EXTENDED REPORT

Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study

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Received 2 February 2012
Accepted 20 May 2012
Published Online First 13 July 2012

ABSTRACT

Background To assess whether, in the real world of three early arthritis clinics, early referral could allow the best outcome, ie, remission, to be reached, and whether reaching the outcome was more dependent on therapy than on disease duration or vice versa.

Methods 1795 patients with early arthritis (symptom duration ≤12 months) were entered into a prospective follow-up study. 711 patients (39.6%) were diagnosed with rheumatoid arthritis (RA). Each RA patient was treated according to the local algorithm, in three tertiary referral centres (representing a small province, a medium sized province and a metropolitan area, respectively). Remission, defined using the disease activity score in 28 joints (DAS28 <2.6) and American College of Rheumatology (ACR) criteria, was the major outcome evaluated at the 12-month follow-up.

Results DAS28 remission was achieved in 34.3% (range 19.5–49%) of RA patients and ACR remission in 15.2% (range 8.5–20.6%). At the multivariate logistic regression analysis only two variables emerged as predictors of the major outcome: being in very early rheumatoid arthritis (VERA; less than 12 weeks symptom duration at the time of first treatment) and being on disease-modifying antirheumatic drugs (DMARD) within 3 months from disease onset. Among RA patients in remission, only 10% of VERA subjects received an anti-TNF blocker compared with 32.2% of non-VERA patients (p=0.002, OR 0.23, 95% CI 0.09 to 0.64).

Conclusions In a real-world setting, the 12 weeks disease duration and an early intervention with DMARD represent the most significant opportunities to reach the major outcome, ie, remission of RA. Moreover, VERA represents a window of opportunity in terms of cost saving.

INTRODUCTION

The early identification of rheumatoid arthritis (RA) represents the crucial step for controlling the progression of the disease. The new deal in rheumatology is early diagnosis and treatment in order to reach the major outcome, ie, remission, quickly RA. In 1970 Jacoby *et al*,[1] reporting on the outcome of RA with early disease, showed that 62 patients presenting with symptom duration less than 3 months had a significantly better outcome than 38 patients referred later. Therefore, already in the 1970s, there were data supporting the importance of an early diagnosis and an early therapeutic intervention. Over the past 10 years data have accumulated, clearly showing in at least four different clinical therapeutic settings, that treating a RA patient within the first 12–16 weeks from symptom onset can really lead to a clinically meaningful different outcome. In 2001 Lard *et al*,[2] when treating patients very rapidly after the first visit (within 15 days) compared with a slower intervention (4 months), showed that the radiographic progression in the rapid intervention subset was flat after the first 6 months, whereas it progressed over time up to 24 months in the slower intervention arm. The FinRACo trial[3] showed that a delay of 16 weeks in using disease-modifying antirheumatic drugs (DMARD) could lead to a lower chance of reaching remission. More recently, in the early arthritis clinics in Leiden, it was shown that a short symptom duration and an earlier therapeutic intervention before 12 weeks was associated with a greater chance of reaching drug-free remission.[4] In our own experience, 12 weeks disease duration was the best predictive factor for reaching disease activity score in 28 joints (DAS28) and/or American College of Rheumatology (ACR) remission, in a tight-aggressive therapeutic approach to early RA.[5] These data have been confirmed in another recent Dutch trial.[6] Therefore, both monocentric clinical cohorts and formal clinical trials suggest that a window of opportunity to reach the best outcome in RA really exists.

In 2007 (until 2009), the Italian Ministry of Health supported an observational prospective longitudinal study in three Italian referral centres, all with already active early arthritis clinics, in order to observe the behaviour of the referral, the delay before referral, through whom the referral occurred (general practitioners (GPs), other specialists or direct patient call), and the outcome of an early arthritis cohort referred to three different clinical settings, a small province, an intermediate province and a metropolitan area, using tight control strategies. The main purpose was to understand the role of an early referral on early RA outcome from diagnosis to therapy, to limit the costs related to this disease. Data suggest that in a real-world setting very early rheumatoid arthritis (VERA) represents the best opportunity to reach the major outcome, ie, full disease remission.

