Anti-TNF treatment response in rheumatoid arthritis patients with moderate disease activity: a prospective observational multicentre study (MODERATE)

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Abstract

Objective

Rheumatoid arthritis (RA) patients with moderate disease activity show progression of joint damage and have impaired quality of life, physical function, work and daily activities. Little is known about management of patients with moderate RA. The aim of the study was to assess the 1-year response to anti-TNF in biologic-naïve RA patients with moderate (3.2 <DAS28 ≤5.1) disease activity despite DMARD treatment, in the Italian clinical practice.

Methods

The MODERATE study is a multicentre prospective, cohort non-interventional study, conducted in 19 Italian rheumatology sites. Patients with moderate RA, diagnosed according to the 2010 American College of Rheumatology (ACR)/EULAR criteria, were enrolled if they also were aged ≥18 years, had disease onset after 16 years old, moderate disease at baseline (DAS28 score >3.2 and ≤5.1), and were naïve to anti-TNF treatment.

Results

Among 157 RA patients, 93 (59%) underwent etanercept, 43 (22%) adalimumab, 26 (17%) certolizumab, 10 golimumab and 2 infliximab; 80% of patients were still in treatment after 12-month observation. One-year clinical remission was achieved by 27 RA patients (21%), reduction of DAS28 score greater than 1.2 was observed in 75 (58%) patients. Moderate and good response according to EULAR criteria was observed in 59 (46%) and 45 (35%) patients, respectively.

Conclusion

Results confirm the efficacy of anti-TNF alpha also in moderate RA patients, who may achieve a substantial decrease of disease activity, and improve their quality of life. The low rate of patients achieving remission may suggest that therapeutic strategies should be more timely and aggressive.

Key words

moderate rheumatoid arthritis, observational study, anti-TNF-alpha, treatment persistence, DAS28

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Introduction

Rheumatoid arthritis (RA) is a multifactorial inflammatory disease involving 0.5–1% of the general population. The environmental and genetic factors interplay determining disease susceptibility and phenotype (1). RA primarily involves the joints, with the development of progressive joint destruction and consequent loss of function, restriction of daily living and the deterioration of quality of life (2).

Current recommendations for RA treatment suggest the introduction of an adequate treatment as soon as possible, not only to limit symptoms and clinical manifestations but also to prevent irreversible joint damage associated with disease progression (2). An early and aggressive treatment with DMARDs seems effective in controlling the inflammatory process and the erosive damage progression in many patients. Conversely, a delay in the introduction of DMARD treatment may lead to worse clinical outcome (3).

As recommended by the European League Against Rheumatism (EULAR), Methotrexate (MTX) represents the first choice for the treatment of RA due to its efficacy both as monotherapy and in combination with other drugs. As well established, the administration of biological agents, including those directed against tumour necrosis factor (TNF) in refractory or intolerant patients, can improve the clinical outcome of RA patients with a severe disease activity (4).

Several evidences demonstrated that patients with moderate disease activity show progression of joint damage and have an impaired quality of life, physical function, work and daily activities. This subset of patients represents 40% of whole RA population (5). Nonetheless, only few studies have been specifically conducted on RA patients with moderate disease activity (5, 6). Moreover, the use of biologic agents in this population is restricted in some countries.

These data suggested us the need for additional information on the management of patients with moderate RA. Thus, in this multicentre longitudinal non-interventional study, we aimed to assess the response to anti-TNF in biologic-naïve RA patients with moderate (3.2 >DAS28 ≤5.1) disease activity despite DMARD treatment in the Italian clinical practice.

Materials and methods

This multicentre, observational, prospective, cohort study was conducted in 19 Italian rheumatology sites.

Patients with moderate RA, diagnosed according to the 2010 American College of Rheumatology (ACR)/EULAR criteria, were enrolled (7). The patients had to fulfill the following inclusion criteria: age ≥ 18 years, onset of disease at age grater then 16 years, active disease at baseline and DAS28 score >3.2 and ≤5.1. All patients had received a previous treatment with DMARDs and/or corticosteroids and started for the first time an anti-TNF treatment at enrolment. The protocol study included the following exclusion criteria: (i) presence of at least one of the following concomitant diseases ongoing at the time of enrolment: cancer or history of cancer (other than resected cutaneous basal cell or squamous cell carcinoma) within 5 years before baseline, serious infections including HIV+ and tuberculosis (TB), other ongoing autoimmune connective tissue disorders, congestive heart failure (class III/IV NYHA, New York Heart Association), kidney significant disease according to clinical opinion; (ii) pregnant or breast-feeding females; (iii) concomitant assumption of prednisone (or an equivalent drug) >25mg/day; (iv) immunodeficiency symptoms; (v) inclusion in a clinical trial or applying to a clinical trial at the time of the enrolment.

