Management of inadequate response to TNF-α antagonist therapy in rheumatoid arthritis: what are the options?

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Citation

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Abstract

The advent of tumor necrosis factor (TNF)-α antagonists for the treatment of rheumatoid arthritis (RA) has led to considerable improvements in effective disease management in patients with an inadequate response to traditional disease-modifying antirheumatic drugs. However, the available TNF-α antagonists have yet to meet the needs of all patients with RA; some patients may have an inadequate clinical response, lose their responsiveness over time, experience unacceptable side effects or have medical issues precluding the use of these medications. An inadequate response is generally determined in the context of a deteriorating clinical state, although there is no standardized definition. This review evaluates the role of two newly available biologic therapies - rituximab and abatacept - within the challenging treatment context of patients who fail to have an adequate response to TNF-α antagonists. Both medications downregulate the immune inflammatory reaction, albeit via different mechanisms, and have been shown to impede the progression of joint deterioration, providing potential options for these difficult-to-treat patients.

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INTRODUCTION

The success of biologic disease-modifying antirheumatic drugs (DMARDs) targeting tumor necrosis factor (TNF)-α has dramatically raised therapeutic expectations in rheumatoid arthritis (RA). Outcomes that previously were seldom achieved are now realistic treatment goals. Three drugs of this class have received United States (US) Food and Drug Administration approval for use in patients who have previously demonstrated an inadequate or failing response to traditional DMARDs, such as methotrexate (MTX), etanercept (Enbrel®, Amgen, Thousand Oaks, CA), infliximab (Remicade®, Centrococ, Malvern, PA) and adalimumab (HUMIRA®, Abbott Laboratories, Chicago, IL) (1,2,3,4).

Despite the proven efficacy of TNF-α antagonists, these agents have yet to meet the needs of all patients (5). A significant number of patients fail to respond satisfactorily to TNF-α antagonists, do not respond at all (6,7,8), or show an initial improvement but lose responsiveness over time (9). In some patients, this may be the result of antibody formation against the biologic therapy, thereby mitigating its efficacy (10). Other patients are ineligible for TNF-α antagonists treatments due to injection/infusion reactions (10) or the development of adverse toxicity issues, such as recurring infections or various skin conditions (11,12). Moreover, the presence of comorbid conditions, such as significant congestive heart failure, recurring/chronic infections and demyelinating diseases, precludes the use of these biologic agents (13).

Until recently, treating patients who experienced an inadequate response to TNF-α antagonists posed a significant problem to the rheumatologist, as there were limited alternatives. This left a treatment void in a patient population that typically has active and/or unremitting disease despite the fact that they have progressed a substantial way through the RA treatment paradigm.

The purpose of this review is to evaluate strategies for treating patients with an inadequate response to TNF-α antagonist therapy, for whom there exists an unmet treatment need.

DEFINING AN ADEQUATE RESPONSE TO TREATMENT

There is no clear consensus on what constitutes an inadequate response to TNF-α antagonist therapy. It is generally anticipated that using maximum dosing regimens...
of TNF-α antagonists should lead to significant, durable improvements in clinical manifestations and laboratory parameters within 12 weeks \( (s_{11},s_{12}) \). When this is not achieved, the decision to escalate a current therapy, prescribe an additional DMARD or switch to another medication is frequently challenging.

Since RA is a heterogeneous disease, responses to a particular medication can vary markedly from patient to patient. Individual patients often exhibit differences in their response to standard DMARDs and biologic response modifiers as well as in their perception of the severity of their disease and the significance of its clinical manifestations. However, uncontrolled disease activity and likelihood of subsequent clinical deterioration is often signaled by persistent and recalcitrant synovitis, inflammatory changes in previously uninvolved joints or the development of extra-articular manifestations. This persistence of unchecked disease activity may often be confirmed by the presence of elevated serum C-reactive protein levels on sequential laboratory testing. Accurate determination of disease status and the ability to prognosticate potentially aggressive disease should help physicians select the most appropriate ‘therapeutic package’ both at the outset of treatment and during subsequent evaluations \( (s_{13}) \).

Objective evidence of diminished disease activity may be assessed using the Disease Activity Score 28 (DAS28; a DAS28 score of <2.6 is considered to indicate clinical remission). In the context of clinical trials, another indication of a successful treatment response would be the achievement of a major clinical response (MCR), in which an American College of Rheumatology (ACR) 70 or greater response is maintained for at least 6 consecutive months \( (s_{13}) \).

