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Rheumatoid Arthritis

Strategies in the Management of Patients Showing an Inadequate Response to TNFα Antagonists

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Abstract

The introduction of medications that target specific proinflammatory cytokines has revolutionized the management of patients with rheumatoid arthritis. The agents that antagonize the effects of tumour necrosis factor (TNF)-α – infliximab, etanercept and adalimumab – have consistently shown very good efficacy for controlling the clinical and radiographic manifestations of the disease. However, it has become apparent that some patients will receive no clinical benefit, gradually lose the effect over time or experience adverse effects with the TNFα antagonists. The management of these patients is challenging and there are no clear guidelines.

The concomitant administration of a disease-modifying antirheumatic drug, such as methotrexate, has been shown to improve outcomes. Optimization of the methotrexate or TNFα antagonist dose may lead to improved responses, as demonstrated in some dose escalation studies. Switching to another TNFα antagonist is a step that is supported by small, mostly uncontrolled studies. Finally, the T-cell co-stimulation antagonist abatacept, as well as the B-cell depleting agent rituximab, are also available for use in patients who have had an inadequate response or intolerance to the TNFα antagonists.

Genotypic studies have identified TNF and TNF receptor polymorphisms that appear to predict independently whether a patient will respond to a TNFα antagonist, but genotyping is not available for routine use in clinical practice.

Until such tools for predicting response are widely available, the management of patients with poor responses to TNFα antagonists will have to depend upon the wishes of the patient regarding medication dosage schedules and adverse effect profiles, as well as how comfortable the treating physician is with the available biological medications. In this article, we review the current data and construct an algorithm to help guide clinicians in the management of patients with inadequate responses to the TNFα antagonists.

Rheumatoid arthritis is a chronic, progressive and inflammatory polyarthritis that can be disabling and often involves erosion of the joints.[1] Advances in the understanding of the disease process have led to the development of biological agents for the treatment of rheumatoid arthritis.[2,3] With the use of four currently approved cytokine-specific agents (infliximab, etanercept, adalimumab and anakinra), as well as the newer agents rituximab and abatacept, the goal of therapy has evolved from that of symptomatic relief to clinical remission.

Most patients will receive some benefit from the current biological agents. Clinical trials with these drugs have generally reported American College of Rheumatology (ACR) 20, 50 and 70 response criteria (table I) in 40–85%, 20–50% and 10–30% of patients, respectively.[4] However, a substantial number will obtain no improvement, achieve only a partial response or develop adverse events related to their treatment.[5] Approximately 30% of subjects in one large database discontinued the initial tumour necrosis factor (TNF)-α antagonist within 12 months because of lack of efficacy and/or adverse effects.[6,7]

Table I. American College of Rheumatology (ACR) response criteria[8] (an ACR 50 or ACR 70 response indicates a 50% or 70% improvement, respectively, in the measures listed below)

ACR 20 response criteria
≥20% improvement in swollen joint count, and
≥20% improvement in tender joint count, and
≥20% improvement in at least three of the following five:
patient's global assessment of disease activity
physician's global assessment of disease activity
patient's assessment of pain (VAS)
acute phase reactants (CRP or ESR)
disability (measured with HAQ)

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **HAQ** = Health Assessment Questionnaire; **VAS** = Visual Analogue Scale.

TNFα is a proinflammatory cytokine closely linked to synovial inflammation [9] (a clinical sign of active disease) and plays an important role in joint erosion[10] (a radiographic sign of disease).[11,12] Both clinical disease activity and radiographic erosions are associated with functional disability.[13,14] Studies with the three TNFα antagonists infliximab, etanercept and adalimumab have consistently shown that TNFα antagonism effectively suppresses both of these disabling processes.[15,16]

In clinical trials involving patients with rheumatoid arthritis, efficacy is typically measured by using ACR or European League Against Rheumatism (EULAR) response criteria (table I and table II)[8,17,18] and quantitative radiographic scoring methods.[19-21] It is important to remember that two large trials have shown that even patients who obtain no apparent clinical benefit with a TNFα antagonist are likely to benefit structurally by the slowing of the progression of radiographic joint erosion.[22-25] We therefore believe that patients with no apparent clinical benefit from TNFα antagonists should not be considered treatment 'failures', and in this review we use the term 'inadequate response' to describe these individuals.

There is no universally accepted 'gold standard' for defining whether a patient has had an 'adequate' or 'inadequate' response in clinical practice.[26] The routine use of the disease activity score (DAS) has been recommended to guide therapy (table III),[27] while others have suggested that patient questionnaires may be a better method for following the disease course in the clinic.[26] In practice, the determination of an inadequate response to a TNFα antagonist often incorporates the expectations of the

Table II. European League Against Rheumatism (EULAR) response criteria[18]

Current DAS28	Improvement in DAS28		
	>1.2	0.6–1.2	<0.6
<3.2	Good response	Moderate response	No response
3.2–5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

DAS28 = Disease Activity Score 28.

patient as well as the physician's overall clinical impression.

