Drug outcome survey to evaluate anti-TNF treatment in rheumatoid arthritis: an Italian observational study (the DOSE study)

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Abstract

Objective

The aim of this paper is to analyse the use of anti-TNF drugs in current Italian practice, evaluate clinical responses to treatment, and identify possible predictors of negative response in patients with rheumatoid arthritis (RA).

Methods

DOSE is a non-interventional, prospective study of patients with active RA treated for the first time with anti-TNF agents in 21 Italian hospitals. Demographic and clinical characteristics of patients, treatments and outcome measures were assessed. Outcome measures used were EULAR response, DAS28 remission and HAQ remission at 12 months. A stepwise logistic regression model was used to study the predictors of non-response.

Results

Of 299 RA patients (mean 53.8±12.8 years, 76.1% female), DAS28 was >5.1 in 60.5% of patients and HAQ was >1 in 65.9%. Etanercept was the most prescribed anti-TNF. DMARDs were used in 77.6% of patients (methotrexate in 59.2%). Significant improvements in clinical and laboratory parameters were observed at 12 months. The proportion of patients classed as non-responders remained high, and varied according to assessment criteria. The main predictors independently and significantly associated with a high risk of non-response were: age and female gender for all outcome criteria; high DAS28 value for disease remission; and HAQ >1 for disability remission.

Conclusion

In Italian anti-TNF treatment for RA, age, gender, and high values of both disease activity and disability were predictors of non-response to first-line therapy with anti-TNF drugs. Future studies should consider optimal second-line therapies for RA patients who do not achieve remission to their first anti-TNF treatment.

Key words
rheumatoid arthritis, etanercept, adalimumab, infliximab

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Introduction

Rheumatoid arthritis (RA) is a complex inflammatory disease resulting in substantial joint damage and progressive disability (1). It is associated with a reduced life span and lost work productivity; compared with other common chronic illnesses, RA is among those with the worst quality of life (2-5). The development of biological disease-modifying antirheumatic drugs (DMARDs) targeting specific mediators of inflammation, such as tumour necrosis factor-alpha (TNF-α), has led to several highly successful therapies (6-7). Blockers of TNF-α (anti-TNF agents) are extremely effective in controlling signs and symptoms of RA and delaying or arresting joint destruction (8-9). However, a significant proportion of patients do not respond to anti-TNF drugs. Only 50–70% of patients receiving anti-TNF therapy achieved at least a 20% response on American College of Rheumatology criteria (ACR20) in clinical trials (10). Data from the Danish DANBIO registry (11) showed that, while two-thirds of patients starting anti-TNF treatment achieved a "good" European League Against Rheumatism (EULAR) response after 6 months, remission was achieved in only a minority of RA patients. Thus, to improve management of RA, anti-TNF response rates must be evaluated in normal clinical practice and predictors of outcomes identified. Despite many national and international recommendations (12-15) and studies of current RA treatments (16-21), gaps in our knowledge of the use of biological DMARDs in day-to-day clinical care of RA (22) suggest the need for further research. Specifically, evaluation is needed of clinical responses in terms of disease activity, assessed by standardised measures of RA disease activity (23), and functional capacity, because reducing disability is a key goal of antirheumatic therapy.

Factors predicting response to biological therapies and rates of survival on treatment have been intensively studied (5, 18, 24-29). Unfortunately, there is little overlap between the predictors identified in these studies (24). Identifying patients who do and do not respond to anti-TNF therapy is essential to reducing the risk of treatment failure and any associated worsening of disease and prolongation of suffering.

A prospective, multicentre observational survey of patients with established RA refractory to traditional DMARDs was conducted by the Drug Outcome Survey to Evaluate biological treatment in rheumatoid arthritis (DOSE) study group. It aimed to:

i) analyse anti-TNF use in Italian practice and describe patient clinical profiles, prescribing patterns and therapeutic algorithms;

ii) evaluate clinical responses to treatment associated with disease activity, and disease and disability remission;

iii) identify the proportion of non-responding patients and factors associated with negative responses.

