Very early rheumatoid arthritis is the major predictor of major outcomes: clinical ACR remission and radiographic non-progression

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ABSTRACT

Objectives To identify predictors of clinical remission as well as of no x-ray progression in a cohort of early rheumatoid arthritis (ERA) treated with a tight-control protocol.

Methods A total of 121 consecutive patients with ERA were treated to reach European League Against Rheumatism (EULAR) and/or American College of Rheumatology (ACR) clinical remission with methotrexate (MTX) for 3 months, then with a combination with anti-tumour necrosis factor if the patient did not achieve a 44-joint Disease Activity Score (DAS44) ≤2.4. At baseline and after 12 months all the patients had hand and foot joint radiographs. Very early rheumatoid arthritis (VERA) was defined as a disease with symptoms of less than 12 weeks.

Results In all, 46.3% of the patients reached DAS remission and 24.8% achieved ACR remission. More than 60% of patients reached remission with MTX. Male sex and an erythrocyte sedimentation rate <35 mm/h at onset arose as significant predictors of EULAR remission, while VERA disease was the only predictor of ACR remission. At baseline, 28.1% of the patients were erosive. Multivariate analysis demonstrated that the only independent predictor of erosiveness was 'not having VERA disease'. After 12 months, VERA was the only factor predicting a lack of new erosions.

Conclusions VERA represents the best therapeutic opportunity in clinical practice to achieve a complete remission and to stop the erosive course of rheumatoid arthritis.

INTRODUCTION

One of the most interesting findings obtained in early rheumatoid arthritis (ERA) trials (ie, the BeST trial) has been the disappearance of any predictor of remission in patients treated ab initio with methotrexate (MTX) plus anti-tumour necrosis factor α (TNFα).[1] However, in the MTX-treated arms of trials, disease duration, disease activity and Health Assessment Questionnaire (HAQ) disability scores at baseline were best predictors of a good European League Against Rheumatism (EULAR) response.[2 3]

In patients under TNFα blockade treatment, the percentage of patients reaching clinical remission is high, but the percentage of patients demonstrating no radiographic progression is even higher, whereas in patients treated with conventional disease-modifying antirheumatic drugs (DMARDs), clinical remission can also be observed in a high percentage of patients but x-ray progression appears to be less favourable.[1 4–6]

When the concept of a very early treatment was introduced, even with DMARDs, a disease duration of less than 4 months emerged as a predictor of remission in ERA.[7–9]

In this study we focused our attention on possible predictors, either in terms of clinical remission as well as in terms of x-ray remission (or lack of progression), in a cohort of ERA prospectively treated according to a very strict protocol.

PATIENTS AND METHODS

The study included 121 consecutive patients with ERA (disease duration <12 months) fulfilling the 1987 and 2010 American College of Rheumatology (ACR) criteria for RA[10] who were attending our early arthritis clinic and that reached a follow-up of 12 months. All patients gave their informed consent to enter into the study, which was approved by our Ethics Institutional Committee.

The disease duration was considered from the onset of the symptoms to baseline that corresponded with the point of diagnosis and with the start of treatment. When disease duration was less than 3 months, patients were defined as having 'very early rheumatoid arthritis' (VERA). In our cohort 44 patients (36.4%) had VERA (supplementary table 1).

The visits were performed every month up to 3 months and every 3 months thereafter, and at each visit all clinical (Disease Activity Score (DAS), HAQ, joint count), immunological (rheumatoid factor (RF)-IgA, RF-IgM, anti-cyclic citrullinated peptide antibodies (ACPA) and anti-mutated citrullinated vimentin antibodies) and laboratory (erythrocyte sedimentation rate (ESR), C reactive protein) data were registered. (For more details on patient characteristics, treatment and follow-up see supplementary data file and supplementary table 1).

At the first visit, once the diagnosis was confirmed, patients began taking MTX (up to 20 mg weekly) and when necessary a low dosage steroid. Patients were evaluated at each control visit and a combination treatment with anti-TNF (adalimumab 40 mg/every 2 weeks or etanercept 50 mg/week) was begun if patients did not achieve a low DAS44 (≤2.4). At month 12, 73 patients (60.3%) were in monotherapy with MTX, while 20 patients (16.5%) were receiving an association with adalimumab and 28 patients (23.2%) an association with etanercept.

A patient was considered in clinical DAS44 remission if he/she reached a DAS value of <1.6[11] for at least two consecutive visits 3 months apart, and if

they also had no disease flare within the previous 6 months, stable treatment for 6 months and no clinical indication for a change of treatment.