While recommendations for the initiation of anti-TNFα therapy have been published,[27,28] the treatment of rheumatoid arthritis in patients who discontinue one of these agents is unclear. In this article, we review the available data regarding the management of patients who have had an inadequate clinical response with, or intolerance to, the TNFα antagonists.

A literature search was performed using MEDLINE, focusing on full text articles in English with the keywords 'rheumatoid arthritis', 'methotrexate', 'infliximab', 'etanercept', 'adalimumab', 'anakinra', 'abatacept', or 'rituximab'. Reference sections from the available articles as well as abstracts from EULAR and ACR annual conferences related to switching among TNFα inhibitors were also scanned for relevant articles.

1. Possible Mechanisms for an Inadequate Response to Tumour Necrosis Factor (TNF)-α Antagonist Therapy

Although most patients achieve at least a partial clinical response to TNFα antagonists,[5,7] some will show no initial response, also known as a primary lack of efficacy. Others may receive an initial positive response but lose it over time (a secondary loss of efficacy), or experience intolerable adverse effects necessitating drug discontinuation. The mechanisms leading to primary lack or secondary loss of efficacy remain to be fully characterized.

Table III. Disease Activity Score 28 (DAS28).[17] The DAS28 calculation is based upon the number of tender and swollen joints (out of 28 possible joints) as well as the erythrocyte sedimentation rate or C-reactive protein level and the patient's general health on a visual analogue scale

Disease activity level	DAS28
High	>5.1
Moderate	3.2–5.1
Low	2.6–3.2
Remission	<2.6

Different pharmacokinetic profiles of the TNFα antagonists may partially account for variations in the efficacy of these agents. After subcutaneous administration, etanercept and adalimumab yield uniform concentration-time profiles at steady-state, while infliximab, which is given via an intravenous infusion, has high peak-to-trough ratios and substantial variability between trough levels.[29,30] Only half of the patients taking infliximab with serum concentrations <0.1 μg/mL achieved an ACR 20 response in one study, whereas half of those with serum concentrations >1 μg/mL had at least an ACR 50 response.[29] Additionally, nearly one-quarter of patients receiving infliximab were reported to have serum concentrations 'below the quantification limits' by the end of a typical 8-week dosage schedule.[29]

Another important determinant of the response to TNFα antagonists may be antibody-mediated clearance of the TNFα antagonists. Antibodies to infliximab, etanercept and adalimumab develop in approximately 7–21%, 2% and 6–12% of patients, respectively.[31] In a retrospective cohort study, higher human anti-chimeric antibody concentrations were found in patients taking infliximab who required dose escalation in order to maintain clinical response than in those not requiring dose elevation,[32] suggesting a secondary loss of efficacy after repeated infusions. Wolbink et al.[33] reported that the presence of anti-infliximab antibodies was associated with a reduced response. Conversely, another study reported no difference in ACR 20 responses between anti-infliximab antibody-positive and -neg-

ative patients,[34] leaving uncertainty about the effect of antibody levels on efficacy. Serum antibodies directed against adalimumab were reported to be significantly more common in those patients regarded as non-responders on the EULAR response scale compared with those showing a good response.[35] However, anti-infliximab and anti-adalimumab antibody levels are significantly reduced by the coadministration of methotrexate.[35-37]

A few other biological differences between the TNFα antagonists have been uncovered. Etanercept alone has the ability to bind lymphotoxin α (TNFβ). Lymphotoxin α was identified in synovial biopsy specimens taken from a patient with disease unresponsive to infliximab who subsequently had an excellent response to etanercept.[38] Another study reported no difference in synovial lymphotoxin α immunohistochemical expression between 12 patients on infliximab who achieved an ACR 50 or 70 response and five patients with no apparent clinical or biochemical response.[39] Infliximab and adalimumab can activate complement and initiate antibody-dependent cytotoxicity in TNFα-expressing cells.[40] Both drugs have been shown to cause apoptosis of peripheral blood monocytes, whereas the soluble receptor etanercept does not.[41] The pharmacological and clinical significance of the biological differences between these three anti-TNFα drugs is unknown.