Materials and methods

Design

DOSE is a non-interventional, prospective, multicentre study of patients with active RA treated for the first time with anti-TNF agents. Patients from 21 hospital rheumatology centres distributed throughout Italy were assessed at baseline and every 3 months for 12 months. Each participating centre used a multidisciplinary research team (hospital pharmacist, nurse and rheumatologist) to collect data and monitor patients.

Study implementation was managed and monitored according to ICH-GCP (30), Good Pharmacoepidemiology Practices (31) and Italian law on observational studies (32). Final study documentation was reviewed and approved by Independent Ethics Committee(s) (IEC) at each participating investigational centre. Written informed consent was obtained from each patient before enrolment. The study began in June 2008 with recruitment of the first patient, and ended in April 2011 with the last follow-up visit.

Patients and therapy

All patients attending the centres during the enrolment period were considered for inclusion. Inclusion criteria were: age ≥18 years, diagnosis of RA according to the 1987 American College Rheumatology (ACR) criteria (33), anti-TNF naïve patients whose rheuma-

tologists considered anti-TNF therapy to be appropriate. When the study started, Italian and International guidelines (12) were followed, which recommended treatment with biological agents in patients with active RA (defined as a 28-joint disease activity score [DAS28] >5.1) after a failure of an adequate trial of another effective DMARD, including methotrexate (MTX) (≥15 mg/week for ≥12 weeks). Patients with contraindications to anti-TNF agents were excluded, as were those involved in any current or previous interventional clinical trial. At the time the trial was initiated, available anti-TNF drugs were adalimumab, etanercept and infliximab. Regimens followed usual clinical practice, *i.e.* dosages of anti-TNF agents and concomitant medications were prescribed and administered according to rheumatologists' decisions.

Clinical data

Patient data were recorded at baseline and each follow-up visit. At inclusion, age, sex, employment status, diagnosis, disease duration, extra-articular manifestations, current co-morbidities, and previous and concomitant treatment with DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids were recorded. Clinical data on disease activity including swollen and tender joint counts (SJC and TJC, based on 28-joint count), duration of morning stiffness, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), physician's and patient's evaluations of global disease activity (using a 0–10cm visual analogue scale [VAS]), patient's assessment of pain (0–10cm VAS) and general health (GH, 0–10cm VAS) were collected at baseline and at each control visit. Data on antinuclear antibodies, hepatic enzymes, and haematological and biochemical measures were also evaluated. At each visit, patients completed the validated Italian version of the Health Assessment Questionnaire (HAQ) (34). At inclusion and 12-month follow-up, the Medical Outcome Survey Short Form-36 (SF-36) (35) was completed. During follow-up, changes in anti-TNF therapy (dosage, discontinuation, or switch to another biological drug) were recorded, including the reason for the change.

Outcome and predictors of non-response

Treatment outcomes were assessed at 12 months. Changes from baseline in all clinical and laboratory parameters were considered. Clinical response (good, moderate, none) was assessed using EULAR criteria (36). Disease remission was defined as DAS28 <2.6 (37). DAS28 was calculated using SJC-28, TJC-28, ESR and GH on a VAS (36). HAQ was used to evaluate disability, with values ≤0.5 suggesting low, 0.6 to 1 suggesting moderate, and >1 indicating high disability. Disability remission was defined as a HAQ value ≤0.5 (38). Since the study intended to evaluate clinical outcomes after 12 months of treatment, patients who discontinued anti-TNF before 12 months for whom there were no 12-month data were excluded from the outcome analysis.

Patients were classified as responders or non-responders. Those who did not achieve a "good" EULAR response (classified as no-EULAR), or disease remission (DAS28 value <2.6), or disability remission (HAQ value <0.5) were classed as non-responders; all others were responders. Predictors of non-response were assessed. In this analysis, all evaluable patients were considered, including those who discontinued treatment because of inefficacy or adverse events (who were classed as non-responders). Patients lost to follow-up, and for whom no outcome data were available, were excluded.

