

Remission in early, aggressive rheumatoid arthritis: a multicentre prospective observational Italian study ARPA (Artrite Reumatoide Precoce Aggressiva)

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Abstract Objectives

To provide a survey of disease activity in patients treated with standard care in Italian clinical practice.

Methods

This was an observational prospective cohort study in patients with early, aggressive rheumatoid arthritis (RA; duration ≤ 2 years but ≥ 6 weeks; DAS28 > 3.2) naïve to anti-tumour necrosis factor (TNF) therapy who were treated with disease-modifying anti-rheumatic drugs (DMARDs) and/or biologics according to standard practice at 15 Italian ARPA (Artrite Reumatoide Precoce Aggressiva) centres. Patients were evaluated at baseline and after 6, 12 and 24 months. The primary endpoint was the proportion of patients achieving remission, as defined by disease activity score in 28 joints (DAS28) < 2.6 , after 1 year.

Results

Among the 152 patients enrolled, 92 were evaluable after 1 year and 77 after 2 years for DAS28. At baseline, patients had a mean DAS28 of 6.1 ± 1.0 . At 12 months, 62.6% of patients were treated with DMARDs (in monotherapy or in combination), and 37.4% with anti-TNFs (in monotherapy or in association with DMARDs). At 24 months, 35.1% were receiving anti-TNF therapy. The rate of DAS28 remission rates at 12 months and 24 months were 28.3% (95% confidence interval [CI] 19.1–37.5) and 41.6% (95% confidence interval [CI] 30.6–52.6), respectively.

Conclusions

The remission rate was lower at 12 months compared with previous large randomised clinical trials for early, aggressive RA, but significantly improved at 24 months. These results suggest that patients in real-world clinical settings in Italy may experience a delay in receiving the best possible care.

Key words

rheumatoid arthritis, remission, anti-TNF, DMARDs

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease affecting primarily the joints and involving approximately 0.5–1% of the general population. Both environmental and genetic factors seem to be responsible for the susceptibility and phenotype. Indeed, genetic factors have been demonstrated in twin and family studies to be responsible for approximately 60% of susceptibility (1).

It is established that in patients with RA, progressive joint destruction causes loss of function (2), with the restriction of daily living and the deterioration of quality of life (QoL). This condition results in high indirect costs (3) and can lead to increased mortality (4). It is now well established that treatment of RA should be started early and should be aggressive to suppress active inflammation status and to slow disease progression (5, 6).

Joint destruction may occur very early in the course of RA, with 40% of patients presenting radiographically detectable joint erosions 6 months after the onset of symptoms (7). Magnetic resonance imaging examination can detect bone oedema and soft tissue lesions at an even earlier stage of the disease. These appear to be predictive of bone erosions, as demonstrated in a 2-year follow-up study (8). However, RA patients with long-standing disease are less likely to respond to treatment (9). In spite of traditional therapy, RA often progresses over the years and produces disabling damage to soft and hard joint tissue (10). The current consensus is that early treatment, with the goal of achieving clinical remission, is required to prevent permanent damage (11, 12).

Disease-modifying anti-rheumatic drugs (DMARDs) alone or in combination have been the mainstay of treatment for RA (13–15). Nevertheless, before the recent era of biological therapy, clinical remission was not commonly reported with conventional DMARDs (16), unless an aggressive multidrug combination therapy or a tight control strategy is used (17). Combination therapy with methotrexate (MTX) and anti-tumour necrosis factor (TNF) agent seems to be the most efficacious

in this respect, nearly halting structural progression and producing clinically relevant responses, as demonstrated in several trials (18–20).

There are no data describing treatment of early, aggressive RA in routine clinical practice in Italy. Thus, the aim of this study was to provide a survey of routine practice in Italian rheumatology units, and to report the observed response to current treatments in Italian patients outside of the controlled clinical trial setting.

Methods

This multicentre, observational, prospective study was conducted in 15 Italian rheumatology centres. A total of 152 patients with early, aggressive RA, diagnosed according to the American College of Rheumatology (ACR) 1987 criteria, were enrolled (21).

Patients in the Artrite Reumatoide Precoce Aggressiva (ARPA, *i.e.* early, aggressive RA) study fulfilled the following criteria: age ≥ 18 years with active RA at enrolment (disease activity score in 28 joints [DAS28] > 3.2); having a disease duration of ≤ 2 years but at least 6 weeks from the onset of symptoms; rheumatoid factor (RF) > 20 UI/dl and/or a positive result for anti-citrullinated peptides/proteins antibodies (ACPA); erythrocyte sedimentation rate (ESR) ≥ 28 mm/h (Westergren method) or C-reactive protein (CRP) ≥ 20 mg/l. Enrolled patients were naïve to anti-TNF and DMARD treatment, including MTX, or were receiving one or more DMARD(s) without complete response. Patients who had participated in an interventional clinical study during the preceding 2 years were excluded.

