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Switching TNF-alpha antagonists in rheumatoid arthritis: The experience of the LORHEN registry

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ABSTRACT

New biologic agents have changed the paradigm of rheumatoid arthritis treatment, leading to improvement in managing patients' refractory to classical DMARDs. Anti-TNF-alpha is used as first-line treatment in patients failing to respond to classical DMARDs. However, up to 50% of patients fail to respond to these drugs or develop adverse events leading to treatment discontinuation: in these cases the optimal treatment strategy is still a matter of debate even if trying with a second anti-TNF-alpha is considered a good option. We report data of patients switching from a first to a second anti-TNF-alpha from an Italian registry of patients with rheumatoid arthritis, showing that switching is valuable in patients stopping a first anti-TNFα drug. The patients with higher disease activity levels and those stopping the first anti-TNFα treatment because of a lack of efficacy are very likely to respond to the second treatment.

Contents

The evolution of the treatment of rheumatoid arthritis (RA) over the last ten years, with the introduction of anti-TNFα agents, has led to improvements in controlling the signs and symptoms of RA refractory to classical DMARDs, and in slowing joint destruction [1,2]. Although no head-to-head comparative trial of the three anti-TNFα agents (adalimumab, etanercept and infliximab) has been carried out, the existing data suggest that their efficacy and safety profiles are similar whether used alone or in combination with methotrexate (MTX) [3,4].

However, some patients do not respond (or respond suboptimally) to anti-TNFα agents, fail to maintain an initially good response over time, or develop adverse events leading to treatment discontinuation [5,6]. Adalimumab, etanercept and infliximab all block TNFα, but have different molecular structures, sites of action and dosing regimens, and also differ in the generation of autoantibodies, and the type and frequency of adverse events, which suggests that switching to a second anti-TNFα agent after the failure of a first may be beneficial and not necessarily associated with an increased adverse event rate. Although the published studies vary widely in terms of population

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sizes (most have been based on small case series), designs and outcome measures [7–26], the latest and most interesting data come from analyses of large registries of patients treated with anti-TNF agents in different countries.

However, as new biological drugs have also been approved for the specific purpose of treating patients who have failed on anti-TNFα agents, clinicians may find it difficult to decide the most appropriate treatment after a first TNF failure: this is still a subject of debate and may have important clinical and economic implications in everyday practice [5].

As data from an Italian registry of RA patients treated with anti-TNFα agent have recently been published [27], the aim of this paper is to describe the clinical characteristics and response rates of patients switching from a first to a second anti-TNFα agent.

1. Patients and methods

1.1. Patients

Since 1999, all patients with RA diagnosed on the basis of the American College of Rheumatology (ACR) criteria [28] and treated with at least one dose of an anti-TNFα agent have been recorded in a database shared by four rheumatology centres in Lombardy (Northern Italy): the Lombardy Rheumatology Network (LORHEN) registry. The registry describes the efficacy and safety of the first three years of treatment in a large cohort of patients receiving the three currently available TNFα inhibitors – etanercept (ETA), infliximab (INF) and adalimumab (ADA) – the data of which have been recently published [3,4,6,27]. The present study considers all of the patients who switched from their first to a second anti-TNFα agent. In all cases, a standard form was used to collect demographic data, the individual components of the DAS28 [29], details of current DMARD or steroid treatment, and comorbidities at baseline (i.e. the visit before starting the second anti-TNFα agent) and six and 12 months later.

1.2. Assessments

At baseline, and six and 12 months later, the treating rheumatologist recorded the number of swollen and tender joints of each patient (28-joint count), the erythrocyte sedimentation rate (ESR), rheumatoid factor level and current RA therapy (DMARDs and steroids), as well as the patient's assessment of pain and overall assessment of general health (in both cases using a 100 mm visual analogue scale, VAS). At baseline, the reason(s) for stopping the first anti-TNF treatment were recorded and classified as a lack of (primary or secondary) response, adverse events, or other reasons, which included pregnancy, patient decision, poor compliance, or unspecified causes. At each visit, all of the patients also completed the Italian version of the Disability Index of the Health Assessment Questionnaire (HAQ) [30], and their response to treatment was evaluated on the basis of the EULAR criteria and classified as good, moderate or none [29].

