Treatment Patterns of Anti-TNF Agents in Italy: an observational study

Pattern di trattamento con farmaci anti-TNF in Italia: uno studio osservazionale

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INTRODUCTION

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory rheumatism. This autoimmune disease leads to progressive joint damage, functional disability, impaired quality of life and, in some cases, shortened life expectancy (1, 2).

Several treatment options are available for patients with RA; however, none of them has a clear advantage over another (3). Traditional therapy for RA included corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, which slow down disease progression. More recently, biologic DMARDs specifically targeting cytokines, mainly Tumour Necrosis Factor (TNF), have been introduced. A large proportion of patients receiving these agents achieve moderate to good responses as defined by the European League Against Rheumatism (EULAR) criteria based on the Disease Activity Score (DAS-28) (4-8). Anti-TNF agents may improve symptoms of disease and physical function, and slow down joint damage (3, 9, 10). Moreover, this class of drugs is considered to be associated with an overall favorable tolerability profile (9), even if patients treated with anti-TNF agents carry a slightly increased risk of opportunistic infections and, possibly, of lymphoma and other malignancies (11).

Clinical experience suggests that a considerable proportion of patients does not show a sustained response or may not respond to anti-TNF therapy (11). As a consequence, dose escalations, drug switching or drug discontinuations because of lack of efficacy are frequently reported (11-15); of these, drug discontinuations are of particular concern (11-15). In addition, drug discontinuation can result from poor or absent tolerability (16). These modifications in treatment regimens have also a direct impact on...
annual cost as well as cost-effectiveness of these drugs, and this should be taken into account by health policy decision makers.

At present, data on dose escalation, drug switching or drug discontinuation of anti-TNF agents in the Italian scenario are quite scant and were mainly collected in small observational studies or by the analysis of local registries (17-19).

The aim of this observational study was to provide a description of real life treatment patterns of biologic anti-TNF, including the discontinuation rates, the dose changes and the frequency of switches in a large number of Italian Rheumatology centers in the Northern, Central and Southern areas of the Country.

**MATERIALS AND METHODS**

**Study design**

This observational, multicenter, retrospective study was designed to evaluate Italian patients with RA. In total, 23 centers (9 in the Northern Italy, 10 in the Central Italy, and 4 in the Southern Italy) participated in this study. The study was assessed and approved by the local Ethics Committees of each centre and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for their participation in the study.

In order to select a representative sample of patients, a chart review was performed and patients were recruited according to the following criteria:

- a) >18 years of age;
- b) diagnosis of RA (as defined by the American College of Rheumatology [ACR] revised criteria 1987);
- c) treatment with the first biologic anti-TNF agent between the 1st July 2002 to the 31st March 2004;
- d) evaluation at the same center for at least 12 months. Patients who were participating in other trials at the time of enrollment or who had been included in other trials which involved dose modifications or dose maintenance with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, DMARDs or anti-TNF therapies in three years prior to enrollment were excluded from the study.

In total, patients underwent six visits during the study period: baseline and at 3, 6, 12, 24 and 36 months after initiating anti-TNF therapy (visits 1, 2, 3, 4 and 5, respectively). At baseline, inclusion and exclusion criteria, as well as baseline characteristics (demographics including body weight, duration of disease, DAS-28 at diagnosis and at initiation of anti-TNF therapy, concentration of rheumatoid factor, radiographic alterations, last therapy administrated before the initiation of anti-TNF therapy and EULAR classification) were collected. From visit 2, treatment discontinuations, dose changes and/or switch to another anti-TNF drug, were monitored and reasons for these decisions were recorded. Concomitant drug usage was also recorded. Depending on the drug administered, dose escalation of anti-TNF agents was defined as follows:

1) intravenous infliximab administered at doses higher than 3 mg/kg or more frequently than every eight weeks;
2) subcutaneous etanercept administered more frequently than twice a week;
3) subcutaneous adalimumab administered at doses higher than 40 mg or administered more frequently than every other week.

**Study objectives**

The primary objective of the study was to estimate the proportion of RA patients ever treated with an anti-TNF agent who discontinued therapy within 36 months of initiation and the reasons for discontinuation.

Secondary objectives included the assessment of anti-TNF dosage patterns in patients remaining on their first biologic, considering the average dose and the proportion of patients needing dose escalation and evaluating the costs associated, and the description of the proportion of patients switching to another anti-TNF drug.