Standard protocol approvals and patient consents

The regional competent ethical standards committees on human experimentation approved the MODERATE study. A written informed consent was obtained from all participants in the study according to the Declaration of Helsinki, other than a privacy consent.

Clinical and laboratory evaluation

The study protocol included a baseline visit at enrolment and follow-up assess-

ments at 3, 6 and 12 months. Clinical evaluation included tender and swollen joint counts (0–28), patient's assessment of pain on visual analogue scale (VAS, 0–100) and global health assessment by the patient and the physician (GH, 0–100). The erythrocyte sedimentation rate (ESR, mm/h) and C-reactive protein levels (CRP, mg/dl) were also measured. Disease activity was calculated by means of disease activity score (DAS) in 28 joints, according to the algorithm of Prevoo *et al*. (8).

The 2011 ACR/EULAR definition of remission (9) could not be considered as it was not yet published at the moment of the MODERATE study protocol design (in 2010). Nevertheless, the new CDAI index was computed as additional analysis and applied to our study in order to have a deeper evaluation of the disease activity. We evaluated the response to treatment according to the EULAR criteria and by using the ACR 20, 50 and 70 criteria for clinical improvement (10-11).

Moreover, all patients completed the disease-specific Stanford Health Assessment Questionnaire (HAQ) (12, 13).

End Points

The primary end-point of the present study was the evaluation of changes of disease activity, assessed by means of DAS28, at the 12-month follow-up. As secondary end-points we aimed at evaluating disease activity changes also after 3 and 6 months from baseline, the proportion of the responder patients according to ACR 20, ACR 50, ACR 70 after 3, 6 and 12 months of follow-up and of patients in remission according to DAS28 values (<2.6) after 6 and 12 months of observation. Moreover, we aimed at describing the pharmacological RA treatments received both before enrolment and during study observation period, and the modifications of HAQ values during follow-up.

Safety

All the adverse events (AEs) occurring during the study follow-up were recorded on study case report form. The percentage of patients with at least one AE during the 12-month follow-up period was calculated. An AE was defined as every sign, symptom or any unwanted or unexpected clinical condition occurring after the sign of the informed consent form until the end of patient's observation period. Serious AEs were those resulting in death, congenital anomaly/birth defect, persistent or significant disability/incapacity or disease that was life threatening and/or that required inpatient hospitalisation or prolongation of a hospital stay. Serious and non-serious AE rates were provided.

Sample size

Sample size was evaluated considering data from a previous study conducted by Marotte *et al*. (10) on subjects with RA in treatment with anti-TNF drugs, where 64% of patients with a DAS28 at 12 months variation greater than 1.2 was observed. A sample of 200 patients was expected, corresponding to 140 evaluable patients at 12 months follow-up, assuming a 30% drop-out rate. With such sample size, the two-sided 95% confidence interval (CI) for the proportion of patients with a DAS28 improvement of at least 1.2 points after 12 months was expected to be equal to 64% ± 7.95%, corresponding to a relative error (ratio between 95% confidence interval half width and expected proportion) of 12%. In the MODERATE study, a number of enrolled patients lower than predefined (168 *vs*. 200) was observed at baseline, but a drop-out rate lower than 30%, allowed use to observe a number of eligible patients at 12 months higher than expected (157 *vs*. 140 expected).

Statistics

All patients who met inclusion-exclusion criteria were considered evaluable for the analyses. The summaries include descriptive statistics [mean, standard deviation (SD), median, interquartile range, minimum, maximum, sample size] for the continuous parameters, and absolute frequencies and percentages for categorical parameters. Statistical tests were performed to evaluate changes from baseline in clinical parameters of RA.

