Unresolved Issues in Identifying and Overcoming Inadequate Response in Rheumatoid Arthritis: Weighing the Evidence

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ABSTRACT. Rheumatoid arthritis (RA) is a chronic, multisystem, inflammatory disorder of the joints that affects about 1% of the world population. The ultimate goals of therapy include remission of disease and prevention of joint damage. Reaching these goals has become a realistic outcome for an increasing number of patients as treatment options have expanded over the past 3 decades. In addition to older therapies, such as methotrexate (MTX), other disease modifying drugs (DMARD), and tumor necrosis factor (TNF) inhibitors, newer biologic treatments have become available. For the substantial number of patients who experience an inadequate response to standard medications, biologic response modifiers (BRM) provide an important therapeutic alternative. The availability of multiple treatment options in the absence of clear definitions or criteria for remission and inadequate response, however, makes clinical decisions about measuring outcomes, predicting response to treatment, and prescribing pharmacologic therapies challenging. In this program, distinguished rheumatologists weigh the evolving body of clinical evidence to draw sound conclusions and resolve key issues in managing inadequate response to treatment and in achieving optimal outcomes in RA. (J Rheumatol 2008;35 Suppl 81:4-30)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INADEQUATE RESPONSE DISEASE ACTIVITY INDICES TREATMENT OUTCOME

INTRODUCTION

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Methotrexate (MTX) and disease modifying antirheumatic drugs (DMARD) have revolutionized the management of rheumatoid arthritis (RA). Once limited to palliative management with cautious use of single agents, rheumatologists can now significantly reduce or halt disease progression with early aggressive treament using combination therapies and biologics (Figure 1). As the number of treatment options for RA has expanded and increased expectations for patient outcomes, however, the lack of standardized definitions and criteria for remission and inadequate response makes clinical decisions about measuring outcomes, predicting response to treatment, and prescribing pharmacologic therapies increasingly complicated. The challenges of assessing treatment response pose a significant barrier to the utilization of available therapies and hinder clinicians' ability to duplicate the tight control achieved in clinical trials[1,2].

Lack of consensus among rheumatologists and pharmacoepidemiologists about definitions of remission and inadequate response stems primarily from the complex nature of RA, with its broad spectrum of clinical presentations and variability in disease course and outcomes. Whereas other chronic conditions, such as hypertension, dyslipidemia, and diabetes, have uniform measures and widely accepted definitions and cutoffs for treatment, numerous interrelated clinical, structural, and functional factors must be considered concurrently in the management of RA[3-5]. Evaluating response to therapy involves appropriate use of outcome assessment measures, intensity of patient monitoring and treatment, awareness of potential drug toxicities and patient comorbidities, and tailoring therapy based on drug kinetics/dynamics, patient profiles, and predictors of response. The multitude of variables that influence outcomes in RA, thus, makes universally applicable definitions of remission and inadequate

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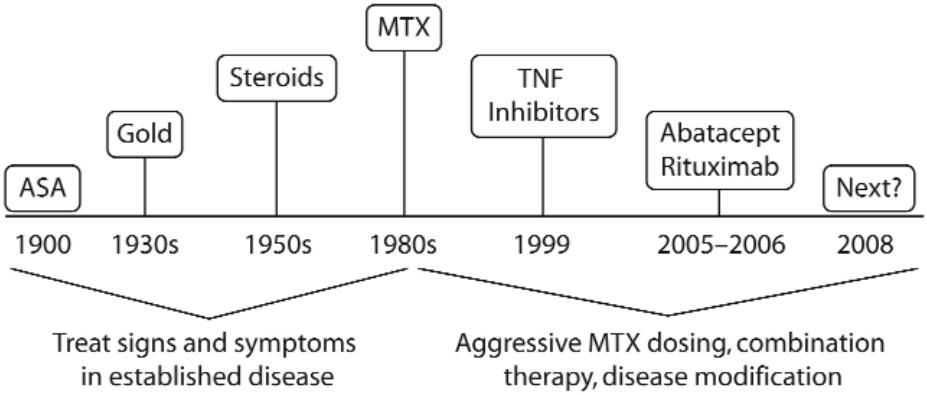


Figure 1. RA medication timeline. ASA: acetylsalicylic acid.