**Data analysis**

Baseline characteristics were stratified according to anti-TNF agent, age, gender,
duration of follow-up, rheumatoid factor, EULAR classification, DAS-28, duration of disease, radiographic alteration and last therapy administrated before the initiation of anti-TNF therapy. Body weight was measured in the entire cohort and reported in terms of percent distribution of patients in predefined classes of weight. The proportion of patients discontinuing therapy was evaluated using a Kaplan-Meier survival analysis, where discontinuation of therapy or switching to alternate therapy was considered an event. The differences between the survival curves were assessed using the log-rank test, applying Bonferroni’s correction when appropriate. The reasons for discontinuation of therapy were stratified according to the drug at different timepoints. A Kaplan-Meier survival analysis was also used to evaluate modifications in dosage regimens where increases in dose or frequency of administration were considered as events. Moreover, an evaluation of therapy costs (as available on December 2007) associated with these dosage modifications was performed. Overall differences between drugs were assessed using the analysis of covariance (ANCOVA) followed by the Tukey test for multiple comparisons (continuous variables) or the chi-square test applying Bonferroni’s correction when appropriate. A p value <0.05 was considered statistically significant.

## RESULTS

### Baseline characteristics

In total, 703 patients (mean age 53.4±13.1 years), of which 80.8% were female, were included in the observation. Data on body weight were available for 446 patients; body weight was distributed as follows: <60 kg, 29.8% (n=133), 60-70 kg, 39.5% (n=177), 70-80 kg, 21.8% (n=96), 80-90 kg, 9.2% (n=42), >90 kg, 1.2% (n=6).

<table>
<thead>
<tr>
<th>Table I - Baseline characteristics of the patients involved in the study.</th>
<th>Total</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>703</td>
<td>248 (35.28%)</td>
<td>259 (36.84%)</td>
<td>196 (27.88%)</td>
<td>NA</td>
</tr>
<tr>
<td>Age, years*</td>
<td>53.41 (13.09)</td>
<td>52.51 (13.26)</td>
<td>54.11 (13.78)</td>
<td>53.63 (11.88)</td>
<td>0.37</td>
</tr>
<tr>
<td>Males</td>
<td>135 (19.2%)</td>
<td>48 (19.35%)</td>
<td>54 (20.85%)</td>
<td>33 (16.84%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Duration of observation, months*</td>
<td>39.71 (11.78)</td>
<td>39.31 (12.46)</td>
<td>38.75 (11.03)</td>
<td>41.49 (11.71)</td>
<td>NA</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>256 (64.32%)</td>
<td>75 (59.52%)</td>
<td>95 (64.19%)</td>
<td>86 (69.35%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Total number of patients evaluated</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>EULAR classification</td>
<td>7 (1.85%)</td>
<td>0 (0.00%)</td>
<td>2 (1.35%)</td>
<td>5 (4.67%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Good</td>
<td>152 (40.10%)</td>
<td>47 (38.52%)</td>
<td>46 (31.08%)</td>
<td>58 (55.14%)</td>
<td>43 (40.19%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>220 (58.05%)</td>
<td>75 (61.48%)</td>
<td>102 (68.92%)</td>
<td>107 (100%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>379 (100%)</td>
<td>122 (100%)</td>
<td>150 (100%)</td>
<td>107 (100%)</td>
<td></td>
</tr>
<tr>
<td>Total number of patients evaluated</td>
<td>379 (100%)</td>
<td>122 (100%)</td>
<td>150 (100%)</td>
<td>107 (100%)</td>
<td></td>
</tr>
<tr>
<td>DAS-28*</td>
<td>5.30 (1.21)</td>
<td>5.31 (1.10)</td>
<td>5.46 (1.21)</td>
<td>5.10 (1.29)</td>
<td>0.018</td>
</tr>
<tr>
<td>Total number of patients evaluated</td>
<td>543</td>
<td>183</td>
<td>193</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>Duration of disease, years*</td>
<td>9.33 (7.46)</td>
<td>9.64 (7.86)</td>
<td>9.92 (7.47)</td>
<td>8.19 (6.83)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total number of patients evaluated</td>
<td>670</td>
<td>235</td>
<td>243</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>Radiographic alterations</td>
<td>456 (91.38%)</td>
<td>150 (90.36%)</td>
<td>186 (94.42%)</td>
<td>120 (88.24%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Yes</td>
<td>499 (100%)</td>
<td>166 (100%)</td>
<td>197 (100%)</td>
<td>136 (100%)</td>
<td></td>
</tr>
<tr>
<td>Total number of patients evaluated</td>
<td>499 (100%)</td>
<td>166 (100%)</td>
<td>197 (100%)</td>
<td>136 (100%)</td>
<td></td>
</tr>
<tr>
<td>Last therapy administrated</td>
<td>91 (13.1%)</td>
<td>17 (7.00%)</td>
<td>49 (19.1%)</td>
<td>25 (12.8%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Only corticosteroids and/or NSAIDs</td>
<td>602 (86.9%)</td>
<td>225 (93.00%)</td>
<td>207 (80.9%)</td>
<td>170 (87.2%)</td>
<td>195 (100%)</td>
</tr>
<tr>
<td>Also DMARDs</td>
<td>693 (100%)</td>
<td>242 (100%)</td>
<td>256 (100%)</td>
<td>195 (100%)</td>
<td></td>
</tr>
<tr>
<td>Total number of patients evaluated</td>
<td>693 (100%)</td>
<td>242 (100%)</td>
<td>256 (100%)</td>
<td>195 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