Finally, genetic variation in the human leukocyte antigen (HLA)-coding region may explain some of the variability in clinical responses to the TNFα antagonists. Patients with early rheumatoid arthritis who have inherited two copies of the shared epitope, an amino acid sequence shared by DRB1 alleles of the HLA-DR molecule on antigen presenting cells that is strongly associated with rheumatoid arthritis in many ethnic groups, are three to four times more likely to have an ACR 50 response with the combination of etanercept and methotrexate than those with one or no copies of the shared epitope.[42] Another study involving patients with established rheumatoid arthritis showed that nonresponders to etanercept were much more likely to be negative for the shared epitope than responders.[43] Additionally, genotype analyses have revealed TNF and TNF receptor polymorphisms that independently predict the response of a patient to anti-TNFα therapy.[44-47]

2. Management after an Inadequate Response to TNFα Antagonists

Currently, there are no published guidelines for the management of patients with an inadequate response (primary or secondary) to TNFα antagonists, used with or without disease-modifying antirheumatic drugs (DMARDs). The available data regarding these patients are reviewed and our recommendations are summarized in a treatment algorithm (figure 1).

2.1 Optimization of Disease-Modifying Antirheumatic Drug Dosage

Combination therapy with a DMARD and a TNFα antagonist improves both clinical and radiographic outcomes compared with TNFα antagonist monotherapy.[48,49] However, it is unclear whether the initiation of a DMARD to a patient who has had an inadequate response to a TNFα antagonist leads

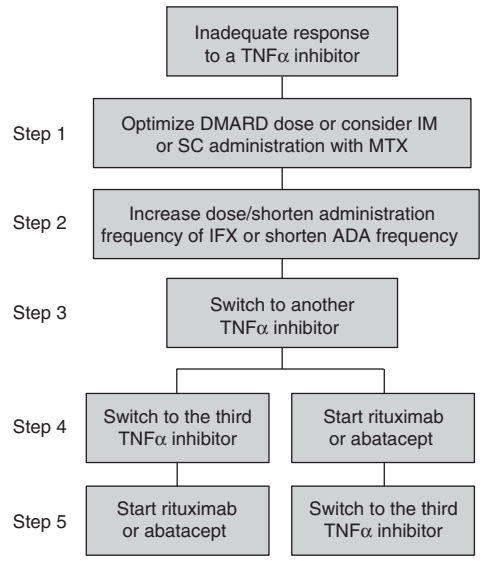

Fig. 1. Strategies in the management of patients showing an inadequate response (primary or secondary) to TNFα antagonists. **ADA** = adalimumab; **DMARD** = disease-modifying antirheumatic drug; **IFX** = infliximab; **IM** = intramuscular; **MTX** = methotrexate; **SC** = subcutaneous; **TNF** = tumour necrosis factor.

to a significant benefit. Although intensification of concomitant DMARD therapy is a reasonable step and can be considered in case of a lack of response (step 1 in figure 1). Methotrexate is the most commonly used DMARD[50] and was the DMARD of choice in the large TNFα antagonist trials.[15,16,22,23,36,48,51-54] A week 12 interim analysis from the ReAct (Research in Active Rheumatoid Arthritis) trial[55] revealed that similar outcomes were achieved with adalimumab whether the concomitant DMARD was methotrexate, leflunomide, sulfasalazine, an antimalarial agent or combinations of these DMARDs. Other than these very short-term data, little else has been reported regarding the role of other DMARDs with TNFα antagonist therapy. The remainder of this section relates to the optimization of the methotrexate dosage.

A dose-response relationship has been established with a methotrexate dose of 7.5–25 mg in patients with rheumatoid arthritis[56,57] and it seems plausible that increased methotrexate bioavailability has the potential to improve efficacy. The bioavailability of methotrexate was reported to be 28% higher when oral dosages of 25–35 mg/week were given in two divided doses rather than once a week.[58] At maintenance dosages averaging 17 mg/week, the area under the concentration-time curve was significantly higher with intramuscular administration than with oral administration.[59] At doses greater than 25 mg, bioavailability was highly variable and nearly two-thirds lower when administered orally than when given subcutaneously.[60]

Whether enhanced bioavailability actually translates into improved outcomes without increased adverse effects is not entirely clear. In a double-blind controlled trial of 384 methotrexate-naive patients, subjects who were randomized to receive subcutaneous methotrexate 15 mg/week achieved statistically significant ACR 20 responses (but not ACR 50 or 70) compared with 15 mg/week orally.[61] Another study of 54 patients showed no evidence of improved disease control after increasing an intramuscular dose of methotrexate beyond 15 mg/week (up to a maximum dose of 45 mg), although a few patients did appear to benefit from switching from oral to intramuscular administration.[62] However, these studies did not involve the TNFα antagonists. Efficacy outcomes with a methotrexate dosage of 15 mg/week were similar for the various routes of administration (oral, intramuscular and subcutaneous) in the ReAct trial when methotrexate was administered with adalimumab.[63]

2.2 Optimization of the TNFα Antagonist Dose Regimen

When a partial response or a secondary loss of efficacy is observed despite administration of the standard infliximab dosage (3 mg/kg every 8 weeks), therapeutic options include increasing the dose or shortening the dose-administration interval (step 2 in figure 1). Pharmacokinetic analysis of samples taken from the ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy) study showed that patients receiving a dosage of 10 mg/kg or a treatment interval of every 4 weeks had lower rates of undetectable serum concentrations.[29] In this study, higher serum infliximab concentrations were associated with increased clinical response and reduced radiographic progression, suggesting a dose-response relationship.