Almost invariably, patients recognize the serious nature of their disease when their health-related quality of life (HRQoL) begins to deteriorate. Recent surveys have highlighted that over one third of patients report their HRQoL issues as being half of what is commonly considered to be normal \( (s_{14}) \). A deteriorating clinical state, then, may well be best determined by a patient’s feedback. Several tools are available that measure patient-centered perceptions of function and HRQoL, which can provide additional guidance in judging a treatment response. These tools include the Health Assessment Questionnaire, developed as a validated quantitative measure to accurately assess a patient’s physical disability, and the Short Form-36 (SF-36), which includes eight subscales measuring social functioning, vitality, health perceptions, pain, general mental health and limitations due to emotional issues and physical problems. More recently, the Routine Assessment of Patient Index Data test has been developed to monitor the performance of a patient’s current therapy. This index measures only three patient-reported outcome measures: physical function, pain and patient’s global estimate of disease activity. It has been demonstrated to distinguish active from control treatments in clinical trials as effectively as ACR or DAS criteria and highly correlates with DAS28 \( (s_{15},s_{16}) \).

In those patients who have achieved a measurable but suboptimal clinical response to TNF-α antagonist therapy, management may be more difficult. It is clear that ‘symptom’ control does not necessarily imply ‘disease’ control. Currently, effective management of RA should target multiple aspects of disease such as inflammatory joint pain, morning stiffness, evident synovitis, serum markers of inflammation, structural deterioration \( (s_{13}) \) and HRQoL determinants.

**CURRENT STRATEGIES FOR PATIENTS WITH AN INADEQUATE RESPONSE TO TREATMENT WITH TUMOR NECROSIS FACTOR ANTAGONISTS**

For those patients who are resistant to or lose their initial responsiveness to TNF-α antagonists, treatment options include increasing the dose of the current background non-biologic DMARD therapy, introducing additional standard DMARDs \( (s_{11},s_{17}) \), or adding low dose corticosteroids either chronically by mouth or intermittently by intra-articular injection to particularly recalcitrant joints \( (s_{10}) \). Another treatment option would be to alter the dosage of the current biologic drug, either by increasing the dose or decreasing the dosing interval. However, there is no firm evidence to suggest that these changes would be efficacious in all patients. Moreover, an apparent initial clinical benefit may regress over time \( (s_{11},s_{12}) \), and an increase in dosage of any biologic or standard DMARD therapy allows for potential increased toxicity \( (s_{17}) \).

Probably the most frequently-used practice is to switch from one TNF antagonist to another \( (s_{19},s_{20}) \). However, to date, no large, controlled, prospective, randomized and blinded clinical trials have been conducted examining the effectiveness of this approach. Additionally, no clear evidence exists to define the optimal sequence in which
these therapies should be used (21). Switching between TNF-α antagonists commonly succeeds in producing an initial, satisfactory clinical outcome (22,23,24), however, it has been the author’s personal experience that the early improvement is often not durable. A recent editorial by van Vollenhoven highlighted the need for randomized, controlled clinical trials to accurately evaluate the effect of switching from one TNF-α antagonist to another, avoiding the potential issues encountered in interpreting data from observational studies (26). Such observational studies may be subject to a bias known as “regression to the disease mean”, whereby natural fluctuations in disease activity may influence the initial perception of a treatment response. Switching between therapies may often be invoked at times of high disease activity; however, due to natural fluctuations, it is unclear whether improvements following switching should be attributed to the effect of a new therapy or whether they are, in fact, due to chance fluctuations in disease activity (26). The OPPOSITE (Open-label, Pilot Protocol Of patients with RA who Switch to Infliximab after an incomplete response To Etanercept) trial was the first open-label trial to evaluate switching from one TNF-α antagonist to another. This 28–patient study randomized patients who had an incomplete response to etanercept 1:1 to receive either their previous etanercept regime (25 mg twice weekly) or infliximab (3 mg/kg at weeks 0, 2, 6, 14 and 22). Although the study was limited by the small sample size (preventing adequate statistical powering) and the lack of definition for a prior inadequate response to etanercept, efficacy data showed a clear benefit of switching to infliximab (25). Another study, based on patients registered in DANBIO (Danish database for biological treatments), evaluated the efficacy of switching from infliximab to a second TNF-α antagonist following discontinuation due to either lack of efficacy or adverse events (AEs). Analysis of this registry showed that patients who discontinued their first TNF-α antagonist due to lack of efficacy, generally, had an improved response to a second agent; while patients who discontinued due to AEs responded similarly to a second agent. Efficacy benefits were shown to be similar regardless of the second TNF-α antagonist used (26). Other studies that examined whether the reason for discontinuing one TNF-α antagonist has any influence on the discontinuation of the second demonstrated that the reasons for the discontinuation of a second TNF-α antagonist (e.g. lack of efficacy) are often the same as with the first (26).