PATIENTS AND METHODS

All the patients referred to the early arthritis clinics of three tertiary referral centres (Ancona–Università Politecnica delle Marche, Pavia–Policlinico San Matteo and Rome–Catholic University of the Sacred Heart) between February 2007 and July 2009

were collected. Entry criteria for the first examination at the early arthritis clinics were two or more swollen joints dating from more than 2 weeks, but less than 12 months. All the subjects fulfilling the 1987 classification criteria for RA[7] at the first visit were defined as having early RA. All these early RA patients also retrospectively met the new 2010 RA classification criteria.[8] Among subjects diagnosed as having early RA, those with symptom duration of 3 months or less were defined as VERA.

The type of referral was recorded (GP, orthopaedic, physiatrist, other specialists, others). Patients satisfying RA criteria were collected in the database and followed up for at least 12 months. The follow-up study had the main aim of determining the major outcome of RA, and was restricted to the patients having moderate–high RA activity at baseline (DAS28 >3.2), in order to highlight more stringent results.

Clinical (DAS28, health assessment questionnaire; HAQ) as well as laboratory (acute phase reactants, IgM-rheumatoid factor, anticitrullinated protein autoantibodies; ACPA) data were collected over time. Seropositivity was defined as previously described.[9]

The follow-up visits were made at weeks 0, 4, 12, 20, 24, 36 and 52.

Local ethics committees gave approval to the study protocol.

Clinical assessments

Clinical assessments included tender joint count (28 joints), swollen joint count (28 joints), erythrocyte sedimentation rate, C-reactive protein and morning stiffness duration. Patient-reported outcomes included global assessments of pain and general health on 100 mm visual analogue scales and HAQ disability index.[10 11]

Workability was evaluated as described in a previous paper.[12] Data on comorbidities were collected from the clinical history of patients.

Study outcomes

The primary outcome was disease remission after 12 months of follow-up, according to a very liberal therapeutic protocol (according to local decisions), although strict and tight in terms of assessment timing. For the evaluation of disease activity, we used two sets of criteria: DAS28 and the ACR criteria for clinical remission in RA.[13] Disease activity according to DAS28 was interpreted as remission (DAS28 <2.6), low (2.6≤ DAS28 ≤3.2), moderate (3.2< DAS28 ≤5.1) and high (disease activity score in 44 joints >5.1) activity.

Treatment

Therapy adjustments were protocolised to occur at every visit and, based on the DAS28 assessment, treatment was intensified if the predefined targets (ie, DAS28 <2.6 for treatment with conventional DMARD and DAS28 <3.2 for treatment with anti-tumour necrosis factor alpha (TNFA) therapy) were not met.

At baseline, methotrexate was prescribed to all patients at an initial dose of 15 mg/week, and it was increased, if required, up to 25 mg/week. Once the patient, after 3 months of methotrexate, had not reached the major outcome, the use of a DMARD combination therapy or the addition of a biological anti-TNFα agent was adopted, according to the local physician's decision. The three centres managed their patient treatment according to their own decision, and no centralised protocol was used.

All patients gave their consent to enter into the study.

Radiology

Radiographs of hands and feet were taken at baseline and then annually. Radiographs were evaluated in chronological order by two observers (consensus score FS and EG) according to the modified Sharp–van der Heijde score.[14] Patients were classified as 'erosive' if the erosion score was 1 or greater, and progression was defined once a new erosion occurred, compared with baseline.

Statistical analysis

Categorical and quantitative variables were described as frequencies, percentages, means and standard deviations (mean±SD). The non-parametric Mann–Whitney U test was used to compare the continuous variables. Categorical variables were analysed using χ^2 test or Fisher's exact test. Differences among centres were analysed using the Kruskal–Wallis non-parametric test. The significance level was set at a p value less than 0.05.

A multivariate analysis was performed to examine which factors were associated with DAS28 remission at the 12th month of therapy in early RA patients with high–moderate disease activity at baseline. The variables related to 'DAS28 remission at the 12th month of therapy' with p≤0.10 in the univariate analysis were included in a multivariate logistic regression model with stepwise backward Wald elimination. The goodness of fit of the models was performed using the Hosmer–Lemeshow test. Results are expressed as OR and 95% CI.

