Original article

# Remission in early rheumatoid arthritis treated with conventional DMARDs. Results of a two-year follow-up study of El Ayachi Moroccan cohort

Karima Benbouazza [a], Hanan Rkain [a,*], Bahia Benchekroun [a], Bouchra Amine [a], Fatiha Bzami [a], Leila Benbrahim [a], Ouafa Atouf [b], Malika Essakalli [b], Redouane Abouqal [c], Maxime Dougados [d], Najia Hajjaj-Hassouni [a]

[a] Rheumatology Department, Mohamed Vth University Souissi, El Ayachi Hospital, Salé, Ibn Sina Universitary Hospital, Rabat, Morocco
[b] Blood Transfusion and Hemovigilance Department, Laboratory of Immunology, Mohamed Vth University Souissi, Ibn Sina Universitary Hospital, Rabat, Morocco
[c] Laboratory of Biostatistics, Clinical and Epidemiological Research, Faculty of Medicine and Pharmacy, Mohamed Vth University Souissi, Rabat, Morocco
[d] Rheumatology B Department, Cochin Hospital, UPRES-EA 4058, René-Descartes University, 75014 Paris, France

## ARTICLE INFO

## ABSTRACT

Objective: This study aimed to evaluate remission in patients with early RA treated by conventional DMARDs and to identify its possible predictor factors.
Methods: Patients with early RA (< 12 months) were enrolled in a 2-year follow-up study. Standard evaluation completed at baseline and at 24 months included clinical, laboratory, functional and structural assessment. Clinical remission after 2 years of follow-up was defined when DAS28 was less than 2.6. Possible predictor factors for remission were analyzed.
Results: Fifty-one patients (88.2% women, mean age of 46.9 [24–72] years, mean disease duration of 24 [6–48] weeks) were enrolled in this study. The delay in referral for specialist care was 140 [7–420] days. Rheumatoid factor, anti-CCP, HLA-DRB1*01 and DRB1*04 alleles were present respectively in 62.5, 56.6, 11.8, and 45.1% of patients. At 24 months, 77.2% received a median dose of 5 (0–8) mg/day of prednisone and 65.2% was taking methotrexate (MTX). 13.6% of patients had stopped their DMARD because of socioeconomic difficulties. At 24 months, we noted a significant improvement of morning stiffness, pain score, swollen joint count, ESR, CRP, DAS28 and HAQ scores. Remission at 2 years was noted in 34.8% of patients and was significantly associated in univariate but not in multivariate analysis to male sex ($P = 0.02$) and to short delay in referral for specialist ($P = 0.03$).
Conclusion: In this cohort of early RA patients treated with conventional DMARDs, especially with methotrexate in monotherapy, remission at 2-year of follow-up was obtained in one third of patients. No predictor factors of remission were found out. These results should be verified by further studies.

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints and one of the most prevalent autoimmune diseases in the world. RA is a highly heterogeneous disease characterized by disease activity and bone destruction resulting in joint destruction, functional impairment and increased mortality [1,2]. RA has a major socioeconomic impact on patient and his entourage in Moroccan context [3]. Early recognition of RA and intervention appear to be keys to optimal management of this chronic disease [4]. Therefore, new therapeutics has revolutionized the treatment of RA, and remission is regarded as the goal of the contemporary management of this rheumatism [5,6]. In the context of developing countries as in Morocco, use of biotherapy agents is limited by precarity of social security systems and socioeconomic difficulties [7]. Consequently, classic disease-modifying anti-rheumatic drugs (DMARDs) continue to be widely used in RA treatment [7].

The purpose of this study is to study remission in a population of early RA patients receiving conventional DMARDs. We would like also to determine if there are any possible predictor factors of this remission.

## 2. Methods

### 2.1. Patients

A cohort of consecutive adults patients with RA aged between 18 and 70 years, who suffered from the disease for less than 1 year, was recruited in this study between January 2005 and December 2006. RA patients were diagnosed by rheumatologists with reference to

* Corresponding author.
 E-mail address: hananrkain@yahoo.fr (H. Rkain).

the American College of Rheumatology (ACR) classification criteria [8]. Patients followed by their rheumatologist were addressed for a supplementary assessment as outpatients in El Ayachi hospital (public structure and referral hospital of Rheumatology in Morocco) at recruitment and 2 years thereafter.

