
Switching between biological agents

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ABSTRACT

The TNF- α antagonists infliximab, etanercept and adalimumab have similar efficacies in clinical trials in the rheumatic diseases, and this efficacy may be related primarily to their neutralizing free TNF- α . Thus, a reasonable question for clinicians is whether patients who have failed one TNF- α antagonist could reasonably be given a trial with another such agent, or whether this is simply a waste of time and money. Several published studies have addressed this important practical issue and are reviewed in this paper.

Data from the Stockholm TNF- α follow-up registry "STURE" that address this issue are described in detail. The overall conclusion appears to be that such switches of biologicals can be effective. Nonetheless, further attention should be paid to the details of various clinical scenarios in which this question can arise and the methods by which comparisons are made of treatment effects occurring during sequential therapies.

Introduction

The TNF α antagonists adalimumab, etanercept and infliximab are efficacious in a variety of clinical settings in the treatment of RA (1-3) and/or other inflammatory arthritides (4, 5). There have been no clinical trials directly comparing the three agents in the treatment of any disease. Comparisons of results seen in randomized clinical trials with each agent separately suggest approximately equal clinical efficacy for the three TNF α blockers, whether such comparisons are performed by simply "eyeballing" the results or by employing formal comparisons (6). Likewise, in longitudinal follow-up studies etanercept and infliximab have shown similar efficacy (see for example Geborek *et al.*, ref. 7). Intriguingly, the efficacy of TNF α antagonists is strikingly dissimilar in Crohn's disease, in which infliximab is a very effective

therapy (8,9) whereas etanercept has no meaningful benefits. Data on the efficacy of adalimumab in Crohn's disease are eagerly awaited. In juvenile chronic arthritis (JCA), etanercept has well-established efficacy (10), whereas that of infliximab in JCA has not been demonstrated and may be less. Finally, these TNF α blockers appear to have similar efficacy in psoriatic arthritis, whereas the effects on the skin disease may not be entirely equivalent.

Mechanisms of action

The therapeutic efficacy of TNF α antagonists appears to be in large part due to the binding of free soluble TNF α , thereby preventing its binding to the TNF α receptor, and this effect is shared by all three agents. There are, however, biological differences between these agents that may or may not be important with respect to efficacy. Thus, the IgG1 antibody molecules infliximab and adalimumab can in principle activate complement or initiate antibody-dependent cellular cytotoxicity (ADCC), thereby causing cytolysis of cells bearing TNF α on their surface, such as activated macrophages. The dimeric p75-receptor IgG fusion product etanercept does not activate these effector pathways. In contrast to the monoclonal antibodies, etanercept can, besides blocking TNF α , also block lymphotoxin (formerly known as TNF β), but the pharmacological significance of this is not known. Haraoui has suggested that lymphotoxin may play a more important pathophysiological role in JCA than in RA (11).

An additional difference in the mechanisms of action may be related to the induction of apoptosis. In the lamina propria of patients with Crohn's disease, infliximab but not etanercept was shown to induce apoptosis in T lymphocytes (12). In contrast, whether apoptosis is induced in synovial cells by either TNF blocker has remained unclear. Smeets *et al.* (13) presented data sug-

gesting that apoptosis did not play an important role in the down-regulation of synovial inflammation by infliximab, but recent data from our own unit suggest that both infliximab and etanercept do indeed induce synoviocyte apoptosis (14). In addition to these differences in mechanisms of action, the TNF α blockers also possess different pharmacokinetic properties, in part due to intrinsic differences in the molecules, and in part due to the different routes of administration.

Published studies on switching between biologicals

Not all patients respond to treatment with TNF α blockers, and some who do respond develop treatment-limiting side effects. In these situations, an important practical question is whether there is a rationale for prescribing another TNF α blocker, or whether this is simply a waste of time and money. A number of studies have addressed this question (summarized in Table I).

Brocq *et al.* (15) treated 8 patients with etanercept after they had failed infliximab, and 6 patients with infliximab after they had failed etanercept. Favorable results were seen in about half of these patients. The reasons for failure with the first drug were heterogeneous in these groups of patients,

and no formal comparison of results with the two agents were performed.