The proportion of patients with significant change in DAS28 score (*i.e*. ΔDAS28 >1.2) after 3, 6 and 12 months of observation was calculated as the ratio between subjects with greater than 1.2 DAS28 score variation from baseline and all evaluable subjects with DAS28 score available at follow-up visit. DAS28 was evaluated using ESR or CRP, follow-up DAS28 score was evaluated with the same method (ESR or CRP) used at baseline. Clinically meaningful improvement in HAQ was defined as reduction from baseline ≥0.22. A Kaplan-Meier analysis was performed to evaluate anti-TNF drug persistence. Time to treatment withdrawal was the time elapsed between the first anti-TNF start date and the date of the first anti-TNF withdrawal. Patients were censored if they dropped out for reasons out of anti-TNF withdrawal or they were still taking the first anti-TNF at the end of observation period. Overall and stratified by anti-TNF active Kaplan-Meier curves were provided.

Data were analysed using SAS for Windows, release 9.2 (SAS Institute Inc). Statistical analyses, project management, clinical and site monitoring and quality control were performed by MediData (Modena, Italy) using internal procedures, in compliance with the Italian privacy law.

Results

Overall, 168 RA patients were enrolled in the study, of whom 157 were eligible for the analysis (M/F 20/137; mean age 54.7±12.8 years; mean disease duration 5.4±5.8 years; mean time occurred from the symptoms onset 6.8±6.1 years). Fifty-two patients (33.1%) suffered from past or ongoing concomitant diseases; the most common comorbidities were cardiovascular diseases (29; 18.5%), followed by endocrine diseases (12; 7.6%) and gastrointestinal diseases (8; 5.1%). At enrolment 49 (31.2%) patients showed erosions.

All patients received a previous treatment with DMARDs and/or corticosteroids, mainly methotrexate (140; 89.2%), corticosteroids (100; 63.7%), hydroxychloroquine (40, 25.5%) and leflunomide (33, 21%). The majority of patients who received methotrexate and corticosteroids were still in treatment at baseline (96 out of 140 patients

who received methotrexate and 95 out of 100 patients who received corticosteroids, respectively).

According to study protocol, all the patients started anti-TNF treatment at the baseline: 109 (69.4%) of them started it as add-on therapy (anti-TNF plus ongoing DMARDs). Etanercept was administered to 59.2% of patients (n=93), 21.7% (n=34) of patients received adalimumab. Certolizumab, golimumab and infliximab were administered to 16.6% (n=26) , 6.4% (n=10) and 1.3% of patients (n=2), respectively. Moreover, biological drugs other than anti-TNF were prescribed during the follow-up: specifically, abatacept was prescribed in two patients (1.3%) and rituximab in one case. Methotrexate was the DMARD treatment most frequently associated with biological therapy (96 patients, 61.1%).

Table I displays clinical and laboratory data of the RA patients at the 4 timepoints evaluated in the study protocol. All the parameters showed a significant reduction from baseline at each timepoint. DAS28 at baseline was computed using ESR or CRP in 127 (80.9%) and 30 (19.1%) subjects, respectively.

At the 12-month follow-up, 27 RA patients (20.9%) reached a clinical remission, defined as a DAS28 value lower than 2.6 and low disease activity (DAS28 <3.2) was achieved by 50% of patients (n=64) (Fig. 1).

At the same time point, 13% of patients (n=16) showed remission and 55% (n=70) low disease activity, according to CDAI index. CDAI disease activity at each time point is displayed in Figure 2.

At 12 months, 75 patients (58.1%) showed a reduction of DAS28 >1.2. The evaluation of EULAR response demonstrated that good/moderate/no response was reached by 44 (33.1%)/ 40 (30.1%)/ 49 (36.8%) patients after 3 months, compared with 47 (37.3%)/ 35 (27.8%)/ 44 (34.9%) after 6 months, and 59 (45.7%)/ 45 (34.9%)/ 25 (19.4%) at 12 months (Fig. 3A). Therefore, a significant increase of responder patients percentage was noted (3 months *vs*. 12 months, p=0.002; 6 months *vs*. 12 months: p=0.01). Moreover, we evaluated the prevalence of response according to ACR criteria: fifty-six patients (39.4%) reached the ACR20 response after 3 months, with a significant increase of this percentage after 12 months (85 patients, 63.4%, p<0.0001) (Fig. 3B).

Older mean age at enrolment was the only factor associated with a poor response: a statistically significant difference in terms of mean age was

Table I. Clinical and laboratory parameters at baseline, 3-, 6- and 12-month follow-up visits.

