In early inflammatory polyarthritis more intensive management according to the 2010 ACR/EULAR criteria leads to higher rates of clinical remission: comparison of two cohorts treated according to different treat-to-target protocols

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Abstract

Objective

The aim of this study was to compare the 12-month probability of remission in early inflammatory arthritis with a milder treatment based on the 1987 criteria or a more intensive protocol based on the 2010 criteria.

Methods

Patients with rheumatoid arthritis (RA) or undifferentiated arthritis (UA) (2005-2012) were included. Before October 2010, patients fulfilling the 1987 criteria received methotrexate (MTX) and possibly low-dose prednisone, while UA hydroxychloroquine (HCQ) (1987-driven cohort). From October 2010, patients fulfilling the 2010 criteria received higher dose MTX and low-dose prednisone, while UA HCQ (2010-driven cohort). Treatment was increased to achieve DAS28 low disease activity. Clinical remission, defined by DAS28, was evaluated at subsequent visits in the whole population. Hazard ratios (HR) adjusted for age, sex, baseline DAS28, symptoms duration, MTX dose and prednisone were calculated by Cox regression.

Results

677 patients were included (468 in 1987-driven cohort, 209 in 2010-driven cohort), with no significant differences in age, gender, autoantibodies and pain. The 2010-driven cohort had significantly fewer tender and swollen joints, lower acute phase reactants, DAS28 and HAQ and achieved more frequently remission even when the analysis was adjusted for all confounders (adjusted HR (95% CI) 1.73 (1.34, 2.22)) and limited to per protocol patients (adjusted HR (95%CI) 1.49 (1.11, 2.02).

Conclusion

Treating patients with early arthritis according to a more intensive protocol leads to higher remission rate. The results of this study support the use of a strategy led by the 2010 criteria with more intensive treatment strategies in the management of early arthritis.

Key words

csDMARDs, early arthritis, remission, treatment

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Introduction

Early diagnosis and treatment significantly improved the management of rheumatoid arthritis (RA) in the last decades (1). Clinical remission has therefore become one of the major targets of treatment, driving relevant outcomes such as structural damage, function and survival (2, 3). Due to this change of perspective, management strategies based on early, intensive and targeted interventions have been increasingly promoted in the last decade (4, 6).

In this context, the 1987 American College of Rheumatology (ACR) classification criteria for RA have shown a limited diagnostic performance in early arthritis (6, 7). For this reason in 2010 the ACR and the European League Against Rheumatism (EULAR) jointly developed new classification criteria for RA with the purpose to allow earlier classification and treatment (8). The criteria were developed on data from early arthritis cohorts and the use of disease-modifying anti-rheumatic drugs (DMARDs) within the first year of follow-up was chosen as reference standard to classify RA in order to minimise the influence of expert opinion on diagnosis, although even this approach does not fully compensate the lack of a reliable reference standard (9).

After their presentation the 2010 criteria were tested in external early arthritis populations, showing an overall performance comparable to that of the old ones (10, 11). Despite the criteria were developed for classification, and the interest of research focused on their diagnostic accuracy, the impact of classification on clinical decisions and therefore on clinical outcomes might be even of higher interest.

Since the 2010 criteria have shown a limited specificity, their early application might also classify as RA subjects with self-remitting forms of arthritis or patients with different diseases. This might lead to the overestimation of treatment effectiveness in trials performed after 2010 and it does not allow a direct comparison with patients classified with the 1987 criteria. The aim of this study is to evaluate two different treatment strategies based on the ACR 1987 criteria and the 2010 ACR/EULAR criteria, with different treatment protocols, in cohorts of patients with early inflammatory arthritis, including RA and undifferentiated arthritis (UA) in terms of achievement of a 12-month clinical remission.

Materials and methods

Consecutive patients presenting with joint symptoms referred to the Early Arthritis Clinic of the University Hospital of Pavia between January 2005 and December 2012 were considered for inclusion. Referral criteria and the detailed protocol are reported elsewhere (12, 13). Patients with a diagnosis of inflammatory arthritis were enrolled, after the exclusion of patients in which joint symptoms were caused by diseases other than RA or UA. At baseline, swelling and tenderness on 58 and 60 joints, erythrosedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), symptoms duration, hands and feet radiographs were evaluated. Visual analogue scale (VAS) for general health (GH), patient's global assessment (PtGA) and pain were recorded. Functional disability was measured through the Italian version of the Health Assessment Questionnaire (HAQ) (14). DAS28 was recorded at each visit. Patients in whom joint symptoms could be explained by diseases other than RA or undifferentiated arthritis (UA) and patients with less than 12 months of follow-up were not included in the analyses (Fig. 1). Before October 2010, the classification of patients and the subsequent selection of treatment was performed according to the ACR 1987 criteria and to the Visser criteria for prognostic stratification in UA (1987-driven cohort) (6, 15). Patients classified as RA or with UA and unfavourable prognostic features were treated with MTX starting from 10 mg/week, increased up to 20 mg/week to achieve low disease activity (DAS28 <3.2). Low-dose oral prednisone (12.5 mg/day for 2 weeks and 6.25 mg/day subsequently) was randomly assigned to about half of patients (11). The remaining patients with UA were treated with hydroxychloroquine (HCQ)