response challenging to formulate. Moreover, randomized clinical trials (RCT) have provided inadequate insight into the degree of treatment response that clinicians should expect in practice and how best to monitor attainment of treatment objectives. Differences in patient populations and outcome measures used in RCT versus those in clinical practice and the tendency for most practicing rheumatologists to misjudge the magnitude of response in their patients hamper the interpretation and application of results from RCT into practice. While RCT have defined the expected level of treatment response, these responses were achieved in patients with far worse disease than those seen in clinical practice, using measures of response or inadequate response that are seldom employed in practice[6]. Ambiguous parameters for inadequate response and incomplete data on therapeutic approaches taken by patients prior to trial entry also limit the extent to which results from RCT that evaluate treatment alternatives in inadequate responders to TNF inhibitors can be generalized to patients in clinical practice[7,8].

In this continuing medical education (CME) initiative, a panel of leading rheumatologists weighs the evolving body of clinical evidence to draw sound conclusions and resolve key issues in managing inadequate response to treatment and in achieving optimal outcomes in RA. The 8-member panel identified specific issues through a survey and teleconferences. A comprehensive literature review using Medline subsequently was conducted to answer specific questions about the following:

- Validated outcome measures/tools
- Predictors of response
- Overcoming inadequate response through assessment of:
  - primary and secondary response failures and withdrawal due to toxicity
  - efficacy of cycling and dose escalation
  - the role of rituximab and abatacept
- The safety of biologics

Levels of evidence were graded using the American Academy of Family Physicians' Family Physician Strength of Recommendation Taxonomy to facilitate objectivity and evidence-based conclusions[9]. The panel then convened to present and assess the data and apply their conclusions to patient case studies that typify the challenges of identifying and overcoming inadequate response currently confronting clinicians. Based on critical evaluation of the available evidence, this educational activity is intended to help rheumatologists, rheumatology fellows, and other healthcare professionals who care for patients with RA meet the educational objectives stated above.

VALIDATED OUTCOME MEASURES/TOOLS

John J. Cush, MD

Determining the appropriate goals of therapy for patients with RA and how best to assess and achieve treatment objectives is fraught with dilemmas. Remission is frequently cited as the ultimate goal of therapy; however, despite the abundance of validated outcome measures and tools available, there is no consensus on the definition of remission or minimally clinically important response. Because of a lack of clear guidelines for the use and interpretation of these measures, lingering doubts about their value in changing outcomes, and the time and expense for using them, it is not surprising that many rheumatologists forego quantitative measures in favor of qualitative assessment and clinical gestalt.

Case study. The following case study illustrates some of the complexities of assessing response to therapy. A 24-year-old Vanderbilt University student relocates and is referred to you by her rheumatologist. She was diagnosed with RA 3 years before when she presented with swollen metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints and positive rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP). She

Table 1. Case study: outcome measures from a 24-year-old woman with RA.

Measure	Therapy				
	Onset Ibuprofen	At 4 Mo Naproxen	At 12 Mo Prednisone, MTX 15	At 24 Mo Prednisone, MTX 15, ADA	Today Prednisone, MTX, ADA
TJC	9	12	3	1	
SJC	7	11	2	0	
ESR	88	79	9	2	
Pain	5	6	1	1	What
MDGA	6	8	3	1	should
PGA	6	6	2	2	be
HAQ	1.8	2.2	0.4	0.2	measured?
CDAI	28	37	10	4	
DAS28	5.64	6.01	2.93	1.07	
GAS	24	34	7	3	

reports that her deceased grandmother had severe RA. The patient's medications include MTX 15 mg weekly, folate 1 mg daily, naproxen 500 mg twice daily, and adalimumab 40 mg every other week. She feels worse since her move to the area. She hands you a table of her past outcome measures, shown in Table 1, and asks what evaluations you will use for your treatment decisions.

This case study raises the following important questions regarding the role of outcome measures and tools in assessing and managing an inadequate response in RA:

- Is the patient's current treatment regimen adequately controlling her disease?
- What are the goals of therapy for this patient, and is remission attainable?
- Which outcome measures should be performed to guide the physician's treatment decisions?
- What lessons have been learned from quantitative assessments and definitions of response/disease activity used in the context of clinical trials and/or clinical practice?
- Would using objective measurements have any significant influence on the patient's outcome?
- How is outcome affected when quantitative assessments are performed but are not used to guide treatment decisions, or when routine care is provided without the benefit of quantitative assessments compared to when outcomes are measured and used to direct RA management?

