The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis

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Abstract

Objective

To determine whether it may be successful to try another TNF-α antagonist (infliximab or etanercept) when one has failed due to non response or the development of side effects.

Methods

In a cohort of 282 patients with rheumatoid arthritis treated with infliximab or etanercept, we observed 38 patients who had received both agents.

Results

Twenty-four patients received infliximab first and 14 received etanercept first. Discontinuation was due to a lack of efficiency for 29 patients and to the occurence of an adverse effect for 9 patients. For 25 out of the 38 patients, the switch was a success according to the global physician's assessment 3 months after switching. This result was correlated to a significant decrease of DAS 28 measurements and CRP values (p < 0.05). The response after switching was recorded as a success for 18 out of the 24 patients who were treated with infliximab first, and for 12 out of the 14 patients who were treated with etanercept first. There was no statistical difference concerning the response after the switch between the two groups. Among the 29 patients who discontinued the first anti TNF-α treatment due to lack of efficiency, only 6 did not respond to the second anti TNF-α treatment. Only one out of the 9 patients who stopped a first anti TNF-α treatment after developing a side effect underwent an adverse event with the second anti TNF-α treatment.

Conclusion

Our study suggests that switching between TNF-α antagonists seems to be relevant, regardless of which one was used first. It is legitimate to try to switch TNF-α blockers before contemplating other therapeutic strategies.

Key words

Anti-TNF therapy, etanercept, infliximab, treatment switching.

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Introduction

TNF-α antagonists completely changed the management of severe rheumatoid arthritis. The use of these agents has increased over the past years. Three drugs are now commercially available. Two of them are monoclonal antibodies directed against TNF-α: infliximab is a chimeric antibody and adalimumab is a human recombinant antibody. The third one, etanercept, is a soluble TNF-α receptor. These three agents, which block TNF-α, have a similar mechanism of action and, although no clinical trial established a direct comparison between these agents, they seem to be comparable in terms of efficiency and tolerance, whether the drugs are used alone or with methotrexate (1-8). Besides, there are about 30% of non responders to each treatment, according to the ACR criteria.

In spite of these similarities, there are clinical and pharmacological differences between these agents. For example, only infliximab proved its effectiveness in Crohn's desease, allergic reactions differ according to the type of anti TNF-α, and the incidence of tuberculous reactivations might be higher with infliximab (9, 10). Considering the pharmacological aspect, differences may be found in relation to the half life period, the affinity with TNF-α, which is higher with monoclonal antibodies, and the specificity with regard to TNF-α (etanercept blocks TNF-α and TNF-β, whereas monoclonal antibodies block only TNF-α). Moreover, there are differences in the mechanism of the neutralization of TNF-α: both monoclonal antibodies and soluble receptors stop TNF-α action on the receptor when they merge with it, but only infliximab and adalimumab can also induce cell lesions.

In consideration of these variabilities, can we expect that a patient who does not respond to one of the anti TNF-α agents will respond to another anti TNF-α agent? The objective of this retrospective study is to determine whether we may successfully try another TNF-α blocker when one fails due to non-response or the development of side effects.

Materials and methods

Patients

In this retrospective study, we selected patients with rheumatoid arthritis according to the ACR criteria (11) who have been successively treated with etanercept and infliximab in the Department of Immuno-rheumatology, Montpellier (France) from February 2000 to March 2004. These patients belong to a cohort of 282 patients with RA, treated with these two TNF-α antagonists.

Treatments

Etanercept was always prescribed initially in monotherapy at 25 mg subcutaneously twice a week. In case of lack of efficiency, methotrexate or another disease modifying antirheumatic drug (DMARD) was added. Infliximab was always given in association with a DMARD at 3 mg/Kg intravenously at 0, 2, and 8 weeks and every 8 weeks thereafter. In case of lack of efficiency, infliximab infusions were done every 6 weeks and/or increased to a 5 mg/Kg.