Treatments

Patients were not randomised and physicians selected the most suitable treatment for each patient according to routine clinical practice at the centre. Treatments received at 12 months were defined as follows:

- 1) Patients receiving anti-TNF – those who had received at least one of these agents for at least 6 months and were still receiving it, or had stopped within 6 months of follow-up;
- 2) Patients receiving DMARDs – those

who had received at least one of these agents, were still receiving it, and had not received anti-TNF or other biologics;

- 3) Patients receiving corticosteroids – those who had received at least one of these agents, were still receiving it at follow-up, and had not received anti-TNF, other biologics or DMARDs.

At 24 months treatments were defined as follows:

- 1) Patients receiving anti-TNF – those who had received at least one of these agents during 24 months follow-up.
- 2) Patients receiving DMARDs – those who had received at least one of these agents during 24 months follow-up and had not received anti-TNF or other biologic agents.
- 3) Patients receiving other biologics – those who had received at least one of biologic agents during 24 months follow-up and had not received anti-TNF.
- 4) Other – those who had received other treatments during observation period.

Evaluation

Patients were evaluated at baseline and every 6 months thereafter. Evaluations included tender and swollen joint counts (0–28), visual analogue scale (VAS) for pain, and global health assessment by the patient and the physician. ESR and CRP levels were also registered. Disease activity was calculated by means of disease activity score (DAS) in 28 joints, according to the algorithm of Prevoo *et al.* (22). QoL was evaluated using the general (Medical Outcomes Study (MOS) 36-Item Short Form Health [MOS-SF-36] and Euro-Qol [EQ-5D]) and disease-specific Stanford Health Assessment Questionnaire (HAQ) instruments after 12 and 24 months of follow-up. The response to therapy was evaluated according to the European League against Rheumatology (EULAR) guidelines (23) and by using the ACR 20, 50 and 70 criteria for clinical improvement (24).

End points

The primary end point was the proportion of patients in remission, as defined

by DAS28 <2.6 at 12 months. Secondary end points were the proportion of patients in DAS28 remission after 24 months, ACR 20, 50 and 70 responses, and the evaluation of QoL and safety after 12 and 24 months of follow-up.

Safety

During the follow-up, all adverse events (AEs) were recorded at each visit on study Case Report Forms. Tolerability was evaluated by calculating the percentage of patients with at least one AE during the 12- and 24-months follow-up. All early and late AEs were recorded. An AE was defined as the appearance of any unfavourable or unintended sign, symptom or disease that could be associated with the use of a drug. Serious AEs were those resulting in death, persistent or significant disability or disease that was life-threatening and/or that required hospitalisation or prolongation of a hospital stay. Serious and non-serious AE rates and those for infusion-related AEs (those occurring during or 24 hours after completion of an infusion) and infectious AEs were calculated separately.

Statistics

The summaries include descriptive statistics [mean, standard deviation (SD), sample size] for the continuous parameters, and absolute frequencies and percentages for categorical parameters.

Two statistical analyses were performed: one was executed on patients observed for 1 year (with baseline and 12-month follow-up visits completed; $n=107$) in order to evaluate the primary endpoint, the other one on patients observed for 2 years (with baseline, 12-month and 24-month follow-up visits completed; $n=94$) in order to evaluate secondary endpoints.

The proportion [and its 95% confidence interval (CI)] of patients in remission (DAS28 <2.6) after 1 year of observation was calculated as the ratio between patients with DAS28 <2.6 at 12-month follow-up visit and patients observed for 1 year. Similarly patients with DAS28 <2.6 after 2 years have been taken into account with respect to all the patients observed for 2 years.

The EULAR response criteria classify

patients as good, moderate or non-responders, using the individual amount of change in DAS28 (low, moderate or high) and the DAS28 reached (20). The proportion of patients who achieved good, moderate or no response after 24 months was evaluated. The reduction in intensity and number of signs and symptoms was described by the ACR 20, 50 and 70 criteria. The frequency of patients who reached, respectively, 20%, 50% and 70% improvement after 24 months was estimated (24).

Scores from the SF-36 eight health domains were calculated and summarised by descriptive statistics. Response to items of EuroQol were described by absolute and relative frequency.

Changes in HAQ score during the follow-up period and the proportions of patients with HAQ >0.5 and HAQ ≤0.5 at baseline and after 2 years were calculated. The correlation between the changes in HAQ score and in DAS28 score from baseline visit was evaluated by Pearson and Spearman correlation coefficients. Similarly, the correlation between the variation of HAQ score and the variation of ESR score from baseline visit was calculated.

Finally, safety was assessed by calculating the proportion of patients with at least one AE occurring during the 2-year observation period.

To calculate an adequate sample size for evaluating the primary objective of DAS28 remission after 1 year, the results of a previous randomised controlled clinical trial with early RA (25) were considered, wherein 15% of patients treated with MTX and 31% treated with MTX combined with anti-TNF achieved remission after 12 months. Given that the choice of therapy was made by the clinical investigators according to local clinical practice, the lowest remission rate was considered. A sample of 200 patients would have allowed to evaluating 15% of patients in remission $\pm 5.5\%$ (95% confidence interval), assuming a 20% drop-out rate. The observed sample size was lower than previewed, but the extent of the observed phenomenon was higher. The study was conducted according to good clinical practice and patients provided written informed consent at the