*mean ± (SD)

DAS-28 = Disease Activity Score; DMARDs = disease-modifying anti-rheumatic drugs; EULAR = European League Against Rheumatism; NSAID = non-steroidal anti-inflammatory drugs; RF = rheumatoid factor.
Baseline demographic characteristics are summarized in Table 1. The mean duration of observation was slightly longer than 3 years (39.7±11.8 months). Only 398 (56.6%) charts contained data on rheumatoid factor; 256 (64.3%) patients were positive for rheumatoid factor. The mean duration of RA was 9.3±7.5 years. DAS-28 was 5.3±1.2 in 543 (77.2%) patients for whom data were available. Only 379 (53.9%) patients were classified according to the EULAR criteria at baseline.

Of these, 220 (58.1%) of patients were poor responders and 7 (1.8%) subjects were good responders to previous therapy. Radiographic evaluations were reported in 456 (71.0%) patients, of whom 456 (91.4%) showed alterations. Data regarding the last therapy prior to the initiation of anti-TNF was reported in 693 (98.6%) patients, of which 602 (86.9%) were treated with DMARDs and 91 (13.1%) were medicated with corticosteroid and/or NSAIDs therapy. Stratification of baseline data according to anti-TNF agent showed that 248 (35.3%) patients were treated with infliximab, 259 (36.8%) with etanercept and 196 (27.9%) with adalimumab. Significant differences between treatment groups were observed for EULAR classification, DAS-28, duration of disease and the last therapy administered before the initiation of anti-TNF therapy (Table I).

**Proportion of patients discontinuing anti-TNF therapy and reasons for discontinuation**

First course of therapy with infliximab was associated with lower cumulative drug survival than the other two agents (chi-square = 24.0, p<0.001), indicating a higher incidence of discontinuation (Fig. 1). No differences were observed between etanercept and adalimumab therapy in terms of drug survival. At 36 months, 74.7% of patients on etanercept, 72.0% of those on adalimumab and 57.7% of subjects receiving infliximab were still on therapy. The discontinuation rate of infliximab was statistically higher compared with either etanercept or adalimumab (p=0.0001 and p=0.0002, respectively).

Overall, infliximab was associated with the highest incidence of discontinuation because of adverse events (14.5% vs 7.7% and 11.2 for etanercept and adalimumab, respectively; p=not significant) or insufficient response (20.2% vs 11.6% and 10.7 for etanercept and adalimumab, respectively; both p=0.01) at 36 months (Fig. 2).

**Anti-TNF dosing patterns and associated costs**

Apart from one patient, all patients initiated adalimumab therapy at a dose of 40 mg, while 237 (91.5%), 21 (8.1%) and 1 (0.4%) of patient(s) started etanercept therapy at doses of 25, 50 and 20 mg, respectively. None of the patients treated with adalimumab and 7 (2.7%) patients treated with etanercept required a dose escalation. With regard to infliximab therapy, 155 (62.4%), 55 (22.3%) and 28 (11.3%) patients initiated therapy at doses of 3, 4 and 5 mg/kg, respectively; 10 (4.0%) subjects initiated therapy at other dosages. Over-
all, 54 (22.2%) patients receiving infliximab therapy required a dosage escalation. Moreover, a dose escalation was required in more patients receiving infliximab 3 or 4 mg/kg (27.9% and 16.5%, respectively) than those receiving other dosages (12.5%, 3.6% and 0.0%, for patients receiving 2, 5 and 6 mg/kg, respectively) of the drug. Furthermore, a numerically higher proportion of patients receiving infliximab compared with etanercept or adalimumab therapy required an increase in the frequency

**Figure 2** - Incidence of discontinuation of therapy because of insufficient response or adverse events in patients receiving infliximab, etanercept or adalimumab at 36 months.

