR response (%)	50	20.9	0.003
12 months			
DAS28, mean $\pm$ S.D.	3 $\pm$ 1.2	4.2 $\pm$ 1.2	< 0.0001
DAS28 < 2.6 (%)	51.5	10.1	< 0.0001
ACR50 (%)	61.8	36.6	0.03
ACR20 (%)	82.4	69	0.23
Whole EULAR response (%)	91.2	71.8	0.04
Good EULAR response (%)	64.7	21.1	< 0.0001

Table V. Baseline characteristics in the cohort of patients with early RA with and without clinical remission. Results of the univariate analysis.

Baseline variable	Clinical remission (n = 34)	No remission (n = 71)	OR	95% CI	p
Gender (% women)	67.6	87.3	0.30	0.11; 0.82	0.020
Age (yrs.)	52.8 ± 16	56.1 ± 14.3	0.98	0.95; 1.01	0.287
Disease duration (months)	9.1 ± 6.6	10.4 ± 6.8	0.97	0.91; 1.03	0.359
Tender joint count	10.1 ± 6.8	10.1 ± 5.5	1	0.93; 1.07	0.960
Swollen joint count	8.9 ± 4.7	8 ± 3.8	1.04	0.95; 1.15	0.337
DAS28 > 5.1	57.6	82.5	0.25	0.10; 0.65	0.004
VAS pain (0-100 mm)	47.7 ± 22.4	53.1 ± 21.2	0.98	0.96; 1	0.232
ESR (mm/h)	32.9 ± 24.3	42.7 ± 24.1	0.98	0.96; 1	0.061
CRP (mg/dL)	2.6 ± 2.7	2.9 ± 3	0.95	0.82; 1.1	0.588
Hemoglobin (mg/dL)	13.1 ± 1.3	12.5 ± 1.4	1.03	1; 1.06	0.043
mHAQ (0-3)	1 ± 0.6	1 ± 0.6	0.97	0.46; 2.04	0.945
RF positive (%)	64.7	78.9	0.49	0.19; 1.21	0.124
Anti-CCP positive (%)	70.6	70.3	1.01	0.40; 2.52	0.977
Erosion joint count	0.4 ± 0.9	0.3 ± 1	1.04	0.67; 1.63	0.835
Larsen	1.6 ± 3.3	1.1 ± 2.3	1.07	0.92; 1.24	0.354
Shared epitope (%)	67.6	72.1	0.81	0.33; 1.97	0.645
SE homozygous (%)	26.5	17.6	1.29	0.41; 4.04	0.656
DRB04 (%)	38.2	47.1	0.69	0.30; 1.61	0.398

Results are expressed as means ± S.D. or percentages. OR: odds ratio, CI: confidence interval.

and EULAR therapeutic responses after 6 and 12 months were significantly higher in patients in remission after 2 years compared to those not in remission. Furthermore, the proportion of remission at 2 years was higher in patients with a marked clinical response at 6 months. Forty-four percent of patients with an ACR50 response at 6 months achieved remission, compared to 20% of patients with no response ($p = 0.03$). Similar results were observed when analysing the good EULAR response (54.8% to 25.7%) ($p = 0.01$).

Remission and radiographic progression

Radiographic progression (increase in the Larsen score > 4 at month 24) was observed in 33% of patients. Progression was observed in 27.3% of patients with remission after 2 years compared to 34.3% of patients with no remission ($p > 0.05$). However, the rate of progression was significantly lower in the 15 patients with remission at three of the four time points (13.3%, $p = 0.04$).