Statistical analysis

Patients' baseline characteristics are reported as percentages, means and standard deviation (SD), median and interquartile range (IQR). Changes from baseline to 12 months were evaluated by Wilcoxon signed rank test for continuous data. The percentage of non-responders to each anti-TNF agent was evaluated using the Pearson's χ^2 test. Non-response associated with specific patient characteristics was first assessed in univariate analyses. The covariates tested were: gender, age, comorbidity, disease duration, extra-articular manifestations, RF, anti-cyclic citrullinated peptide antibody (anti-CCP), DAS28 and HAQ values and concomitant therapy with DMARDs, NSAIDs and corticosteroids. A stepwise logistic regression model was used to evaluate clinical characteristics associated with the outcomes analysed. Results are expressed as odds ratio (OR) values with 95% confidence intervals (95%CI). A p-value <0.05 was considered to be statistically significant. All analyses were performed using the SAS Statistical Package Release 9.3 (SAS Institute, Cary, NC, USA).

Results

Patient and disease characteristics

Demographics at baseline for 299 anti-TNF naïve patients included in this survey are reported in Table I. Patients were mainly female (76.1%) and had a mean age of 53.8±12.8 years. Comorbidities were present in 49.5% of patients, with osteoporosis, hypertension and thyroid disease occurring most frequently (32.9%, 31.1%, and 15.5%, respectively). Extra-articular manifestations of RA occurred in 47 patients. Among these, 41 patients had 1 extra-articular manifestation and 6 had 2 manifestations. Sjögren's syndrome and rheumatoid nodules were the most common extra-articular manifestations, each reported in 21 patients.

Disease activity (DAS28) and disability score (HAQ) were high at baseline. DAS28 was >5.1 in 181 patients (60.5%) and between 3.2 and 5.1 in 118 (39.5%). HAQ values in 197 patients (65.9%) were >1, for 63 patients (21.1%) ranged from 0.6 to 1, and for 39 (13.0%) were ≤0.5.

Most patients received etanercept, with very few receiving infliximab (Table I). The 3 biological drugs were prescribed mainly according to recommended dosages (etanercept 25 mg twice a week; adalimumab 40 mg every 2 weeks; infliximab 3 mg/kg every 8 weeks following an initial dose escalation). Seven patients (3.5%) receiving etanercept were prescribed less than the recommended dose (25 mg weekly) and 1 adalimumab patient received a higher than recommended dose (40 mg weekly).

At baseline, most patients (93.7%) received other drugs for RA (Table I).

Table I. Patient characteristics at the start of anti-TNF treatment.

Characteristics (n=299)	
Female, n (%)	230 (76.1)
Age, years	53.8 (12.8)
Comorbidity, n (%)	148 (49.5)
Disease duration, years (median [IQR])	5.0 (2-10)
Extra-articular manifestations, n (%)	47 (15.7)
Disease activity	
Tender joints, n	11.0 (7.1)
Swollen joints, n	7.3 (5.3)
Morning stiffness, min	61.8 (48.0)
CRP, mg/dL	3.2 (6.1)
ESR, mm/h	32.9 (22.0)
RF positivity, %	163 (54.5)
Anti-CCP positivity, %	124 (41.5)
DAS28 score	5.4 (1.2)
HAQ score	1.4 (0.7)
Treatment	
Anti-TNF, n (%)	
Etanercept	200 (66.9)
Adalimumab	80 (26.8)
Infliximab	19 (6.3)
Co-therapy, n (%)	280 (93.7)
DMARDs	232 (77.6)
Steroids	221 (73.9)
NSAIDs	134 (44.8)

Values are mean (standard deviation) or number of patients (%), unless otherwise stated.
DMARDs: disease-modifying anti-rheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; anti-TNF: anti-tumour necrosis factor; anti-CCP: anti-cyclic citrullinated peptide antibody; DAS28: Disease Activity Score in 28 defined joints; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SD: standard deviation; IQR: interquartile range; RF positivity: rheumatoid factor positivity.

Table II. Changes in clinical parameters from baseline to 12-month follow-up.