We have not excluded patients already receiving corticosteroids and/or a DMARD. All patients were subsequently treated with DMARDs that could be modified during the study according to efficacy and side effects. The choice of treatment in this cohort according to the protocol was left to the discretion of the treating physicians in order to simulate a 'real-life'-like situation. None of patients received biologic agents because of socioeconomic difficulties.

All patients agreed to enrollment in a 2-year follow-up study and signed written informed consent. The study was approved by the ethics review.

## 3. Patients' features and disease characteristics

Patients' features and disease characteristics were assessed at the study entry baseline and 2 years after. Thus, the following parameters were collected at baseline: age, sex, educational level, adherence to a health insurance system, disease duration, patient's assessment of pain (on a visual analog scale), number of swollen and tender joints (both by 28-joint count), extraarticular manifestations, functional status evaluated by the Moroccan adapted version of Health Assessment Questionnaire (HAQ) [9], erythrocyte sedimentation rate (ESR), C reactive protein (CRP) level, IgM or IgA rheumatoid factor (RF) positivity (20 IU/mL and 7 units/mL, respectively), anticyclic citrullinated peptide (anti-CCP) positivity using second generation anti-CCP assay (CCP2) of Elisa and finally frequency of HLA-DRB1*01 and DRB1*04 alleles tested by "polymerase chain reaction sequence specific primers" (PCR-SSP).

At 24 months, the clinical assessment included number of swollen and tender joints (both by 28-joint count), HAQ and pain scores. The laboratory investigations included ESR and CRP dosages.

Radiographs of the hands and feet were obtained at baseline and 2 years thereafter. Structural damage was assessed by counting the number of erosions and grading the joint space narrowing (JSN) according to the Sharp and van der Heijde method [10].

Concerning treatments, we recorded at baseline and at 24 months doses of oral corticosteroids and type of DMARDs received by patients.

### 3.1. Disease activity and remission

The disease activity was evaluated by the 28-joint Disease Activity Score (DAS28). The DAS28 was calculated according to the published algorithm using the swollen and tender joint count of 28 joints, patient's global assessment, and erythrocyte sedimentation rate (ESR) in millimetre per hour. We assessed patient disease status at study entry and 2 years thereafter. Thus, we determined in our early RA cohort the proportion of patients in remission at baseline and at 2 years. As proposed by Prevoo et al., the remission was defined by a DAS28 score less than 2.6 [11]. DAS28 values less or equal to 3.2 are regarded as representing low disease activity and DAS28 values greater than 5.1 as representing high disease activity [11].

## 4. Statistics

Descriptive statistics of the patients and disease characteristics were completed. Student's $t$ test and the Chi-squared test were used as appropriate to compare the evolution of clinic, biologic and radiographic parameters between outset and 24 months there-

after. Outcome variable was dichotomized into qualitative variable: presence or absence of remission.

Univariate analysis tested most of the clinical, biologic, immunologic and genetic factors that were previously reported to be possibly related to remission in RA.

Multivariate logistic regression analyses were also conducted. A statistical significance level of $P < 0.05$ was used in all statistical tests performed. Analyses were performed using the SPSS program (version 13.0; SPSS Inc., Chicago, IL, USA).

## 5. Results

### 5.1. Patients' and diseases' features at baseline

Fifty-one patients (45 women, six men) were enrolled in this study. Data on 46 patients were available for analysis after 2 years of follow-up.

At baseline, the mean age of patients and the mean disease duration were respectively 46.9 (24–72) ± 10.8 years and 24 (6–48) ± 13.9 weeks. The delay in referral for specialist care was 140 (7–420) ± 43 days.

Thirty patients (62.5%) were IgM or IgA RF positive. HLA-DRB1*01 and DRB1*04 alleles were present respectively in 11.8% and 45.1% of patients. Anti-CCP positivity was recorded in 56.6% of patients. At baseline, DAS28 and HAQ mean scores were respectively 6.9 (3.7–9.9) ± 1.3 and 2.2 (0.7–3) ± 0.6.

At study entry, 18 patients (35.3%) were already taking corticosteroids with a median dose of 0 (0–8) mg/day and four patients (7.8%) were under conventional DMARDs (methotrexate alone and methotrexate associated to chloroquine in one and three cases respectively).