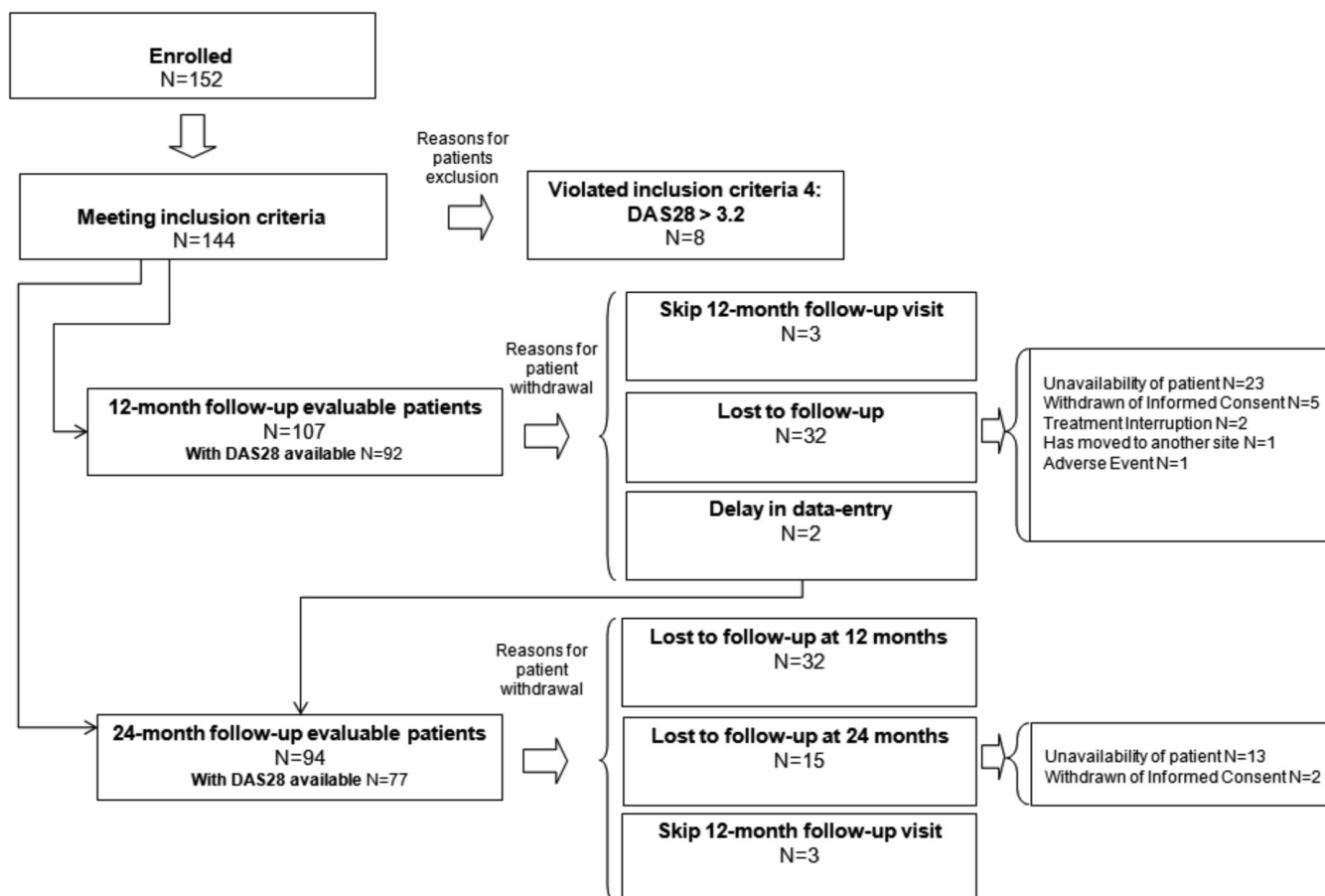


Fig. 1. A patient disposition chart with the identification of the patients considered during statistical analysis.

screening visit. The study protocol was approved by the local ethics committee and registered with ClinicalTrials.gov (no. NCT00267852).

Results

The ARPA study was conducted from 2005 to 2010. A total of 152 patients

were enrolled. At baseline, 91% of patients were receiving any therapy for RA. Specifically, 63% were receiving DMARDs (76% of which, MTX); according to inclusion criteria, no patients were receiving anti-TNFs. At baseline, 129 patients (95.6%) were RF positive.

At the 12-month follow-up, 107 patients (70.4%) were evaluated; at 24-month follow-up, 94 (61.8%) were evaluated, with respectively 92 and 77 patients evaluable for DAS28 score (Fig. 1). Subjects excluded from statistical analyses were compared to evaluable patients for clinical and

Table I. Clinical and laboratory characteristics of the patients' cohort at baseline and after 12 and 24 months of follow-up.

