Switching to etanercept in patients with rheumatoid arthritis with no response to infliximab.

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ABSTRACT

TNF-α is thought to play a pivotal role in the initiation and perpetuation of the chronic inflammatory process in rheumatoid arthritis.

TNF-α blockers such as infliximab and etanercept are currently used in the treatment of active rheumatoid arthritis (RA) when traditional DMARDs have failed and are effective in a significant proportion of patients. However, about one third are non-responders to anti-TNF-α.

The aim of this study was to verify whether rheumatoid patients, after failing infliximab, can benefit from etanercept.

We analysed 18 patients with active RA with no response to at least 3 DMARDs and where infliximab therapy had failed. The patients had received infliximab associated with methotrexate: eleven of them did not show any significant response, while seven patients, after a good response, relapsed. Etanercept was then started. EULAR criteria of response were used with calculation of activity index DAS28 at baseline, after 2 weeks, 3 months and every third month until last follow-up.

A moderate or good response was achieved with etanercept in 13 out of 18 patients.

From our experience, etanercept can be considered as a good alternative choice when infliximab has failed.

Introduction

Tumor necrosis factor a (TNF-α) is thought to play a pivotal role in the initiation and perpetuation of the chronic inflammatory process in rheumatoid arthritis (1).

TNF-α blockers are currently used in the treatment of active rheumatoid arthritis (RA) when traditional DMARDs have failed and are effective in a significant proportion of patients (2, 3).

Currently three TNF-α blockers are available with different way of administration, pharmacokinetic and probably different mechanisms of action. Infliximab is a chimeric monoclonal IgG1 antibody against TNF-α given intravenously, etanercept is a recombinant TNF-α receptor fusion protein given subcutaneously twice a week and adalimumab is a recombinant humanized IgG1 monoclonal anti-TNF-α antibody given subcutaneously every two weeks (2, 3).

Overall about one third of rheumatoid patients fail to respond to TNF-α blockers (2, 3).

On the other hand, switching from one TNF-α antagonist to another when the first agent has demonstrated lack of efficacy may prove of value. In particular, Brocq *et al*. described 14 rheumatoid patients, 8 switched from infliximab to etanercept and 6 from etanercept to infliximab because of inefficacy or adverse event: a good clinical improvement was shown in about half of the patients (4).

Our purpose was to evaluate the clinical efficacy of etanercept on rheumatoid patients where infliximab therapy had proved ineffective.

Materials and methods

We longitudinally evaluated 18 patients affected by RA, as defined by the 1987 American College of Rheumatology criteria (5) and who had failed at least 3 DMARDs. These patients were 15 females and 3 males with mean age 52.0 ± 17.0 years. Previously, all of them had received monotherapy with a single DMARD and then combination therapy with methotrexate + cyclosporin A + chloroquine or sulfasalazine without any significant efficacy. At the basal evaluation DAS28 resulted 6.7 ± 1.0.

Initially the patients received infliximab 3 mg/Kg intravenously at time 0, after 2, 6 weeks and then every 8 weeks always associated to methotrexate. Infliximab was then discontinued due to lack of response in 11 patients and due to relapse after an initial good response in 7 patients.

One patient relapsed at six months (month +6) after the beginning of infliximab treatment, one at month +9, one at month +12, one at month +13, one at month +15, one at month +21 and one at month +22. The mean ± SD duration of infliximab treatment was 13.7 ± 9.6 months (range 6-41).

After at least 3 months of washout, etanercept was started at the dose of 25 mg subcutaneously twice a week maintaining methotrexate at the unchanged

dose. The mean ± SD etanercept-treatment duration was 10.5 ± 10.9 months (range 3-33).

EULAR criteria of response were used with calculation of activity index DAS28 at the basal level, after 2 weeks, 3 months and every third month until the last follow up. A good clinical response was defined by a DAS28 reduction of at least 1.2 points from basal level, a moderate clinical response a DAS28 reduction of 0.6-1.2 when basal DAS28 was ≤ 5.1. When DAS28 reduction was the same as or inferior to 1.2 in patients with basal DAS28 > 5.1 or was the same as or inferior to 0.6 in patients with basal DAS28 ≤ 5.1, the patient was considered having no response to treatment. Clinical remission was defined by a DAS28 inferior to 2.6 (6).

Safety measures included regular clinical assessment record of laboratory data, infusion reactions, infections and other possible side effects.

Results

Seven of 11 patients with no response to infliximab improved with etanercept: four had a good clinical response and three a moderate clinical response with a mean DAS28 reduction from 6.4 ± 1.1 to 4.4 ± 0.9 (p = 0.001). Four patients did not gain any advantage from etanercept (Fig. 1A).

Six of 7 relapsers on infliximab treatment responded to etanercept: three had a good clinical response and three a moderate one with a mean DAS28 reduction from 6.3 ± 0.6 to 4.2 ± 1.7 (p = 0.001) (Fig. 1B).

The mean baseline DAS28 of responders to etanercept was not statistically different from mean basal DAS28 of the patients who did not gain any advantage from either infliximab or etanercept.

In conclusion, etanercept was effective in 13 out of 18 patients where infliximab had failed (72%) with a median DAS28 reduction from 6.4 ± 0.9 to 4.3 ± 1.3 (p = 0.000). However, only one patient of the 13 responders to etanercept achieved clinical remission.