Ang and Helfgott (16) studied 29 patients who had switched from etanercept to infliximab or vice versa. They compared the clinical responses by determining the correlation coefficients for joint counts and acute phase reactants obtained with each therapy, and the monitored side effects. Interestingly, no correlations were observed between the clinical outcomes with the two agents, with the exception of the adverse event of anaemia which, if it had occurred with the one agent, was likely also to occur with the second. The authors conclude that patients who fail one TNF α antagonist can respond to the other.

Sanmarti *et al.* (17,18) studied 12 patients with RA who were switched from infliximab to etanercept. The patients had responded initially to infliximab, but a secondary loss of efficacy occurred after a mean of 16 months. After starting treatment with etanercept, 10 of these patients achieved a EULAR response, and the DAS28 values achieved the same favourable level as had earlier been achieved with infliximab. Thus, this study described a clearly defined clinical scenario and addressed the results using appropriate quantitative comparisons: the report demon-

strates that for most patients who experience a secondary loss of efficacy from infliximab, etanercept is a useful therapeutic option that can achieve roughly the same levels of response.

Hansen *et al.* (19) performed a retrospective study of 93 patients who had been started on infliximab as an add-on to leflunomide. Of these patients, 20 had previously undergone treatment with etanercept, which had been discontinued in most of them due to lack of efficacy. When comparing these 20 patients to the 73 for whom infliximab was the first biological treatment, no differences emerged with respect to the clinical efficacy, but dosages of infliximab in the "switchers" were significantly higher. The results obtained with infliximab in these patients were not formally compared to the results seen previously in the same patients with etanercept. In direct contrast to these data, Yazici and Erkan (20) reported in a letter that in their experience patients who had previously failed etanercept responded less well to infliximab than patients who were naïve to TNF α blockers.

Favalli *et al.* (21) reported in a letter on 14 patients who switched from infliximab to etanercept and one who made the opposite switch. Six-month results suggested good efficacy in most pa-

Table I. Overview of published studies on switching between biological agents.

Authors	Ref.	no.	Switched from	Reason for switching	Switched to	Results
Brocq <i>et al.</i>	15	8 6	INF ETA	Miscellaneous	ETA INF	Favourable results in about half of all patients
Ang & Helfgott	16	29	INF ETA	Miscellaneous	ETA INF	Efficacy of second agent <i>not</i> predicted by that of the first
Sanmarti <i>et al.</i>	17, 18	12	INF	Secondary loss of efficacy	ETA	ETA as effective as INF had been initially
Hansen <i>et al.</i>	19	20	ETA	Lack of efficacy	INF	INF as effective in switchers as in ETA-naïve pts.
Yazici & Erkan	20	21	ETA	Miscellaneous	INF	INF not as effective as in ETA-native patients
Favalli <i>et al.</i>	21	14	INF	Miscellaneous	ETA	Efficacy in some but not all
Van Vollenhoven <i>et al.</i>	22	18 13	ETA INF	Lack of efficacy Side effects	INF ETA	Better efficacy with second agent At least equal efficacy with second agent
Wick <i>et al.</i>	23	17 6	INF ETA	Secondary loss of efficacy	ADA	ADA as effective as INF/ETA had been initially

ADA: adalimumab; ETA: etanercept; INF: infliximab.

tients, while some had to discontinue the second agent due to side effects (in some instances, they showed the same type of hypersensitivity reaction with each agent). No formal comparison of the results seen with the two agents was performed.

Some additional studies have been reported in abstract form only. Most of these give the same general impression, namely that patients being treated with a second TNF α blocker in many instances respond well to this therapy. Unfortunately, formal quantitative comparisons of therapeutic efficacy with sequential biological therapies were not employed in the vast majority of these reports. In our own studies addressing these issues, we have endeavoured to develop a methodology for accomplishing such comparisons.