	Baseline	3 months	6 months	12 months	*p*-value
DAS28 (mean±SD)	4.5 ± 0.5	3.7 ± 1.2	3.4 ± 1.1	3.2 ± 0.9	<0.0001*
no. tender joints (mean±SD)	5.7 ± 2.8	3.7 ± 3.6	3.2 ± 3.5	2.3 ± 2.6	<0.0001*
no. swollen joints (mean±SD)	2.9 ± 2.6	1.8 ± 2.4	1.2 ± 1.8	0.8 ± 1.3	<0.0001*
ESR, mm/h (mean±SD)	28.3 ± 20.9	22.1 ± 15.8	21.1 ± 15.3	20.5 ± 14.0	0.0005° <0.0001§
CRP, mg/dl (mean±SD)	3.9 ± 8.9	2.1 ± 3.3	1.8 ± 2.7	1.6 ± 2.5	<0.04*
Patient's global assessment (VAS, 100 mm; mean±SD)	55.9 ± 19.5	41.3 ± 24.1	38.0 ± 23.5	32.7 ± 21.0	<0.0001*
Physician's global assessment (VAS, 100 mm; mean±SD)	49.8 ± 17.3	31.6 ± 19.1	29.4 ± 17.3	24.4 ± 15.3	<0.0001*
HAQ (mean±SD)	1.2 ± 0.8	0.8 ± 0.7	0.8 ± 0.7	0.7 ± 0.7	<0.0001*

t-test of parameter variation at each follow-up visit from enrolment. Test performed out of the total number of patients with parameter available at each visit. *All the comparisons *vs*. baseline; °3 months *vs*. baseline; §6 months *vs*. baseline and 12 months *vs*. baseline.

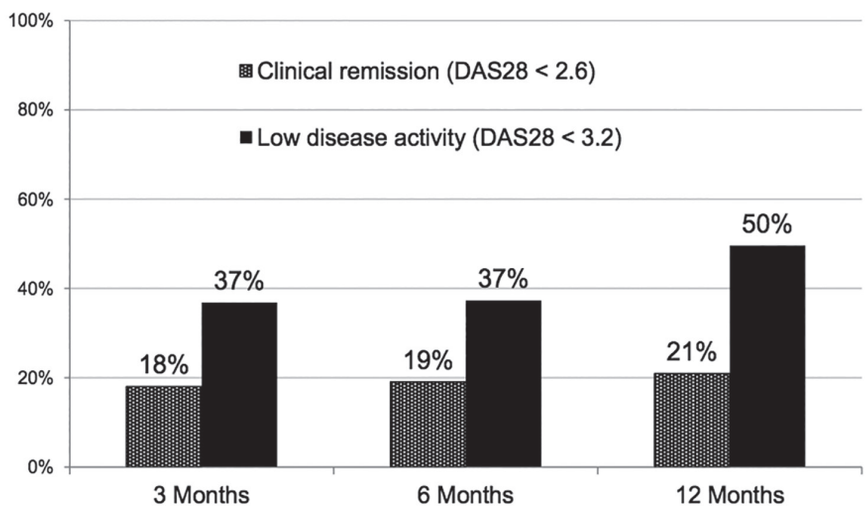

Fig. 1. Clinical remission (DAS28 < 2.6) and low disease activity (DAS28 < 3.2) at each follow-up visit.

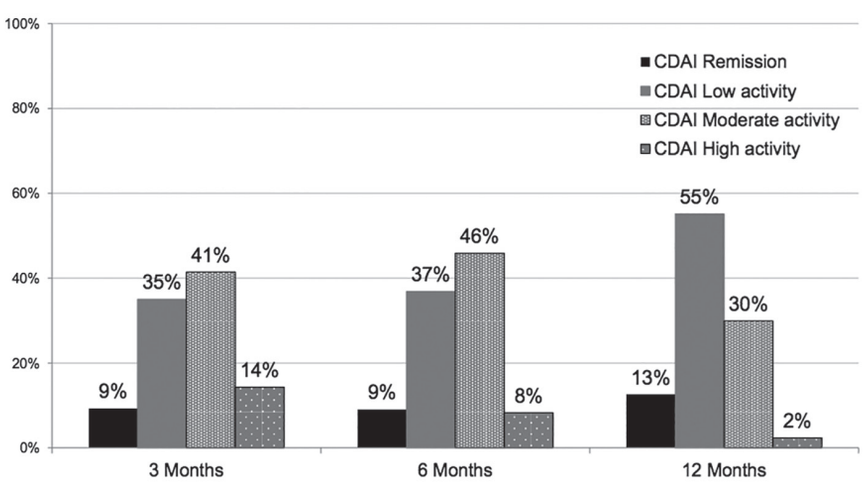

Fig. 2. CDAI disease activity at each follow-up visit.