Data were analysed using SPSS 17.0 software for Windows and Graph Pad Prism 5.0 software.

RESULTS

In the timeframe February 2007 to July 2009, 1795 patients with early arthritis were assessed. The diagnosis of RA was made in 711 (39.6%) of evaluated patients. In the remaining 1084 subjects, the following diagnosis was recorded: 550 (50.7%) undifferentiated polyarthritis (UPA); 227 (20.9%) psoriatic arthritis; 115 (10.6%) spondyloentesoarthritis; 56 (5.1%) microcrystal-related arthritis; 41 (3.8%) polymyalgia rheumatica; 22 (2.0%) reactive arthritis; 19 (1.8%) undifferentiated connective tissue disease. In 54 subjects a specific diagnosis was not made.

In particular, of the 1795 total early arthritis cohort, 355 patients were referred to the early arthritis clinic in Pavia, 948 patients in Ancona and 482 in Rome.

Referral

In the early arthritis clinics of Pavia and Ancona 60.1% of patients were referred by GPs, and the remaining by other specialists (20.4% by orthopaedics, 15.3% by physiatrists and 4.2% by other specialists). In Rome, 45% of patients were referred to the centre by physicians, while 55% of patients were directly referred to the early arthritis clinic (through a call centre organised for this purpose, and made known by brochures, internet, newspapers, TV).

UPA follow-up

All the subjects initially diagnosed with UPA were asked to have a follow-up. After 12 months, 463 out of the 550 UPA patients could be re-evaluated and 181 of them (39.1%) were diagnosed with RA during a further 12 months follow-up.

RA follow-up

Among the 711 subjects initially diagnosed with RA, 74% were women and the mean age was 54.7±12.4 years. Symptom duration at the time of RA diagnosis was 6.4±4.4 months and 148 (20.8%) subjects had VERA. The autoimmune phenotype was found in 46.3% of the patients who were ACPA positive and in 51.6% who were rheumatoid factor positive, with important differences among the three centres (table 1); 213 patients

Table 1 Summary of the outcomes according to the three different referral centres therapeutic approaches

	EAC 1	EAC 2	EAC 3	p Value 1 vs 2	p Value 1 vs 3	p Value 2 vs 3
Sex, female	78.8%	68.6%	74.5%	0.02	0.8	0.3
Age, years	53.8±13.5	54.2±8.8	57.3±14.8	0.8	0.01	0.003
Disease duration (months)	5.8±3.4	7.7±2.5	5.5±7.0	<0.001	0.001	<0.001
VERA (≤12 weeks)	32.6%	1%	49.6%	<0.001	0.01	<0.001
RF, % positive	67.8%	35.7%	51.2%	<0.001	0.002	0.01
Anti-CCP, % positive	68.6%	26.7%	38.2%	<0.001	<0.001	0.1
DAS28 T0	5.4±1.3	5.8±0.7	5.0±1.1	<0.001	0.008	<0.001
DAS28 T12	2.8±1.3	4.0±1.3	3.0±1.1	<0.001	0.03	<0.001
HAQ T0	1.2±0.7	1.1±0.4	1.2±0.7	0.3	0.7	0.1
HAQ T12	0.4±0.5	0.7±0.4	0.4±0.6	<0.001	0.6	<0.001
DMARD only T12 (% of patients)	78.5%	58.6%	98.6%	0.006	<0.01	<0.001
Anti-TNF therapy T12 (% of patients)	31.5%	41.4%	1.4%	0.14	<0.001	<0.001
DAS28 remission T12 (% of patients)	49%	19.5%	36.6%	<0.001	0.09	0.006
ACR remission T12 (% of patients)	20.6%	13.3%	8.5%	0.03	0.03	0.4

It can be seen that the approach was substantially different in the three early arthritis clinics.
ACR, American College of Rheumatology; CCP, cyclic citrullinated protein; DAS28, disease activity score in 28 joints; DMARD, disease-modifying antirheumatic drug; EAC, early arthritis clinic; HAQ, health assessment questionnaire; RF, rheumatoid factor; TNF, tumour necrosis factor; T0, baseline; T12, 12-month follow-up; VERA, very early rheumatoid arthritis.