The answers to these questions remain a subject of considerable debate. Although most would agree that standardization of outcome measures facilitates the collection of conclusive, reproducible, and comparable endpoints in clinical trials, rheumatologists often settle for more subjective measures in routine practice.

A recent online survey of practice patterns among US rheumatologists determined that the majority relied heavily upon qualitative assessments (physician overall assessment, symptom review, morning stiffness, and complaint-focused joint examinations) and laboratory measures [complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hepatitis screens, antinuclear antibodies (ANA)] when assessing and treating patients with RA. In contrast, quantitative measures that comprise validated outcome tools [28 total joint count (TJC) and swollen joint count (SJC), physician and patient global assessments, functional measures] were less commonly used and ranked less important (Table 2). Radiographs were variably performed, as nearly three-quarters stated that they would take baseline radiographs, half would perform yearly hand radiographs, and one-quarter would routinely take foot radiographs. Uncommonly used measures included a scored Health Assessment Questionnaire (HAQ, 12.3%), magnetic resonance imaging (MRI, 5%–8%), joint ultrasound (1%–2%), Disease Activity Score (DAS, 6%), or an American College of Rheumatology 20% improvement (ACR20) or continuous measure of clinical improvement ACR-N outcome (1.8%)[10]. Contrary to current opinions and practices, a growing body of evidence suggests that using quantitative assessments to treat to a predefined target raises the standard of care and has a measurable positive effect on patient outcomes.

Table 2. Physician assessment of treatment response[10]. Importance ranked (1-7) from most important (1) to never important (7) (n=880).

Assessment	Weighted Importance	How Often Done?
Physician joint examination	1.69	27%
Patient assessment of response	1.88	39%
Drug tolerability	2.04	41%
MDGA	2.14	32%
Radiographic assessments	2.94	51%
ESR or CRP	3.18	68%–80%
Functional outcome measures	4.20	15%
DAS28	5.41	7%

What are the goals of therapy in RA, and is remission attainable?

National guidelines and recommendations from the US Food and Drug Administration (FDA) generally agree on the following goals of RA therapy[11-13]:

- Induce complete remission (ultimate goal)
- Alleviate pain
- Maintain function for essential activities
- Maximize quality of life
- Prevent or control joint damage

Whether remission is an attainable objective depends upon the definition of remission used. The RCT that

evaluate the efficacy of pharmacologic therapies and treatment approaches as well as prospective cohort studies have shown that remission or very low level of disease activity has become an achievable goal for a large number of patients[7,8,14-26].

In RCT evaluating the efficacy of DMARD and TNF inhibitor therapies, 25% to 46% of patients with early disease achieve remission or near-remission if ACR 70% improvement (ACR70) response or DAS-defined remissions are accepted as surrogate measures for a superlative response or remission. The FDA requires ACR70 of 6 months' duration when defining a major clinical response (Table 3)[7,8,14-22]. Patients with advanced disease experience remission less frequently, 10% to 27%, presumably from deformity, underlying joint destruction, and secondary degenerative changes[19-22]. Among patients who experience inadequate response to TNF inhibitor therapy, an additional 10% to 12% subsequently achieved remission with abatacept and rituximab, respectively[7,8]. Note that direct comparison of remission rates among different therapies is problematic because no head-to-head trials have been performed, and patient demographics and treatment dosages vary from study to study.

In a one-year followup study of 948 patients with RA who received routine clinical care, 34% to 43% of the patients had at least one remission during a visit, using the remission criteria defined by the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), DAS28, or modified ACR remission criteria (mACR). Sustained remission (remission on 2 consecutive visits) was seen in 17% to 20% of patients. Patients with SDAI and CDAI remissions had fewer residual swollen joints than those with DAS28 and mACR remissions, although the vast majority of patients overlapped among the differently defined remission criteria[23].

An overall remission rate (DAS < 1.6) of 32% at 1 year was reported in 508 patients with early RA allocated to one of 4 treatment strategies in the BeSt study (Dutch acronym for "treatment strategies"). Treatment groups included sequential monotherapy, step-up combination therapy, initial combination therapy with tapered high-dose prednisone, or initial combination therapy with infliximab[24]. During the second year of followup, 42% of patients achieved remission[24]. In the Tight Control for Rheumatoid Arthritis (TICORA) study, 65% to 71% of 111 patients with RA of less than 5 years' duration (n = 55) randomly assigned to intensive management were in remission criteria at 18 months based on European League Against Rheumatism (EULAR) remission and ACR70 response, respectively[26]. With reported remission rates in clinical trials as high as 71%, the bar for setting and meeting treatment objectives is clearly higher than ever before.

