Switching Anti–TNF-α Agents: What is the Evidence?

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The availability of biologic agents targeting tumor necrosis factor (TNF)-α represents a significant advance in the management of rheumatoid arthritis. Anti–TNF-α therapy has been associated with dramatic improvements in the clinical signs and symptoms of rheumatoid arthritis and has been shown to greatly retard the destructive process that too often characterizes this condition. Although effective and well-tolerated in a substantial proportion of patients, primary and secondary failures of anti–TNF-α strategies have been well described, affecting up to one-third to one-half of subjects treated with these agents. Switching from one anti–TNF-α agent to a second (or even third) anti–TNF-α therapy has emerged as a means of addressing treatment failures with this drug class. This review examines data addressing the practice of switching anti–TNF-α agents in the context of initial treatment failure, with a focus on data from peer-reviewed reports.

Introduction

Tumor necrosis factor (TNF)-α inhibitors have significantly enhanced the treatment of rheumatoid arthritis (RA), dramatically changing the way rheumatologists treat active disease. With the addition of TNF-α inhibitors to the treatment armamentarium, we have been able to successfully implement new combinations of disease-modifying antirheumatic drugs (DMARDs) and abandon others that have traditionally proven either ineffective or poorly tolerated. Three selective TNF-α inhibitors have been approved by the US Food and Drug Administration and the European Union for the treatment of active RA: etanercept, infliximab, and adalimumab. Despite their effectiveness and favorable safety profiles in randomized clinical trials and long-term observational studies, many patients demonstrate an inadequate initial response to TNF-α inhibition, side effects, or loss of effectiveness with continued use. These effects have led to the natural consequence of TNF-α inhibition "switching," which has become routine practice for many rheumatologists. This review examines the issues surrounding the practice of switching anti–TNF-α agents, with a focus on data that has emerged from peer-reviewed reports.

TNF-α in Rheumatoid Arthritis

TNF-α is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Playing a critical proinflammatory role in RA, TNF-α has two distinct receptors, a 55-kDa protein and a 75-kDa protein, which exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biologic activity of TNF-α is dependent on binding to either cell surface receptor. Consequently, selective TNF-α inhibition leads to predictable biologic changes including a potent reduction in inflammatory signaling and reduced cellular expression of other proinflammatory molecules such as interleukin-1. Although the available TNF-α–inhibiting agents all work by targeting this central proinflammatory molecule, these agents have important molecular and pharmacologic differences [1]. It may be these differences that explain why one strategy of TNF-α inhibition demonstrates inefficacy or toxicity while another strategy simultaneously results in clinical efficacy for an individual RA patient.

Agents Targeting TNF-α

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the 75-kDa TNF-α receptor linked to the Fc portion of immunoglobulin (Ig) G. Etanercept inhibits binding of both TNF-α and TNF-β (also known as lymphotoxin [LT]-α) to cell surface TNF-α receptors, rendering TNF-α biologically inactive. Cells expressing transmembrane TNF-α that bind etanercept are not lysed in the presence or absence of complement. Through decreasing TNF-α activity, etanercept, like the other TNF-α–inhibition agents, can modulate responses including expression of adhesion molecules, serum levels of other proinflammatory cytokines, and serum concentrations of matrix metalloproteinases. Following a single

25 mg subcutaneous dose, the half-life of etanercept is 102 ± 30 hours (approximately 4 days) [2]. Although antibodies against etanercept have been observed with its use, these antibodies do not appear to have a neutralizing effect on the agent.

Infliximab is a chimeric (human-murine) IgG monoclonal antibody targeting TNF-α. Infliximab inhibits the biologic activity of TNF-α by binding the soluble and transmembrane forms of TNF-α and inhibiting the binding of TNF-α to its cell surface ligand, but unlike etanercept, it does not inhibit LT-α [3–5]. It is administered intravenously and shows a linear relationship between the dose administered and the maximum serum concentration. At doses of 3 mg/kg, the terminal half-life of infliximab is 8 to 9.5 days. Clearance of infliximab is increased with the development of human antichimeric antibodies (HACA), or the so-called HACA response [3]. In addition to decreasing its therapeutic effect, HACA responses may predispose patients to greater risk of infusion reactions [6]. The coadministration of methotrexate with infliximab has been shown to substantially diminish HACA responses, improving both the magnitude and durability of treatment response with this agent [7]. In contrast to etanercept, infliximab may also fix complement leading to lysis of inflammatory cells and reduced expression of interferon-γ [1].