Assessment

Collected data included age, sex, rheumatoid factor positivity, presence of erosion or joint space narrowing by standard radiographs, and DMARDs taken in combination or previous to infliximab or etanercept. A physician's global evaluation including swollen joint count, tender joint count (28 joint count), erythrocyte sedimentation rate, C reactive protein and DAS 28 score (12) was performed at the onset of the first anti TNF-α treatment, after 3 months of therapy, and when treatment was switched to the other anti TNF-α agent. The reason for switching was recorded. An assessment of the efficiency of the second TNF-α blocker was done after 3 months of therapy as well. Side effects were noted at each visit. The primary criterion for this study was the physician's global assessment, separating the patients in 2 groups: those for whom the switch was a success and those for whom it was a failure (lack of efficiency or side effect). Since they were not available for all patients, the variation of DAS 28 and the Eular response criteria (13) were

considered as secondary criteria only. The follow up of efficiency and tolerance to the second TNF-α blocker was also performed.

Statistical analysis

The statistical analysis was done using the BMDP software packages on Vax. A repeated measures analysis for DAS 28 score and CRP was perfomed with the Friedman test. A p level < 0.05 was considered as significant. The distribution of qualitative variables between groups was compared using the Chi 2 test. When the calculated frequency of the categorical data of the contingency table did not allow the use of the Chi 2 test, the Fisher's exact test was performed. Quantitative variables (such as "periods") were compared using the Wilcoxon test.

Results

Patients' characteristics (Table I)

Thirty-eight patients out of the 282 patients had been treated with both etanercept and infliximab. There was a majority of women (31 women/7 men) with a mean age of 54.4 (range 28-72) years, a disease duration before TNF-α antagonist treatment of 13.5 (1-36) years, a positive serum test for rheumatoid factor in 97% of the cases, the presence of erosion or joint space narrowing in 100% of the cases, a mean number of DMARDs previously used of 4.3 ± 1.8 and a DAS 28 baseline of 5.7 ± 1.7.

Reasons for switching

The reason for switching was the lack of efficiency for 29 patients and side effects for 9 patients.

Clinical responses after switching for the whole group

According to the physician's global evaluation 3 months after the switch, the second anti-TNF-α treatment was a success for 29 patients (76%) and a failure for 9 patients. The DAS 28 score and CRP significantly decreased between the assessment performed before and 3 months after the switch (DAS 28 in 31 patients: p = 0.0001; CRP in 30 patients: p = 0.0097) (Figs. 1 and 2). According to the EULAR re-

Table I. Patients' characteristics.

	Patients treated first with infliximab, then with etanercept	Patients treated first with etanercept, then with infliximab	Whole group
Number of patients	24	14	38
Sex (female/male)	21/3	10/4	31/7
Age (years) ± SD	53.6 ± 11.3	55.8 ± 12.8	54.4 ± 11.8
Disease duration (years)	12.2 ± 9.6	15.7 ± 8.9	13.5 ± 9.4
Number of DMARDs	4.1 ± 1.8	4.6 ± 1.8	4.3 ± 1.8
Baseline DAS 28	5.6 ± 1.1	5.9 ± 1.2	5.7 ± 1.7

sponse criteria, there were 15 good responses, 7 moderate responses, 11 absence of response.

The mean duration of follow-up after the switch was 11.5 (1-36) months. The second anti-TNF-α treatment was stopped in 15 cases (lack of efficiency in 8 cases, 6 adverse events and 1 pregnancy case).

When the first TNF-α antagonist was stopped due to lack of efficiency (n = 29), the response to the switch according to the physician's global evaluation was a success in 19 cases, a lack of efficiency in 6 cases and an adverse event for 4 patients. When the first TNF-α antagonist was stopped due to adverse events (n = 9), the response to the switch was a success in 6 cases, a lack of efficiency in 2 cases and an adverse event for 1 patient.