	Baseline (n=152)	12 months (n=107)	24 months (n=94)	p-value
M/F	31/121	24/83	22/72	–
Age years (mean±SD)	52.3 ± 14.0	52.3 ± 15.1	51.8 ± 14.6	–
Disease duration years (mean±SD)	0.53 ± 0.59	1.6 ± 0.61	2.55 ± 0.62	–
DAS28 (Mean±SD)	6.11 ± 0.99	3.29 ± 1.41	3.11 ± 1.36	<0.0001*
Number of tender joints (mean±SD)	12.1 ± 6.4	3.41 ± 3.91	2.51 ± 3.37	<0.0001*
Number of swollen joints (mean±SD)	8.6 ± 5.7	1.71 ± 2.35	1.47 ± 2.76	<0.0001*
ESR mm/h (mean±SD)	40.2 ± 21.4	20.55 ± 16.3	21.64 ± 18.71	<0.0001*
CRP mg/dl (mean±SD)	7.4 ± 31.5	1.37 ± 3.78	1.90 ± 7.13	<0.0001*
VAS for pain (mean±SD)	65.0 ± 21.4	30.94 ± 25.81	27.27 ± 23.88	<0.0001*
VAS for global health assessment by the patient (mean±SD)	63.4 ± 16.1	29.07 ± 24.59	25.66 ± 23.41	<0.0001*
VAS for global health assessment by the physician (mean±SD)	71.1 ± 17.4	21.45 ± 20.15	17.76 ± 17.77	<0.0001*
Morning stiffness (minutes, mean±SD)	75.6 ± 53.7	19.72 ± 27.68	25.66 ± 23.41	<0.0001*

M: male; F: female; DAS28: disease activity in 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; VAS: visual analogue scale. *p-value is significant for both 12 and 24 months compared to baseline.

demographic characteristics, namely age, gender, DAS28, number of painful and swollen joints (on 28 joints), ESR, CRP, RF, patients assessment of pain (VAS 0-100), general health or patient's global assessment of disease activity, physician's global assessment of disease activity, morning stiffness. No statistically significant differences were observed ($p>0.14$ for each variable; data not shown).

The demographic, clinical and laboratory characteristics of the patients' cohort at baseline and after 12 and 24 months of follow-up are reported in Table I.

Clinical efficacy

A significant reduction in all of the clinical and laboratory parameters ($p<0.0001$) was observed at 12 and 24 months of follow-up compared with baseline. Considering the primary end point of our study, 28.3% (26/92) of evaluable patients showed remission (defined as DAS28 <2.6) at 12 months. The rate of patients in remission at 24 months was 41.6% (32/77 evaluable patients). In particular, looking at the subgroup of patients for which DAS28 mean score was assessable at 12 and 24 months, a significant reduction was observed during the follow-up: DAS28 mean score was 6.09 (SD=1.06) at baseline; 3.29 (SD=1.41) at 12 months and 3.11 (SD=1.36) at 24 months. The improvement of DAS mean score at follow-up versus baseline was statistically significant ($p<0.01$) (Fig. 2).

At 12-months follow-up, 62.6% of evaluable patients received therapy with DMARDs alone, while 37.4% received anti-TNF for at least 6 months (in monotherapy or in association with DMARDs). After 24-months follow-up, the percentage of patients treated with anti-TNF increased to 41.5%, while 54.3% of patients received therapy with DMARDs alone. Finally, 4.3% of patients were treated with biologics other than TNF antagonists (rituximab, three patients, and abatacept, one patient).

At 12 and 24 months, 92.5% and 89.6% of patients, respectively, showed any response according to EULAR criteria; at 12 months 51.3% (41/80) of evaluable patients achieved a good response and

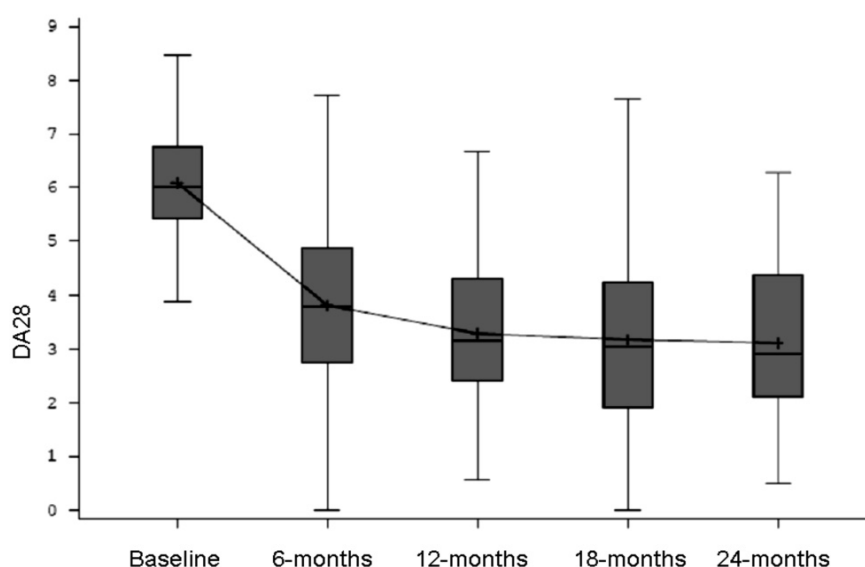


Fig. 2. Changes in mean DAS28 values during the follow-up. DAS28: disease activity in 28 joints.