Studies from the Stockholm biologicals registry "STURE"

In a previously published study (22), we selected patients from the Stockholm TNF α follow-up registry (STURE database) who had been treated with both etanercept and infliximab, in either order. Thirty-one such patients were identified: 18 who had been treated with etanercept first and then switched to infliximab, and 13 in whom the order was the reverse. Etanercept was always given at 25 mg subcutaneously twice weekly. Infliximab was dosed according to the product resumé, that is, at 3 mg/kg/infusion, given intravenously at 0, 2, and 6 weeks and every 8 weeks thereafter.

The measures of greatest interest for this study were the best outcomes obtained with each drug in each patient. Thus, for each patient the best DAS28 (23) and best swollen joint count (SJC) with each drug were selected and used for formal comparisons. We also calculated the ACR-N at each time point (24) and compared the best ACR-N in each patient with either drug. Obviously, this also allowed comparisons of the number of ACR20 responders (25). In addition, the values immediately prior to starting each treatment and at the point of discontinuation of each treatment were also analysed.

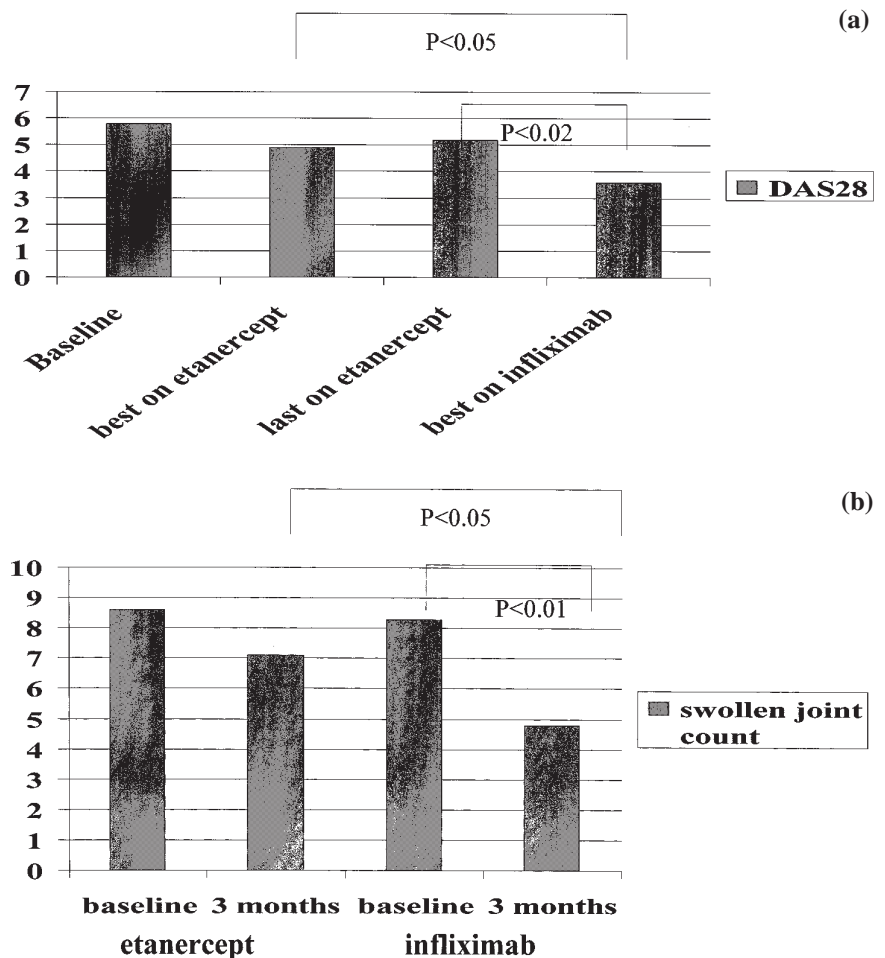


Fig. 1. (a) Disease activity by DAS28 in patients treated first with etanercept, then with infliximab. Values shown are the mean value at baseline (prior to etanercept treatment), mean best value during etanercept therapy, mean value at last visit while on etanercept (when the decision to switch was made), and mean best value on infliximab. Comparisons are by the paired 2-tailed Student t-test.

(b) Swollen joint count in patients treated first with etanercept, then with infliximab. Values shown are the means at baseline and after 3 months for each treatment. Comparisons are by the paired 2-tailed Student t-test.