There was no significant difference in the physician's global evaluation at 3 months and at the end of the study regardless of which anti TNF-α treatment was used first (p = 0.68 and p = 0.72 respectively).

Clinical responses for patients first treated with infliximab (Table II)

Twenty four patients were first treated with infliximab (63%) for a mean duration of 9 (2-19) months before switching to etanercept. Twenty-one were females, with a mean age of 53,6 (28-72) years, a mean disease duration of 12.2 (1-36) years, a mean number of DMARDs used previously of 4.1 ± 1.8 and a baseline DAS 28 of 5.6 ± 1.1 (Table I). The reason for switching to etanercept was an adverse event in 8 cases (infusion reactions 7, pleuritis
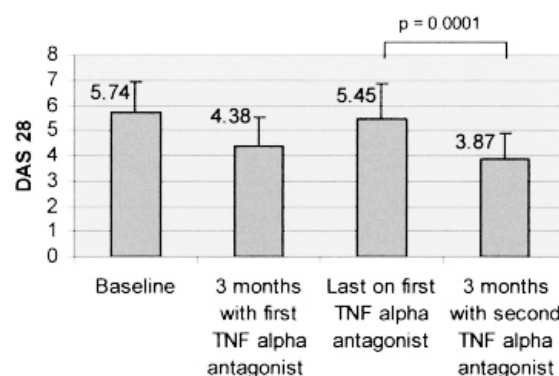

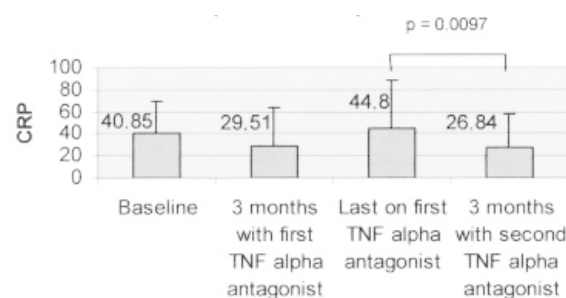**Fig. 1.** Variation of DAS 28 for the whole group (mean ± SD).

Fig. 2. Variation of CRP for the whole group (mean ± SD).

tuberculosis 1) and a lack of efficiency for 16 patients. The DMARDs used in combination with infliximab was methotrexate for 16 patients, leflunomide for 6 patients and azathioprine for 2 patients. When treatment was switched to etanercept, MTX was maintained for one patient and readministered for 4 patients due to inadequate response.

According to the physician's global evaluation, the initial response after switching to etanercept was a success in 18 (75%) cases and a failure in 6 cases. Figure 3 shows the DAS 28 variations during treatment with the two agents. A significant response was observed with etanercept 3 months after the switch (p = 0.0029). With the EULAR response criteria, there were 11 good responses, 3 moderate responses and 5 absence of response.
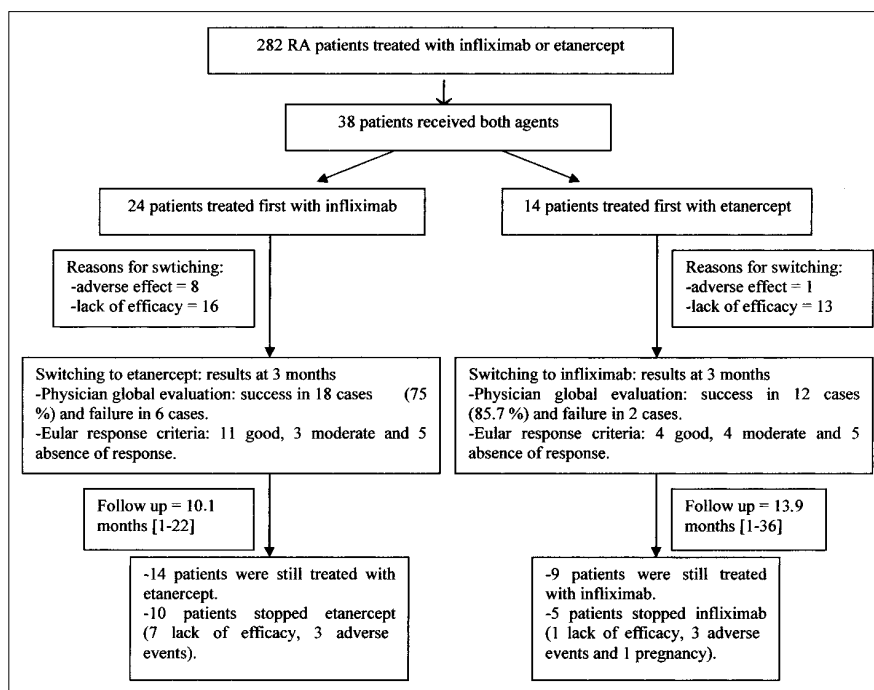
The mean duration of the follow-up after the switch was 10.1 (1-22) months. Fourteen patients were still on treatment. Etanercept was stopped in the 10 other cases [7 cases due to lack of efficiency and 3 adverse events (one pulmonary nocardiosis, one recurrent bronchitis and one rash)].