Disease activity	Baseline (n=299)	At 12 months (n=216)	Change
Number of tender joints	11.0 ± 7.1	2.8 ± 4.5	-8.3 ± 7.5*
Number of swollen joints	7.3 ± 5.3	1.1 ± 2.3	-6.1 ± 5.2*
Morning stiffness, min	61.8 ± 48.0	12.4 ± 15.8	-48.1 ± 48.2*
CRP, mg/dL	3.2 ± 6.1	1.1 ± 1.8	-1.9 ± 5.1*
ESR, mm/h	32.9 ± 22.0	18.6 ± 14.5	-13.7 ± 20.3*
DAS28 score	5.4 ± 1.2	3.3 ± 1.2	-2.1 ± 1.4*
HAQ score	1.4 ± 0.7	0.6 ± 0.6	-0.7 ± 0.7*
Physician's Global Assessment	6.1 ± 1.7	2.2 ± 2.0	-4.1 ± 2.5*
Patient's Global Assessment	6.6 ± 2.1	2.7 ± 2.3	-3.9 ± 3.0*
Patient's VAS score for pain	6.7 ± 2.2	2.7 ± 2.4	-3.9 ± 3.1*
Global Health Assessment score	5.3 ± 2.2	4.7 ± 3.0	-0.6 ± 3.8§

Values are mean±standard deviation.
CRP: C-reactive protein; DAS28: Disease Activity Score in 28 defined joints; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; VAS: visual analogue scale.
*p<0.0001; §p=0.0351.

Table III. Patients with different categories of response at 12 months, listed by assessment criteria.

Outcome	Patients, n	%
DAS28 Remission	56	25.9
EULAR response		
Good	102	47.2
Moderate	76	35.2
None	38	17.6
Disability (HAQ)		
Low (≤0.5)	123	57.5
Moderate (0.6–1)	39	18.2
High (>1)	52	24.3

EULAR: European League against Rheumatism; HAQ: Health Assessment Questionnaire.

DMARDs were used in 232 patients and, among these, MTX was prescribed to 177 patients (78.3% of DMARDs users, 59.2% of all patients). Corticosteroids were given to 221 patients (73.9%) and NSAIDs to 134 (44.8%). The frequency of DMARD co-therapy was 89.5% (n=17) with infliximab, 80% (n=64) with adalimumab, and 75.5% (n=151) with etanercept. MTX co-therapy was prescribed to 49 adalimumab patients (61.2% of this group), 118 etanercept patients (59%), and 10 infliximab patients (53%).

Follow-up

During the study, 27 patients (9.0%) were lost to follow-up and 56 (18.7%) discontinued therapy before 12 months. Reasons of discontinuation included inefficacy (29 patients), adverse events (20 patients), or other reasons (abnormal biochemical data in 3 patients, non-compliance in 2 patients, other reasons in 2 patients). Patients who interrupted treatment due to inefficacy comprised 26.3% of infliximab recipients (5/19), 10.0% of adalimumab recipients (8/80), and 8.0% of those receiving etanercept (16/200). Discontinuation due to adverse events occurred in 15.8% (n=3), 6.2% (n=5) and 6.0% (n=12) of patients receiving infliximab, adalimumab and etanercept, respectively.

Twenty-two patients (7.4%) switched between anti-TNF agents: 14 patients receiving etanercept (7.0%, 14/200) and 8 receiving adalimumab (10.0%, 8/80). One patient switched twice: from etanercept to adalimumab and back to etanercept. Inefficacy was the most common reason for a switch (17 patients, 77.3%), followed by adverse events (3 patients, 13.6%). Dosages changed in 8 patients (2.7%): 6 had reductions (5 etanercept and 1 adalimumab recipient) and 2 had increases (1 each receiving adalimumab and infliximab).

Clinical outcome

Clinical response was evaluated in 216 patients after 12 months. Fifty-six patients were excluded because of they discontinued treatment before 12 months; 12 patients were lost to follow-up. Excluded patients did not different significantly from those included in the analysis (data not shown).