Furthermore, pharmacokinetic models have suggested that higher trough concentrations are better achieved by reducing the interval rather than increasing the dose, a finding since supported in a small open-label study.[64] Higher infliximab trough concentrations and greater improvement in the DAS have been reported in responders compared with nonresponders.[65] Higher doses have also been associated with a lower incidence of anti-infliximab antibodies.[37] However, there is a concern that higher doses may lead to higher rates of adverse events,[66] although this was not apparent in 90 patients who completed a dose escalation study.[67]

In a nonrandomized, open-label study from Belgium, patients who were regarded by the treating physician to be unresponsive to infliximab at 22 weeks were given an extra 100 mg of infliximab at each subsequent 8-week infusion.[68] Between weeks 30 and 54, the proportion of patients with ACR 20 and 50 scores increased from 34% to 61%

and 12% to 25%, respectively. Data from the START (Safety Trial for Rheumatoid Arthritis with Remicade® [1] Therapy) trial showed that patients initially started on infliximab at dosages of either 3 mg/kg or 10 mg/kg every 8 weeks had similar ACR 20 responses at 22 weeks.[69] In the group of patients who either failed to obtain a response or initially responded but later experienced a disease flare, a dose escalation study (an increase of 1.5 mg/kg every 8 weeks if there was less than a 20% improvement in swollen and tender joints) was performed.[67] In the group with a primary lack of efficacy, 41 of 53 patients (77%) had a more than 20% improvement in swollen and tender joint counts after receiving an infliximab dose escalation. Similarly, 39 of 47 patients (83%) who initially responded to 3 mg/kg but had a disease flare also responded to dose escalation. van Vollenhoven et al.[70] reported that while modest but statistically significant clinical improvement did occur with increased infliximab doses, similar benefits were obtained in two comparison groups receiving standard-dose infliximab and etanercept. van Vollenhoven et al.[70] were of the opinion that the improvements seen with dosage escalation may, in fact, be related to a 'regression-like effect'.

A few studies have investigated the consequences of increasing the adalimumab dose or shortening the dose-administration interval in patients with suboptimal responses to adalimumab (step 2 in figure 1). In a phase II trial, 80 mg given every other week was no more effective than the typical dose of 40 mg every other week.[36] Results from the PREMIER trial showed that changing to weekly dose administration in patients not achieving an ACR 20 response had minimal effect on the percentage of patients reaching ACR 20 or 70 responses.[23] However, van de Putte et al.[71] reported a trend towards improved ACR responses with 40 mg administered every week as opposed to every other week, but this study was not powered to detect differences between the two dosage schedules of adalimumab.

2.3 Treatment with Another TNFα Antagonist

Despite ostensibly similar mechanisms of action and the ultimate result of TNFα inhibition, it has been apparent that lack of success with one TNFα antagonist does not preclude successful treatment with another (step 3 in figure 1). In fact, when one TNFα antagonist has been ineffective, responses to a second or even a third agent often appear to be as robust as those seen with the initial agent. Table IV highlights the studies that have been reported to date regarding medications used, sample size, population characteristics and outcomes.

Although it is difficult to draw definitive conclusions from the heterogeneous, small, nonrandomized, open-label and often retrospective studies, some interesting trends and differences appear. It must be emphasized that the definitions of 'inadequate response' and 'loss of efficacy' are not universally agreed upon. Many of the reports involving switching TNFα antagonists define these conditions differently and some do not separate patients with a primary lack from those with a secondary loss of efficacy. It is also not typically apparent from the reports how long patients were treated or whether the dose of the concomitant DMARD or TNFα agent was optimized before declaring an 'inadequate response'.

Overall, patients who do not achieve an adequate clinical response to an initial TNFα antagonist have still received significant benefit after switching to another agent in all but one small study.[84] Subjects who had received prior TNFα antagonist therapy had lower response rates than biological agent-naive patients in a few studies,[78,82] but other studies reported similar responses among the two groups.[80,81] There is a suggestion from two studies that adalimumab was more effective in patients who developed toxicity or a secondary loss of efficacy with infliximab compared with those patients who never responded to infliximab.[78,79] Conflicting results were seen when patients were switched from infliximab to etanercept. Buch et al.[39] reported that patients with a primary lack of efficacy with inflix-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table IV. Outcomes after switching to a different tumour necrosis factor (TNF)-α antagonist