One alternative treatment open to these patients is anakinra (Kinere®; Amgen, Thousand Oaks, CA), which downregulates the biologic effects of interleukin (IL)-1. However, anakinra has not been widely used, since the rapid, dramatic improvements commonly observed with TNF-α inhibitors are not as apparent with this agent.

NOVEL APPROACHES FOR A NEW ERA

Until recently, available biologic therapies directly targeted pro-inflammatory cytokines generated downstream in the immunopathogenesis of RA. A more comprehensive understanding of the cellular elements involved in RA immunopathology has led to the development and approval of two medications with alternate mechanisms of action – abatacept (ORENCIA®, Bristol-Myers Squibb, Princeton, NJ) (28) and rituximab (RITUXAN®, Genentech Incorporated, San Francisco, CA) (29). Unlike the TNF-α antagonists, abatacept and rituximab target earlier, initiating events in the immune cascade that, ultimately, result in the downregulation of pro-inflammatory cytokines (26,29) (Figure 1). These newer agents act via the depletion of B cells (rituximab) and by the modulation of a necessary second co-stimulatory signal required for full T-cell activation (abatacept). Both agents have demonstrated effective and sustained reductions in rheumatoid disease activity and provide new treatment options for those patients experiencing an inadequate response to TNF-α inhibition.

Figure 1

Figure 1: Immunopathogenesis of rheumatoid arthritis, depicting the targets of biologic therapies

IL=interleukin; TNF=tumor necrosis factor; RF=rheumatoid factor; IL-6R=interleukin 6 receptor; MMP=matrix metalloprotease. [Cohen M. Internet J Rheum; 3(1). Copyright © (2007) Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.]
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ABATACEPT

Abatacept, a selective co-stimulation modulator of T-cell activation, is a first-in-class agent for the treatment of RA. As monotherapy or concomitantly with non-biologic DMARDs, abatacept is indicated for reducing signs and symptoms, inducing a MCR, inhibiting the progression of structural damage and improving physical function in patients with moderate to severe RA. It was the first therapy to be approved in the US for the treatment of patients with active RA and an inadequate response to either traditional or biologic DMARDs (28).

MECHANISM OF ACTION OF ABATACEPT

Abatacept is a soluble, fully-human fusion protein, consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen-4, linked to the modified Fc (hinge, CH2 and CH3 domains) portion of human immunoglobulin GI (IgG1). Abatacept modulates the full activation of T cells, an event that occurs early in the immune cascade, which, if unopposed, may lead to the progressive inflammatory and destructive changes characteristic of RA (30).

T cells require an antigen-specific and a co-stimulatory signal (of which there are several) in order to become fully activated (30,31,32). The engagement of CD80/CD86 on antigen presenting cells (APCs) with CD28 on T cells is the best characterized of the co-stimulatory pathways (30,34,35). By competitively binding to CD80/CD86 on APCs, abatacept prevents their interaction with CD28 on T cells (34) (Figure 2), inhibiting the full activation of T cells, and thereby suppressing multiple downstream events in the immunopathology of RA. These include a dampening of B-cell activation and its consequent auto-antibody formation and B-cell cytokine release, as well as the inhibition of macrophage activation, thereby preventing the production of TNF-α, IL-6 and other pro-inflammatory mediators (25,30).

Figure 2

Figure 2: Mechanism of action of abatacept and rituximab

APC=antigen presenting cell; MHC=major histocompatibility complex; TCR=T-cell receptor; ADCC=antibody-dependent cell-mediated cytotoxicity; NK=natural killer. [Cohen M. Internet J Rheum; 3(1). Copyright © (2007) Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.]

ADMINISTRATION OF ABATACEPT

Abatacept is given as a 30-minute intravenous (IV) infusion at a fixed dose approximating 10 mg/kg, according to weight and is administered at 2 and 4 weeks after the first infusion, and every 4 weeks thereafter (28). Pre-medication prior to the infusion is not required.

