Original article

Outcome and safety of TNFα antagonist therapy in 475 consecutive outpatients (with rheumatoid arthritis or spondyloarthropathies) treated by a single physician according to their eligibility for clinical trials

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ABSTRACT

Objective: To investigate the effectiveness and safety of TNFα antagonists in patients with rheumatoid arthritis (RA) or spondyloarthropathies (SpA) treated by a single physician, according to the presence of the inclusion and non-inclusion criteria used to select patients for pivotal clinical trials.
Methods: Effectiveness was evaluated based on four categories defined by the DAS28-ESR and BASDAI values, from a very good response (mean DAS-28-ESR less than 3.2 and mean BASDAI less than 2.0) to failure (DAS28-ESR unchanged or greater than 5.1 and BASDAI unchanged). Serious adverse events were defined as events that required permanent TNFα antagonist discontinuation or that led to sequelae, hospital admission, or death.
Results: The study included 475 patients, 230 with RA, 226 with SpA, 10 with juvenile-onset arthritis, and nine with unclassifiable arthritis. Mean number of TNFα antagonists used per patient was 1.3 and mean duration of TNFα antagonist treatment was 28 ± 23 months. Overall, 41% of patients met the inclusion and non-inclusion criteria used in pivotal trials; the proportion was 43% in the RA group and 40% in the SpA group. These patients had a 3-fold higher rate of very good responses (54 versus 19%) and a 5-fold lower rate of failures (5 versus 25%) compared to the other patients. Of the 15 (3%) patients who died, none met pivotal trial criteria. The group that met pivotal trial criteria had a significantly lower rate of serious adverse events (11 versus 16%; Chi^2, $p = 0.0001$), although age was similar in the two groups (53 ± 16 years versus 57 ± 14 years).
Conclusion: Patients meeting the selection criteria used in pivotal trials had a higher response rate and significantly fewer serious adverse events.

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The efficacy and safety data obtained in trials of TNFα antagonist therapy cannot be directly generalized to the real-life clinical setting [1,2]. A study from The Netherlands showed that 56% of patients with rheumatoid arthritis (RA) given TNFα antagonist therapy did not meet the criteria used to select patients for a clinical trial [3]. In the US, higher proportions of 80% in New York [4] and 87% among 825 veterans [5] were reported. Studies in patients with RA [3,4] or spondyloarthropathies (SpA) [6] who did not meet trial selection criteria found decreases in both effectiveness and safety compared to the data from trials.

Registries of patients given TNFα antagonist therapy in everyday clinical practice have been established in Sweden (STURE) [7], the UK (BSR) [8], Denmark (DANBIO) [9], Spain (BIOBADASER) [10], Germany (RABBIT) [11], The Netherlands (DREAM) [12], and the US

(RADIUS) [13]. However, differences in patient profiles may exist across these registries, as the recommendations for using TNFα antagonists vary from one country to the next. For instance, British recommendations require a considerably higher level of disease activity than do French recommendations [14]. Furthermore, the registries in Spain, Germany, and the US included only a small fraction of the patients treated with TNFα antagonists, and patients not given these agents and included as controls in some registries had less severe disease [13]. Finally, very few data are available on the effects of TNFα antagonists on SpA in the everyday clinical setting [15].

We studied outcomes in consecutive patients given TNFα antagonist therapy by a single physician in France. The objectives of the study were as follows: to describe patients started on TNFα antagonist therapy for joint disease; to determine the proportion of patients who refused TNFα antagonist therapy because of concerns caused by the information they received; to determine the percentage of RA and SpA patients who did not meet the selection

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criteria used in clinical trials; and to determine the rate of serious adverse events (SAEs) in the groups that did and did not meet trial selection criteria.

1. Methods

A list of all adults given TNFα antagonist therapy by a single physician was established and reported to the French Computerized Data and Freedom Committee (CNIL). The medical records of the first 500 patients were reviewed retrospectively between December 2008 and March 2009. The duration of actual TNFα antagonist use was determined in each patient.

Patients were classified as having SpA if they met Amor's criteria [16] and as having RA if they met 1987 American College of Rheumatology criteria [17]. Of the 10 patients with childhood-onset disease, four met criteria for juvenile-onset RA [18] and three criteria for juvenile-onset SpA [19]. We determined whether patients with RA or SpA met the recommendations issued by the French Society for Rheumatology (SFR) for the initiation of TNFα antagonist therapy [20,21]. Psoriatic arthritis (PsA) was classified in the SpA group, and nine patients with predominantly peripheral arthritis were also counted in the RA group. Patients with predominant polyenthesitis were classified in a specific subgroup and patients with concomitant fibromyalgia in another subgroup. The diagnosis of fibromyalgia was based on the presence of hyperpathia and of at least 10 of the 18 tender points, although this diagnostic criterion has been criticized [22].