Besides EULAR remission, in order to define whether stricter criteria could reflect a better concordance between clinical involvement and radiological damage, we also assessed a sustained ACR remission defined as fulfilling five of the ACR remission criteria for two consecutive visits.[12]

All the patients had hand and foot radiographs taken at baseline and after 12 months of treatment. Radiographs were scored according either to Larsen score[13] or using the Sharp/van der Heijde[14] method, but in this case considering only the erosion score. Patients presenting a new erosion or the worsening of 1 or more points of Larsen and/or Sharp/van der Heijde erosion score were considered as radiological progressors.

RESULTS

After 12 months of treatment, 56 patients (46.3%) reached DAS remission (DAS44<1.6) (table 1) and 26 more patients had reached a low disease activity (DAS44≤2.4). According to the ACR criteria, 30 patients (24.8%) reached remission (table 2). A total of 91 patients (75.2%) reached a HAQ score of ≤0.5. Patients that did not reach DAS remission presented at baseline a higher ESR (42.0±24.0 mm/h), DAS (3.6±0.7) and HAQ (1.4±0.7) with respect to patients that reached DAS remission (ESR 31.6±25.0 mm/h, p=0.01; DAS 3.0±0.8, p<0.0001; HAQ 1.1±0.7, p=0.04; respectively). Thus, patients with a high ESR, DAS and HAQ less frequently reached DAS remission (table 1).

At the 12-month follow-up 60.3% of patients were receiving only MTX, and 39.7% were receiving MTX and anti-TNFα.

We observed a highly significant fall of RF-IgM, of RF-IgA and a smaller decrease of ACPA levels and, as expected, a highly significant improvement in all the clinical variables (see supplementary figures 1 and 2 and supplementary table 1). ACPA positivity was found in 65.3% at the end of the follow-up versus 72.7% at baseline (p=0.001), RF-IgM positivity was seen in 31.4% versus 67.8% (p<0.0001) and RF-IgA positivity was seen in 16.5% versus 37.2% (p<0.0001).

The variables that arose as significant predictors of EULAR remission were male sex (OR 2.5 (Confidence Intervals (CI): 1.1–5.9)) and 'having at onset an ESR<35 mm/h' (OR 2.4 (CI: 2.2–5.1)).

Patients that did not reach ACR remission presented a longer disease duration at onset (6.4±3.6 months) with respect to patients that had reached ACR remission (3.8±2.4 months) (p<0.0001) (table 2). The only variable that arose a significant predictor of ACR remission was 'having VERA disease' (OR 5.3 (CI: 2.1–13.0)).

Patients with erosions at baseline (28.1%) presented a longer disease duration (7.1±3.0 months), with respect to patients without erosions at diagnosis (5.2±3.4 months) (p=0.005) and a higher (though not statistically different) ESR, DAS, HAQ, RF-IgM and RF-IgA at onset (table 3).

While erosions were present in a similar percentage of patients that would reach EULAR remission (26.8%) and of patients that would not (29.2%), radiological damage was less frequent in patients that would reach ACR remission (16.7%) than in patients that would not (31.9%) (table 2).

Multivariate analysis demonstrated that the only independent predictor of erosiveness at baseline was 'not having a VERA disease' (OR 3.9 (CI: 1.5–10.7)).

After 12 months, 14 patients (11.6%) became erosive, 13 patients (10.7%) presented a worsening of at least 1 point of Sharp and/or Larsen score, while 73 patients (60.3%) were still not erosive.

The percentage of patients erosive at the end of the follow-up was strikingly different in the VERA subset (13 patients (27.1%)) versus the non-VERA subset (35 patients (45.4%)), (p=0.005). Multivariate analysis demonstrated that the only independent predictor of erosiveness at month 12 was 'not having a VERA disease' (OR 2.4 (CI: 1.1–5.6)).

Considering the group of patients that presented a progression of the Sharp erosion score, seven patients progressed 1 point, three patients 2 points and one patient 4 points. Considering the

Table 1 Baseline and 12-month follow-up clinical and biological characteristics of patients reaching DAS remission and not reaching remission at follow-up