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Clinical responses in patients treated first with etanercept, then with infliximab

Of the 18 patients who were treated with etanercept first, the reason for switching to infliximab was lack of efficacy in 14, side effects from etanercept in 2 (rhinorea 1, nasal congestion 1), and unknown in 2 patients. Fourteen of these patients had rheumatoid arthritis (RA) and 13 were seropositive, 2 had a diagnosis of juvenile chronic arthritis but were now adults with an RA-like clinical course, and 2 had a spondyloarthropathy with predominantly peripheral joint involvement.

Fifteen were female, the mean age was 53 years, the mean disease duration was 15 years, and the mean number of DMARDs used previously was 5.8. These patients had been treated with etanercept for a mean of 6.8 ± 1.7 months before switching to infliximab. Of these 18 patients, 11 had been given methotrexate along with etanercept treatment. When treatment with infliximab was begun, MTX was continued in those 11, and MTX was added to the treatment in an additional 4 patients, whereas 3 patients did not receive MTX even when they were treated with infliximab.

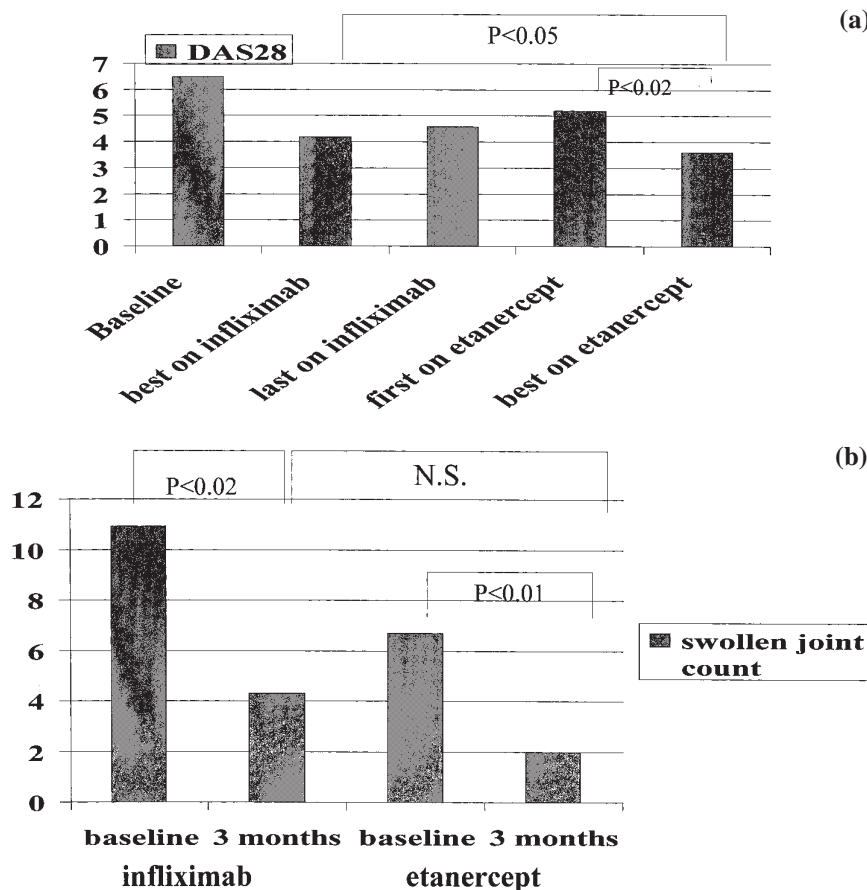


Fig. 2. (a) Disease activity by DAS28 in patients treated first with infliximab, then with etanercept. Values shown are the mean value at baseline (prior to infliximab treatment), mean best value during infliximab therapy, mean value at last visit while on infliximab (when decision to switch was made), mean value just prior to starting etanercept treatment, and mean best value on etanercept. Comparisons are by the paired 2-tailed Student t-test.

(b) Swollen joint count in patients treated first with infliximab, then with etanercept. Values shown are the means at baseline and after 3 months for each treatment. Comparisons are by the paired 2-tailed Student t-test.