At 24 months assessment, 34 patients (77.2%) received a low dose of prednisone with median dosage at 5 (0–8) mg/day. During follow-up, all patients were receiving conventional DMARDs in monotherapy. At the 24 months assessment, methotrexate (MTX) was the most frequently prescribed DMARD, being taken by 65.2% of patients and followed by sulfasalazine and chloroquine (10.8% for each of them). Six patients (13.6%) had stopped the DMARD for socioeconomic difficulties. None of patients received combination therapy or biologic agents.

Table 1 shows the patients' and diseases' characteristics at baseline.

### 5.2. Early RA evolution between baseline and at 24 months

Table 2 shows a comparison of clinical and biologic parameters of RA between baseline and 2 years thereafter. These results revealed a significant global improvement of the disease status including morning stiffness, pain score, swollen joint count, DAS28 and HAQ scores, ESR and CRP. Structural progression between baseline and 2-year of follow-up occurred in 15 patients. The median of total damage score, erosions score, and joint space narrowing score increased respectively from 1 (0–5) to 4 (1–10); $P < 0.001$, from 0 (0–1) to 0 (0–2); $P < 0.001$, and from 1 (0–3) to 3 (1–8); $P < 0.001$.

### 5.3. Disease activity and remission

The DAS28 decreased significantly from an initial mean score of 6.9 (3.7–9.9) ± 1.3 in range of high disease activity to 3.7 (0.5–9.2) ± 1.9 into the range of moderate disease activity; $P < 0.001$. At the end of second year, a DAS28 of less than 3.2 (range of low disease activity) was observed in 50% of the RA patients versus none patients at baseline; $P < 0.001$, (Fig. 1).

Sixteen patients (34.8%) were in remission at 2 years whereas there were no patients in remission at baseline; $P < 0.001$. Four

**Table 1**
Patients and disease characteristics at baseline.

| Baseline variable | Value |
|---|---|
| Sex, % women | 88.2 |
| Age, years | 46.9 (24–72) ± 10.8 |
| Disease duration, weeks | 24 (6–48) ± 13.9 |
| Referral to specialist delay, days | 140 (7–420) ± 43 |
| Extraarticular manifestations, % | 1.8 |
| ESR, mm/hour | 57.2 (5–115) ± 25.8 |
| CRP, mg/L | 26.8 (0–96) ± 22 |
| RF positivity, % | 62.5 |
| Antinuclear antibody positivity, % | 7.8 |
| Anti-CCP positivity, % | 56.6 |
| HLA-DRB1*04, % | 45.1 |
| HLA-DRB1*01, % | 11.8 |
| Patient global assessment (0–10) | 3.4 (0–8) ± 1.6 |
| Physician global assessment (0–10) | 6.2 (1–10) ± 1.7 |
| Patient pain assessment (0–10) | 6.6 (1–10) ± 1.8 |
| Tender joint count (0–28) | 20.4 (8–48) ± 10.1 |
| Swollen joint count (0–28) | 9.6 ± 6.5 |
| HAQ (0–3) | 2.2 (0.7–3) ± 0.6 |
| Total Sharp score | 1 (0–5)[a] |
| Erosion score | 0 (0–1)[a] |
| Joint space narrowing score | 1 (0–3)[a] |
| Treatment received | |
| Corticosteroids, % | 35.3 |
| DMARD, % | 7.8 |

RA: rheumatoid arthritis: RF: rheumatoid factor; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; DMARDs: disease-modifying anti-rheumatic drugs. Values are presented as mean or percentage.

[a] Values are presented as median and quartiles.