Significant improvement was seen in all clinical and laboratory parameters during anti-TNF therapy (Table II). Mean DAS28 scores decreased and HAQ scores improved. Assessments of GH, disease activity and pain intensity also showed a general improvement. After 12 months (Table III), a "good" EULAR response was achieved in 47.2% of patients. About 26% of patients exhibited disease remission and 57.5% showed a disability remission. Responses differed between treatment groups (Fig. 1). A

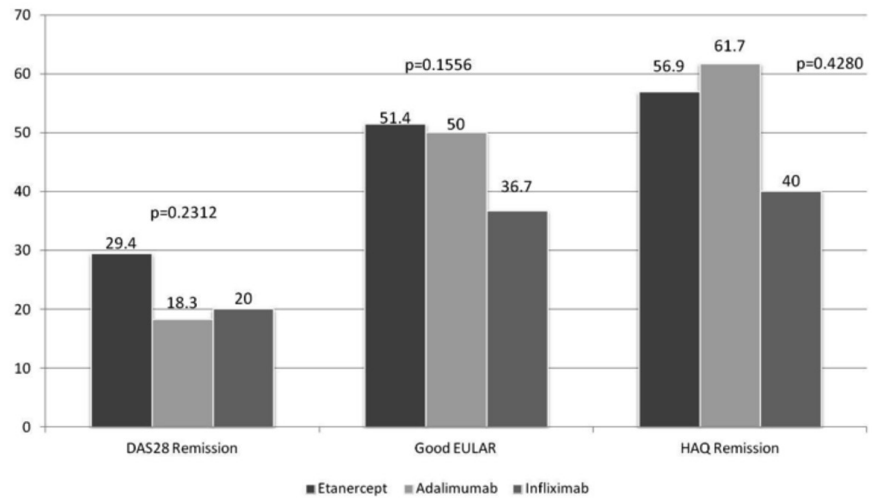

Fig. 1. "Good" EULAR response, disease (DAS28) remission and disability (HAQ) remission occurring in each group of anti-TNF agent, etanercept, adalimumab, and infliximab (percentage).
DAS28: Disease Activity Score in 28 defined joints; EULAR: European League Against Rheumatism classification criteria; HAQ: Health Assessment Questionnaire.

"good" EULAR response was achieved in 51.4% of etanercept, 50.0% of infliximab, and 36.7% of adalimumab recipients. Similarly, DAS28 remission at 12 months was more frequent with etanercept (29.4%) than with infliximab (20.0%) or adalimumab (18.3%). HAQ remission occurred in 61.7% of adalimumab, 56.9% of etanercept, and 40.0% of infliximab patients.

Predictors of non-response

Univariate and multivariate analysis of demographic and clinical factors associated with non-response are presented in Table IV. With the exclusion only of patients who were lost to follow-up, results from 272 patients were used to evaluate predictive factors.

Non-response to treatment appeared to depend on the criteria used to assess response. In the univariate analysis, age >50 years and baseline HAQ values >1 were associated with non-response regardless of evaluation criteria (EULAR "good", remission on DAS28 or HAQ). Female gender was associated with both no EULAR response and no disease remission, but did not affect disability remission. The presence of comorbidity and disease duration of >5 years were predictors of non-response in disability remission alone. DAS28 >5.1 at baseline and concomitant use of NSAIDs were predictors of no disease remission.

Multivariate analysis confirmed age as an independent predictor of non-response according to all 3 outcome criteria. However, female gender (OR 2.35, 95%CI 1.29–4.27; p=0.0051) and lack of concomitant therapy with steroids (OR 1.91, 95%CI 1.03–3.35; p=0.0404) were independently associated with a higher risk of no EULAR response. In terms of disease remission, female gender (OR 3.17, 95%CI 1.59–6.31; p=0.0011) and high baseline DAS28 values (OR 2.18, 95%CI 1.16–4.11; p=0.0156) were independent predictors of non-response, associated with a more than doubling of

Table IV. Univariate and multivariate analysis of predictors of a lack of response to anti-TNF treatment (n=272).