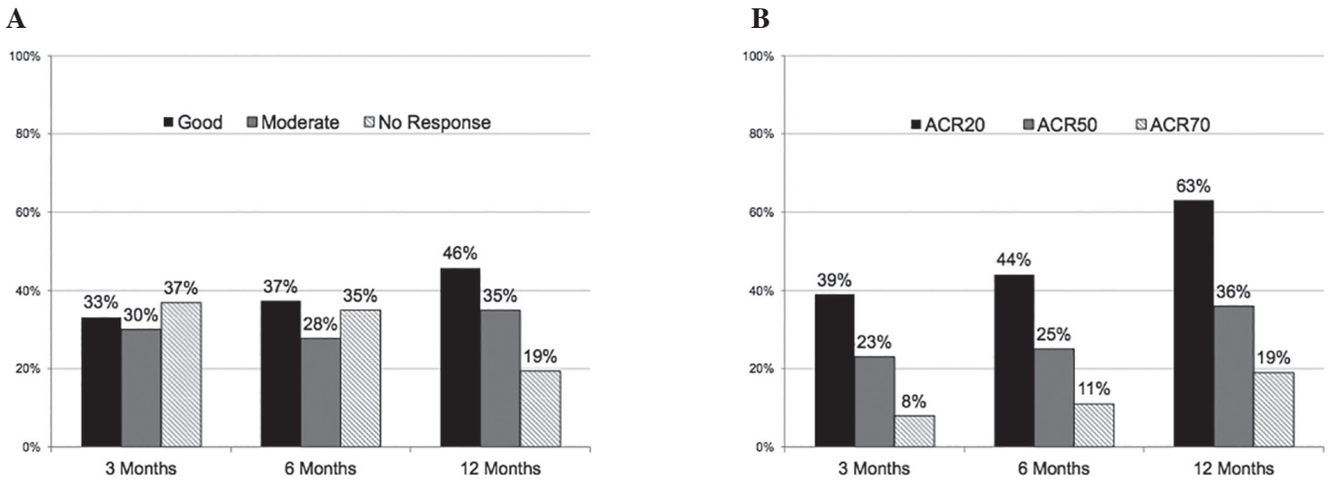

Fig. 3. Percentage of patients reaching a clinical response according to EULAR and ACR definitions.