CLINICAL EFFICACY OF ABATACEPT IN INADEQUATE RESPONDERS TO TUMOR NECROSIS FACTOR-α ANTAGONIST THERAPY

Several randomized, double-blind, placebo-controlled trials have evaluated the efficacy and safety of abatacept in patients with an inadequate response to MTX, including a Phase IIb trial (37,38) and the Phase III AIM (Abatacept in Inadequate responders to MTX) trial (39). The ATTAIN (Abatacept Trial in Treatment of Anti-TNF INadequate responders) trial was the first Phase III study specifically designed to examine the efficacy of a non-TNF-α antagonist in patients with an inadequate response to TNF-α inhibition (40). This, 6-month, double-blind trial randomized and treated 258 and 133 patients with active RA who had failed at least 3 months of TNF-α antagonist therapy with etanercept, infliximab or both to receive either abatacept or placebo, respectively (40). Patients discontinued TNF-α antagonist therapy at least 28 days (etanercept) or 60 days (infliximab) prior to randomization, following which they received
abatacept or placebo in addition to at least one traditional DMARD and/or anakinra. At the time of randomization, in the abatacept and placebo groups, respectively, 38.0 and 41.4% of patients were receiving TNF-α antagonists and 62.0 and 58.6% had previously received them but were no longer receiving them at the time of randomization. For abatacept versus placebo, respectively, 32.2 versus 39.8% had received etanercept (n=136), 67.8 versus 60.2% had received infliximab (n=255) and 2.3 versus 1.5% had received adalimumab (n=8; the low number of patients treated with adalimumab was due to the fact that the study was initiated before the use of adalimumab became widespread) (40).

Patients completing the 6-month, double-blind period were eligible to enter an open-label, long-term extension (LTE) period, where all patients (placebo and active arms) received abatacept (41).

In this study, abatacept was shown to provide significant and sustained improvements in the signs and symptoms of RA and reductions in disease activity (Figures 3 and 4) (42,43). Figure 3 presents a summary of the efficacy findings for patients in this trial following 6 months of double-blind treatment with abatacept or placebo. At the end of the double-blind period (6 months), a significantly higher proportion of abatacept-treated patients achieved ACR 20, 50 and 70 responses versus placebo (Figure 3A). Efficacy benefits were observed in these patients regardless of the type and number of prior TNF-α antagonists (42,43).

The efficacy benefits for assessments of ACR, low disease activity state (LDAS) and DAS28-defined remission were maintained through 2 years of abatacept treatment (Figure 4) (41). Patients in the original placebo group, who were switched to abatacept at the end of the double-blind period, exhibited ACR response rates after 18 months of abatacept treatment that were comparable to patients treated with abatacept during both the double-blind and LTE periods (2 years) (41). Similarly, 18.9% of the patients treated continually with abatacept had achieved an MCR (ACR 70 for at least 6 consecutive months), and almost 50% had maintained their ACR 70 response for 9 consecutive months (10.6% of the total) (Figure 4) (41). When disease activity was assessed using the DAS28, the percentage of abatacept-treated patients considered to have LDAS (DAS28 ≤3.2) almost doubled from the end of the double-blind period (18.3%) to 2 years (32.0%). A similar pattern was observed with DAS28-defined remission (11.1% at 6 months and 20.3% at 2 years) (Figure 4B) (41).
Figure 4
Figure 4: Summary of efficacy through 2 years in the abatacept ATTAIN trial

A) ACR responses and B) Low disease activity (DAS28 ≤3.2) and DAS28-defined remission (DAS28 <2.6) through 2 years of abatacept treatment in the ATTAIN trial in patients with an inadequate response to TNF-α antagonist therapy. Results are based on patients with available data at the visit of interest (as-observed data).


HEALTH-RELATED QUALITY OF LIFE AND PHYSICAL FUNCTION

As noted above, multiple surveys have demonstrated the importance of issues relating to HRQoL, including physical disability, pain, fatigue and cognitive function, in patients with RA (14,44,45). Abatacept has been shown to provide clinically meaningful and statistically significant improvements in both physical and mental aspects of HRQoL in patients with an inadequate response to MTX and/or TNF-α antagonists (46-48). Abatacept is also the first biologic therapy to demonstrate significant improvements in all eight subscales of the SF-36, including both physical and mental components (38,40), in these patient populations. As with clinical responses, the ATTAIN trial demonstrated improvements in HRQoL that were either maintained or increased through 2 years of abatacept treatment (40). Clinically meaningful improvements in physical function, noted as early as the first measurement (Day 15) (40), were statistically significantly higher than placebo after 6 months (p<0.001), and were maintained through 2 years (54.4% and 47.9% at 6 months and 2 years, respectively) (40).