Discussion

TNF-α antagonists are effective agents for the treatment of RA and are relatively safe. Nevertheless some patients still have a poorly or incompletely controlled disease (2, 3). There is little information regarding comparison between the different TNF-α-blockers or between TNF-α-antagonists and other DMARDs or combination therapy in RA.

Among the 18 patients who did not improve with infliximab or relapsed after a good-moderate initial response, 13 presented a significant improvement in disease control after treatment with etanercept. Overall, etanercept proved effective in 72% of the patients unsuccessfully treated with infliximab.

Our experience is in accordance with other previous observations in rheumatoid patients who were unresponsive or intolerant to infliximab. Of note, we chose to analyse only the patients who failed infliximab and not the patients who discontinued it for adverse events. Previous lack of efficacy with infliximab does not predict a lack of response with etanercept (4, 7- 9).

These data support the hypothesis that TNF-α-antagonists have different clinically relevant mechanisms of action.

Infliximab, the first approved, is a chimeric IgG1 anti-TNF-α antibody that binds to soluble and membrane-bound TNF-α with high affinity and kills cells that express TNF-α through antibody-dependent and complement-dependent cytotoxicity (10). It is used in combination with methotrexate because of the frequent development of anti-infliximab antibodies. Patients lacking a full response, or having an initial response followed by a relapse, may show a better response either by decreasing the interval between infliximab infusions or increasing the dose (11). In this way, the treatment cost can duplicate and, if anti-infliximab antibodies are present, a significant clinical response could not be achieved.

Etanercept, a soluble TNF-α-receptor fusion protein, binds both TNF-α and TNF-β, thereby blocking their interaction with the corresponding receptors. It is administered subcutaneously twice weekly and reaches a steady state dur-

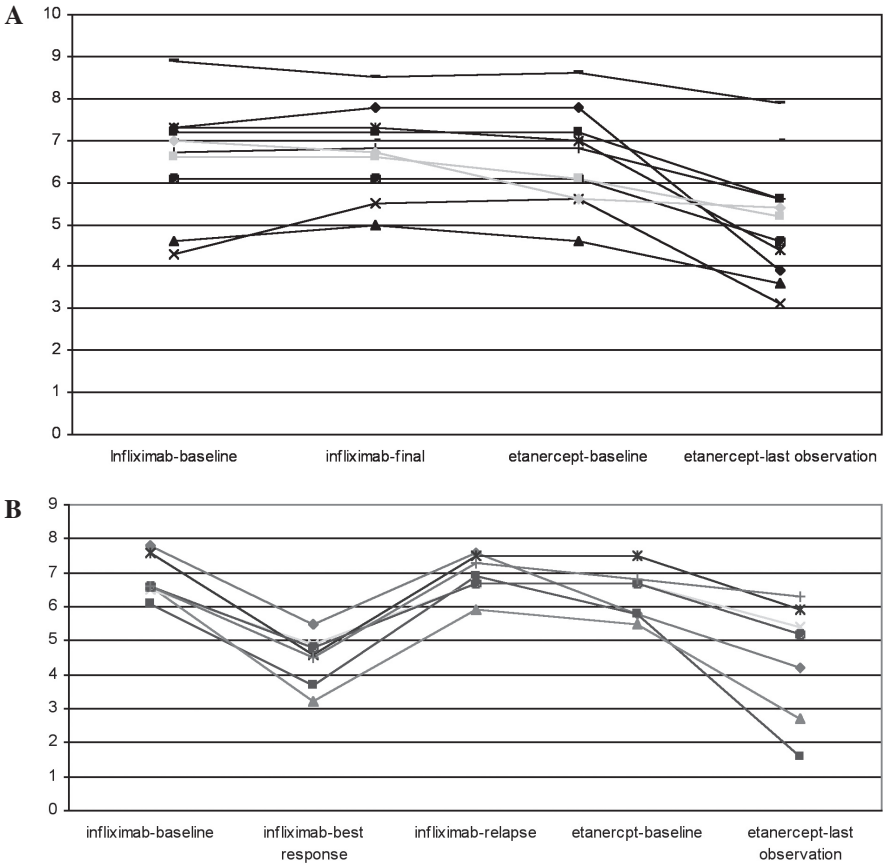

Fig. 1. DAS28 variation in the studied patients: RA patients with no response to infliximab (panel a) and relapsers (panel b), both subsequently treated with etanercept.

ing chronic treatment (12).

Both infliximab and etanercept are very effective in RA, while, in the treatment of Crohn's disease, etanercept is ineffective. Even though both drugs can inhibit soluble TNF-α, infliximab, but not etanercept, can induce peripheral and lamina propria lymphocyte apoptosis in patients with Crohn's disease (13).

Nevertheless, etanercept, but not infliximab, can neutralize lymphotoxin (TNF-β), considered an important cytokine in the complex network of rheumatoid inflammation since it is expressed in the synovial tissue of affected joints and exhibits proinflammatory effects *in vivo* studies of transgenic mice (14).

These differences may account for the different clinical response with the two biologics in the same RA patients.

In addition, a possible association between TNFRII and TNF-α gene polymorphisms and severity of RA is emerging. TNF-α –238 GG homozigosity and TNFRII 196M/R gene polymorphism have been associated to a more severe rheumatoid arthritis (15, 16) and TNFRII 196M/R gene polymorphism seems to predict a poor response to etanercept (15). Additional studies are needed to verify whether these polymorphisms can influence a different susceptibility to different TNF-α-antagonists to better select the initial treatment with biologics.

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