(200mg/twice daily for two months, 200 mg/day afterwards). Low-dose oral prednisone, prescribed based on the opinion of the treating rheumatologist, was permitted in UA.

After October 2010 the classification of patients and the choice of the treatment were performed according to the ACR/EULAR 2010 criteria (2010-driven cohort) (8). Patients classified as RA received MTX starting from 15 mg/week and increased up to 25 mg/week to achieve a DAS28 <3.2. Prednisone (5 mg/day) was prescribed to all patients unless contraindicated. All patients with UA received HCQ following the same protocol applied before 2010, without further prognostic classification.

Patients were seen every two months in the first semester and every three afterwards. The outcome of interest was the achievement of clinical remission, defined as DAS28 <2.6, in at least one follow-up visit in the first 12 months.

Statistical analysis investigated the association between the treatment strategy (1987-driven cohort *versus* 2010-driven cohort) and the probability of DAS28 remission within the first year. Such association was evaluated in two separate logistic and Cox proportional hazard regression models: the first one including all subjects, and a second one including only patients following the therapeutic strategy they were assigned to. Taking into account that historical trends and the different therapeutic regimens might have influenced selection and outcome, leading to better outcomes in and the 2010 cohort, the analyses were also corrected for possible confounders (age, sex, baseline DAS28, symptoms duration, MTX dose and use of prednisone). Proportional hazard assumption was verified. Results were presented as odds ratio (OR), hazard ratio (HR) and 95% confidence intervals (CI). All analyses were conducted using Stata v. 11 (StataCorp, College Station, Texas, USA).

Ethics, consent and permissions

The study was conducted according to the declaration of Helsinki: all patients signed a written informed consent before the inclusion and the study protocol was approved by the ethics committee of the IRCCS Policlinico San Matteo Foundation of Pavia.

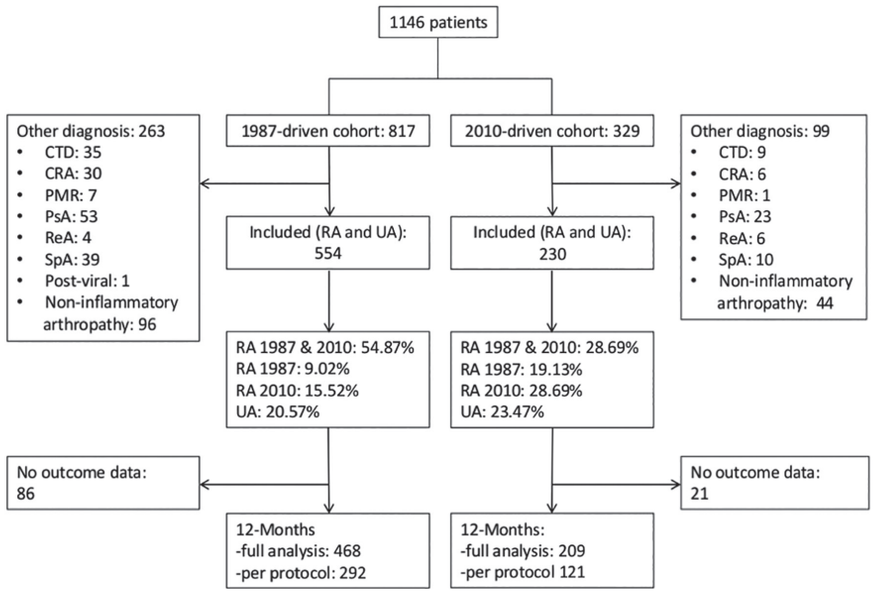

Fig. 1. Flow-chart showing patient selection. Selection process leading to the final composition of the 1987-driven and 2010-driven cohorts. CTD: connective tissue diseases; CRA: crystal-related arthritis; PMR: polymyalgia rheumatica; PsA: psoriatic arthritis; ReA: reactive arthritis; SpA: spondyloarthritis; RA: rheumatoid arthritis; UA: undifferentiated arthritis.