	No EULAR response		No Disability remission (HAQ)		No Disease remission (DAS28)	
Variable	Univariate OR (95%CI)	Multivariate OR (95%CI)	Univariate OR (95%CI)	Multivariate OR (95%CI)	Univariate OR (95%CI)	Multivariate OR(95%CI)
Demographic						
Age (>50 years)	2.24 (1.33–3.78)	2.83 (1.62–4.95)§	2.91 (1.71–4.93)	2.28 (1.29–4.02)†	2.00 (1.10–3.66)	2.22 (1.16–4.28)‡
Gender (female)	2.05 (1.16–3.63)	2.35 (1.29–4.27)§§	1.49 (0.84–2.64)		2.49 (1.31–4.70)	3.17 (1.59–6.31)‡‡
Comorbidities (yes)	1.52 (0.93–2.49)		2.20 (1.35–3.59)		1.29 (0.71–2.32)	
Disease factors						
Disease duration (>5 years)	1.39 (0.85–2.28)		1.91 (1.17–3.10)	2.17 (1.28–3.67)††	0.59 (0.32–1.08)	
Extra-articular manifestations (yes)	1.99 (0.96–4.14)		1.50 (0.77–2.94)		1.20 (0.52–2.75)	
Rheumatoid Factor (positive)	0,90 (0.53–1.50)		1.12 (0.68–1.86)		1.31 (0.71–2.45)	
Anti-CCP (positive)	1.14 (0.64–2.04)		1.11 (0.63–1.94)		1.46 (0.72–2.97)	
DAS28 (>5.1)	1.16 (0.7–1.91)		1.47 (0.90–2.41)		2.56 (1.41–4.66)	2.18 (1.16–4.11)‡‡‡
HAQ (>1)	1.84 (1.11–3.07)		3.77 (2.23–6.40)	3.41 (1.95–5.97)†††	2.39 (1.31–4.34)	
Treatment						
DMARDs (no *vs*. yes)	0.72 (0.40–1.28)		0.94 (0.53–1.66)		0.68 (0.35–1.32)	
NSAIDs (no *vs*. yes)	0.70 (0.43–1.16)		1.06 (0.66–1.71)		0.44 (0.24–0.83)	0.45 (0.23–0.88)‡‡‡‡
Steroids (no *vs*. yes)	1.61 (0.90–2.88)	1.91 (1.03–3.55)§§§	0.88 (0.51–1.52)	1.08 (0.55–2.12)		

§p=0.0003, §§p=0.0051; §§§p=0.0404; †p=0.0045; ††p=0.0040; †††p<0.0001; ‡p=0.0167; ‡‡p=0.0011; ‡‡‡p=0.0156; ‡‡‡‡p=0.0206.
EULAR: European League against Rheumatism response criteria; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score in 28 defined joints; anti-TNF: anti-tumour necrosis factor; DMARDs: disease-modifying anti-rheumatic drugs; anti-CCP: anti-cyclic citrullinated peptide antibody; CI: confidence interval; OR: odds ratio; NSAIDs: non-steroidal anti-inflammatory drugs.

the risk. Concomitant use of NSAIDs also predicted a lack of disease remission. The duration of disease (OR 2.17, 95%CI 1.28–3.67; p=0.0040) and values of HAQ >1 (OR 3.41, 95%CI 1.95–5.97; p<0.0001) were independently and significantly associated with a risk of no remission of disability.

Discussion

The efficacy of anti-TNF agents in clinical trials in the treatment of RA is well documented and their use in clinical practice has dramatically improved the disease course in most patients (9). Nevertheless, real world data show that a significant proportion of patients, particularly those with established RA, do not respond to these drugs (11, 20). Thus, to optimise their use and reduce the risk of treatment failure, there is a need identify patients who do not respond to anti-TNFs in clinical practice. The DOSE study, involving a network of 21 Italian hospital rheumatology centres, has provided a representative description of anti-TNF use in current daily practice. Our data suggest that anti-TNF agents are mainly used in accordance with Italian and International guidelines. As recommended, most of the patients starting treatment with anti-TNFs in real practice had high disease activity (mean DAS28 5.4) and high functional disability (mean HAQ 1.4), consistent with that reported in previous observational studies (11, 17, 27). Nevertheless, there was a percentage of patients with a moderate disease activity (DAS28 3.2–5.1). At the time of the study, the prescription of a biological agent in this setting was not recommended and was therefore off-label. The possible presence of negative prognostic factors in these patients, as well as the clinician's confidence in the efficacy and safety of the anti-TNF agents are possible explanations for the use of anti-TNF patients in this group of patients. In later updates of Italian and International guidelines (13-15), the indication for the use of anti-TNF drugs was extended to patients with moderate disease activity in the presence of unfavourable prognostic factors (*i.e.* positive test for anti-CCP or RF; elevated ESR or CRP). As a result, what was off-label prescribing of anti-TNF agents to patients with moderate RA in 2008 would now be considered in line with treatment recommendations. Our data also show that, on average, the starting doses for biological therapies agreed with label recommendations.