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These 18 patients had modest improvements after etanercept was begun, their best DAS28 values on the treatment being only slightly better than baseline, consistent with the fact that they later were switched to infliximab because of lack of efficacy. At the time point when the switch to infliximab was made, the mean activity was close to the original baseline. After infliximab treatment was started, the DAS28 showed a significant improvement, resulting in a mean best DAS28 value that was significantly better than the value just prior to starting infliximab (5.2 ± 0.9 vs. 3.6 ± 0.6 , $p < 0.02$). More germane to the question addressed in this study, the

best DAS28 on infliximab was also significantly better than the best result obtained with etanercept (4.8 ± 0.6 vs. 3.6 ± 0.6 , $p < 0.05$) (Fig. 1a).

As is generally the case, significant clinical responses to infliximab occurred early, within the first 3 months of therapy, but the mean time point at which the best DAS28 result was obtained in this group was after 6.0 ± 1.4 months. When analysing the swollen joint counts, a similar pattern was seen, that is, a modest response with etanercept, and a more definite improvement with infliximab that was statistically significantly superior to the first response (Fig. 1b). Similarly, the

- (a) best ACR-N responses on infliximab showed a higher mean value than on etanercept, but this difference did not reach statistical significance (17.2 ± 6.65 for etanercept vs. 40.4 ± 10.6 for infliximab, $p = 0.08$; not otherwise shown). Likewise, ACR20 responses were more frequent with infliximab than with etanercept in these patients (64% vs. 36%, not otherwise shown). In the 2 patients who discontinued etanercept due to upper airway symptoms, these symptoms did not recur during infliximab therapy. Thus, in patients who fail to respond to etanercept, better clinical results can be achieved with infliximab.
- (b)

Clinical responses in patients treated first with infliximab, then with etanercept

Of the 13 patients who were treated with infliximab first and then etanercept, the reason for switching to etanercept was an adverse event in 11 (infusion reaction 7, liver toxicity 2, change in olfaction 1, unspecified 1), and miscellaneous in 2. Thus, these patients represented a clinical situation different from the previous group. These patients had been treated with infliximab for a mean of 5.5 ± 1.2 months when this drug was discontinued. All 13 patients had been treated with MTX as well as infliximab. When treatment was switched to etanercept, MTX was continued in 8 and discontinued in 5 patients. The DAS28 values during treatment with the 2 agents are given in Figure 2a. A significant response was seen with infliximab. At the time this agent was discontinued the response had become somewhat less.

Because it could take time in practice to start treatment with etanercept (for which special approval had to be sought due to the limitations on the availability of etanercept in Sweden at the time of this study) an additional worsening was seen by the time etanercept was started, but this second baseline value remained considerably better than the original baseline. However, following the inception of etanercept, a sharp decrease in the DAS28 values was seen, that was highly significant compared to the prior value and also

significantly better than the best result seen with infliximab.

As is generally the case, significant clinical responses to etanercept occurred early, already within the first 3 months of therapy, but the mean time at which the best DAS28 result was obtained in this group was after 7.0 ± 2.3 months. When analysing swollen joint counts, a similar pattern emerged, but the difference between the best results with infliximab and etanercept did not reach statistical significance (Fig. 2b). Moreover, the ACR-N responses to the 2 agents were virtually identical, and the number of ACR20 responders on each drug was similar (not shown). This group of patients continues to be followed in our registry and good clinical responses have been maintained for up to 24 months. The adverse events that led to the discontinuation of infliximab (as described above) all resolved and did not recur during treatment with etanercept. Thus, in patients who discontinued infliximab due to adverse experiences, results can be achieved with etanercept that are at least equal, and in some analyses superior to the results seen with infliximab.

In a more recent study from the STURE database (26), we studied 23 patients (mean age 50.0 ± 15.3 years) who received adalimumab after experiencing a secondary loss of efficacy (i.e., loss of efficacy after having responded initially) with infliximab (group A, $n=17$) or etanercept (group B, $n=6$), as well as 14 patients who were started on adalimumab as the first TNF α antagonist (group C). The methodology used for comparing the results with the first TNF α antagonist to the second agent was the same as that used in our prior study, that is, comparisons were made between the best results seen with each treatment.