**Figure 3** - Incremental cost of different anti-TNF agents at 36 months when considering patients on their first biologic who required dose modification.
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of drug administration (11.3% vs 1.5% and 5.6%, respectively), although a statistical analysis was not performed. Also, numerically more infliximab than etanercept or adalimumab recipients required a reduction in the frequency of administration (8.1% vs 6.6% and 0.5%, respectively); even in this case, a statistical analysis was not performed.

Taking into account changes in both dose and frequency of administration, at 36-month of follow-up mean cost of treatment per patient was € 28,186.60 (standard deviation, SD ±10,236.87) for infliximab, € 36,541.16 (±10,603.65) for etanercept and € 38,215.85 (±11,558.27) for adalimumab. In other terms, considering the entire period of observation, the need for dose modification was associated with a 29.6% incremental cost for infliximab, versus -2.1% and 4.4% for etanercept and adalimumab, respectively (Fig. 3), when compared with the approved therapeutic doses at the time of the observation.

**Switching patterns**

Switching patterns between anti-TNF drugs or between an anti-TNF agent and a conventional DMARD are summarized in Figure 4. Overall, 37.3%, 38.0%, and 88.2% of patients switched from etanercept, adalimumab, and infliximab therapy respectively to another anti-TNF agent. Statistical analysis showed significant differences between the infliximab and etanercept (OR=12.5, Confidence Interval 95%, CI 95%, 5.5-28.5; p<0.001) and

**Figure 4** - Switching patterns between anti-TNF drugs or between an anti-TNF agent and a conventional DMARD.

**Figure 5** - Kaplan-Meier survival curve for infliximab, etanercept or adalimumab as the second anti-TNF treatment over a total period of 24 months.
between the infliximab and adalimumab (OR=12.2, CI 95% 5.2-28.5; p<0.001) treatment groups, indicating that patients receiving infliximab therapy were more likely to switch to another anti-TNF agent than those receiving etanercept or adalimumab.

In total, patients discontinuing a first anti-TNF agent and switching to a second one were 149: 12 switched to infliximab, 112 to etanercept, and 25 to adalimumab, respectively. The survival rate of the second anti-TNF agent, available over a 24-month period, is shown in Figure 5. At 24 months of the second line treatment, 75%, 22%, and 54% of infliximab, etanercept and adalimumab recipients, respectively, had discontinued their second anti-TNF. Overall, the relative risk of discontinuing the second agent with respect to the first anti-TNF drug was 1.31 (CI 95% 0.96-1.83).

# DISCUSSION

The aim of this study was to describe the discontinuation rate and the different treatment patterns of anti-TNF agents (adalimumab, etanercept and infliximab) in patients with RA in a large cohort of Italian patients treated in 23 Rheumatology centers from all areas of the Country. Overall, results presented here demonstrate a higher incidence of discontinuations and dose escalations in patients treated with infliximab compared with etanercept and adalimumab.

The National Institute for Health and Clinical Excellence (NICE) updated guidelines for the treatment of RA (20) recommend adalimumab, etanercept and infliximab as options for adult patients with active RA (defined as DAS28 >5.1 points on two assessments, 1 month apart) who have participated in trials of two DMARDS, including methotrexate unless contraindicated. The NICE guidelines also recommended that continuation of anti-TNF treatment should only occur if there is an adequate response at 6 months follow-up (defined as improvement in DAS28 ≥1.2 points) with further monitoring at a minimum of 6-monthly intervals and treatment withdrawal if an adequate response is not maintained.

Discontinuation of anti-TNF therapy has been extensively investigated in recent years (7, 8, 15-19). However, results have been generally inconclusive: in some studies the incidence of discontinuation was higher in patients with RA or spondyloarthropathies receiving infliximab compared with those receiving etanercept or adalimumab therapy (7, 15), but these findings were challenged (16).

In our study, the discontinuation rates associated with the three drugs were generally similar to those reported in studies evaluating patients with RA or spondyloarthropathies, some of which were conducted in the Italian scenario (7, 17-19, 21-23). Overall, infliximab was associated with a higher discontinuation rate than the other anti-TNF agents.

The most important reasons for discontinuation of therapy in the present study were the occurrence of insufficient response to therapy and of adverse events, which were observed, at different rates, with all anti-TNF agents. A higher proportion of patients treated with infliximab discontinued therapy because of an insufficient response to treatment. These results are in line with other studies, which showed that insufficient response was the most important reason for discontinuation of therapy after one year of infliximab treatment (21, 24). Moreover, there was a trend towards more discontinuations because of adverse events associated with infliximab than etanercept or adalimumab therapy.