Prognostic markers of remission

In the univariate analysis, the baseline parameters associated with remission at 2 years were: DAS28 < 5.1, high hemoglobin levels and male gender. Clear

but not statistically significant trends were observed for old age, low VAS pain, low ESR and negative rheumatoid factor (Table V). Two-year remission was achieved by 56% of patients with moderate disease activity (DAS28 > 3.2 and ≤ 5.1) at baseline and in only 19% of patients with high disease activity (DAS28 > 5.1) at entry ($p = 0.006$). In the multiple regression analysis, the only independent factor associated with clinical remission was a DAS28 < 5.1, with an odds ratio of 4.1 (95% CI 1.56; 10.77, $p = 0.004$). When the therapeutic response at 6 months was included in the multivariate analysis, an ACR50 response and a good EULAR response emerged as independent factors associated with remission at 2 years. In contrast, an ACR20 response and a whole EULAR response at 6 months were not significantly associated with remission at 2 years (Table VI).

Discussion

In this open prospective study, we analysed the rate and predictive factors for remission after 2 years of a structured therapeutic algorithm using gold salts as the first DMARD and very low dose glucocorticoids in a series of patients with early RA. We found that one-third of patients achieved remission, with

the absence of high disease activity at baseline and evidence of a good therapeutic response during the first months of therapy being the main predictive factors of remission at 2 years.

The definition of remission in RA is controversial (20, 21). Two main sets of criteria have been used, the ACR criteria (5) and the DAS criteria (6), with the ACR criteria being more conservative (8, 9). Some modifications in the original criteria have been proposed in recent years, including the modified ACR criteria that exclude fatigue from the variables analysed (6) and the DAS criteria that use the DAS28 score (< 2.6) as the cut-off point instead of the original DAS score (< 1.6) (7). In this observational study we defined remission using DAS28 with the original cut-off point of < 2.6, although new cut off points have been proposed recently (9, 22-24).

Few studies have analysed the proportion of patients in remission using the original DAS score in patients with early RA after the initiation of DMARDs. Gossec *et al.* (12) reported a remission rate of 25% after 3 years. Svensson *et al.* (25) found the prevalence of remission to be 36% after 2 years, while Teir *et al.* (26) in a small study reported a remission rate of 25%. In the TICORA

Table VI. Stepwise logistic regression analysis of predictive factors for remission at 2 years.

	Z	SE	OR	p	95% CI
<i>Without therapeutic response at 6 months</i>					
DAS28 < 5.1	2.87	2.02	4.1	0.004	1.56; 10.77
<i>With ACR response at 6 months</i>					
DAS28 < 5.1	2.87	2.52	4.68	0.004	1.63; 13.46
ACR20	0.74	1.31	1.74	0.462	0.39; 7.62
ACR50	2.17	2.45	3.9	0.03	1.14; 13.38
<i>With EULAR response at 6 months</i>					
DAS28 < 5.1	2.68	2.38	4.34	0.007	1.48; 12.74
Whole EULAR response	1.64	2.13	3.09	0.1	0.8; 11.94
Good EULAR response	2.66	4.29	6.23	0.008	1.61; 24.04

study, a strategy of intensive management and tight control of early RA using combination DMARDs resulted in the highest proportion (65%) of patients in remission after 18 months of follow-up described so far (3). In the BeSt study (27), which compared four treatment strategies in patients with early RA, the overall proportion of patients in remission at one year was 32%, with no differences between the four therapeutic groups. Therefore, the rate of clinical remission at one and two years in our study (23.5% and 32.4%) seems to be similar to previous reports, with the exception of the TICORA study. We are not aware of the existence of any previous studies using the DAS28 as remission criteria in patients with early RA that would allow direct comparison, as those published have been clinical trials using biologics in patients with aggressive RA (28, 29).