**Table 2**
Determinant factors of clinical remission (DAS28 < 2.6) by univariate analysis.

| Items at baseline | Remission (DAS28 < 2.6) | | P |
|---|---|---|---|
| | Yes (n = 16) | No (n = 30) | |
| Age, years | 44.5 (24–60) ± 10.8 | 48 (24–72) ± 10.8 | 0.2 |
| Sex female, % | 68.8 | 97.1 | <0.01 |
| Delay in referral to specialist, days | 90 (48.7–165)[a] | 165 (67–232)[a] | 0.02 |
| Swollen joint count (0–28) | 9 (8–13)[a] | 8 (3–15)[a] | 0.2 |
| DAS28 | 6.9 (5.5–8) ± 0.7 | 6.9 (3.7–9.9) ± 1.5 | 0.4 |
| HAQ | 2.1 (0.7–2.9) ± 0.6 | 2.2 (0.9–3) ± 0.6 | 1 |
| RF, % | 54.3 | 33.3 | 1 |
| CRP, mg/L | 21.1 (0–48) ± 16.4 | 29.3 (0–96) ± 24 | 0.8 |
| ESR, mm/hour | 48 (25–80) ± 17.5 | 59.4 (5–115) ± 28.4 | 0.5 |
| Anti-CCP | 44.9 (2.2–100)[a] | 26.9 (2.2–100)[a] | 0.9 |
| HLA-DRB1*04, % | 31.3 | 52.9 | 0.4 |
| HLA-DRB1*01, % | 12.5 | 11.8 | 1 |

Values are presented as mean or percentage.

[a] Values are presented as median and quartiles.

patients in clinical DAS below 2.6 have had structural progression.

Remission at 2 years of follow-up was significantly associated with male sex (P = 0.02) and with a short delay in referral for specialist (P = 0.03). Logistic regression did not show any independent predictor factor of remission.

## 6. Discussion

This prospective study constitutes a real-life design in a developing African country and provides information about remission in a cohort of early RA patients receiving traditional DMARDs. At 2 years, remission occurs in one third of patients and seems to be not predicted by any of baseline factors.

The DAS28 has significantly improved after the 2 years follow-up. Moreover, practically a third of patients were in remission after this period whereas there were no patients at baseline. Methotrex-



**Evolution of the DAS 28 scores between baseline and 2 year follow-up**
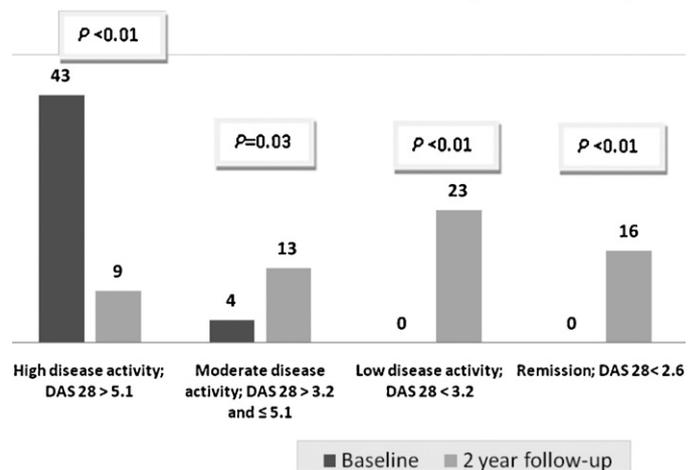
**Fig. 1.** Evolution of the DAS28 scores between baseline and 2 years.

ate was the most frequently used DMARD as monotherapy in our cohort. The significant improvement of the disease status including clinical and biologic parameters under classic DMARDs and especially MTX is in concordance with the literature findings [12,13].

Remission rates range from 3 to 68% [14] in RA studies depending on selection of remission criteria, patient selection, duration of the follow-up period, and therapies.

In our study, we have chosen the remission definition proposed by Prevoo et al. [11]. Even if this method has the advantage of being simple to apply, it should be used with caution in clinical practice and clinical trials because the DAS28 remission at a cutoff level of 2.6 seems to have insufficient construct validity [15].

DAS28 remission criteria have been used in studies concerning traditional DMARDs. In the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo), patients treated with a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone, DAS28 remission rate was 68% at 2 years [16]. In the Tight Control of Rheumatoid Arthritis (TICORA) trial, the DAS remission rate was 65% in patients who received traditional DMARDs according to an intensive strategy and 16% in patients who were treated in routine care [17]. Biologic agents give DAS28 remission levels of 21 to 53% and have the principal advantage of their capacity to stop structural damage more than do DMARDs [18–20]. Furthermore, initial combination therapy consisting of methotrexate plus a biological agent has superior efficacy for the induction of remission at 1 year [21].

Because of the differences existing in the study designs, it is not suitable to compare the remission rate found in our study with literature results. Nevertheless, we think that association of DMARDs and applying intensive therapeutic strategy could be a good alternative which should be encouraged especially in patients with inaccessibility to biotherapies.