Several exploratory, patient-centered endpoints were included in this study (pain, fatigue [measured using a 100 mm visual analog scale] and sleep [measured using the Medical Outcomes Study-Sleep module]). These all demonstrated sustained, clinically-meaningful improvements through 2 years of abatacept treatment (41). As demonstrated with other biologic DMARDs, patients in the ATTAIN trial with less severe disease at baseline showed greater improvements in HRQoL than those with more severe disease. Findings such as these are the basis for promulgating earlier use of biologic DMARDs in the treatment of RA (38,40).

SAFETY OF ABATACEPT

Safety findings from this patient population are consistent with those observed across multiple trials of abatacept (38). In the ATTAIN trial, abatacept was shown to have acceptable safety and tolerability, with an overall frequency of AEs and serious AEs (SAEs) similar to placebo (79.5% vs 71.4%; 10.5% vs 11.3%, for abatacept vs placebo, respectively) (40). The frequency of serious infections was 2.3% with both abatacept and placebo, and no unusual or opportunistic infections were seen (40). Unlike other RA therapies
administered by IV infusion, there is no need for premedication with abatacept treatment (28). Although acute infusional events were more common in the abatacept- than the placebo-treated patients (5.0% vs 3.0%, respectively), overall frequencies were very low and most were mild or moderate in intensity (40).

**RITUXIMAB**

Rituximab is a chimeric mouse–human monoclonal antibody that selectively depletes the CD20+ peripheral B-cell subpopulation. In combination with MTX, rituximab is indicated for reducing the signs and symptoms of RA in adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonists (29).

It is now recognized that antibody-producing B cells play a significant role in the pathogenesis of RA. In addition to producing auto-antibodies, B cells function as highly efficient APCs and, like APCs, express co-stimulatory molecules (53) and secrete chemokines and cytokines (54, 55, 56, 57).

**MECHANISM OF ACTION OF RITUXIMAB**

The surface antigen, CD20, is expressed throughout B-cell differentiation, but it is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues (58). Rituximab is a genetically-engineered, chimeric, murine/human monoclonal antibody directed against CD20 (29), which selectively depletes CD20+ B cells via multiple mechanisms, including antibody-dependent cellular cytotoxicity, complement-mediated lysis and induction of apoptosis (29, 59, 60, 61). Administration of rituximab results in a rapid and sustained depletion of circulating and tissue-based B cells (62), although plasma cells and B-cell lineage are not disrupted, so serum Ig levels are generally maintained (63).

**ADMINISTRATION OF RITUXIMAB**

Rituximab is given as two, 1000mg IV infusions separated by 2 weeks, each administered over a minimum of 4 hours (29). In order to reduce the incidence and severity of infusion reactions, administration of glucocorticoids is recommended (100 mg IV methylprednisolone or equivalent 30 minutes prior to each infusion) (29). The safety, efficacy and timing of re-treatment/re-depletion are currently being investigated in controlled trials (30).

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**CLINICAL EFFICACY OF RITUXIMAB**

As with abatacept, the efficacy and safety of rituximab has been evaluated in both patients with an inadequate response to MTX (34), and in those with an inadequate response to treatment with TNF-α antagonists (35). The Phase III, 6-month REFLEX (Randomized Evaluation of Long-term Efficacy of rituximab in RA) trial evaluated the efficacy and safety of rituximab plus MTX in patients with active RA and an inadequate response to one or more TNF antagonists (36). Patients (n=520) were randomized to receive one course of IV rituximab (consisting of two infusions of 1000 mg each) or placebo, both with background MTX. After 24 weeks, the ACR 20 response rate was significantly higher for patients treated with rituximab compared with those treated with placebo (51% vs 18%, respectively; p<0.0001; Figure 5); the same was true for ACR 50 (27% vs 5%, respectively; p<0.0001) and ACR 70 (12% vs 1%, respectively; p<0.0001) (37). Beyond improvements in signs and symptoms, a significantly higher proportion of rituximab-treated patients achieved good or moderate European League Against Rheumatology responses (good response = DAS28 score <3.2 and an improvement of ≥1.2 units; moderate response= DAS28 <5.1 and an improvement of 0.6–1.2 units) compared with placebo-treated patients (Table 1; p <0.0001). A greater proportion of patients treated with rituximab were also shown to achieve LDAS compared with patients treated with placebo (Figure 5B). Sequential radiographic data from the REFLEX study showed significant reductions in joint-space narrowing versus placebo at 24 weeks (Table 1) (38).
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Figure 5
Figure 5: ACR responses in the REFLEX trial