Study (year)	Agents	Patients	Results	Comments
Brocq et al.[72] (2002)	IFX → ETA	8	5 showed 'good' response	It is difficult to draw conclusions from this small study
	ETA → IFX	6	3 showed 'good' response	
Ang and Helfgott[73] (2003)	IFX ↔ ETA	29	Patients with an inadequate response to one agent can respond to another	A second agent can be used safely after infections or hypersensitivity reactions with the first
van Vollenhoven et al.[74] (2003)	IFX → ETA	13 (11 with AEs)	Patients achieved lower mean DAS28 levels with ETA than with IFX	Study included 6 JIA and SpA patients. Nearly half of patients that failed to achieve an ACR 20 on ETA reached it after starting IFX
	ETA → IFX	18 (14 with lack of efficacy)	Patients achieved lower mean DAS28 levels with IFX than with ETA	
Gomez-Puerta et al.[75] (2004)	IFX → ETA	12 with lack of efficacy	Ten patients had good or moderate EULAR responses	Four patients with a primary lack of efficacy showed 'impressive' responses to ETA
Hansen et al.[76] (2004)	ETA → IFX	20 (17 with lack of efficacy)	There was no statistically significant difference for TJC, SJC,	Similar efficacy was seen for patients who switched from ETA to IFX compared with TNFα antagonist-
	IFX	73 TNFα antagonist-naive patients	CRP, and global assessments between the two groups	naive patients started on IFX
Haraoui et al.[77] (2004)	IFX → ETA	25 (76% with lack of efficacy)	ACR 20, 50 and 70 responses were 64%, 23% and 5%, respectively, in the 22 patients completing the study	In this 12-week prospective, open-label study, none of the patients stopped ETA because of AEs or lack of efficacy
Bennett et al.[78] (2005)	IFX/ETA → ADA	26 with prior biological exposure (IFX in 23 patients)	65% of patients had good or moderate EULAR responses after switching, compared with 85% in 44 biological agent-naive patients	Patients with a secondary loss of efficacy had significantly better DAS28 outcomes than those with primary lack of efficacy to the original TNFα antagonist
van der Bijl et al.[79] (2005)	IFX → ADA	37 with mean disease duration of 12 years	ACR 20 and 50 responses were reported in 49% and 26%, respectively	Patients with a primary lack of efficacy had much lower ACR 20 and 50 response rates than those with a secondary loss of efficacy (33% and 8% vs 61% and 39%, respectively)
Nikas et al.[80] (2006)	IFX → ADA	9 'drug failures'	ACR 20, 50, 70 = 89, 56, 33%, respectively	Similar rates of discontinuation and adverse events were seen among the groups
		15 AEs	ACR 20, 50, 70 = 67, 47, 33%, respectively	
	ADA	25 TNFα antagonist-naive patients	ACR 20, 50, 70 = 75, 50, 33%, respectively	

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Table IV. Contd

Study (year)	Agents	Patients	Results	Comments
Wick et al.[81] (2005)	IFX/ETA → ADA	36 (27 IFX, 9 ETA) with loss of efficacy	75% of patients achieved an ACR 20 response	Response rates were similar among those switching compared with 26 patients without prior TNFα antagonist exposure started on ADA
Burmester et al.[82] (2005)	IFX/ETA → ADA	688 with prior biological agent exposure	ACR 20, 50 and 70 responses met in 57%, 31% and 11%, respectively	Clinical improvement was evident after switching in this large study, although better response rates were seen in 3553 biological agent-naive patients in the ReAct trial. ACR 20, 50 and 70 responses in 68%, 40% and 18% of patients, respectively
Solau-Gervais et al.[83]	IFX/ADA → ETA	32	45% had 'good' response	7 of 20 patients showed a good response after
(2006)	ETA → IFX/ADA	30	45% had 'good' response	switching to a third TNFα antagonist
	IFX ↔ ADA	8	33% had 'good' response	
Yazici and Erkan[84] (2004)	ETA → IFX	21	HAQ, pain scores, and morning stiffness did not improve after switching	IFX was not as effective in patients with an inadequate response to ETA in this retrospective study
Cantini et al.[85] (2005)	IFX/ADA → ETA	22 (15 IFX, 7 ADA)	An ACR 20 response was seen in 12 of 21 patients after 24 weeks	ETA was well tolerated and efficacious in patients with toxicity or inadequate response to IFX and ADA
Navarro et al.[86] (2006)	IFX, ADA, ETA	417 patients given a first agent, 83 given a second agent and 18 a third agent	Moderate or good EULAR responses seen in 75%, 47% and 28% with the first, second and third agents, respectively	Statistically significant improvements in DAS28 scores seen with switching to a second ($p < 0.0001$) but not a third agent ($p = 0.06$)
Bombardieri et al.[87] (2006)	ADA in TNFα antagonist-naive patients	5711	ACR 20, 50, 70 = 70, 41, 19%, respectively	ADA was effective for patients who had previously received IFX and/or ETA but possibly less effective than for TNFα antagonist-naive patients
	IFX → ADA	591	ACR 20, 50, 70 = 64, 34, 13%, respectively	
	ETA → ADA	188	ACR 20, 50, 70 = 57, 34, 13%, respectively	
	IFX + ETA → ADA	120	ACR 20, 50, 70 = 46, 29, 11%, respectively	
Hyrich et al.[88] (2007)	IFX, ADA, ETA	856	70% of patients continued a second agent for ≥6 months	The rate of continuation was similar whether the first agent was stopped because of lack of efficacy or to adverse events. No efficacy data were reported
Buch et al.[39] (2007)	IFX → ETA	34 with primary lack of efficacy	ACR 20, 50, 70 = 42, 30, 15%, respectively	61% of patients achieved moderate or good EULAR responses after switching. Better responses were seen in those with a primary lack of efficacy. None of the 23 patients who discontinued IFX because of toxicity developed toxicity after 12 weeks of ETA