Characteristics	Baseline characteristics of patients achieving DAS remission (56 patients)	Baseline characteristics of patients not achieving DAS remission (65 patients)	Follow-up characteristics of patients achieving DAS remission (56 patients)	Follow-up characteristics of patients not achieving DAS remission (65 patients)
Age, years	52.1±15.1	55.0±11.4	–	–
Sex, no. F (%)	38 (67.9%)	54 (83.1%)*	–	–
Disease duration, months	5.6±3.5	5.9±3.5	–	–
VERA, n (%)	21 (37.5%)	23 (35.4%)	–	–
ACPA, U/ml	81.6±133.7	60.6±45.0	45.7±39.8	43.5±38.4
ACPA+, n (%)	47 (83.9%)	41 (63.1%)	38 (69.1%)	41 (63.1%)
RF-IgM, U/ml	94.6±115.2	92.2±136.3	38.9±73.1	34.2±47.7
RF-IgM+, n (%)	38 (67.9%)	44 (67.7%)	17 (30.6%)	21 (32.3%)
RF-IgA, U/ml	165.1±170.1	179.5±249.1	58.3±114.4	33.8±59.7
RF-IgA+, n (%)	23 (41.1%)	22 (33.8%)	11 (20.0%)	9 (14.1%)
ESR, mm/ l° h	31.6±25.0	42.0±24.0*	9.8±6.2	20.8±16.7†
CRP, mg/litre	19.7±26.6	24.3±32.3	2.6±3.6	5.6±7.8†
DAS44	3.0±0.8	3.6±0.7*	1.0±0.4	2.2±0.8†
HAQ-DI	1.1±0.7	1.4±0.7*	0.2±0.2	0.6±0.6†
Erosives	15 (26.8%)	19 (29.2%)	21 (37.5%)	27 (41.5%)
Sharp erosion score	2.4±2.5	2.5±2.2	2.4±2.5	2.5±2.1
Larsen score	3.8±2.4	4.3±3.3	3.6±2.7	4.2±3.0

Characteristics at baseline and after 12 months of patients reaching DAS remission or not reaching DAS remission after 12 months of follow-up. Values are mean±SD.
*p<0.05 between baseline characteristics of patients achieving and not achieving DAS remission.
†p<0.05 between 12-month follow-up characteristics of patients achieving and not achieving DAS remission.
ACPA, anti-cyclic citrullinated peptide antibodies; CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; RF, rheumatoid factor; VERA, very early rheumatoid arthritis.

Table 2 Baseline and 12-month follow-up clinical and biological characteristics of patients reaching ACR remission or not reaching remission at follow-up

Characteristics	Baseline characteristics of patients achieving ACR remission (30 patients)	Baseline characteristics of patients not achieving ACR remission (91 patients)	Follow-up characteristics of patients achieving ACR remission (30 patients)	Follow-up characteristics of patients not achieving ACR remission (91 patients)
Age, years	55.0±13.3	53.2±13.3	–	–
Sex, no. F (%)	20 (66.7%)	72 (79.1%)	–	–
Disease duration, months	3.8±2.4	6.4±3.6*	–	–
VERA, n (%)	19 (63.3%)	25 (27.5%)*	–	–
ACPA, U/ml	105.5±175.1	59.1±48.1	61.2±45.2	39.8±35.8
ACPA+, n (%)	20 (66.7%)	68 (74.7%)	18 (62.1%)	61 (67.0%)
RF-IgM, U/ml	55.0±71.2	105.5±138.1	33.7±73.4	37.2±56.7
RF-IgM+, n (%)	19 (63.3%)	63 (69.2%)	7 (24.1%)	31 (34.1%)
RF-IgA, U/ml	130.2±121.0	188.8±237.6	41.2±54.3	48.9±14.8
RF-IgA+, n (%)	13 (43.3%)	32 (37.6%)	8 (27.6%)	12 (13.3%)
ESR, mm/ l° h	34.7±24.3	38.0±24.3	10.3±7.3	17.5±15.3†
CRP, mg/litre	19.8±23.7	22.9±31.5	2.6±5.4	4.8±6.6†
DAS44	3.2±0.7	3.4±0.9	0.8±0.3	2.0±0.8†
HAQ-DI	1.0±0.6	1.3±0.8	0.1±0.2	0.5±0.5†
Erosives	5 (16.7%)	29 (31.9%)	9 (30.0%)	39 (42.9%)
Sharp erosion score	1.8±0.8	2.6±2.5	1.6±0.7	2.7±2.5
Larsen score	3.2±1.8	4.2±3.0	2.7±1.7	4.2±3.0

Characteristics at baseline and after 12 months of patients reaching ACR remission or not reaching ACR remission after 12 months of follow-up. The values are indicated as the mean±SD.
*p<0.05 between baseline characteristics of patients achieving and not achieving ACR remission.
†p<0.05 between 12-month characteristics of patients achieving and not achieving ACR remission.
ACR, American College of Rheumatology; ACPA, anti-cyclic citrullinated peptide antibodies; CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; RF, rheumatoid factor; VERA, very early rheumatoid arthritis.