Adalimumab is a recombinant fully human IgG monoclonal antibody also targeting TNF-α. Similar to infliximab, adalimumab also blocks TNF-α binding with the cell surface TNF-α receptors. Adalimumab administration also leads to lysis of inflammatory cells with cell-surface expression of TNF-α in the presence of complement. The overall biologic actions of adalimumab on TNF-α are similar to both etanercept and infliximab. However, unlike etanercept but similar to infliximab, adalimumab does not bind or inactivate LT-α. The mean terminal half-life of adalimumab (dosed subcutaneously) ranges from 10 to 20 days across studies. Although lacking the murine component of infliximab, anti-adalimumab antibodies may develop with its use, increasing medication clearance and leading to diminished clinical responses over time [8]. As with other TNF-α inhibitors, adalimumab appears to be most efficacious when used in combination with weekly methotrexate [7,9,10].

Switching Anti–TNF-α Agents

A number of published articles are relevant to the practice of TNF-α inhibitor switching. Most of these reports have important limitations that make their interpretation challenging, including small sample sizes, short trial durations and lack of randomization or control. In addition, only a few have included all three available TNF-α inhibitors. Moreover, outcomes measures in these reports are not standardized. Some studies use the Disease Activity Score (DAS), and others use the American College of Rheumatology (ACR) criteria of improvement or its core components (ie, joint counts, patient reported measures, or acute phase reactants). Additionally, many of the articles do not provide detailed information concerning dosing regimens (ie, timing of initiation referent to initial withdrawal and doses used), other DMARDs or glucocorticoids that the patients may have taken concomitantly, or perhaps most importantly the reason for switching the patients' TNF-α inhibition therapy in the first place. With this being said, review of the literature still provides useful information for the clinician considering switching TNF-α–blocking agents. As noted earlier, we have focused on peer-reviewed reports to help guide the clinician asking whether failure of one TNF-α inhibitor in a patient with active RA precludes the use of a second or third agent in the same family of treatments.

There are multiple reasons why a patient may "fail" therapy with a TNF-α inhibitor and multiple reasons why a second (or third) agent targeting TNF-α might work where the first (or even second) agent has failed. Failure of adequate response may manifest as a primary nonresponse, partial response, or loss of response. Initial response followed by relapse may be frequent with select agents; a recent report showing that secondary nonresponse occurred within the first year in approximately half of RA patients who initially received and responded to infliximab [11]. Failure may also be related to the occurrence of adverse events or toxicity. All of these indications for switching biologic agents may have an impact on how a patient responds to subsequent therapeutic strategies [12]. For instance, among patients receiving treatment for various forms of inflammatory arthritis, failure of a second anti–TNF-α agent has been reported to be approximately 50% less likely if the first agent was discontinued due to toxicity and more likely in patients over 60 years of age [13]. Several initial studies, most of which were uncontrolled and small, reported on the outcome of switching among the different available agents. As noted, the indications for switching agents were often poorly described and the clinical assessments were completed using different methodologies.

In a small retrospective study, van Vollenhoven et al. [14] examined the effect of switching to infliximab after the primary failure of etanercept and vice versa in 31 RA cases. Of 18 subjects receiving initial etanercept (stopped in 14 subjects due to efficacy failure), the subsequent use of infliximab was associated with significant improvement in DAS28 scores from a pre-infliximab score of 5.2 (0.9) to 3.6 (0.6) ($P < 0.02$). A similar level of improvement was observed with etanercept use in the 13 subjects who had received and failed initial infliximab (due to adverse events in 11 subjects) ($P < 0.05$ for improvement). Importantly, the adverse events observed with initial infliximab dosing did not recur with the subsequent use of etanercept.

In another small open-label study ($n = 25$) examining the use of etanercept following infliximab failure (18 due

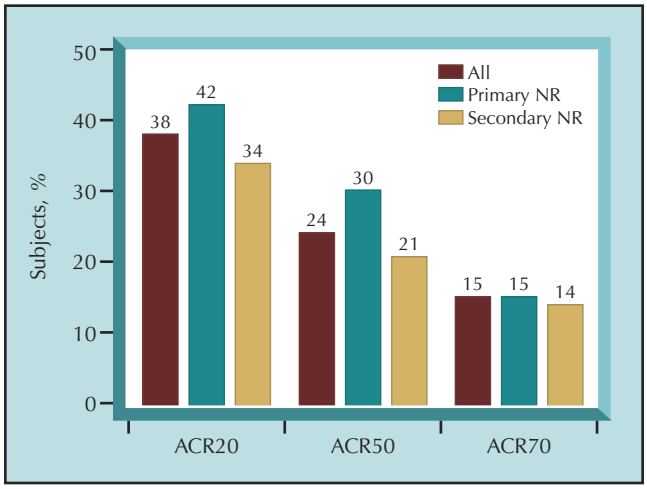

Figure 1. American College of Rheumatology (ACR) response criteria after 12 weeks of etanercept therapy in previous infliximab failures. ACR20—20% improvement based on ACR critiera; ACR50—50% improvement; ACR70—70% improvement. (*From* Buch et al. [20], with permission.)