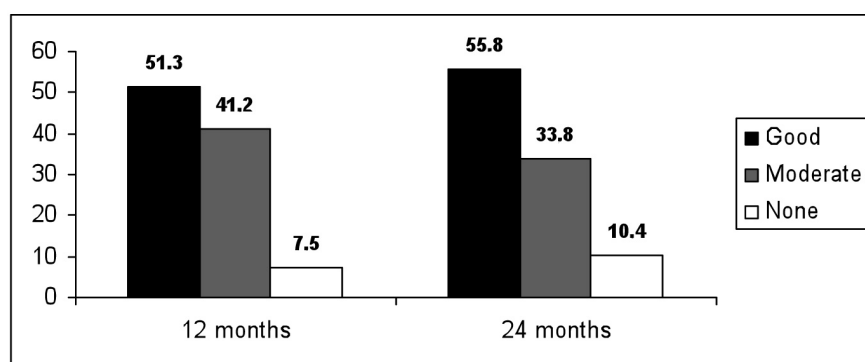


Fig. 3. Distribution of EULAR response at 12 and 24 months. EULAR: European League Against Rheumatology.

41.2% (33 patients) achieved a moderate response. At 24 months, 55.84% (43/77) of evaluable patients achieved a good response and 33.8% achieved a moderate response (Fig. 3).

ACR20, 50 and 70 responses were 73.4% (69 patients), 53.2% (50) and 32.9% (31), respectively, at 12 months; at 24 months, the responses were 75.5% (71 patients), 61.7% (58) and 44.7% (42) for ACR20, 50 and 70, respectively (Fig. 4).

When considering steroid treatment, 42.3% of subjects in remission status at 12 months were receiving steroid treatment. Steroid therapy was assumed by 32% of patients in remission after 24 months of follow-up.

Health assessment and QoL

The changes in HAQ values during

the study are reported in Fig. 5. The mean HAQ values showed a significant decrease from baseline ($p<0.01$) at each time point. Moreover, HAQ changes showed a significant positive correlation with changes in DAS28 and ESR levels at 24 months follow-up ($p<0.0001$ and $p=0.005$, respectively). After 12 months, a reduction in HAQ below 0.5 was registered in 62.5% of patients with HAQ >0.5 at baseline.

Table II shows the values of SF-36 items at baseline and after 24 months of follow-up. A significant reduction in physical and mental health items was observed, with a significant correlation with changes in DAS28 ($r=0.58$ and $r=0.44$, respectively; $p<0.001$ for both correlations). Moreover, a significant improvement in all EuroQol items was

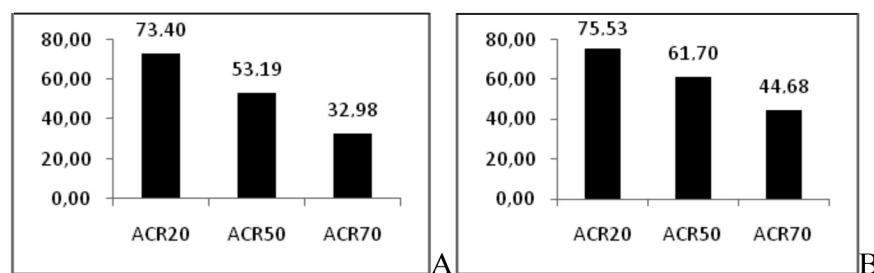


Fig. 4. ACR20, 50 and 70 response at 12 (A) and 24 months (B). ACR: American College of Rheumatology.

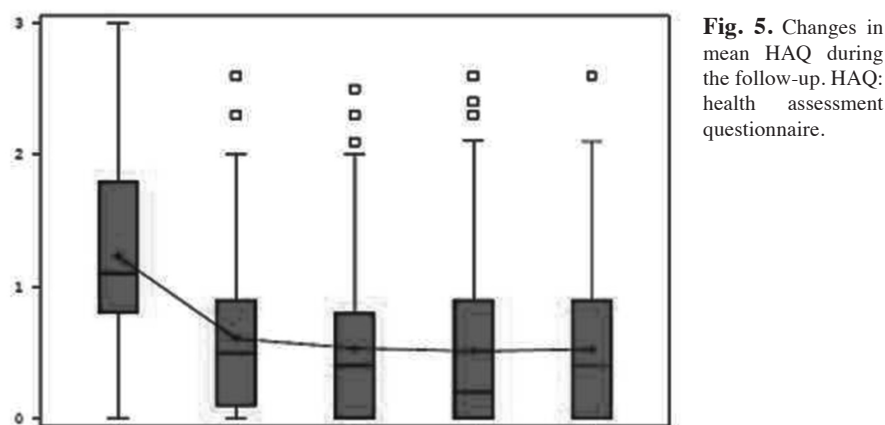


Fig. 5. Changes in mean HAQ during the follow-up. HAQ: health assessment questionnaire.

Table II. Values of SF-36 items, expressed as mean \pm SD, at baseline and after 24 months of follow-up.