The use of prednisone at TNFα antagonist therapy initiation was recorded. For each patient, we determined whether the non-inclusion criteria widely used in clinical trials of TNFα antagonists were met (atypical disease pattern, high-dose glucocorticoid therapy, recent or remote history of significant medical problems, and psychopathology). We did not consider that low disease activity (DAS28-ESR less than 3.2) was a non-inclusion criterion for RA patients, because several trials assessed TNFα antagonist therapy as a means of decreasing the glucocorticoid requirements or preventing structural joint damage. In contrast, in the SpA group, a BASDAI lower than 4.0 at baseline was considered a non-inclusion criterion.

Effectiveness was assessed based on the response to the first TNFα antagonist used, as few patients received more than one TNFα antagonist. However, we separately assessed the response to each TNFα antagonist used in each patient. Effectiveness could not be reliably assessed in the 40 patients with less than 6 months on TNFα antagonist therapy. Furthermore, 25 patients did not take the TNFα antagonist. Therefore, the effectiveness analysis included 435 patients.

Effectiveness [1] was assessed semi-quantitatively [23], given the retrospective study design and fluctuations in RA and SpA activity in individual patients [24,25]. The data in correspondence to the patients' usual physicians were used to classify patients into four subgroups, as follows: very good response (DAS28-ESR usually less than 3.2 and BASDAI usually improved by more than 60% or less than 2.0); satisfactory response (DAS28-ESR usually between 3.2 and 4.0 and BASDAI usually improved by more than 30% or lower than 4.0); fair response (DAS28-ESR between 4.0 and 5.1 and BASDAI usually improved by less than 30% or between 4.0 and 5.0); and failure (DAS28-ESR usually unchanged or greater than 5.1 and BASDAI usually unchanged or worsened). The score fluctuations in individual patients over time precluded the use of the DAS-based EULAR response criteria.

SAEs were defined as events requiring permanent TNFα antagonist discontinuation, events requiring hospital admission, life-threatening events, and events with a potential for causing permanent harm. However, some events that required hospital admission were not classified among SAEs because they had no plausible link with the TNFα antagonist treatment (e.g., motor vehicle accidents).

Vital status was determined for all patients. For patients who died, the cause of death was sought by reviewing the medical records and calling the usual physicians. The safety analysis included the 475 patients who received at least one injection of TNFα antagonist.

2. Results

In France, TNFα antagonist therapy must be initiated in an accredited hospital department. Of the 500 patients, 429 (86%) were referred by office-based physicians. Among them, 25 (5%) did not take the TNFα antagonist, for one or more of the following reasons: improvement of the joint disease, either spontaneously or after treatment adjustments (n = 15); concern about possible side effects (n = 6); plans for a pregnancy (n = 3); detection of a co-morbid condition (cancer, n = 2; and sinus infection requiring surgery, n = 1); dosing schedule incompatible with the patient's lifestyle (n = 3); and refusal of the public health insurance agency physician to grant payment for TNFα antagonist treatment (n = 1, with undifferentiated SpA).

In the 475 patients given at least one dose of TNFα antagonist, theoretical exposure time (from the prescription to the last evaluation) was 39 ± 25 months and actual exposure time was 28 ± 23 months (1584 patient-years). Reasons for not taking the full amount of TNFα antagonist prescribed were side effects, personal convenience and, in only a few cases, a lasting remission [26]. In both the RA and the SpA group, exposure time was not significantly different in the patients with poor responses (15%) and in those with good responses. Thus, the 14% of patients in the failure category used TNFα antagonist therapy for nearly 1.5 years. This conservative attitude explains why 73% of patients received a single agent, 23% two agents, and only 4% the three available agents.

2.1. Patient characteristics

Of the 475 treatment patients, 230 had RA (mean age at treatment initiation, 53.0 ± 13.3 years), 226 had SpA (41.6 ± 12.3 years), 10 had juvenile-onset chronic arthritis (38.5 ± 17 years, with the youngest being 17 years of age at treatment initiation), and nine had unclassifiable chronic arthritis (47.9 ± 18 years) (Table 1).

Of the 230 RA patients, 201 (87%) had radiographic evidence of joint damage and/or positive tests for rheumatoid factors and/or anti-citrullinated peptide antibodies (ACPA). Importantly, 180 (78%) RA patients had a level of clinical activity that was sufficient per se to warrant TNFα antagonist therapy [20] and 142 (62%) had radiographic progression. At TNFα antagonist initiation, 131 (57%) patients were taking prednisone in dosages greater than 7.5 mg/day. Overall, 192 (83%) patients met SFR criteria for initiating a biotherapeutic agent [20].

Of the 226 SpA patients, 143 (63%) had predominantly axial disease, 65 (29%) had PsA (including 56 [86%] with psoriasis), 34 (15%) had enteropathic arthropathy, and 11 (5%) also had manifestations consistent with SAPHO syndrome; the total is greater than 100% because some patients fell into more than one category. Furthermore, in 54 SpA patients the predominant manifestation was polyenthesitis, which was chiefly peripheral with little or no axial involvement in 43 patients, among whom 19 (19/43) were also classified as having fibromyalgia. The most prominent manifestation was refractory heel pain in 15 (7%) patients and progressive hip disease in 15 (7%) patients. At baseline, 18 (9%) patients had a BASDAI value lower than 4.0. Overall, only 135 (59%) SpA patients met SFR criteria for TNFα antagonist therapy initiation [21].