(29.9%) had at least one erosion in hands or feet. Moderate–high disease activity (DAS28 >3.2) was present in 481 out of the 711 RA patients (67.7%), all were available for a full clinical and biological assessment at 12 months. This subgroup represented the cohort of completers-only analysis and the baseline and 12-month characteristics were shown in table 2. The RA patient group considered for the final analysis differed from the overall study cohort only by a higher DAS28 score and a higher percentage of erosions at baseline.

Primary outcome

Considering the primary outcome, 165/481 (34.3%) RA patients reached DAS28 remission at the 12-month follow-up. The other categories of DAS28 activity at 12 months are summarised in table 3. Seventy-three patients (15.2%) satisfied the ACR remission criteria.

Medications

At the 12-month follow-up, 329/481 patients (68.4%) were taking only DMARD (alone or in combination), whereas 152 (31.6%) were in combination therapy with TNFα blockers.

When we divided the RA patients based on the duration of symptoms, we found that at the 12-month follow-up 95 (90.5%) patients with VERA were on DMARD only, while 10 (9.5%) were on biological drugs, compared with 279 (74.4%) and 96 (25.6%), respectively, of patients with symptom duration greater than 3 months (p<0.001, OR 0.31, 95% CI0.15 to 0.61).

Moreover, among the 165 RA patients with disease remission at the 12-month follow-up, only five of 50 VERA subjects

Table 2 Clinical and biological characteristics of the 481 early RA patients who had a follow-up assessment of 12 months

Early RA patients n = 481	Baseline (T0)	Follow-up (T12)
Gender: female, n (%)	358 (74.4)	–
Age, years	54.4±12.0	–
Disease duration, months	6.4±3.3	–
VERA, n (%)	105 (21.8)	–
DMARD only, n (%)	–	329 (68.4)
Anti-TNF, n (%)	–	152 (31.6)
Tender joint count (28 joints)	9.0±5.3	2.8±3.3
Swollen joint count (28 joints)	6.4±4.6	1.8±2.4
PhGA (0–100)	49.8±20.1	24.8±25.4
PGA (0–100)	60.6±19.8	27.0±23.3
VAS pain (0–100)	59.3±22.4	24.4±21.9
GH (0–100)	55.9±19.7	58.7±28.9
HAQ (0–3)	1.15±0.6	0.5±0.5
ESR, mm/1st h	38.9±21.9	23.2±15.5
CRP, mg/l	23.0±26.0	8.6±12.6
DAS28	5.4±1.1	3.4±1.4
Erosive patients, n (%)	168 (34.9)	264 (54.9)

CRP, C-reactive protein; DAS28, disease activity score in 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; GH, general health; HAQ, health assessment questionnaire; TNF, tumour necrosis factor; PGA, patient global assessment; PhGA, physician global assessment; RA, rheumatoid arthritis; VAS, visual analogue scale; VERA, very early rheumatoid arthritis.

(10%) received an anti-TNF blocker, compared with 37/115 (32.2%) non-VERA patients (p=0.002, OR 0.23, 95% CI 0.09 to 0.64), suggesting that VERA requires a much lower use of anti-TNF treatment to obtain disease control.

x-Rays

Of the 481 RA patients, 34.9% were erosive at baseline, 54.9% were erosive at the 12th month. The mean annual progression rate in the overall cohort, according to the modified Sharp–Van der Heijde score, resulted in 5.8±6.2 units.

Comorbidities

Forty-one per cent of the patients had hypertension, 20% diabetes or thyroid diseases, 13% gastrointestinal diseases (gastritis or colitis) and 4.9% central nervous system vascular diseases.