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Table IV. Contd

Study (year)	Agents	Patients	Results	Comments
		38 with secondary loss of efficacy	ACR 20, 50, 70 = 34, 21, 14%, respectively	
Furst et al.[89] (2007)	ETA → IFX	13 with partial ETA response	ACR 20 and 50 = 62 and 31%, respectively	This randomized, open-label, prospective study also reported improved HAQ outcomes but did not report
	ETA continued	14 with partial ETA response	ACR 20 and 50 = 29 and 14%, respectively	p-values
Iannone et al.[90] (2007)	IFX → ETA	37 with AEs	ACR 50 and 70 responses in switchers were 73 and 50%, respectively, compared with 53 and 30% while on IFX	Switching to ETA led to improved responses for patients who had already obtained a good response from IFX but switched because of AEs
Cohen et al.[91] (2005)	IFX → ETA	24 (16 with lack of efficacy, 8 with AEs)	According to the physicians' 'global evaluation', the switch was successful in 75%	Of patients with available DAS28 scores, 11 of 19 had good EULAR responses after switching to ETA and 8 of 12 who switched to IFX had moderate or good responses
	ETA → IFX	14 (13 with lack of efficacy, 1 with an AE)	The switch was successful in 86% of patients	
Di Poi et al.[92] (2007)	IFX → ETA	18 (11 with primary lack and 7 with secondary loss of efficacy)	64% of patients with a lack and 86% with a loss of efficacy obtained a moderate or good EULAR response	72% of patients responded after switching to ETA, but only one achieved a clinical remission
Hjardem et al.[6] (2007)	IFX, ETA, ADA	235 patients with a lack of efficacy or AEs	The median drug survival time for the initial agent in all patients (switchers and non-switchers) and the second agent in switchers was 119 and 92 weeks, respectively	DAS28 improved regardless of the reason for switching. Those who switched because of loss of efficacy obtained statistically significant DAS28 improvements compared with the initial agent at the same time periods
Gomez-Reino et al.[93] (2006)	IFX, ETA, ADA	194 RA switchers	63% of patients were still taking the second agent after 1 year	Second TNFα antagonist survival in the group (68% RA, 11% AS, 11% PsA and 11% other chronic arthritis) was better for those switched because of AEs
Favalli et al.[94] (2004)	IFX ↔ ETA	15 (8 RA, 7 JIA, 1 ETA → IFX)	13 of 15 patients achieved an ACR 20 at 6 months	It is difficult to draw conclusions from this small study with a mixed patient population

ACR = American College of Rheumatology; **ADA** = adalimumab; **AE** = adverse event; **AS** = ankylosing spondylitis; **CRP** = C-reactive protein; **DAS28** = Disease Activity Score 28; **ETA** = etanercept; **EULAR** = European League Against Rheumatism; **HAQ** = health assessment questionnaire; **IFX** = infliximab; **JIA** = juvenile idiopathic arthritis; **PsA** = psoriatic arthritis; **RA** = rheumatoid arthritis; **SJC** = swollen joint count; **SpA** = spondyloarthritis; **TJC** = tender joint count; → indicates switched to; ↔ indicates switched from one agent to the other agent.

imab were slightly more responsive to etanercept than those with a secondary loss of efficacy. Conversely, another small study showed that 7 of 11 patients (64%) who never responded to infliximab obtained a moderate or good EULAR response after switching to etanercept, while 6 of 7 patients (86%) with a secondary loss of efficacy had moderate or good EULAR responses after the switch.[92] These studies did not compare adalimumab and etanercept, so, while it may be tempting, it is not possible to conclude that adalimumab should be used over etanercept after a loss of efficacy to infliximab, or that etanercept would be a better choice than adalimumab in the case of a primary lack of efficacy.