Several baseline parameters emerged as predictive factors of remission at 2 years in the univariate analysis; however, in the regression logistic analysis only low-moderate disease activity (DAS28 < 5.1) was independently associated with remission. Remission at 2 years in patients with DAS28 < 5.1 at baseline was 4 times higher than in patients with a high disease activity (DAS28 > 5.1) at study entry. The few observational studies of the prognostic factors of remission in early RA produced similar results. In a multi-parameter prospective study (12), the independent baseline markers of remission (DAS < 1.6) at 3 and 5 years after initiation of DMARDs were parameters of disease activity such as low DAS, a low Ritchie score, and the

duration of morning stiffness, together with radiographic damage. Verstappen *et al.* (14) analysed the prevalence of remission using the less commonly employed Scott criteria and found that the baseline factors associated with remission after a median follow-up of 62 months were a lower joint score, rheumatoid factor negativity, and a lower pain score. In a Swedish study (25), the predictive factors for remission (DAS < 1.6) after 2 years of DMARDs and/or glucocorticoids in patients with early RA were a low DAS score, male gender and a lower level of disability. All of this evidence supports the view that low disease activity at baseline is the main predictor of remission in early RA after DMARD therapy.

Other baseline factors, such as high hemoglobin and ESR levels or low VAS pain (all surrogate markers of low disease activity), male gender, old age or negative rheumatoid factor were associated (or showed a clear trend) with remission in the univariate analysis. Other studies have reported that males and older patients (> 60 years) are more likely to achieve remission periods than females (30) or young patients (30, 31). Although we found no significant association between RF negativity and remission, a clear trend was evident; the lack of association was probably due to the small percentage of RF negative patients in our series (25.7%). In contrast, anti-CCP antibodies were not associated with remission, as instead was reported in other studies (12). Nor was an association found between the HLA-DRB1 genotype and remission. Patients with a good therapeutic response during the first months of therapy

were more likely to achieve remission after 2 years of follow-up. When the therapeutic response was introduced into the multivariate logistic regression model, a good therapeutic response according to the EULAR criteria using the DAS28 score and an ACR50 response at month 6 were significantly associated with remission. However, this was not the case when the analysis included a whole EULAR response or an ACR20 response. This clearly suggests that we can promptly identify those RA patients with a high probability of remission. Our results are similar to those reported by Verstappen *et al.* (14) in a series of patients with early RA treated with four different DMARD therapeutic strategies; after a mean follow-up of 62 months, a good therapeutic response during the first year was independently associated with remission, rather than the type of DMARD prescribed.

The type of drugs used after 2 years differed significantly between patients with and without remission, although all patients were treated with the same initial structured therapeutic algorithm. Most patients achieving remission were still taking gold whereas only a minority of patients without remission were still on gold, and most of these were treated with methotrexate or even other antirheumatic drugs, including TNF-alpha blockers. This strongly suggests that, as suggested by other reports (32, 33), there is a subgroup of RA patients with a dramatic, persistent response to parenteral gold. The possible role of glucocorticoids in achieving remission merits consideration. Although glucocorticoids were progressively reduced as clinical improvement was achieved

in our patients, a considerable proportion were taking very low doses of glucocorticoids during the follow-up. These doses seem to be relevant not only in reducing radiographic disease progression but also account for the high rates of remission in early RA, as recently reported (34).

Although not the primary objective of the study, we also analysed the association between radiographic progression and remission in our cohort. The percentage of 2-year radiographic progression was similar in the patients with and without remission at 2 years. This may not be surprising, as a considerable proportion of patients achieving remission at 2 years had had inflammatory activity during this 2-year period. When only patients with a DAS28 < 2.6 in three of the four evaluation visits were considered, the proportion of radiographic progression was lower than in the patients without permanent remission. This finding confirms the evidence that persistent remission measured using the DAS28 is associated with a low rate of radiographic progression, but also shows that some patients may suffer from progressive radiographic damage even in the absence of apparent inflammatory activity (35).

In conclusion, up to one-third of early RA patients achieved clinical remission after structured anti-rheumatic strategy using DMARDs (gold salts and/or methotrexate) and very low dose glucocorticoids. Disease activity at baseline and a good therapeutic response during the first months of therapy were the main factors associated with remission at 2 years. A longer follow-up time will be required to determine whether this clinical remission is persistent and long-lasting.

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