Clinical responses in patients first treated with etanercept (Table II)

Fourteen patients were treated with etanercept first (37%) for a mean duration of 16.4 (3-36) months before switching to infliximab. Ten were female with a mean age of 55.8 (29-72) years, a mean disease duration of 15.7 (4-33) years, a mean number of DMARDs previously used of 4.6 ± 1.8 and a baseline DAS 28 of 5.9 ± 1.2 (Table I). Methotrexate was prescribed in combination with etanercept to 6 patients. The reason for switching to infliximab was the lack of efficiency for 13 patients and an adverse effect for one of them (rash).

According to the physician's global evaluation, the initial response after switching to infliximab was a success in 12 cases (85.7%) and a failure in 2 cases. A significant DAS 28 response was observed 3 months after the switch (p = 0.001 for 12 patients) (Fig. 3). The EULAR response was graded as good in 4 cases and moderate in 4 cases; 4 patients were non responders. The

Table II. Response to the switch.

DMARDs used in combination with infliximab were methotrexate for 6 patients, leflunomide or azathioprine for 4 patients. The main follow-up after the switch was 13.9 (1-36) months and infliximab was stopped in 5 cases [due to lack of efficiency in 1 case, 3 adverse events (1 rash, 1 hepatic cytolysis and 1 heart failure) and 1 pregnancy case].

Discussion

When we consider the whole group, the switch turned out to be relevant for 76% of our patients, according to the main criteria. This is confirmed with the secondary criteria: DAS 28 score and CRP significantly decreased in 3 months, and 22 patients out of 33 had a good or moderate response according to the EULAR criteria. For 75% of the
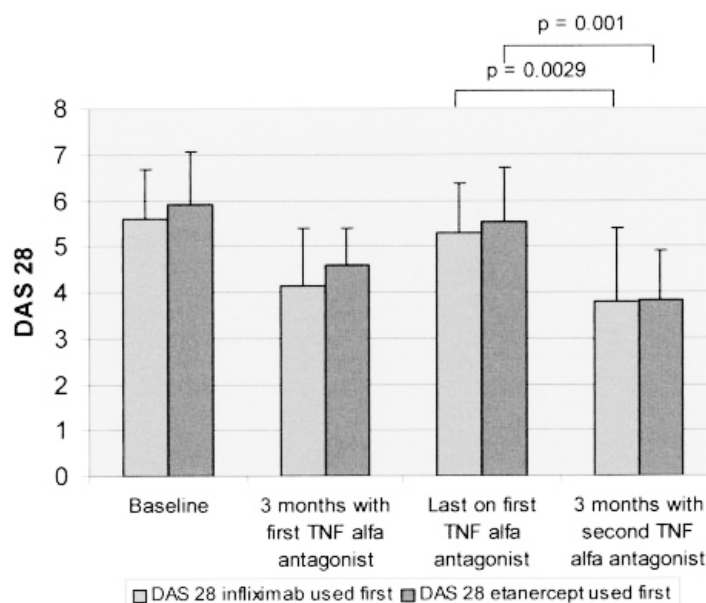