Data from two studies have revealed that the reason for discontinuation of the first TNFα antagonist often predicts the reason for discontinuation of a second agent.[6,88] A large cohort study from the UK reported that if discontinuation of an initial TNFα antagonist was due to lack of efficacy, the risk of discontinuing a second agent due to lack of efficacy, but not toxicity, was increased (hazard ratio [HR] 2.7; 95% CI 2.1, 3.4).[88] Similarly, if the reason for switching was the occurrence of an adverse event, the likelihood of discontinuation of the second drug because of another adverse event, but not lack of efficacy, was increased (HR 2.3; 95% CI 1.9, 2.9). Efficacy outcomes were not reported, but more than 70% of patients continued a second agent for more than 6 months.[88] Similarly, in a retrospective analysis by Hjardem et al.,[6] 32% of patients who had switched because of a lack of efficacy eventually stopped the second agent because of lack of efficacy and only 3% stopped because of an adverse event. Only 15% of patients who switched from the initial agent because of an adverse event had to stop the second because of an adverse event, whereas 25% stopped because of a lack of efficacy.

2.4 Treatment with an Interleukin-1 Receptor Antagonist

Few data are available regarding the use of the interleukin-1 receptor antagonist anakinra after the failure of TNFα antagonists or vice versa. One study reported that only 2 of 26 patients with long-standing rheumatoid arthritis and an inadequate clinical response to TNFα antagonists achieved an ACR 20 response after 3 months of therapy with anakinra.[95]

2.5 Treatment with a B-Cell Depleting Agent

Rituximab is a chimeric monoclonal antibody that targets the B-cell surface antigen CD20. It is expressed on late pro-B cells, pre-B cells, and immature, mature, activated and memory B cells but is not expressed on stem cells, early pro-B cells, plasma cells or other normal tissue.[96] Treatment with rituximab results in peripheral blood B-cell depletion without significantly reducing immunoglobulin levels.[97] Following the results of a randomized, placebo-controlled trial of 161 patients who had an inadequate response to the TNFα antagonists, the greater efficacy of rituximab in combination with methotrexate than methotrexate alone was established,[97] and rituximab was approved for use in combination with methotrexate for these patients (step 4 or 5 in figure 1).

Nearly 500 patients with an inadequate response to TNFα antagonist therapies were enrolled in the REFLEX (Randomised Evaluation of Long-term Efficacy of Rituximab in RA) study comparing rituximab plus methotrexate with methotrexate monotherapy.[98] Two doses of rituximab (1000 mg each) were infused intravenously on days 0 and 14. After 24 weeks, statistically significant improvements were seen in all clinical and patient-reported outcomes in the combined therapy group. There was a suggestion of a radiographic benefit at 24 weeks and this was statistically significant at 56 weeks in the rituximab plus methotrexate group compared with the methotrexate-only group.[99] This was evident even in the group of ACR 20 nonresponders. A second course of treatment appears to lead to comparable, if not improved, responses when compared with the original baseline, without evidence of increased toxicity.[100]

A subgroup analysis from the REFLEX study revealed that rituximab was beneficial for patients with an inadequate response to a single TNFα antagonist or multiple TNFα antagonists.[101] The benefit did seem to be more pronounced in the population

that had been exposed to only one agent compared with two or more (ACR 20 responses in 57% vs 42% of patients, respectively); however, the statistical and clinical significance of this finding is unclear.

Recently, a Swiss prospective cohort study of 116 patients with an inadequate response to at least one TNFα antagonist compared a treatment strategy of initiating rituximab versus switching to another TNFα antagonist.[102] The authors reported that rituximab was more effective than a different TNFα antagonist at reducing the DAS for 28 joints, erythrocyte sedimentation rate and number of tender joints after 6 months of therapy. Only 53% of patients who switched TNFα antagonists were taking methotrexate or leflunomide compared with 68% of the rituximab group (not statistically significant). However, this was not a randomized study and selection bias is a concern. The basis by which some patients were chosen to receive rituximab as opposed to a second TNFα antagonist was not clear. Similar rates of adverse events were reported in both groups of patients.

2.6 Treatment with a T-Cell Costimulation Antagonist

Abatacept has recently been approved by the US FDA for use in patients with moderate to severe rheumatoid arthritis who have not responded adequately to either DMARDs or TNFα antagonists (step 4 or 5 in figure 1). Abatacept is a human recombinant cytotoxic T lymphocyte antigen-4 fused with the Fc portion of an IgG molecule. It prevents the binding of CD80 and CD86 ligands on the surface of antigen-presenting cells with the CD28 receptor on the T-cell surface. Blockade of this costimulatory pathway effectively inhibits T-cell activation and two trials have reported efficacy of abatacept in methotrexate-refractory disease.[103,104] Abatacept is administered via an intravenous infusion over 30 minutes at weeks 0, 2 and 4, and then every 4 weeks thereafter.

ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders), a randomized, double-blind trial, evaluated the efficacy and safety of abatacept in patients with an inadequate response to 3 months of treatment with either etanercept or infliximab.[105] After 6 months, significantly greater improvements in ACR 20, 50 and 70 response criteria were reported in the abatacept group than in placebo recipients. Rates of discontinuation and adverse events were low and similar in the two groups. The ACR responses appear to be maintained for 24 months.[106] A *post hoc* analysis demonstrated that similar benefit was obtained regardless of whether the initial TNFα antagonist was discontinued for a primary lack or secondary loss of efficacy.[107]

Another randomized, placebo-controlled 6-month trial confirmed an improved quality of life, as gauged by the Health Assessment Questionnaire and 36-item Short-Form health survey, with abatacept in patients with rheumatoid arthritis refractory to TNFα antagonists.[108]

Overall, therapy with abatacept carries a slightly higher risk of infection than placebo, but no deaths or opportunistic infections were reported in these studies. Patients with chronic obstructive pulmonary disease in particular appear to experience more adverse effects and infections.[109] Infusion reactions may occur but are typically not severe.[105]

2.7 Addition of Another Biological Agent to a TNFα Antagonist

A few studies have investigated combined biological therapy, but the results have not been promising. In one study, the addition of anakinra to etanercept did not lead to improvement in disease activity and actually resulted in a higher rate of adverse events, including serious infections.[110] In the ASSURE (Abatacept Study of Safety in Use with Other Rheumatoid Arthritis Therapies) trial, the addition of abatacept to a TNFα antagonist provided no additional clinical benefits in physical function or patient global assessment of disease and pain.[111] Importantly, the combination resulted in significantly higher rates of neoplasms and serious infections. At present, the use of biological agents as combination therapy in refractory rheumatoid arthritis cannot be recommended.

3. Discussion and Conclusion

A treatment algorithm has been provided based upon the available data (figure 1). As discussed in this article, other than the trials involving the newest medications approved for the treatment of rheumatoid arthritis, abatacept and rituximab, there are relatively few reliable data from large, prospective, randomized, placebo-controlled trials upon which to base clinical decisions after an unsuccessful trial of a TNFα antagonist. The concomitant administration of a DMARD, most commonly methotrexate, has consistently proven to improve both clinical and radiographic outcomes and should be considered for all patients receiving TNFα antagonists.[49,50] Optimization of the effective dose of methotrexate, whether by increasing the oral dose or switching to intramuscular or subcutaneous administration, is an appropriate next step, although this is not necessarily supported by results from trials involving the TNFα antagonists (step 1 in figure 1). Additionally, there are reasonable, but limited, data[29,65,67,68,70,71] that show that shortening the interval between doses and/or increasing the dose of infliximab, and possibly by changing adalimumab to weekly administration, may also improve outcomes (step 2 in figure 1).

The studies involving switching among the TNFα antagonists consistently reveal that patients with a primary lack of efficacy, secondary loss of efficacy or adverse effects often achieve a response that is similar to, or better than, that seen with the initial agent, and similar to the response seen in TNFα antagonist-naive patients (step 3 in figure 1) [table IV]. While the reason for the discontinuation of an initial TNFα antagonist (lack of efficacy or adverse event) often predicts the reason for stopping a second TNFα antagonist, most patients still tolerate and obtain benefit from the second or even third agent.

Should there be a concern for an exacerbation of congestive heart failure, a demyelinating process or the development of a lupus-like syndrome, then switching to one of the newer biological agents would certainly be appropriate (step 4 in figure 1). Otherwise, the decision whether to switch to a second or even third TNFα antagonist versus starting abatacept or rituximab must be based upon a thorough discussion of the risks and benefits with the patient. Some patients and clinicians may feel more comfortable with the dosage and potential adverse effects of the TNFα antagonists, leading them to switch to another TNFα antagonist (step 3 in figure 1). Others may opt for rituximab or abatacept because of the different mechanisms of action, adverse effect profiles and dosage schedules (step 4 in figure 1). Although this decision should be individualized, in the algorithm we have suggested switching to a second TNFα antagonist before starting either rituximab or abatacept as our personal preference (step 3 in figure 1) because TNFα antagonists have the support of reliable, long-term safety and efficacy data[112,113] that are not yet available for the newer agents in the rheumatoid arthritis population.

The introduction of infliximab, etanercept and adalimumab to the rheumatologist's armamentarium has revolutionized the treatment of rheumatoid arthritis. However, a new challenge that has surfaced is the management of those patients who show an inadequate response to these agents. There are encouraging recent studies[42-47] that have identified genetic differences that independently predict who will be more likely to achieve a favourable response. With further advances, the hope is that these and potentially other tests will enable clinicians to match individual patients with specific effective biological agents.

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