1.3. Statistical analysis

The differences between infliximab, adalimumab and etanercept were analysed on the basis of the data relating to all of the LORHEN patients who switched from one anti-TNFα agent to another, using the Kruskal–Wallis non-parametric test for the continuous variables (mean and standard deviation) and the Chi-squared test for the categorical variables (counts and percentages). The uni- and multivariate analyses were performed using logistic regression models. The response variable was defined as the occurrence of EULAR response criteria (yes/no) after one year of treatment. The baseline variables taken into account were age at the start of therapy, gender, the duration of the first anti-TNF treatment, the DAS28 and HAQ scores, the concurrent use of MTX and corticosteroids, and the reasons for stopping the first anti-TNFα treatment.

All of the analyses were made using SAS version 9.2 (SAS Institute, Inc; Cary, NC), and a p value of 0.05 or less was considered statistically significant.

2. Results

During the three-year study period, 1114 biological agent-naïve RA patients were started on a first anti-TNFα treatment (533 on INF, 332 on ADA, and 249 on ETA), 237 of whom subsequently switched to a second anti-TNF agent and were included in the analysis. Table 1 shows their baseline characteristics, and Table 2 the type of switch. The majority of patients switched from monoclonal antibodies (INF or ADA) to ETA (65% of cases) or from ETA to monoclonal antibodies (13.5%); only 21.5% switched from one monoclonal antibody to another.

2.1. Response rates

Fig. 1 shows the response rates after six and 12 months. On the basis of DAS28, EULAR good responses were achieved by 32 patients (14.9%) after six months and 36 (18.6%) after 12 months and moderate responses by respectively 80 (37.2%) and 103 patients (53.1%); and no response was observed in respectively 103 (47.9%) and 55 patients (28.3%).

In general, the number of responders (those with good or moderate DAS28 responses) after six and 12 months' treatment with the first anti-TNFα agent was respectively 534 (76.1%) and 668 (81.4%); the corresponding figures after treatment with the second agent were respectively 112 (52.1 %) and 139 patients (71.7 %) (p = n.s.).

The patients who started treatment with a second anti-TNFα agent due to lack of response to the first were more frequently responders after six and 12 months (56.7% and 79.7%, respectively) than those who started the second treatment after stopping the first because of adverse events (44.6% and 60.3%). The percentage of non-responders to ADA and INF was higher than the percentage of non-responders to ETA at both time points.

Table 1
Patient characteristics at baseline (237 patients switching to a second anti-TNF), TJC = tender joint count; SJC = swollen joint count; ESR = erythrocyte sedimentation rate; HAQ = health assessment questionnaire; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate.

Age (yrs), mean (SD)	61.0 (13.49)
Females, *n* (%)	195 (82.3)
Disease duration (yrs), mean (SD)	7.9 (7.93)
DAS-28 score, mean (SD)	5.7 (1.29)
28 TJC, mean (SD)	11.1 (6.85)
28 SJC, mean (SD)	9.8 (5.62)
VAS global (mm), mean (SD)	69.0 (23.86)
Physician global assessment (mm), mean (SD)	58.1 (24.90)
ESR (mm/h), mean (SD)	41.3 (21.96)
HAQ score, mean (SD)	1.4 (0.63)
Previous number of DMARDs[a], mean (SD)	3.4 (1.34)
Concurrent corticosteroid use, *n* (%)	
None	34 (14.4)
≤5 mg	139 (58.6)
>5 mg	64 (27.0)
Weekly MTX dose (mg), mean (SD)	12.2 (3.25)
Concurrent MTX use, *n* (%)	207 (87.3)
Concurrent DMARDs other than MTX, *n* (%)	82 (34.6)
MTX + other DMARDs, *n* (%)	77 (32.5)
Reason for stopping previous anti-TNFα therapy	
Adverse events, *n* (%)	77 (32.5)
Primary inefficacy, *n* (%)	86 (36.3)
Secondary lack of response, *n* (%)	59 (24.9)
Others, *n* (%)	15 (6.3)

[a] Includes previous biological drugs.