to efficacy failure), 14 subjects (64%) achieved at least 20% improvement in ACR criteria [15]. Although the study was only 12 weeks in total duration, no adverse events were observed. In a separate study, investigators compared the response of subjects switching from etanercept to infliximab (n = 20) to subjects receiving infliximab as their first TNF-α inhibitor [16]. In both groups, there was significant improvement in several core outcome measures including swollen and tender joint counts, patient and physician global well-being, duration of morning stiffness, and C-reactive protein levels. Importantly, no significant differences were seen between the two treatment groups in terms of clinical response, although the "switchers" received higher doses of infliximab compared to the infliximab-naïve subjects (4.4 vs 3.2 mg/kg, P = 0.006). Taken together, these initial studies support the concept that switching strategies of TNF-α inhibition in the context of drug failure with one agent may result in clinical benefit.

More recent trials have also provided support for the practice of switching agents after failure of prior TNF-α–targeted therapy. One of the largest trials to date to evaluate this question comes from a large UK national registry of RA patients initiating anti–TNF-α therapy [17••]. Of the 6739 patients enrolled, 2826 started with etanercept, 3037 with infliximab, and 841 with adalimumab. Approximately equal numbers of patients stopped their initial anti–TNF-α agent for inefficacy (n = 841) and toxicity (n = 1023). Of the patients who discontinued their first anti–TNF-α agent, 46% (n = 856) switched to a second agent primarily because of initial inefficacy and not adverse events. At the end of the study, 73% of these patients were still receiving therapy with the second agent with at least 6 months of follow-up, which suggests that switching anti–TNF-α therapies may be related to durable clinical responses. Importantly, the authors found that the reasons sited for discontinuing the first anti–TNF-α agent was an important determinant for failure of subsequent agents. Specifically, first drug discontinuation due to efficacy failure was strongly associated with second drug discontinuation from efficacy failure (HR = 2.7; 95% CI, 2.1–3.4) but was not associated with secondary failure due to toxicity. Likewise, first drug discontinuation due to adverse effects predicted an increased incidence of second drug failure due to toxicity (HR = 2.3; 95% CI, 1.9–2.9) but did not predict secondary failure due to efficacy failure. Interestingly, most of the adverse events observed with the second anti–TNF-α strategy were different from those observed with the first anti–TNF-α agent.

Hyrich et al. [17••] did not evaluate specifically whether RA patients who never respond to the first anti–TNF-α agent (primary efficacy failures) are inherently different from those who initially responded to the first anti–TNF-α agent but stopped using the agent because of toxicity or secondary efficacy failure. This important question was preliminarily addressed in a small retrospective study (n = 37) that looked at the efficacy of switching to etanercept treatment in patients with active RA who already responded to infliximab, but were switched to etanercept because of adverse events, primarily infusion reactions [18•]. Although it lacked a comparator group, this study demonstrated that etanercept "maintained" the initial benefit achieved with infliximab based on DAS scores and other measures of disease activity. In a small study of 18 subjects failing infliximab due to inefficacy (11 with primary efficacy failure and 7 with an initial good clinical response followed by relapse), subsequent etanercept therapy led to moderate or good clinical responses based on DAS28 scores in 13 of the subjects [19].

In a more recent investigation, Buch et al. [20] examined the use of etanercept in 95 RA treatment failures with infliximab (34 with primary efficacy failure, 38 with an initial response and subsequent relapse, and 23 with toxicity). A majority of subjects (61%) had a moderate or good treatment response, and no major response differences were observed across groups. Among all subjects with prior infliximab failure, 38% achieved 20% improvement based on ACR criteria (42% for primary nonresponders and 34% for secondary nonresponders) (Fig. 1). The study was only 12 weeks long, but no toxicity was observed in those who had stopped their initial infliximab due to adverse events. Thus, it would appear that switching to a second anti–TNF-α therapy may be a rational strategy for select RA patients who fail initial treatment or who respond to the initial treatment but require drug discontinuation due to either toxicity or later loss of efficacy.