Disability

At baseline, HAQ values in the total RA cohort were 1.2±0.6 and decreased to 0.5±0.5 at 12 months of follow-up. Thirty out of 481 patients (6.2%) maintained a HAQ of 1.5 or greater after 1 year of therapy, despite the early treatment and diagnosis, indicating a moderate grade of disability. Considering

Table 3 Major outcomes at the 12-month follow-up, following DAS28 cut-off points and ACR remission criteria, in the follow-up cohort

Disease activity status (T12)	No (%) of patients (total 481)
ACR remission	73 (15.2%)
DAS28 status	
Remission (≤2.6)	165 (34.3%)
Low disease activity (2.6–3.2)	88 (18.3%)
Moderate disease activity (3.2–5.1)	170 (35.3%)
High disease activity (>5.1)	58 (12.1%)

ACR, American College of Rheumatology; DAS28, disease activity score in 28 joints; T12, 12-month follow-up.

Table 4 Model predicting 12-month DAS28 remission in the follow-up cohort of 481 early RA patients with moderate–high disease activity at baseline

Variables	OR (95% CI)
DAS28 T0, <5.1=1	1.54 (0.94 to 2.51)
HAQ T0, <1.5=1	1.29 (0.75 to 2.23)
VERA, yes=1	**2.03 (1.25 to 3.30)**
Anti-CCP+, yes=1	1.39 (0.94 to 2.07)
Erosions T0, yes=1	0.47 (0.29 to 1.08)
DMARD within 3 months from disease onset, yes=1	**1.65 (1.06 to 2.55)**
Hosmer–Lemeshow test	p=0.59

CCP, cyclic citrullinated protein; DAS28, disease activity score in 28 joints; DMARD, disease-modifying antiheumatic drug; HAQ, health assessment questionnaire; T0, baseline; VERA, very early rheumatoid arthritis.
Bold type indicates that the p value is less than 0.05.

disease activity, 75% of patients in remission reached a HAQ less than 0.5 (no disability) compared with 30.7% of patients not reaching remission (p<0.001). Moreover, 62.7% of VERA patients achieved a HAQ less than 0.5 at 1-year follow-up compared with 41.3% of non-VERA subjects (p<0.001), regardless of achieving remission and despite similar HAQ values at baseline (1.22±0.73 in VERA and 1.11±0.54 in non-VERA, p=0.56).

Work ability

At the 12-month follow-up only 2.9% of the cohort, all patients doing heavy manual works, had lost their working place (data from Ancona and Rome).

Multivariate analysis

In the logistic regression analysis, having VERA (OR 2.02, 95% CI 1.25 to 3.30) and being on DMARD within the 3rd month (OR 1.65, 95% CI 1.06 to 2.55) emerged as predictors of DAS28 remission in the cohort of 481 RA patients (table 4).

DISCUSSION

Over the past few years, new data suggest that there are two main modalities to reach the major outcomes in RA: early and aggressive therapeutic approaches. However, the type and the efficacy of treatment is very much dependent on when the therapies are given. The FinRaCo trial,[3 15 16] showed that: a delay in therapy (>4 months) was the only significant predictor for remission in patients treated with the single-DMARD strategy, while no variable was a significant predictor for remission in those treated using the combination-DMARD strategy; at 2 years, 40% of patients in the combination-DMARD group and 18% in the single-DMARD group achieved remission (p<0.009), but at 5 years the difference between the groups disappeared (28% and 22%). Therefore, the only way to avoid negative structural outcomes is to start the appropriate treatment within 4 months.

In the present study, the mean percentage of remission achieved in early RA patients from the three centres involved, according to DAS28 criteria, was 34.3% (range 19.5–49%). This remission rate is quite similar to that obtained for the groups in the BeSt study (38–46% remission), but lower than other tight control studies (ie, FIN-RACo, TICORA, CAMERA).[3 17 18] It should be considered, however, that all these studies were randomised controlled trials and included established treatment protocols, while our study, being an observational study with broad individual autonomy in the choice of therapeutic regimen, may better reflect what happens in the real world of clinical practice.