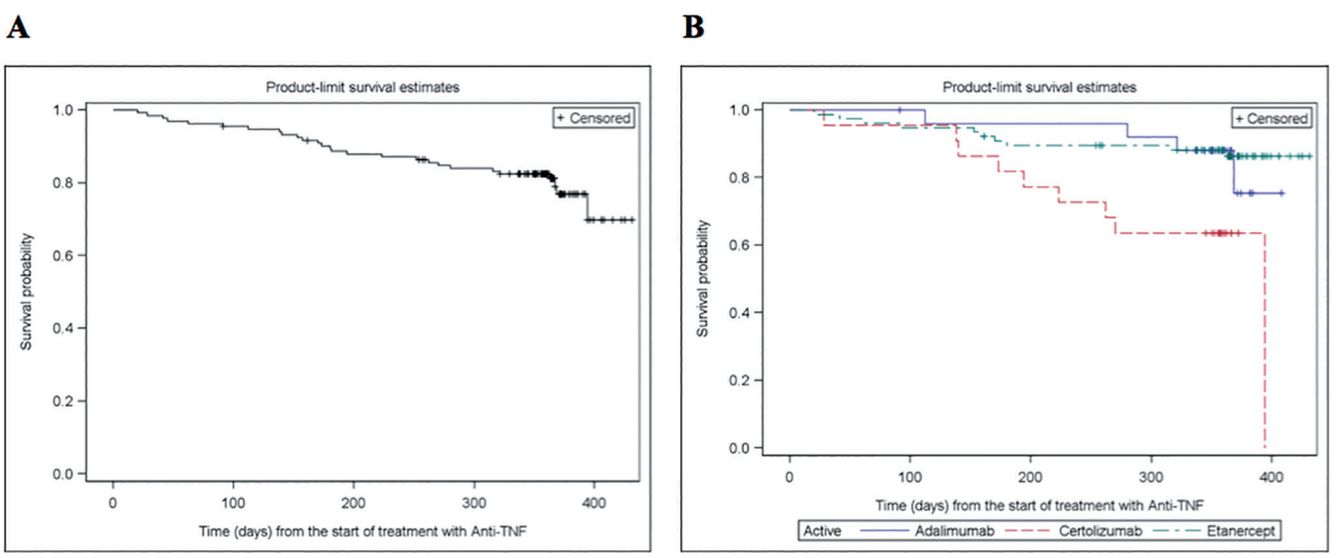

Fig. 4. Overall and stratified anti-TNF persistence (Kaplan-Meier curve).
(**A**) Kaplan-Meier curve of overall anti-TNF persistence during observation period, (**B**) Kaplan-Meier curve of anti-persistence stratified by the most frequently administered drugs (etanercept, adalimumab, certolizumab). Concerning the certolizumab curve, at day 394 we observed the treatment interruption of the only patient who was still treated: therefore, the probability of remaining in treatment is 0 and the Kaplan-Meier curve steps down to a 0 value.

detected between patients reaching a good/moderate response according to EULAR criteria (n=104) compared to non-responders (n=25) at 12 months follow-up (53.1±12.7 *vs*. 58.9±12.4 years; p=0.039).

As reported in Table I, a significant reduction of the HAQ score was observed at each time-point. Moreover, 75 patients (56.0%) showed an HAQ values improvement greater than 0.22. Finally, anti-TNF persistence was evaluated by means of Kaplan-Meier survival curve. Figure 4A displays data concerning the overall anti-TNF survival: according to Kaplan-Meier survival estimates, after 12 months, the cumulative probability of remaining in treatment with the same anti-TNF drug administered at enrolment was 81.2%. Figure 4B shows anti-TNF survival curve stratified by the most frequently administered drugs (etanercept, adalimumab, certolizumab). The Kaplan-Meier curve is higher for adalimumab and etanercept groups than for certolizumab group indicating a longer treatment persistence for the first two drugs. According to log-rank test there is a significant difference among the three Kaplan-Meier curves (p=0.0050).

Safety

During the 12-month follow-up, 34 AEs were registered, 30 of them classified as of mild/moderate intensity. Twenty-four patients (15.3%) experienced at least one AE, three of them (1.9%) had serious AEs. Specifically, one patient developed asthenia in association with high fever, abdominal pain and nausea, requiring hospitalisation. A causal relationship with certolizumab was suspected; the pharmacological treatment was interrupted and the event was solved by the end of observation. One patient developed an infection of lower respiratory tract, requiring the hospitalisation. The clinician suspected a causal relationship with DMARDs and etanercept. The pharmacological treatment interruption and a pharmacological support

Table II. Studies enrolling exclusively or partly RA patients with moderate disease activity.

Study	no. patients	Disease activity status	Treatment	Outcome
Van Riel, 2006 (ADORE) (13)	315 (ETN=160, ETN+MTX=155)	MDA/HDA	ETN *vs*. ETN+MTX	Improvement in DAS28>1.2 at week 16 (ETN 72.8% *vs*. ETN+MTX 75.2%); DAS28<2.6 at week 16 (ETN 14.6% *vs*. ETN+MTX17.3%)
Aletaha, 2007 (ASPIRE, ATTRACT, PREMIER, ERA, DE019, TEMPO) (14)	1342 early RA, 712 late RA	MDA/HDA	MTX=572, aTNF=291, aTNF+MTX=1191	Pts achieving remission at 1 year have lower average SDAI values at all-time points, including baseline than LDA<MDA<HDA pts
Aletaha, 2008 (ASPIRE, ATTRACT, PREMIER, ERA, DE019, TEMPO) (6)	1966 RA	MDA/HDA	MTX=629 *vs*. combination aTNF+MTX 1337	ACR 20 responders at 1 year: HDA 13%, MDA 41%, LDA 18%; remission 28%, higher radiographic progression in ACR50 responders with MDA (37%), *vs*. LDA (23%), *vs*. REM (39%); no differences in radiographic progression in ACR70 responders
van der Heijde, 2008 (extension TEMPO) (15)	227	MDA	addition of ETN to MTX (ETN-added=55) or of MTX to ETN (MTX-added=76), combination ETN+MTX (n=96)	Remission rate: ETN-added 41.8% at week 52 *vs*. MTX-added 36.8%, *vs*. combination 50.0%; EULAR response: moderate/good: ETN-added 63.6%, *vs*. MTX-added 40.8% *vs*. combination 33.3% *assessment with DAS
Hyrich, 2009 (16)	HAD: 4687 anti-TNF+ 344 DMARD pts; MDA: 224 anti-TNF + 300 DMARD pts	MDA/HDA	Anti-TNF/DMARDs	Similar reduction in HAQ score in both DAS28 groups (adjusted mean improvement -0.26 in MDA group).
Bazzani, 2009 (17)	1010	MDA/HDA	aTNF+DMARD *vs*. aTNF	EULAR response aTNF+DMARD *vs*. aTNF good 27.1% *vs*. 18.9%, moderate 56.2% *vs*. 46.7%
Smolen, 2013 (PRESERVE) (18)	604	MDA	ETN 50+MTX (202) *vs*. ETN 25 +MTX (202) *vs*. MTX (200)	At week 88, LDA 82.6% of ETN50+MTX pts *vs*. 79.1% of ETN25+MTX *vs*. 42·6% of MTX
Fleischmann, 2014 (APPEAL, Latin RA) (19)	723	64 MDA /657HDA	478 ETN + MTX *vs*. 245 csDMARD + MTX	Steady state analyses: for MDA patients, similar DAS28 values in csDMARDs + MTX and ETN + MTX group (lower DAS28 values in the ETN + MTX group at 16 weeks)
Smolen, 2014 (CERTAIN) (20)	194 (CZP=96, placebo=98)	LDA/MDA (>90% MDA)	Certolizumab *vs*. placebo	DAS28 remission significantly higher in CZP-treated than placebo-treated patients at week 24 (19.8% *vs*. 3.1%)
Combe, 2015 (ESPOIR) (21)	532 (MDA: MTX=72, TNFi=31; REM: MTX=101, TNFi=11	155 REM / 107 MDA	REM *vs*. MOD	Moderate disease activity during the first year associated with increased radiographic disease progression at 3 years and increased HAQ-DI at 3 and 5 years