SF36 items	Baseline	24-months	p-value
Physical function (Mean \pm SD)	48.2 \pm 28.7	72.0 \pm 25.8	0.001
Role physical (Mean \pm SD)	18.3 \pm 32.8	57.1 \pm 42.9	0.001
Body pain (Mean \pm SD)	38.7 \pm 18.8	49.1 \pm 19.7	0.003
General health (Mean \pm SD)	42.7 \pm 18.4	54.7 \pm 18.7	0.002
Vitality (Mean \pm SD)	53.5 \pm 24.0	75.6 \pm 25.5	0.001
Social function (Mean \pm SD)	38.3 \pm 43.3	75.0 \pm 37.1	0.001
Role emotional (Mean \pm SD)	29.7 \pm 17.9	56.6 \pm 23.2	0.001
Mental health (Mean \pm SD)	54.7 \pm 15.8	62.6 \pm 16.3	0.006

SF-36: short form-36.

registered. Changes in EuroQol items at 24 months of follow-up are shown in Figure 6.

Safety

Treatment was generally well tolerated. The safety evaluation performed after 12 months showed that 81% (87/107) of patients did not report any AE, while 13% (14/107) reported having one AE, 3.7% (4/107) reported two events, and 0.9% (1/107) reported three or four AEs. The most frequent AEs were diarrhoea and increase of liver enzymes (two instances each). No TB events were reported. No serious AEs were

reported during the 24-month observation period.

Discussion

In the ARPA study, we examined treatment practices and outcomes for early, aggressive RA in Italian clinical practice. RA is a chronic inflammatory disorder characterised by progressive inflammatory synovitis and destruction of articular cartilage and marginal bone (26). It has been demonstrated that moderate disability within 2 years of diagnosis is relatively frequent in patients affected by RA, with inability to work after 10 years from diagnosis in

up to 30% of patients (27). Data from a number of studies show that joint erosions may appear within the first 6 months of disease in the majority of patients, with a rapid progression over the first year of disease course (28, 29). Early intervention and combination therapy, rather than monotherapy, appear to provide the most favorable outcomes in patients with early, aggressive RA (30, 31).

In this study, we showed that in Italian clinical practice, more than 90% of patients with early, aggressive RA undergo any form of treatment 6 months from disease onset, with 63% of these are treated with DMARDs. This is in agreement with recent EULAR recommendations that patients should receive DMARDs as soon as a diagnosis is formulated. This can lead to lower disease activity or to remission (32), while a delay in the start of DMARDs may lead to a worse outcome (33, 34). In the majority of the cases in our study (73%), patients were treated with MTX. This drug represented the first line of intervention in most cases, as recommended by EULAR (25, 35).

In recent years, the employment of TNF-antagonists has revolutionised RA clinical practice, provided new treatment options, and established low disease activity and remission as achievable goals (36). The reduction of signs and symptoms of disease and the slowing or inhibition of joint damage progression have been described in several clinical trials involving long-standing and early RA patients treated with TNF-antagonists (25, 37).

The results of the ARPA study document a significant improvement from baseline in all of the response criteria, disease activity scores and QoL questionnaires after 12 and 24 months of observation. In our cohort, 37.4% of evaluable patients started anti-TNF during the first 12 months of follow-up because they were non-responders to conventional therapy. This percentage rose significantly (41.5%) at 24 months, indicating that these patients needed to switch from DMARDs, mainly due to lack of efficacy (as very few AEs were registered). It is also interesting to note that the switch to anti-TNF was pre-

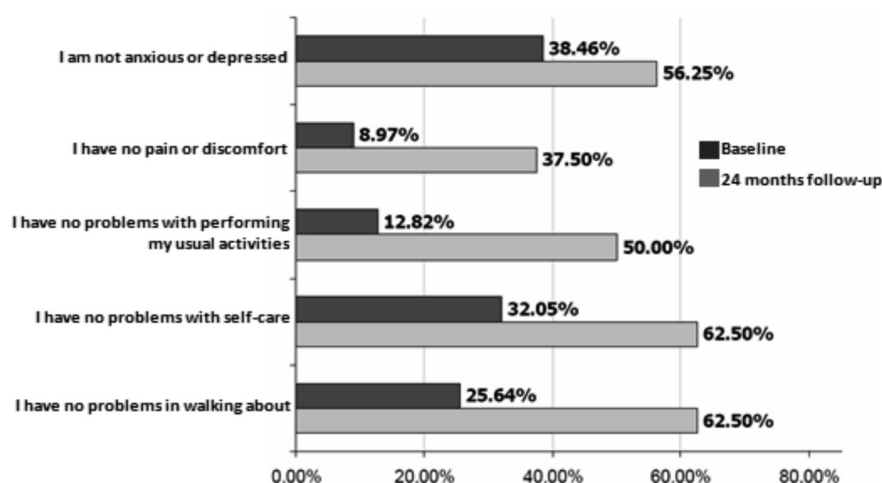


Fig. 6. EuroQoL rate of response at baseline and after 24 months of follow-up.

ferred to combination therapy. This is generally in accordance with EULAR recommendations, suggesting a good fit of Italian clinical practice with published data (32).

Thanks to the innovations in therapeutic approaches in RA, remission is now an achievable goal in many patients in clinical trials and in clinical practice, especially in patients with early disease. A rapid attainment of remission may prevent joint damage irrespective of synthetic or biologic DMARD agents (38, 39). Nonetheless, in spite of the fact that remission cannot always be achieved, low disease activity is desirable, especially in patients with long-standing RA (40).