Figure 6
Table 1: Summary of results from the REFLEX trial

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SAFETY OF RITUXIMAB

In the 6-month REFLEX trial, the overall frequency of AEs through 6 months of rituximab treatment was similar to that observed in patients receiving placebo (85% versus 88%, respectively), with SAEs reported in 7% of rituximab-treated patients and 10% of placebo patients. Infusional events (AEs reported within 24 hours of infusion) were higher with rituximab versus placebo (29% versus 23%, respectively). Acute infusional events were also observed at a higher frequency in the rituximab group versus the placebo group (23% versus 18%, respectively); however, these were shown to decrease during the second and subsequent infusions (8% versus 11%, respectively) (67). Two rituximab-treated patients experienced acute infusion reactions that were considered SAEs (anaphylaxis and hypertension) and five discontinued the study due to infusional AEs. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to infusion (29). Patients requiring close monitoring during the first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions and those with prior clinically significant cardiopulmonary AEs (67). Although serious infections were observed in a higher proportion of rituximab- versus placebo-treated patients (5.2 and 3.7 per 100 patient-years, respectively), no opportunistic infections were reported (67). In studies to date, subsequent rituximab re-treatment courses have demonstrated continued disease suppression with maintenance of a satisfactory clinical response and no evidence suggesting an increase in AEs (67-70). Studies aiming to elucidate the optimal timing of re-treatment and to evaluate the long-term safety and efficacy of long-term B-cell depletion in RA patients are ongoing.

SWITCHING WITHIN VERSUS BETWEEN CLASSES

Data from the ATTAIN and REFLEX trials provide evidence to support the benefit of switching from a TNF-α antagonist to abatacept or rituximab in this difficult-to-treat population. In addition, data from the Swiss Clinical Quality Management RA Cohort study suggest that switching to a therapy with a different mechanism of action may be more beneficial than switching to an alternative TNF-α antagonist (71). This prospective, observational study assigned 116 patients who had previously failed at least one TNF-α to either one cycle of rituximab (n=50) or a second or third alternative TNF-α antagonist (n=66) in 116 patients antagonist. At 6 months, the mean DAS28 had decreased by
-1.61 (95% confidence intervals [CI] –1.97, –1.25) in patients receiving rituximab, and -0.98 (95% CI –1.33, –0.62) in patients receiving a subsequent TNF-α antagonist (\( \alpha \)).

**CONCLUSIONS**

The introduction of biologic RA therapies has elevated the treatment goals and expectations of physicians and patients alike. While a consensus on what constitutes an inadequate response to RA therapy is still evolving, it is clear that not all patients derive an optimal benefit from their current biologic therapy. This may be a consequence of the heterogeneous nature of the inflammatory process in this disease, as well as other factors intrinsic to each individual patient. Until recently, patients with an inadequate response to TNF-α antagonists had limited treatment alternatives and no clear guidelines currently exist regarding their management. The availability of two novel biologic agents targeting alternative elements of the inflammatory cascade provides new options for these patients.

Abatacept is indicated for reducing signs and symptoms of RA, inducing an MCR, inhibiting the progression of structural damage and improving physical function. Since abatacept can be used either as monotherapy or in combination with non-biologic DMARDs in patients with an inadequate response to MTX, as well as in those with inadequate responses to TNF-α antagonist therapy, it constitutes a valuable therapeutic option that can be considered for a wide range of patients with moderate to severe RA. The approval of rituximab in combination with MTX for the treatment of patients with an inadequate response to TNF-α antagonists provides a further option for the latter group of patients.

It is likely that a number of other biologic agents to treat RA will become available over the next few years, making future treatment decisions more complex. Ultimately, the goal of RA therapy is the complete and lasting elimination of inadequate therapeutic responses. Clearly, as long as there remains a population of patients resistant to available medications, the pursuit of more effective and safer therapies is certain to continue.

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I do not hold any stock in any pharmaceutical company.

I am not applying for, nor do I hold, any patents related to the content of this manuscript. I have not received any fees or salary or reimbursements from any organization that hold patents relating to the content of this manuscript.

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