Guidelines and clinical trial data recommend the combined use of anti-TNF agents with other synthetic DMARDs, specifically MTX. Co-therapy with MTX or other DMARDs has greater efficacy and provides better structural protection than anti-TNF monotherapy, with no increase in adverse events (19, 39, 40). In our study, 78% of patients used DMARDs, but MTX was prescribed in only 59.2%, suggesting low compliance with official guidelines in current clinical practice. Adalimumab and etanercept are licensed as monotherapy in RA, whereas infliximab is intended to be used with MTX. The difference between guidelines and approved label indications, as well as the confidence of rheumatologists in anti-TNF drugs, could explain the lower than expected use of MTX. This gap, highlighted in previous studies (25, 26, 28), is still present and recently confirmed. In the last appraisals of the British Society for Rheumatology Register, only 42.5% of total patients received MTX with anti-TNF therapy (41), as did only 25.5% of patients naïve to anti-TNFs (21). By comparison, in Italy, data from the GISEA registry suggest concomitant MTX use is increasing (42). Steroids were also commonly prescribed in association with anti-TNFs in this study (almost 74% of patients). These findings can be considered comforting and in line with recent literature (43-45).

In our study, persistence with anti-TNF treatment was high: only 56 patients (18.7%) discontinued therapy. This lower discontinuation rate than seen in previous studies (29,46) may have occurred because of variations in the duration of follow-up (the percentage discontinuing increases with time) (41), and because our patients were receiving first-line treatment (in second- and subsequent lines the discontinuation rate is greater) (42). Although our study did not intend to compare across drugs, discontinuation for inefficacy was more common in infliximab than in adalimumab and etanercept groups, which agrees with the results of other studies (11, 47, 48). Among our patients, the most common reason for discontinuation of anti-TNF treatment at 1 year was insufficient response to therapy, which matches the results of other studies (47, 49). While loss of anti-TNF efficacy may be due to generation of antibodies against these drugs, concomitant administration of MTX seems to suppress the formation of anti-drug antibodies and prolong the rate of survival on treatment (48). This finding supports recommendations for the combination of MTX with anti-TNF drugs. Thus, the low utilisation of the combination, as previously discussed, could suggest a knowledge gap that needs to be addressed.

The modern treatment goal of disease remission (23, 35) was a clear outcome indicator in our study of anti-TNF therapy. These agents confirmed their efficacy in reducing disease activity and increasing functional capacity; indeed, the parameters we considered showed significant and clinical improvements. Specifically, in line with other studies of anti-TNF agents in RA patients (11, 18, 20, 27, 50), almost 50% of our patients achieved a "good" EULAR response, more than 57% had disability remission according to HAQ scores, and 26% achieved disease remission, according to DAS28 values.

Still, these results still highlight a considerable proportion of non-responders. Characterisation of these patients is essential to improving treatment of long-term and established RA. The predictive value of certain baseline features might depend on the response criteria chosen, as highlighted elsewhere (24); our results confirm this variability. Patients aged >50 years were less likely to achieve "good" EULAR response or remission of either disease or disability. Similarly, females were more likely to see no EULAR response or no DAS28 remission. These findings are consistent with prior studies (25, 26, 28).

