CONCISE REPORT

Decreased flares of rheumatoid arthritis during the first year of etanercept treatment: further evidence of clinical effectiveness in the "real world"

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Objective: To determine the incidence of disease flare during the first year of etanercept treatment for 88 patients with rheumatoid arthritis (RA) and compare it with the incidence of flare in those same patients in the year before etanercept use.

Methods: The outpatient clinic charts of all patients with RA who were prescribed etanercept in or before September 1999, who also had at least one year's follow up in the same outpatient clinic, were surveyed. The primary outcome measure was the number of disease flares in one year before and after etanercept use. The secondary outcome measures included the number of patients who did and did not flare, how flares were treated, and the drug alterations that were necessary during the same two time intervals.

Results: The total number of flares for all patients in the year before etanercept treatment was 214 (mean (SD) 2.43 (1.75)). The number of flares in the first year of etanercept treatment decreased to 83 (mean 0.94 (1.07)) ($p < 0.0001$). The total number of patients who had at least one flare in the year before etanercept use was 80; eight had no flares. In their first year of etanercept treatment, 50 patients had at least one flare; 38 had no flares ($p < 0.0001$). Twenty one patients (24%) stopped using etanercept before completing one year's treatment.

Conclusion: This study of patients with RA in the "real world" shows that etanercept is effective in reducing the number of RA flares.

The course of rheumatoid arthritis (RA) is best described as fluctuating. Throughout the chronic course of RA, periods of increased disease activity or "flare" alternate with periods of relative quiescence. RA flares are often a cause of intermittent patient discomfort and decreased quality of life, even if only for a short period. These flares often require medical intervention in order to regain control of the acute clinical manifestations of the disease.

Clinical trials with etanercept, the tumour necrosis factor α receptor antagonist, have demonstrated sustained clinical efficacy over a two year period.^{1,2} A decrease in overall RA activity, as assessed by improvement in the composite measures of disease activity, improvement in individual measures of active disease, and slowing of radiographic progression due to RA, has been reported. However, the incidence of RA flares requiring medical intervention during etanercept use has not been determined in the "real world".

We conducted a retrospective chart review of our patients with RA who were being treated with etanercept to determine their rate of flare during the first year of treatment and compared this with the rate of flare among the same patients in the year before etanercept use.

METHODS

Patients were selected from the RA registry and repository maintained at the Hospital for Special Surgery. The registry is a prospective longitudinal database that records clinical information relevant to RA (that is, demographics, American College of Rheumatology (ACR) criteria, RA drugs, RA signs and symptoms) for every patient with RA seen at our tertiary care institution.

We identified all patients with RA contained in the registry who had been prescribed etanercept treatment before or during September 1999 to ensure at least one year's exposure to the drug at the time of our analysis. We then performed a retrospective chart review on each patient for the year before and the first year of etanercept treatment. We were specifically looking for the number of flares occurring in each of these one year periods. Flare was defined based on the principle of the doctor's intention to treat. A flare was said to have occurred if there had been a change in the patient's "baseline" treatment for the purpose of alleviating signs and symptoms of increased RA activity or there was a mention by the doctor of "flare" and "increased activity" in the charts. The therapeutic measures to treat individual flares, changes in standing medical regimens, incidence of infections, and reasons for discontinuation of etanercept were also recorded.

Our primary outcome was the number of flares that had occurred during the two time intervals. Secondary outcomes included the number of patients who did or did not flare, treatment of flare, change/discontinuation of antirheumatic drugs, especially etanercept, for each one year interval. Rates and differences in intervention were compared for the year before and the first year of etanercept treatment. McNemar's χ^2 test for paired observations was used for statistical analysis.

RESULTS

The Hospital for Special Surgery RA registry and repository contains 613 patients meeting the ACR classification criteria for RA. One hundred and thirty two of these patients who had been treated with etanercept were identified. Of these, 88 patients had started treatment before September 1999 (mean (SD) age 57.3 (12.9) years, mean duration of disease 16.8 (10.8) years, female 79, white 56, Hispanic 16, Asian 8, black 8). All patients were followed up by the same rheumatologists during both time intervals.

The total number of flares for all the patients in the year before etanercept treatment was 214 (mean 2.43 (1.75)). The number of flares for this cohort in the first year of etanercept treatment decreased to 83 (mean 0.94 (1.07)) ($p < 0.0001$).