The results show that in group A the baseline DAS28 at infliximab institution was 5.3 ± 0.2 . During infliximab-treatment, the mean best DAS28 was 3.7 ± 0.2 ($p < 0.0001$), but had increased to 5.4 ± 0.4 by the time infliximab had to be stopped after 1.3 ± 0.2 years. Adalimumab was started 0.4 ± 0.1 years after the stop of infliximab. During that time, the mean DAS28 increased to 5.7

± 0.4 . After 3 months on adalimumab, the mean DAS28 decreased to 4.3 ± 0.4 ($p < 0.001$) and to 3.9 ± 0.3 at 6 months ($p < 0.001$). At 6 months, 67% of the patients fulfilled the ACR20 response criteria.

In group B, the baseline DAS28 at etanercept institution was 6.7 ± 0.7 . During etanercept treatment, the mean best DAS28 was 4.3 ± 0.6 ($p < 0.03$ vs. baseline), but had increased to 5.5 ± 0.6 by the time etanercept had to be stopped after 2.5 ± 0.6 years. Adalimumab was started 0.3 ± 0.1 years after interrupting etanercept treatment. During that time, the DAS28 increased to 6.2 ± 0.2 . After 3 months on adalimumab, the mean DAS28 decreased to 5.1 ± 0.4 ($p < 0.03$), and to 4.5 ± 0.4 at 6 months ($p < 0.001$ vs. baseline). At 6 months, 4 of 6 patients fulfilled the ACR20 criteria.

In group C, the mean baseline DAS28 was 5.5 ± 0.4 . After 6 months of adalimumab-therapy, the DAS28 decreased to 3.7 ± 0.5 ($p < 0.001$), and 9 patients fulfilled the ACR20 response criteria. These results are summarized in Table II. Thus, in this study, for patients who failed infliximab or etanercept, switching treatment to adalimumab restored a marked clinical response already after 3 months of therapy. The clinical improvements in such patients were similar to the improvements of patients for whom adalimumab was chosen as the first TNF- α blocker.

Discussion

An important question for practising physicians is whether it makes sense to prescribe a second (or third) TNF α blocker if the patient has already failed

one such agent. While in many instances the alternatives are few and the physician as well as the patient might be motivated to "try anything", it would nonetheless be important to avoid a therapeutic trial of an agent that has no likelihood of being effective, particularly in view of the risks that do exist with TNF α blockers and the costs associated with the treatment. Moreover, the number of treatment options is steadily increasing, and in the not so distant future physicians may have to weigh the potential benefit of a second or even a third TNF α blocker against a plethora of other biological and pharmacological treatment options.

The published data from the STURE database (22) address these questions in several specific situations. First, for those patients whose clinical results with etanercept are inadequate, it appears that a considerable gain can be achieved with infliximab. In our study, approximately half of those who failed to reach ACR20 responses with etanercept did achieve that response with infliximab. However, it is important to emphasise that this result was obtained in a setting in which only about half the patients were treated with MTX while on etanercept, but 15 of 18 were given MTX with infliximab. Thus, it would be more correct to state that in patients who fail etanercept with or without MTX, infliximab with MTX can give a significantly higher number of responders.

The second group of patients had failed infliximab treatment primarily because of adverse events. In fact, these patients had excellent responses during inflix-

Table II. Patients treated with adalimumab (ADA) after having experienced secondary loss of efficacy with infliximab (INF, group A) or etanercept (ETA, group B), compared to patients for whom adalimumab was the first biological agent (group C). From Wick *et al.* (26).