RA: rheumatoid arthritis; MDA: moderate disease activity; HAD: high disease activity; REM: remission; MTX: methotrexate; ETN: etanercept; CZP: certolizumab; TNFi: TNF inibithor.

therapy with antibiotic drugs solved the event. One patient experienced dyspnea, defined by the physician as a life-threatening important medical event, requiring hospitalisation. No suspicion of the relation with the administration of any drug was posed. Nonetheless, pharmacological treatment was interrupted, and a pharmacological support therapy was required to solve the event.

Discussion

The multicentre longitudinal non-interventional MODERATE study aimed at evaluating, in the Italian real-world clinical practice, the extent of disease activity changes over 12 months in a cohort of patients with moderate RA and treated for the first time with anti-TNF drugs. The results of the present analysis confirmed the efficacy of these agents also in a moderate subset of RA patients. A significant reduction of DAS28 values at all time-points was noted; moreover, 58% of the population showed a reduction of DAS28 score greater than 1.2 after 12 months, when a moderate/good response according to EULAR criteria was observed in 45.7% and 34.9%, respectively. In terms of remission, defined as a DAS28 value lower than 2.6, only 20% of our patients reached this condition. Moreover, our analysis demonstrated good results in terms of treatment survival, showing that up to 80% of the enrolled patients were still in treatment after 12 months of observation.

The most novel aspect of the present observational multicentre study was the choice to focus on RA patients with moderate disease activity, a subset scarcely evaluated in the scientific literature. In fact, the great majority of randomised controlled trials, performed to evaluate the efficacy of biologics, included mainly RA patients with high disease activity. Nevertheless, patients with high disease activity represent only a portion of RA patients, while in the clinical practice physicians more frequently deal with patients with low or moderate disease activity.

Table II summarises the studies published so far enrolling exclusively or partly RA patients with moderate disease activity.

In only two studies, this specific subset of patients was selectively enrolled. The first one is an extension of the TEMPO trial, demonstrating a higher remission rate in patients treated with etanercept compared to those treated by MTX (17). In the second study, recently published by Smolen and colleagues (PRESERVE), significantly higher percentages of patients with a low disease activity were registered in patients treated with etanercept (25 mg or 50 mg/weekly) compared to MTX (19). Moreover, in the ESPOIR cohort, a comparison between patients with moderate activity and remission has been performed, identifying an increased radiographic disease progression at 3 years in patients with moderate status (21).