Abbreviations: ACR, American College of Rheumatology; DMARD, disease modifying antirheumatic drug; RA, rheumatoid arthritis

Table 1 Number of RA flares and how they were treated before and after the initiation of etanercept treatment

Intervention	Before etanercept	After etanercept
PO Pred (temp)	12	19
IA Pred	34	12
IM Pred	1	0
IV Pred	10	3
MTX	3	4
LEF	1	0
SSZ	2	0
HCQ	0	1
NSAID (temp)	6	3
AZA	2	1
Gold	0	0
CYC	0	0
Opioids (temp)	1	1
MIN	0	0
↑ Pred	82	17
↑ MTX	22	7
↑ HCQ	2	0
↑ NSAID	5	1
↑ CYC	1	0
↑ AZA	4	0
↑ Gold	1	0
Combination treatment	12	1
No treatment	13	13
Total	214	83

PO, oral; IA, intra-articular; IM, intramuscular; IV, intravenous; (temp), temporary; ↑, increase; Pred, prednisone; MTX, methotrexate; LEF, leflunomide; HCQ, hydroxychloroquine; AZA, azathioprine; IM, intramuscular; CYC, cyclosporin; SSZ, sulfasalazine; MIN, minocycline; NSAID, non-steroidal anti-inflammatory drugs.

The total number of patients who had at least one flare in the year before etanercept treatment was 80; eight patients had no flares. After starting etanercept, in their first year of treatment, 50 patients had at least one flare; 38 patients had no flares ($p < 0.0001$).

The most common intervention for the treatment of the 214 RA flares in the year before etanercept treatment started was a temporary increase in the patient's established dose of steroid in 82 (38%) cases. This was followed by the use of intra-articular steroid injections in 34 (16%) cases, an increase in the current dose of methotrexate in 22 (10%), and temporary addition of oral steroids for patients who were not already using them in 12 (6%). Thus, a total of 94 (44%) flares were treated with oral steroids. Twelve episodes of flare were treated with a combination of interventions (table 1).

Temporary addition of oral steroids in 19 (23%) cases was the most common intervention for the 83 flares recorded in the first year of etanercept treatment. An increase in the standing dose of oral steroids in 17 (20%) cases, the use of intra-articular steroid injections in 12 (14%), and an increase in the standing methotrexate dose in seven (8%) followed as the next preferred treatment interventions. Only one of these flares was treated with multiple modalities (table 1).

In the pre-etanercept period, 32/88 (36%) patients used steroids and a disease modifying antirheumatic drug (DMARD), 21 (24%) patients used oral steroids alone, and seven (8%) patients took only methotrexate. Twenty one (24%) patients used no steroids or DMARDs (table 2).

During the year of etanercept treatment, the most common additional treatment for individual patients was oral steroids in 20 (23%), methotrexate in eight (9%), and oral steroid with methotrexate in five (6%). No patients required the use of three DMARDs in addition to etanercept. Forty five (51%) patients were using etanercept alone (table 2).

A total of 21 (24%) patients in our cohort stopped using etanercept before completing one year's treatment. Eleven of

Table 2 Numbers of patients using DMARDs before and after the initiation of etanercept

DMARDs	Before etanercept	After etanercept
Pred	21	20
MTX	7	8
LEF	0	1
HCQ	3	4
AZA	0	1
Gold (IM)	0	1
Pred+AZA	7	0
Pred+CYC	1	0
Pred+MTX	15	5
Pred+MTX+HCQ+AZA	1	0
Pred+LEF	1	0
Pred+LEF+gold	1	0
Pred+SSZ	2	0
Pred+HCQ	2	1
Pred+HCQ+MIN	1	0
Pred+MTX+LEF	1	0
MTX+LEF	0	1
MTX+gold	1	0
MTX+LEF+SSZ	1	0
MTX+HCQ	1	1
LEF+SSZ	1	0
Total	67	43

Pred, prednisone; MTX, methotrexate; LEF, leflunomide; HCQ, hydroxychloroquine; AZA, azathioprine; IM, intramuscular; CYC, cyclosporin; SSZ, sulfasalazine; MIN, minocycline.

these patients discontinued because the drug was ineffective and seven because of side effects or associated adverse events. The reasons for stopping were not recorded for the remaining three patients.