Results

A total of 1146 patients were evaluated. After the exclusion of patients with diagnoses other than RA or UA (in particular seronegative spondyloarthritis, crystal-related arthritis and connective tissue diseases) and patients not reaching a 12-month follow-up, we analysed 677 patients, 468 enrolled before October 2010 (1987-driven cohort) and 209 afterwards (2010-driven cohort) (Fig. 1). There were no statistically significant differences between the two cohorts for age, sex, VAS pain, RF and ACPA positivity. The proportion of patients seen within six weeks from symptom onset was not significantly different between the two populations as well. Patients on the 2010 cohort had less tender and swollen joints, lower ESR and CRP, lower mean DAS28 and median HAQ (Table I).

At 6 months 73/166 (43.8%) patients in the 2010 cohort were in remission, compared to 121/417 (29.0%) in the 1987 cohort (crude OR 1.92 (95%CI 1.32, 2.78)). The higher probability of remission in the 2010 cohort was still significant after adjusting for age, sex, baseline DAS28, symptoms duration, MTX dose and use of prednisone (adjusted OR 2.09 (95%CI 1.27, 2.45)).

Evaluating the probability of a first DAS28 clinical remission over the first 12 months of follow-up, the 2010 cohort had a significantly higher probability of remission in the analysis including all the patients (Crude HR (95%CI) 1.83 (1.5, 2.22)), even adjusting for age, sex, baseline DAS28, symptoms duration, MTX dose and use of prednisone (adjusted HR (95%CI) 1.73 (1.34, 2.22)). The higher probability of clinical remission in the 2010 cohort was confirmed when we limited the analysis to patients following the assigned therapeutic strategy (n=413) after the adjustment for the confounders (HR (95%CI) 1.49 (1.11, 2.02)) (Table II; Fig. 2).

Discussion

In the treatment of RA, it has been clearly shown that targeted strategies with DMARDs aiming at low disease activity or clinical remission lead to better outcomes (16) and the validity of this approach has also been demonstrated in patients with UA (17). In addition, the role of an early diagnosis and the early achievement of remission has been underlined (17, 3).

In this context, the 2010 ACR/EULAR criteria were developed to allow earlier

Table I. Baseline clinical and demographic characteristics of patients.

	1987-driven cohort	2010-driven cohort	*p*-value
Number (n)	468	209	
Female, n (%)	342/468 (73.1)	155/209 (74.2)	0.80
Age (years), mean (SD)	58.2 (14.6)	56.1 (15.7)	0.09
RA (2010 classification), n (%)	270/384 (70.3)	103/163 (63.2)	0.10
RA (1987 classification), n (%)	291/455 (63.9)	86/204 (42.2)	<0.0001
Symptom duration <6 weeks, n (%)	39/386 (10.1)	17/163 (10.4)	0.91
SJC28, median (IQR)	6 (3-10)	4 (2-7)	<0.0001
TJC28, median (IQR)	5 (2-10)	4 (2-8)	0.02
VAS pain (mm), median (IQR)	53 (39-80)	54 (30-74)	0.31
ESR (mm/h), median (IQR)	22 (13-39)	19 (10-34)	0.007
CRP (mg/dl) , median (IQR)	0.7 (0.31-2.09)	0.4 (0.3-1.2)	0.001
RF positivity, n (%)	156/416 (37.5)	57/145 (39.3)	0.69
ACPA positivity, n (%)	90/440 (20.5)	39/165 (23.6)	0.39
DAS28, mean (SD)	4.74 (1.25)	4.44 (1.14)	0.005
HAQ, median (IQR)	1 (0.5-1.625)	0.75 (0.375-1.25)	0.0001

Baseline clinical and demographic characteristics of patients with early inflammatory arthritis (either rheumatoid or undifferentiated) included in the study. n: number; SD: standard deviation; RA: rheumatoid arthritis; SJC28: swollen joint count on 28 joints; TJC28: tender joint count on 28 joints; IQR: interquartile range; VAS: visual analogue scale; ESR: erytrhosedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; DAS28: disease activity score on 28 joints; HAQ: health assessment questionnaire.

Table II. Probability of clinical remission within the first 12 months.

	Crude HR (95%CI)	Adjusted*HR (95% CI)
Full cohort (RA and UA)	1.83 (1.5, 2.22)	1.73 (1.34, 2.22)
Patients following the assigned strategy (RA and UA)	1.79 (1.39, 2.29)	1.49 (1.11, 2.02)

Hazard ratio of achieving for the first time clinical remission (DAS28<2.6) in the first 12 months of treatment. HR: hazard ratio; 95% CI: 95% confidence interval; RA: rheumatoid arthritis; UA: undifferentiated arthritis. *Adjusted for age, sex, baseline DAS28, symptoms duration, MTX dose and use of prednisone.