Another important issue concerns the factors that may affect the achievement of remission. In the BeST trial, it was clearly shown that even the worst prognostic factors (rheumatoid factor, ACPA, shared epitope positivity) disappeared when patients were treated aggressively and promptly.[19] In the subgroup treated conventionally, all these factors persisted as negative prognostic markers. The main conclusion could be that only being aggressive in the therapeutic protocol can really lead the majority of patients to reach major outcomes, but the focus of these studies was on the therapeutic approach. In our report, the major predictor of remission was to have VERA, along with being on DMARD within 3 months from disease onset. Certainly, the study presents some limitations, mainly related to the variability of the patient baseline characteristics and to the different management and therapeutic strategies in the three centres. However, despite these differences, a symptom duration of less than 12 weeks emerged as a determinant of a really hard outcome such as remission. Moreover, having obtained these data in the real world adds strength to what has been seen recently in formal trials such as COMET, which showed important better outcomes in patients treated within 4 months from symptom onset.[20]

This finding is even more important because, unlike disease activity, erosions and autoantibody positivity, VERA is a modifiable factor through interventions on patient referral.

In a large cohort of early arthritis, van der Linden *et al*[4] recently found that only 31% of patients were evaluated within 12 weeks (the 'window of opportunity' period), yet the delay greatly influenced the outcome in terms of x-ray progression, as well as in terms of persistent remission. In our study, the percentage of RA patients seen within 12 weeks from symptom onset ranged between 1% and 50%, reflecting what was recently observed by Raza *et al*[21] in 10 centres from eight European countries. These results suggest that, to improve the outcomes in RA patients further, an important challenge is to ensure that patients with arthritis will be seen by a rheumatologist as early as possible after symptom onset.

Our observational study in a real-life setting allowed us to draw a clear-cut conclusion. The most important result is that the percentage of patients, with all their comorbidities, that can achieve remission is really high now. Despite the different results in terms of major outcomes among the three early arthritis clinics, starting therapy within 3 months' disease duration played the most important role, along with the early use of DMARD to achieve remission. VERA thus seems to represent a real window of opportunity, not only in terms of clinical outcomes but also in terms of pharmacoeconomy. In fact, we observed that patients with VERA achieve remission with a significantly lesser use of anti-TNF drugs compared with RA patients with a symptom duration of more than 3 months. This finding could enable savings to be made in pharmacological costs only by starting treatment as early as possible. Moreover, as it has been established that the annual RA costs have increased to €20 000 with a HAQ increase from 0.5 to 2, and that decreasing HAQ from 1.5 to 0.5 means a gain of at least US$4385 per year,[22] the significant decrease in HAQ values obtained with an early intervention, and in particular in VERA patients as seen in our study, appears to be cost saving.

Another important finding arising from this study is that referral is really different in a small province and in a metropolitan area. We observed that, in the metropolitan area, the minority of patients arrived through their GPs and the majority from

the call centre. The GPs seem to be really active in a small province, where it can be easier to create a collaboration network between the referral centre and the GPs, while the patient is more prone to decide himself in a metropolitan area. For this reason, in metropolitan areas, it seems appropriate to use the media (eg, internet, newspaper, TV, brochures) to raise awareness among the population, other than educating primary care physicians.

The take-home message that arises remains: diagnose early and treat to target within 12 weeks from symptom onset. The recommendation of the EULAR committee stating that 'Patients presenting with arthritis of more than one joint should be referred to and seen by a rheumatologist, ideally within 6 weeks after the onset of symptoms' remains of fundamental importance and appears to be increasingly supported by evidence-based data.[23] In this setting, it is crucial to minimise the delay in patient referral and interventions are required at all levels (patients, physicians and health systems) to ensure timely treatment for RA patients.

Contributors Study conception and design: EG, FS and GF. Acquisition of data: SLB, AC, FBP, EG and RC. Analysis and interpretation of data: EG, SLB, FS and GF.

Funding The study was supported by a grant from the Ministry of Health—protocol no. DGPREV F.3.a.d/2009/274. This funding source had no role in the design and conduct of the study, in collection, management, analysis and interpretation of the data and in preparation, review or approval of the manuscript.

Competing interest None declared.

Patient consent Obtained.

Ethics approval Local ethics committees gave approval to the study protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

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