We have previously reported that in the year before etanercept treatment 24 patients had 32 infections compared with 26 patients with 51 infections during the first year of etanercept treatment ($p = \text{NS}$)³ (full manuscript in preparation). Most of the infections before and during etanercept treatment were respiratory (17 v 27), and did not require admission to hospital. Among the most serious infections were two cases of empyema, one each before and during etanercept treatment, and methicillin resistant *Staphylococcus aureus* sepsis and infected total hip replacement in one patient during etanercept use. No patients died during the course of this study.

DISCUSSION

Evidence for the efficacy, safety, and tolerability of etanercept has been reported in clinical trials.⁴⁻⁶ After the approval of any drug, clinical response in general medical practice often differs from the rather artificial scenario of the formal clinical trial for many reasons. Firstly, without the limitations of stringent inclusion and exclusion criteria necessary for scientific evaluation in clinical studies more diverse groups of patients are treated with the regimen studied. Secondly, clinical trials are conducted on only a small number of subjects and the incidence of specific adverse events is low. Also, the clinical outcomes assessed by doctors for individual patients often differ from those designed for research purposes. It is these bedside evaluations that guide therapeutic decision-making and ultimately determine the effectiveness of any drug in the "real world".

This retrospective survey of patients with RA in the "real world" demonstrates the effectiveness of etanercept. The drug reduced the number of episodes of increased RA activity that required a change in medical treatment. In addition to the reduced number of flares while receiving etanercept treatment, fewer patients required chronic oral steroids to control their RA, and patients required fewer additional DMARDs or

combinations of DMARDs. Also, more patients were “flare-free” during their first year of etanercept treatment than in the year before changing from their previous RA regimens to etanercept.

Etanercept use in general medical practice was associated with a low incidence of discontinuation because of either a total lack of efficacy or the development of side effects.

The purpose of this investigation was to enhance our knowledge of the “efficacy” of etanercept by defining its “effectiveness” in general medical practice. We wished to identify the drug’s actual performance in the unconstrained environment that is requisite for a clinical trial.

The ACR response criteria are very explicit. Day to day, few rheumatologists perform standardised joint counts or administer health assessment questionnaires, and even fewer would base their decision-making on these structured measures. Given the retrospective nature of our study, we had to employ a practical method of detection of success versus failure of etanercept that described the de facto management. The definition of increased RA activity or “flare” was felt to best reflect clinical practice. Although our definition is not nearly as uniform or as operationalised as the outcomes used in clinical trials, and although it is likely that each rheumatologist maintains his or her own threshold for considering a change in RA treatment, we felt our definition best represented therapeutic success in the “real world”.

Furthermore, while discontinuation/dropout rates from clinical trials are recorded, the ACR response criteria detect rates of improvement at predetermined cutoff points only; minor improvements are not identified. The 20% improvement (that is, ACR20) required by the Federal Drug Administration for drug approval may not be sufficiently clinically significant for all patients with RA to warrant their continuation or discontinuation of any regimen. Patients with RA may have some clinical improvement while taking etanercept that is suboptimal for that particular person, either transient or long lasting.

Thus our definition of effectiveness—that is, the doctor’s view that further intervention is needed, allows us to identify clinically important improvement that would otherwise be undetected.

The use of patients with RA as their own controls reduces the possibility of introducing several biases, including those related to disparities in baseline characteristics of disease such as disease severity and comorbid conditions.

Patients with RA are known, by their doctors and themselves, to have their own patterns of disease activity and flares. The patient-doctor pair for each evaluation is the same for the periods before and after etanercept use, and therefore clinical diagnosis and chart documentation, triggers for intervention and specific treatment algorithms for RA flares are not

expected to change. Also, the individual character of the disease usually becomes clear within the first two years of diagnosis. RA progresses over many years, but dramatic changes in rates and quality of progression are not usual. Although, possibly, the overall clinical status of a patient with RA might change significantly over the course of two years, the likelihood of this occurrence is minimal. If anything, using patients with RA as their own controls with time as an independent variable, would bias our results such that during the second of the two years of follow up—that is, during etanercept exposure, patients would fare much worse. This is likely to be true of their RA and any other progressive comorbid condition, such as diabetes mellitus or congestive heart failure. In fact, our study shows that with time, our patients did better during the subsequent year. This further underlines the idea that etanercept is effective in general medical practice.

To the best of our knowledge this study provides the first evidence that etanercept reduces the number of RA flares requiring treatment and the number of additional DMARDs that patients with RA use. A prospective study specifically examining this question is needed to determine definitively whether these perceptions are valid.

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