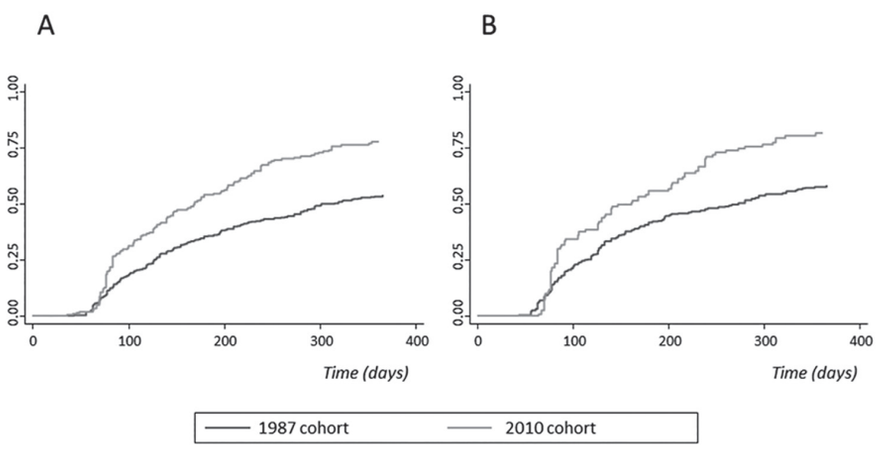

Fig. 2. Cumulative probability of the achievement of clinical remission.
Kaplan-Meier curves comparing the cumulative probability of achieving first clinical remission in patients treated following the 1987 criteria and the 2010 criteria. The results were adjusted for all the relevant confounders. **A**: analysis based on the entire population; **B**: analysis limited to patients following the therapeutic strategy they were assigned to (per protocol). Patients in the 2010-driven cohort achieved clinical remission more rapidly and frequently compared to patients in the 1987-driven cohort.

classification and treatment. Following their presentation they have been tested in external cohorts showing a good sensitivity but a lower specificity, although their usefulness to lead early treatment in a clinical setting had not been investigated yet. Considering the diagnostic performance of the criteria, a risk of overtreatment due to their use might be hypothesised, with the possible classification of self-remitting forms of arthritis or different diseases as RA. This does not allow a direct comparison of populations enrolled based on the 1987 or 2010 criteria, with the latter selecting patients who are more likely to achieve better clinical outcomes. In our study, the impact of the criteria was tested in two cohorts of early arthritis, including both RA and UA, enrolled based on the same features, so that the same proportion of subjects of self-remitting arthritis could be expected in the two populations. Patients presenting with features suggesting other disease were not included, although a proportion of misclassification might have occurred.

The two cohorts were significantly different in terms of extent of joint involvement, ESR and disability, suggesting the enrolment of patients with less severe clinical presentation in the 2010-driven cohort .

When we evaluated the impact of treatment driven by different sets of criteria, patients treated with higher DMARDs and corticosteroids, according to the 2010 criteria, had a greater probability to achieve clinical remission. This result was also supported by the secondary analysis based on patients following the assigned therapeutic strategy.

The presence of confounders, due to baseline differences between the groups in therapeutic protocol, has been taken into account in the analysis. After the correction for all confounders, and assuming the same proportion of subjects with self-remitting disease in both groups, patients treated following the 2010 criteria still achieved significantly more frequently early clinical remission.

The unsatisfactory diagnostic performance of the 2010 criteria emerged by their application in historical populations of early arthritis, while the present study enrolled a population of consecutive inflammatory arthritis patients. In this context, the use of the 2010 criteria for selecting treatment approach allowed more frequently the achievement of incident clinical remission during the first year of follow-up. This result is likely driven by the earlier introduc-

tion of MTX and, in general, to a more intensive treatment approach in patients presenting with milder disease than those that would be classified following the 1987 criteria. This is in line with the purpose for which the criteria were developed, that is to say earlier diagnosis and earlier exposure to DMARDs, however it cannot be excluded that the better clinical response in these populations might be partially due to the inclusion of patients with milder presentation or misclassification.

The study presents some limitations. First, an appropriate analysis on adverse events and on long-term functional and structural outcomes could not be performed because of missing data. Despite the adjustment, some further confounders with an impact on the results might still be present, possibly depending on the different recruiting periods and the use of different criteria. Moreover, the concurrent change of treatment strategies and classification criteria does not allow to evaluate these two aspects separately. Despite these possible limitations, this is to our knowledge the first prospective application of the classification criteria for RA to guide the choice of the treatment in a context of clinical practice, showing a potential benefit when considering consecutive patients presenting with inflammatory arthritis (UA or RA).

Further studies investigating concurrent cohorts and comparing classification criteria, clinical diagnosis and different treatment strategies might help fully clarify the applicability of this approach in clinical practice.

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