Table 3 Baseline and 12-month follow-up clinical and biological characteristics of patients with and without erosions at diagnosis

Characteristics	Baseline characteristics of erosive patients at diagnosis (34 patients)	Baseline characteristics of not erosive patients at diagnosis (87 patients)	Follow-up characteristics of erosive patients at diagnosis (34 patients)	Follow-up characteristics of not erosive patients at diagnosis (87 patients)
Age, years	57.7±10.6	2.1±13.9	–	–
Disease duration, months	7.1±3.0	5.2±3.4*	–	–
VERA, n (%)	6 (17.6%)	28 (32.2%)*	–	–
ACPA, U/ml	60.6±57.1	74.1±108.2	39.3±38.4	46.7±39.1
ACPA+, n (%)	27 (79.4%)	61 (70.1%)	22 (66.7%)	57 (65.5%)
RF-IgM, U/ml	122.4±158.2	79.3±107.6	52.9±76.7	29.4±51.2
RF-IgM+, n (%)	25 (73.5%)	57 (65.5%)	14 (42.4%)	24 (27.6%)
RF-IgA, U/ml	186.6±230.9	164.0±203.8	40.9±67.6	49.8±104.8
RF-IgA+, n (%)	16 (47.1%)	29 (33.3%)	5 (15.2%)	15 (7.4%)
ESR, mm/ l° h	41.5±25.0	35.5±24.6	20.1±19.2	14.0±11.1†
CRP, mg/litre (T=0)	27.4±33.7	20.1±27.9	4.8±9.4	4.0±4.8
DAS44	3.5±0.9	3.2±0.8	1.8±0.8	1.6±0.9
HAQ-DI (T=0)	1.3±0.8	1.2±0.7	0.5±0.6	0.3±0.5
DAS remission	–	–	15 (44.1%)	41 (47.1%)
HAQ remission	–	–	22 (64.7%)	69 (79.3%)
ACR remission	–	–	9 (26.5%)	34 (39.1%)

Clinical and biological values of variables in patients that were erosive or not erosive at baseline. The values are indicated as the mean±SD.
*p<0.05 between baseline characteristics of patients with and without erosion at diagnosis.
†p<0.05 between 12-month characteristics of patients with and without erosion at diagnosis.
ACR, American College of Rheumatology; ACPA, anti-cyclic citrullinated peptide antibodies; CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; RF, rheumatoid factor; VERA, very early rheumatoid arthritis.

Larsen's score, four patients presented a worsening of 1 point, four patients of 2 points, two patients of 4 points and one patient of 5 points.

DISCUSSION

The goal of our study was to find predictors of remission and radiographic progression in a cohort of patients that followed a therapeutic protocol aiming at remission, in a real world tight-control setting. Our data show that an aggressive therapeutic approach can lead to a major response in a high percentage of patients, and more importantly that an ACR remission can be a realistic clinical outcome in clinical practice.

Other clear-cut messages arose: first, the major determinant of an ACR clinical remission is VERA; second, the major risk factor for being erosive at onset is being a 'no VERA patient'; third, the erosivity after 12 months under a strict and aggressive therapeutic protocol depends on a major risk factor, being or not in VERA at the point of diagnosis. Therefore all the data lead to the clinically relevant issue of early diagnosis and early therapeutic intervention within the window of opportunity of 3 months.[7 15 16] Also, the effect of a later diagnosis did not disappear when an aggressive treatment strategy was applied.[7]

Unfortunately, despite aiming at remission, and despite leading to DAS remission in a high percentage of patients and to

low disease activity the majority of our cohort, we still had 11.6% of patients becoming erosive, as already reported.[17 18] The radiological progression was small in our cohort, and definitely hardly clinically significant. In a recent study, an initial combination of MTX and adalimumab compared to an initial monotherapy with MTX allowed a faster control of disease activity but did not increase the number of patients for whom anti-TNFα treatment was not needed after 12 weeks nor a better subsequent clinical or radiological outcome than a 3-month delayed initiation of anti-TNF in patients with still active disease despite MTX.[19] Of interest, DAS remission was seen more often in the arm receiving MTX first than in the combination treatment since the beginning. About 50% of the patients progressed in both arms, but progression was quite minimal.

Summarising all the studies from the literature, indirect data suggest a clear-cut role of the 3-month symptom duration as a possible window of opportunity.[20] Our study provides prospective data suggesting that VERA represents the ideal target for stopping the erosive course and leading the patient into remission. In this setting even an aggressive protocol, used beyond the window of opportunity, cannot be used to fully avoid progression, even though the radiological progression is minimal.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Catholic University of the Sacred Heart Ethics Committee.

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