Our data suggest that not achieving disability remission is associated with a greater degree of disability at baseline (HAQ) and longer disease duration, 2 factors that are related to disease sever-

ity. HAQ score is, especially in established RA, directly related to the level of joint damage. Patients with high HAQ scores are more likely to have irreversible damage. Data from clinical trials and observational studies have demonstrated that disease duration may influence functional response, with less improvement in disability seen among those with the longest disease duration. Patients with longer disease duration are more likely to have joint damage, which is in itself a plausible explanation for the lower potential of these patients for a good functional response to anti-TNF agents (51).

Higher DAS28 at baseline was associated with a higher risk of no disease remission. Although this result may seem obvious (*i.e.* more aggressive disease does not respond as well as less aggressive disease), the finding has practical implications. The criteria for remission do not reflect the magnitude of change in disease activity but instead show whether disease activity (DAS28) is reduced below a certain threshold. Thus, reaching these absolute DAS28 scores is more likely for patients with lower baseline values. Patients who start with a high level of DAS can get a "good" EULAR response, but, to obtain remission, the DAS value at baseline should reflect the less aggressive phenotype.

A lack of concomitant treatment with corticosteroids was a negative predictor of EULAR response, and this is supported by recent literature (43-45). However, there was no disease remission among patients receiving NSAIDs, a finding also observed previously (25). NSAIDs may interfere with the effects of anti-TNF agents through enzyme induction or other pathways. More likely, they have no effect on response, but serve as a marker for comorbidity. The negative prognosis associated with NSAIDs persisted after adjusting for comorbidities. Furthermore, NSAID use may act as a marker for inflammatory symptoms and worsening of overall clinical condition.

One important limitation of our study is the fact that the survey started more than 6 years ago. Current clinical practice now includes a "treat to target" approach (52, 53) and new biological agents are now available. Nevertheless, the three anti-TNF agents studied remain the most commonly prescribed biological agents for the treatment of RA, meaning that our data are still useful for clinical practice in Italy. In addition, the endpoints used (*e.g.* DAS28, HAQ, EULAR response) are objective measures that are still in widespread use. The nonrandomised design of this observational study is also associated with methodological limitations. Factors affecting the choice of therapy and confounding by indication could produce selection bias. The three anti-TNF groups varied widely in numbers of patients enrolled. Since the purpose of the study was to observe real practice without interference, we verified that the difference observed in the frequency of use of the 3 anti-TNF agents reflected clinical practice in the involved centres and conformed both to market data and to data from epidemiological registries of RA patients. Moreover, in terms of predictors of response, all anti-TNF agents were grouped together, with no separate statistical analysis. Follow-up duration is another potential limitation of our study. Although a 12-month study may be considered relatively short for a chronic condition like RA and for administration of chronic treatment with biologic agents, this duration was chosen it is longer than that in many clinical trials (24 weeks) and allowed determination of longer term effectiveness and safety. Moreover, a recent long-term study (up to 7 years) documented that anti-TNF therapy resulted in rapid improvement in DAS28 score and inflammatory markers in the first year of treatment (46). Our data on percentages of patients responding to treatment were in line with previous studies, and allowed us to identify patients who did not respond to anti-TNF agents.

Conclusion

We can conclude that, in our nationwide cohort of anti-TNF naïve patients with established RA treated in routine clinical practice, the use of anti-TNF agents is in accordance with label recommendations. All 3 agents seemed to be effective for controlling active, long-standing and disabling RA. Etanercept was the most frequently used anti-TNF and, although our study was not designed to compare between agents, appeared to be associated with less discontinuation for inefficacy and with a higher percentage of patients in disease remission. At the end of follow-up, a reasonably high proportion of patients treated with anti-TNFs were non-responders. Older age, lower functional status, and higher disease activity were negative predictors of a treatment response or of remission of disease or disability. Since these characteristics indicate more severe disease and the likelihood of irreversible damage, early use of anti-TNFs seems desirable. The role of biological therapies in the treatment of RA continues to evolve, and further research will be useful to identify the optimal sequence of treatments according to patient characteristics, response and tolerance to previous drugs, and to define the comparative effectiveness of available biological agents.

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