DAS28	A (n = 17)	B (n = 6)	C (n = 14)
Baseline before INF / ETA	5.3 ± 0.2	6.7 ± 0.7	-
Best on INF / ETA	$3.7 \pm 0.2^*$	$4.3 \pm 0.6^{\S}$	-
Last on INF / ETA	5.4 ± 0.4	5.5 ± 0.6	-
Baseline before ADA	5.7 ± 0.4	6.2 ± 0.2	5.5 ± 0.4
After 6 months on ADA	$3.9 \pm 0.3^*$	$4.5 \pm 0.4^*$	$3.7 \pm 0.5^*$

* $p < 0.001$ vs. baseline; $\S p < 0.05$ vs. baseline.

imab treatment, but it was of interest to note that the clinical responses had worsened by the time the infliximab treatment was discontinued. Nonetheless, at the time when the etanercept treatment was subsequently started, the activity indices were still somewhat better than at baseline. This leaves open the possibility that some measure of carry-over was still present from the infliximab treatment, consistent with the long half-life of that drug. In this group of patients, the overall results with infliximab were good. When infliximab was discontinued due to adverse events and etanercept was given subsequently, similar and in some analyses even better results were obtained with etanercept. In addition, the two patients who had discontinued infliximab due to lack of efficacy illustrate that even in such patients a switch to etanercept can be successful.

Taken together, the data in that paper provided an indication of results that can be seen in clinical practice when switching between the TNF α antagonists etanercept and infliximab. However, since the numbers in this study were small, and several patients in each group had diagnoses other than RA, and because there were differences in the concurrent use of MTX, these results should be interpreted with caution. Moreover, because the reasons for discontinuing the first TNF-antagonist were dissimilar between the two groups, this study does not allow for a direct comparison between the two groups or between the relative efficacies of the second agent in each situation. The fact that most of the patients who first received infliximab discontinued due to adverse events despite having achieved good clinical responses made the *a priori* likelihood of showing a better response to etanercept smaller than in the reverse situation.

The more recent data from the STURE database presented in abstract form (26) address the more specific situation that arises when a patient who initially showed a favourable response to a TNF α antagonist subsequently begins to respond less well, which we have denoted as secondary loss of efficacy. When such a secondary loss of efficacy

occurred with etanercept or with infliximab, excellent clinical responses were obtained with adalimumab, suggesting that the latter agent is an appropriate therapeutic alternative for such patients. Likewise, the majority of studies referred to above support the use of an alternative TNF α antagonist in a variety of clinical scenarios. Taken together, one may conclude that "switching" between biologicals remains reasonable in selected patients in clinical practice, while further studies are needed to more exactly to define the efficacies in each specific situation.

These studies illustrate some of the practical issues that clinicians face when trying to use the new antirheumatic agents optimally, and indicate that a systematic registry of newer biological drugs is a useful tool to answer daily practice questions. We are continuing our own efforts in the Swedish ARTIS and STURE registries, and encourage others who use such agents to engage in similar longitudinal efforts.

Cautionary notes

Published studies have indicated that patients who have "failed" a TNF α blocker can "respond" to another one. However, "failure" in this context represents a heterogeneous mixture of situations, such as the absence of any response to the first agent (primary lack of efficacy), the disappearance of an initial favourable response later during treatment (secondary loss of efficacy), or the emergence of limiting side effects. Likewise, a response to the second agent can be defined with respect to the baseline for that agent (using the ACR or the EULAR improvement criteria) or to the baseline for the first agent (which might be more fair, in view of potential carry-over effects from the first therapy) or simply to what is perceived as a favourable clinical development.

All this depends critically on the actual question being addressed. If the first agent was discontinued due to toxicity, then an equivalent result with the second agent may be entirely acceptable and adequate (as we demonstrated for switching from infliximab to etanercept). If the first agent was effective

initially but a secondary loss of efficacy occurred, then efficacy for the second agent is only relevant inasmuch as it may represent a different biological mechanism and/or if the efficacy can be shown to be (more) sustained (as we showed in part for the switch from infliximab and etanercept to adalimumab). And if the first agent was simply not effective at all, then the second agent would have to demonstrate better efficacy for the "switch" to be considered successful (as was indeed the case in our experience with switches from etanercept to infliximab). In our registry, we feel that the most scientific means of comparing two sequential agents has to include a comparison of the best results obtained with each agent as well as the comparison to each baseline.

In summary, switching between different biologicals can benefit the individual patient and can teach us important lessons about these agents. However, studies of such switches must be conducted with attention to defining the issues and using the appropriate methodologies.

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