In the other studies, reported in Table II, patients with different activity degrees were enrolled and it was not possible to extrapolate precisely data on the moderate subset. Anyhow, data from the literature seem to suggest a better response in RA patients with lower disease activity compared to those with severe activity. The subanalysis of the ASPIRE, ATTRACT, PREMIER, ERA, DE019, TEMPO trials conducted by Aletaha *et al*. in 2007, demonstrated that RA patients with lower disease activity at the baseline were more likely to reach a status of remission or low disease activity (18). More recently, a *post-hoc* sub-analysis of data from the TEMPO and ERA trials compared patients with severe and moderate disease activity by using different outcomes, including remission as defined by DAS28 values (23). Patients with moderate disease activity achieved better outcomes at 6 and 12 months of follow-up in terms of remission, irrespective to the adopted therapeutic strategy. Within this study, only the data extrapolated from the TEMPO study can be compared with ours, since the ERA included patients with early disease activity while our population and that from the TEMPO are characterised by a similar disease duration (around 6 years) and by a high percentage of patients treated with MTX. The results from TEMPO show that patients with moderate disease activity achieved DAS28 remission in a percentage of 38% and 77% when treated with etanercept or etanercept plus MTX, respectively. Despite this result is higher compared with our cohort, where 20.9% of patients showed a DAS28 <2.6 after 12 months of follow-up, there may be a bias in their population size. Indeed, only three patients treated with etanercept and only 13 with etanercept plus MTX reached remission over a population of overall 41 moderate patients. Furthermore, we can hypothesise that at least in our cohort, chronic structural damage in these patients with established disease did not allow the achievement of higher rates of remission. Indeed, the absence of a radiological assessment is a limitation of our study. To date, x-ray evaluation is the gold standard to assess the joint damage in patients affected by RA. According to the Italian clinical practice, radiological assessment is not routinely performed during one year. Moreover, the non-interventional observational design of MODERATE did not allow a centralised – thus uniform – execution and evaluation of x-rays.

Furthermore, a description of the serological status of patients would have allowed a better prospective indication of the RA prognosis. However we observed that serological exams (*i.e*. ACPA and RF) are not routinely performed in the Italian clinical practice, therefore few data were available about these laboratory tests (only 9 and 19 patients performed ACPA and RF at each study visit, respectively).

Such limitation may have prevented the evaluation of the impact of chronic damage on disease activity. Nonetheless, another study compared patients from the TEMPO trial with an observational registry (Rheumatoid Arthritis DMARD Intervention and Utilisation Study [RADIUS II]). An extrapolation of the results may suggest that the percentage of patients treated with etanercept in monotherapy who achieved remission (according with the Clinical Disease Activity Index remission [CDAI ≤2.8]) at 52 weeks of follow-up was similar to our (approximately 20%). In TEMPO, patients with simultaneous initiation of etanercept and methotrexate achieved sustained remission sooner and at higher proportions than patients who received etanercept monotherapy in either TEMPO or RADIUS II. The data from this large observational study suggest that, in real practice, remission is reached later and at lesser extent (24). However, the mean DAS28 value at baseline (4.5±0.5) and the mean disease duration (about 6 years) of selected patients in our cohort define a subset of moderate rheumatoid arthritis characterised by a significant disease activity; there is great probability that this kind of patient will still develop structural damages, such as erosions, inducing a lower probability to achieve disease remission or low desease activity.

Taken together, the results of our analysis and the data from the literature suggest the need to deeper investigate the correct therapeutic approach in the different RA subpopulations. The possibility to use an aggressive DMARD treatment should not be neglected. As demonstrated by recent studies published in the literature, the comparison between different biologics and the triple therapy with hydroxychloroquine/sulphasalazine/MTX with concomitant glucocorticoids showed similar results in terms of efficacy, especially after 24 months of treatment (25-27). Based on a treat-to-target approach with a realistic target of remission in patients with early RA or low disease activity in established disease, these abovementioned strategies obtained similar re-

sults also in terms of radiological damage progression (25-28).

Finally, in the present cohort an average disease duration of about 5 years have been registered at the time of biological treatment beginning. Several reasons could explain this interval: in our opinion, the most important could be the observational design of the study, allowing the administration of the treatment according with physician evaluation. Moreover, the multicentre enrolment could determine a difference among the centres in terms of biological drugs availability for patients with moderate disease activity.

In conclusion, moderate RA (3.2 <DAS28 ≤5.1) patients treated with an anti-TNF, both in monotherapy and in combination with DMARDs, according to the Italian clinical practice, may achieve a substantial decrease of disease activity, and reduce their disability status. The low rate of patients achieving remission may suggest that therapeutic strategies should be more timely and aggressive.

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