Knowledge about factors that are possibly associated with remission is limited. Recently, several predictor factors of remission were reported. It appears that men achieve remission as assessed by the DAS28 more often than women [22]. This could be possibly due in women to higher pain perception and less muscular strength and maybe because men overestimate their functional capacity.

In a cohort of 191 early RA patients followed up prospectively for 5 years, Gossec and al. [23] showed that remission at 3 years and persistent remission at 5 years were closely correlated with baseline DAS values, C reactive protein level, Ritchie score, health assessment questionnaire score, duration of morning stiffness, and

to a lesser extent baseline total radiological scores and rheumatoid factor negativity. In our study, none of those factors were in relation with remission.

In our data, remission at 24 months of follow-up was associated as shown in univariate analysis to male sex ($P < 0.01$) and to a short delay in referral to specialist ($P = 0.02$). Nevertheless, none of those candidate predictors of remission was revealed as independent factor after the logistic regression analysis. This finding may be due to the small number of our cohort.

Some limitations should be recognized in our study. Because of technical and financial considerations, we have not included in the design study regular assessment throughout the 2 years of follow-up. Thus, we were unable to verify remission persistence. Furthermore, we think that the ACR remission criteria should be used instead of the DAS28 remission criteria since it is a more rigorous tool for assessing remission.

We are well aware that this is a study of a small number of patients with early RA. Where it is unique is in its geographical setting – namely in North Africa. Thus, since use of biotherapy agents is limited in this area by socioeconomic difficulties, this study offers a unique opportunity to evaluate remission in early RA patients treated by classic disease-modifying anti-rheumatic drugs (DMARDs).

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

## References

[1] Pincus T, Callahan LF. What is the natural history of rheumatoid arthritis? Rheum Dis Clin North Am 1993;19:123–51.
[2] Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481–94.
[3] Rkain H, Allali F, Jroundi I, et al. Socioeconomic impact of rheumatoid arthritis in Morocco. Joint Bone Spine 2006;73:278–83.
[4] Combe B, Landewe R, Lukas C, et al. EULAR evidence recommendations for the management of early arthritis. Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2007;66:34–45.
[5] Berthelot JM, Benoist-Gérard S, le Goff B. Outcome and safety of TNFα antagonist therapy in 475 consecutive outpatients (with rheumatoid arthritis or spondyloarthropathies) treated by a single physician according to their eligibility for clinical trials. Joint Bone Spine 2010;77(6):564–9.
[6] Aletaha D, Ward MM, Machold KP, et al. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum 2005;52:2625–36.
[7] Mody GM, Cardiel MH. Challenges in the management of rheumatoid arthritis in developing countries. Best Pract Res Clin Rheumatol 2008;22:621–41.
[8] Arnett FC, Edworthy SM, Block DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
[9] Abourazzak FE, Benbouazza K, Amine B, et al. Psychometric evaluation of a Moroccan version of health assessment questionnaire for use in Moroccan patients with rheumatoid arthritis. Rheumatol Int 2008;28:1197–203.
[10] Van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999;26:743–5.
[11] Prevoo ML, Van Gestel AM, Van Thma, et al. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35:1101–5.
[12] Van Dongen H, Van Aken J, Lard LR, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2007;56:1424–32.
[13] Bijlsma JW, Jacobs JW. Methotrexate: still the anchor drug in RA treatment. Joint Bone Spine 2009;76:452–4.
[14] Mäkinen H, Hannonen P, Sokka T. Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomized clinical trials for the rate of remission. Clin Exp Rheumatol 2006;24:S22–8.
[15] Landewe R, Van Der Heijde D, Van Der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28-remission definition due to the omission of the lower extremity joints: a comparison with the original DAS-remission. Ann Rheum Dis 2005;5:637–41.
[16] Rantalaiho V, Korpela M, Hannonen P, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum 2009;60:1222–31.
[17] Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263–9.
[18] St Clair EW, Van Der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432–43.
[19] Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26–37.
[20] Van Der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: Two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006;54:1063–74.
[21] Kuriya B, Arkema EV, Bykerk VP, et al. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis 2010;69:1298–304.
[22] Tengstrand B, Ahlmen M, Hafstrom I. The influence of sex on rheumatoid arthritis: a prospective study of onset and outcome after 2 years. J Rheumatol 2004;31:214–22.
[23] Gossec L, Dougados M, Goupille P, et al. Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. Ann Rheum Dis 2004;63:675–80.