In the ARPA study, one-third of patients went into remission after 12 months of follow-up, a percentage that increased to 40% at 24 months follow-up. Moreover, any response to therapy (EULAR criteria) was achieved in 92.5% and 89.6% of patients after 12 and 24 months of follow-up, respectively. ACR20, 50 and 70 were obtained in 73.4%, 53.2% and 33.0% of patients, respectively, at 12 months of follow-up, and in 75.5%, 61.7% and 44.7% of patients, respectively, at 24 months.

When considering patients treated in this cohort of subjects, despite treatment, the percentage of patients achieving remission was lower compared with those in randomised trials on biologics. In fact, the percentage of remission was 28.3% after 12 months of follow-up in our study, while it was 43% in

the PREMIER study (adalimumab + MTX vs. placebo) and 50% in COMET study (etanercept + MTX vs. placebo) (20). A lower percentage of patients in the ARPA study achieved ACR50 at 12 months (53.2%) compared with the PREMIER and COMET studies (71% and 62%, respectively).

More recently, Shahouri *et al.* described the application of ACR/EULAR remission criteria for RA in clinical practice, confirming the discrepancy between remission in clinical trials and remission in clinical practice (41).

Several reasons could explain this discrepancy in remission rate, despite the comparable demographic characteristics among RA populations. Indeed, there are some fundamental differences between the design and conduct of randomised controlled trials and community-based studies. In randomised trials, an idealised clinical environment is used to test drug efficacy. Often, patients with comorbidities (multi-morbidity) and elderly patients are excluded. Moreover, the protocol defines the treatment strategies, drug doses and combinations. In contrast, community-based studies are conducted in a 'real-life' situation, involving a wide spectrum of clinical situations in the (relative) absence of exclusion criteria. These substantial differences may influence the outcomes and the lower remission and response rates registered in our population compared with a randomised trial.

Relatively few data are available from European registries regarding clinical

outcome measure in the real-life scenario, probably because of the nature of observational studies, which are not exactly appropriate to measure efficacy objectives. Nevertheless, a recent analysis from the British Society for Rheumatology Biologics Register (BSRBR) described patient characteristics at initiation of biologic treatments and relative clinical outcome, including DAS28 remission rate. Interestingly, in the period observed (2001–2008), there was a significant trend towards an earlier use of anti-TNF therapies in patients with less severe disease, which also correlated with higher rate of DAS28 remission at 1 year (42). In line with this result, the Canadian CORONA registry showed a greater likelihood of remission in RA patients treated earlier rather than later in disease course (43). In Europe, the NOR-DMARD registry supports significantly better responses for the MTX + anti-TNF than for MTX + DMARD combination for most disease outcomes at both 3 and 6 months. Subjects who started MTX + anti-TNF after two synthetic DMARD regimens had failed had a tendency to less favourable disease states after 3 months than patients who switched directly from MTX to MTX + anti-TNF (44). More recently Descalzo *et al.*, in a large cohort of patients with early RA in Spain, underlined as patients may benefit from attending structured and organised programs for the management of disease. Disease activity, evaluated by means the DAS28, improves in patients with early referral, early diagnosis, and early therapy (45).

With regard to patient-reported outcomes, patients in the ARPA study significantly improved in health-related QoL as well as in disability indexes. Such improvement could be related to amelioration of disease activity and, thus, reduction of disability. Regarding the safety of the therapies prescribed, treatments were generally well-tolerated, as shown by the absence of serious AEs. Also, the reported AEs were sporadic in nature, with no more than two each for any event.

In conclusion, given the importance of achieving remission as early as possible, together with the efficacy of an

early, aggressive intervention, making remission an achievable goal, routine standards of care for patients with early RA could be improved in Italian clinical practice. Moreover, we suggest that further data on patients with early RA are needed.

The study was conducted in 15 centres in Italy: Arenzano, Bari, Brescia, Ferrara, Genova, Jesi, Messina, Napoli, Padova, Palermo, Pavia, Pisa, Roma, Siena, Torino.