Fig. 3. Variation of DAS 28 according to the first anti-TNFα used.

patients who received infliximab first, the response after switching was a success. As there is no significant difference between the two groups, a first point that arises from this study is that switching between anti TNF-α agents can be relevant, regardless of which one was used first. It is important to note that the two groups were comparable for all the registered characteristics (sex, age, duration and severity of the disease, DMARDs used first).

Since 2002, several studies have already investigated the clinical response in rheumatoid arthritis patients when a second anti TNF-α treatment was used after a first one had failed (14). All were open-label studies, conducted on a limited number of patients, and all concluded to a benefit of the switch. Three of these works concerned the switch from infliximab to etanercept and vice versa. Brocq et al. (15) registred good results in the two groups after switching for 8 of the 14 patients. Most patients from the van Vollenhoven et al. study (16) improved after switching in the two groups, but the reason for switching was different according to the first TNF-α blocker that was used; most of the patients who started with infliximab stopped it due to the development of an adverse event, when most of the patients who had started with etanercept stopped it due to lack of efficiency. For Ang et al. (17), there was no link between the joint count response and the acute phase reactant responses with the use of etanercept and infliximab for the same patients. The number of patients in the group which used infliximab first was quite limited (5) compared to the number of patients in the group which used etanercept first (24). Two studies (18-19) concerned only the switch from etanercept to infliximab. Shergy et al. (18) reported that 16 out of 17 patients had significantly improved. These were all patients who had discontinued etanercept treatment due to lack of efficiency. With a different study design, Hansen (19) suggested that there was no significant difference in improvement after introducing infliximab between a group of patients who had failed to etanercept and a group of

patients with no prior anti TNF-α therapy. In his abstract, Gomez (20) reported 10 cases of good response after switching to etanercept for 12 patients who had stopped infliximab, due to lack of efficiency.

When we analyzed the results of our study with respect to the reason for discontinuing the first anti TNF-α treatment, it appears that only a few patients did not respond to any of the two anti TNF-α agents used successively. Among the 29 patients who had switched due to the lack of efficiency of the first anti TNF-α treatment, only 6 did not respond to the second anti TNF-α treatment. We can also notice that only one of the 9 patients who stopped a first anti TNF-α treatment after developing side effects underwent an adverse event with the second anti TNF-α treatment. In this case, the side effects consisted in hypersensitivity reactions. It seems to arise from our results, first that a lack of efficiency of a first anti TNF-α agent does not predict failure with the second one, secondly that the occurence of an adverse event with one agent does not predict the occurence of an adverse event with the other agent. This study confirms the results of the other open studies (15-20), and was conducted on a larger number of patients.

The mean follow-up after the switch was about one year, and at that point 39% of the patients had stopped the second anti TNF-α treatment, in the same proportion in the two groups.

A weakness of this study is its retrospective design, leading to incomplete data concerning essentially the assessment criteria for each patient. The physician's gobal assessment may be considered as subjective for a primary criterion, but the results are related to more objective criteria such as DAS 28 and CRP variations, or the Eular response.

We may consider that the switch between etanercept and infliximab which seems logical with respect to the clinical and pharmacological differences between these agents appears to be clinically relevant in case of failure or occurence of a side effect following the use of an anti TNF-α agent, whichever was used first. It would be interesting

to conduct a large prospective study to confirm that this practice shall be taken into account in the management of rheumatoid arthritis and that it is legitimate to try it before contemplating the use of other biotherapy agents.

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