Data in the literature also suggest that patients receiving infliximab frequently require dose escalations to achieve a response (7, 14, 25) and similar results have been reported in Italy (17). In contrast, studies suggested that dose escalations were less frequent with etanercept and adalimumab than infliximab therapy (7, 14). Data in the present study support these findings and show a significantly higher incidence of dose escalations with infliximab than with etanercept or adalimumab at 36 months. Similar results were observed with respect to the frequency of administration.
It must be observed, however, that a statistical analysis was not performed for these two parameters, and therefore these results should be regarded as indicative and not definite findings.

Of note, drug discontinuations, dosage adjustments and the need to switch to another anti-TNF agent may pose important concerns from a pharmacoeconomic perspective. In our study, the evaluation of total costs (including incremental costs) associated with different anti-TNF agents suggested that these drugs present an overall similar impact to healthcare expense. In fact, although infliximab is associated to the lowest mean cost when compared to etanercept and adalimumab, the frequent need for dose adjustments with this drug accounts for a higher incremental cost.

Data from our study regarding switching to an alternative anti-TNF agent are of particular interest. Most patients switched from infliximab to etanercept (65.6%), with fewer patients (18.3%) switching to DMARDs other than anti-TNF agents. These results are overall similar to those reported in the literature (26,27), although some authors have also suggested a switch from infliximab to adalimumab (28, 29).

One surprising finding of this study is the relatively low proportion of patients for whom an assessment of the RF status was available (56.6%): according to this result, in Italy the evaluation of RF in clinical practice is still suboptimal.

It must be acknowledged that this is an observational study and therefore may only infer associations, and not cause-effect relationships, which can be only addressed by a randomized trial. However, the precise aim of this analysis was to evaluate anti-TNF patterns of usage in a real-life scenario, since data on discontinuation, dose adjustments of and switch between different anti-TNF agents are unlikely to be retrieved from randomized trials (11).

Moreover, our analysis reports the results of a large observational study, with well-defined inclusion and exclusion criteria: we speculate that a similar design may strengthen the overall validity of the resulting evidence.

Conclusions and possible implications for clinical practice

The results of this large multicenter observational study, conducted in a real-life scenario, suggest that anti-TNF agents may be associated with a rather high incidence of discontinuation and dose adjustments over a 36-month period in patients with rheumatoid arthritis, with a possible effect on healthcare expense. In particular, infliximab appeared to be associated with a higher incidence of discontinuations and dose escalations, compared with etanercept and adalimumab.

Taking these findings together, we speculate that other therapeutic options with a different mechanism of action (e.g. abatacept, rituximab, and tocilizumab) should be considered in clinical practice, in particular in patients who fail the first anti-TNF treatment (11). Such an approach was recently acknowledged in the new EULAR recommendations for the management of RA that report the high level of evidence (RCTs) supporting other mechanisms of action than TNF antagonism as valid treatment choices as of first anti-TNF insufficient response (30). In particular, evidence suggests that abatacept may be a cost-effective strategy in patients discontinuing anti-TNF agents (31, 32). This finding has been very recently strengthened by the results of a cost-effectiveness study, conducted in the US, which underlined the cost-effectiveness of abatacept, when compared to rituximab, in patients affected by rheumatoid arthritis (33). Similar pharmacoeconomic evaluations concerning the Italian reality are ongoing and will likely shed new lights on the cost-effectiveness of these new molecules (manuscript in preparation).

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Objective: This study aims to provide a description of real life treatment patterns of biologic anti-TNF in 23 Italian Rheumatology centers.

Methods: This was an observational, multicenter, retrospective study. Patients >18 years of age, diagnosed with rheumatoid arthritis and treated with the first biologic anti-TNF agent between the 1st July 2002 to the 31st March 2004 were included. Total follow-up was 36 months.

Results: In total, 248 patients were first treated with infliximab, 259 with etanercept and 196 with adalimumab. First course of therapy with infliximab was associated with lower cumulative drug survival than the other two agents. At 36 months, 74.7% of patients on etanercept, 72.0% of those on adalimumab and 57.7% of subjects receiving infliximab were still on therapy. In total, 149 patients switched to a second anti-TNF agent. At 24 months of the second line treatment, 75%, 22%, and 54% of infliximab, etanercept and adalimumab recipients, respectively, had discontinued their second anti-TNF.

Conclusions: Anti-TNF agents may be associated to a rather high incidence of discontinuation and dose adjustments over a 36-month period, with a possible effect on healthcare expense. In particular, infliximab was associated with a higher incidence of discontinuations compared with etanercept and adalimumab.

Parole chiave: Anti-TNF; artrite reumatoide; pattern di trattamento.

Key words: Anti-TNF; rheumatoid arthritis; treatment patterns.
REFERENCES