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References

- PERRICONE C, CECCARELLI F, VALESINI G: An overview on the genetic of rheumatoid arthritis: a never-ending story. *Autoimmun Rev* 2011; 10: 599-608.
- WOLFE F, HAWLEY DJ: The longterm outcomes of rheumatoid arthritis: Work disability: a prospective 18 year study of 823 patients. *J Rheumatol* 1998; 25: 2108-17.
- YELIN E, WANKE LA: An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. *Arthritis Rheum* 1999; 42: 1209-18.
- WOLFE F, MITCHELL DM, SIBLEY JT *et al.*: The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 481-94.
- HARAOUI B, POPE J: Treatment of early rheumatoid arthritis: concepts in management. *Semin Arthritis Rheum* 2011; 40: 371-88.
- 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.
- ANDERSON PJ: Tumor necrosis factor inhibitors: clinical implications of their different immunogenicity profiles. *Semin Arthritis Rheum* 2005; 34: 19-22.
- HANNONEN P, MOTTONEN T, HAKOLA M, OKAM: Sulfasalazine in early rheumatoid arthritis. A 48-week double-blind, prospective, placebo-controlled study. *Arthritis Rheum* 1993; 36: 1501-9.
- MCQUEEN FM, BENTON N, CRABBE J *et al.*: What is the fate of erosions in early rheumatoid arthritis? Tracking individual lesions using x rays and magnetic resonance imaging over the first two years of disease. *Ann Rheum Dis* 2001; 60: 859-68.
- SYMMONS D, TRICKER K, HARRISON M *et al.*: Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs – results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial. *Rheumatology* (Oxford) 2006; 45: 558-65.
- KNEVEL R, SCHOELS M, HUIZINGA TW *et al.*: Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 987-94.
- 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.
- BOERS M, VERHOEVEN AC, MARKUSSE HM *et al.*: Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; 350: 309-18.
- O'DELL JR, HAIRE CE, ERIKSON N *et al.*: Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; 334: 1287-91.
- DOUGADOS M, COMBE B, CANTAGREL A *et al.*: Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999; 58: 220-5.
- WOLFE F, HAWLEY DJ: Remission in rheumatoid arthritis. *J Rheumatol* 1985; 12: 245-52.
- SOKKA T, MAKINEN H: Remission makes its way to rheumatology. *Arthritis Res Ther* 2010; 12: 129.
- 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.
- VAN DER BIJLA AE, GOEKOOP-UITERMAN YP, DE VRIES-BOUWSTRA JK *et al.*: Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 2129-34.
- EMERY P, BREEDVELD FC, HALL S *et al.*: Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008; 372: 375-82.
- ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
- PREVOO ML, VAN 'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LB, VAN RIEL PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
- FRANSEN J, VAN RIEL PL: The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* 2005; 23 (Suppl. 39): S93-9.
- FELSON DT, ANDERSON JJ, BOERS M *et al.*: American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
- 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.
- LEE DM, WEINBLATT ME: Rheumatoid arthritis. *Lancet* 2001; 358: 903-11.
- SOKKA T, HÄKKINEN A: Poor physical fitness and performance as predictors of mortality in normal populations and patients with rheumatic and other diseases. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S14-20.
- VAN DER HEIJDE DM, VAN LEEUWEN MA, VAN RIEL PL, VAN DE PUTTE LB: Radiographic progression on radiographs of hands and feet during the first 3 years of rheumatoid arthritis measured according to Sharp's method (van der Heijde modification). *J Rheumatol* 1995; 22: 1792-6.
- LINDQVIST E, JONSSON K, SAXNE T, EBERHARDT K: Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 611-6.
- O'DELL JR, LEFF R, PAULSEN G *et al.*: Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46: 1164-70.
- PINCUS T, O'DELL JR, KREMER JM: Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: a preventive strategy. *Ann Intern Med* 1999; 131: 768-74.
- SMOLEN JS, LANDEWE R, BREEDVELD FC *et al.*: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; 69: 964-75.
- NELL VP, MACHOLD KP, EBERL G, STAMM TA, UFFMANN M, SMOLEN JS: Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology* (Oxford) 2004; 43: 906-14.
- LARD LR, VISSER H, SPEYER I *et al.*: Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001; 111: 446-51.
- VERSTAPPEN SM, JACOBS JW, VAN DER VEEN MJ *et al.*: Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007; 66: 1443-9.
- FURST DE: Development of TNF inhibitor

- therapies for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2010; 28 (Suppl. 59): S5-12.
37. EMERY P, FLEISCHMANN RM, MORELAND LW *et al.*: Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naïve patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009; 60: 2272-83.
 38. MIERAU M, SCHOELS M, GONDA G, FUCHS J, ALETAHA D, SMOLEN JS: Assessing remission in clinical practice. *Rheumatology* (Oxford) 2007; 46: 975-9.
 39. SOKKA T, HETLAND ML, MAKINEN H *et al.*: Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries. *Arthritis Rheum* 2008; 58: 2642-51.
 40. SMOLEN JS, ALETAHA D, BIJLSMA JW *et al.*: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; 69: 631-7.
 41. SHAHOURI SH, MICHAUD K, MIKULS TR *et al.*: Remission of rheumatoid arthritis in clinical practice: application of the American College of Rheumatology/European League Against Rheumatism 2011 remission criteria. *Arthritis Rheum* 2011; 63: 3204-15.
 42. HYRICH KL, WATSON KD, LUNT M, SYMONS DP: Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. *Rheumatology* (Oxford) 2011; 50: 117-23.
 43. FURST DE, PANGAN AL, HARROLD LR *et al.*: Greater likelihood of remission in rheumatoid arthritis patients treated earlier in the disease course: results from the Consortium of Rheumatology Researchers of North America registry. *Arthritis Care Res* (Hoboken) 2011; 63: 856-64.
 44. LIE E, VAN DER HEIJDE D, UHLIG T *et al.*: Treatment strategies in patients with rheumatoid arthritis for whom methotrexate monotherapy has failed: data from the NOR-DMARD register. *Ann Rheum Dis* 2011; 70: 2103-10.
 45. DESCALZO MÁ, CARBONELL J, GONZÁLEZ-Álvarez I *et al.*: Effectiveness of a clinical practice intervention in early rheumatoid arthritis. *Arthritis Care Res* (Hoboken) 2012; 64: 321-30.