Most studies to date have dealt with switching from one anti–TNF-α agent to a second agent, but few investigations have examined outcomes associated with switching

Table 1. Clinical response after 12 months of adalimumab treatment in patients with RA and previous treatment failure with infliximab

	Switchers			Controls
	Drug failure (*n* = 9)	Adverse events (*n* = 15)	All (*n* = 24)	(*n* = 25)
Patients achieving, *n* (%)				Table body
ACR20	8 (89)	10 (67)	18 (75)	19 (76)
ACR50	5 (56)	7 (47)	12 (50)	14 (56)
ACR70	3 (33)	5 (33)	8 (33)	9 (36)
EULAR	7 (78)	10 (67)	17 (71)	18 (72)
DAS28, mean (SD)				
Baseline	5.4 (0.7)	5.7 (0.8)	5.6 (0.8)	5.9 (0.9)
12 months	3.3 (0.6)	3.2 (0.6)	3.2 (0.6)	3.2 (0.7)

No significant differences were seen between any group of switchers and the control group according to the chi-squared test for categorical parameters and Wilcoxon test for continuous variables. ACR—American College of Rheumatology; DAS—Disease Activity Scale; EULAR—European League Against Rheumatism, RA—rheumatoid arthritis.
(*From* Nikas et al. [22].)

to a third agent. However, this issue was recently evaluated by Solau-Gervais et al. [21•]. In their retrospective study of 70 patients receiving at least two anti–TNF-α agents, 20 subjects had received all three agents. Patients were switched because of ineffectiveness or adverse events, but the specifics of these failures were not detailed. Of 32 subjects switching from a monoclonal antibody to etanercept, 45% had a good clinical response based on European League Against Rheumatism response criteria. Similarly, of 30 subjects switching from etanercept to an anti–TNF-α monoclonal antibody, 45% had a good clinical response. Of the 20 patients receiving all three drugs, all had received etanercept and one of the monoclonal antibodies as their initial two agents, and response to the third agent (infliximab or adalimumab) was suboptimal in a majority of subjects (seven subjects had stopped the third therapy altogether due to efficacy failure). These data suggest that sequential efficacy failure with etanercept and one of the monoclonal antibodies predicts poor treatment response to the third anti–TNF-α agent.

As previously noted, of the three TNF-α–inhibiting agents presently available, two are anti–TNF-α antibodies: infliximab and adalimumab. Based on the data above and the biologic relatedness of the monoclonal antibodies, it might be expected that a switch between them would be of limited effectiveness. Nikas et al. [22] examined 24 RA patients who were treated with infliximab and switched to adalimumab, and compared them to 25 patients who were treated with adalimumab as their first anti–TNF-α agent. After 12 months, the degree of clinical response (ACR20) was similar in both groups (75% vs 76%). Although a trend seemed to favor those stopping initial infliximab due to inefficacy, no major differences appeared to exist in groups based on the initial indication for switching (previous adverse event versus efficacy failure) (Table 1).

This result was very similar to another study of 13 patients who had initially responded to infliximab but failed to maintain that response [23]. In this study, 77% responded to adalimumab therapy following secondary efficacy failure with infliximab. In another study from the Stockholm TNF-α follow-up registry (STURE), investigators examined the use of adalimumab following failure of prior anti–TNF-α treatment, including 27 subjects with secondary loss of efficacy following infliximab [24]. In this group, subsequent adalimumab therapy was associated with significant improvement in DAS28 scores and an ACR20 response of approximately 70%. Although they seem counterintuitive, these data suggest that switching from one monoclonal anti–TNF-α antibody to another may be a rational therapeutic strategy in the context of treatment failure.

Conclusions

Anti–TNF-α therapies have clearly revolutionized our management of RA. Despite this significant advance, a substantial proportion of patients, in both clinical trials and "real-life" practice, fail to achieve even minimal treatment responses. Although limited in their design and size, several studies have now examined the impact of switching anti–TNF-α therapies as a means of addressing prior treatment failures with other TNF-α–targeted strategies. Together, these reports suggest that switching anti–TNF-α agents is indeed a rational treatment strategy; however, the reason for discontinuation of the first agent may be a robust determinant of the reasons for failure of subsequent agents.

Both abatacept and rituximab, the most recently approved biologics for the treatment of RA, have mechanisms of action that are distinct from the anti–TNF-α therapies. As a result, these emerging therapeutic strategies represent additional important options for patients failing conventional DMARDs, DMARD combinations, and therapy with anti–TNF-α agents.

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