Table 3. Remission rates with DMARD and TNF inhibitors[7,8,14-22]. Approximately 12 months' treatment unless otherwise stated.

Treatment	Early RA	Advanced RA
LEF + MTX	—	10% (6 mo)
SSZ + MTX	32% (10 mo)	—
Etanercept	25%	15% (6 mo)
Etanercept + MTX	43%	27% (6 yrs)
Infliximab + MTX	33%	10%
Adalimumab + MTX	46%	23%
Abatacept + MTX	—	10% (6 mo)
Rituximab + MTX	—	12% (6 mo)

What outcome measures/tools and definitions of response/disease activity have been validated and used in the context of clinical trials and/or clinical practice?

Numerous outcome measures and tools for evaluating clinical, structural, and functional outcomes have been developed and validated. Composite measures most often used in clinical trials for quantifying disease activity and response to therapy include the ACR response and DAS. Other indices measured include the SDAI, CDAI, and Global Arthritis Score (GAS). The calculation of these indices is shown in Table 4[27-29]. Cutoffs for remission and low and high disease activity have been established for each of the composite indices with the exception of the ACR response. The ACR Guidelines for the Management of RA: 2002 Update defines complete remission as the absence of symptoms of active inflammatory joint pain,

Table 4. Calculation and criteria for disease assessment tools[27-29].

Measurement	Calculation	Remission	Low Disease Activity	High Disease Activity
ACR response	% improvement in TJC % improvement in SJC plus % improvement in 3 of the following 5 criteria: Patient's pain assessment PGA MDGA Patient self-assessment of physical function Acute-phase reactant value	ACR70	—	—
DAS28	$0.56 \times \sqrt{(TJC28)} + \sqrt{(SJC28)} + 0.70 \times \ln ESR + 0.014 \times GH$	≤ 2.6	≤ 3.2	> 5.1
SDAI	TJC(0-28) + SJC(0-28) + PGA (0-10 cm VAS) + MDGA (0-10 cm VAS) + CRP	≤ 3.3	≤ 11	> 26
CDAI	TJC(0-28) + SJC(0-28) + PGA (0-10 cm VAS) + MDGA (0-10 cm VAS)	≤ 2.8	≤ 10	> 22
GAS	Patient pain (0-10 scale) + MHAQ score (range 0-24) + TJC (0-28)	≤ 3	≤ 7	> 20

Table 5. Benefits and limitations of current validated disease indices.

Index	Benefit	Limitation
ACR	• Useful for efficacy studies in clinical trials	• Measures relative change but not disease status at a given point in time
DAS (includes ESR)	• Measures disease activity at a given point in time	• Limited usefulness in office setting unless ESR level drawn prior to office visit so ESR level is available for calculation • Complex equation used in calculation of score • Low DAS score possible with persistent symptoms
SDAI (includes CRP)	• Measures disease activity at a given point in time • Simple calculation	• Limited usefulness in office setting unless CRP level drawn prior to office visit so CRP level is available for calculation
CDAI	• Measures disease activity at a given point in time, but without CRP or ESR, negating need for previsit blood testing • Simple calculation	• Does not measure acute-phase reactants, pain, or function
GAS	• Measures disease activity at a given point in time • Simple calculation • Uses both patient and physician reported measures	• Does not measure acute-phase reactants • Limited clinician experience with new tool

morning stiffness, fatigue, synovitis on joint examination, progression of radiographic damage on sequential radiographs, and elevated ESR or CRP level[11]. The ACR70 response, which represents a major clinical improvement, is generally interpreted as a surrogate for remission or near-remission in clinical trials[13,27]. To support a claim of reduction of signs and symptoms in RA, the FDA requires a minimal clinical endpoint of ACR20[11]. As more efficacious treatment options have become available, many believe that the bar for determining efficacy should rise to an endpoint of ACR 50% improvement (ACR50).

Although generally underutilized in clinical practice, the various benefits and limitations of different composite indices favor the use of some over others in the office setting. Table 5 summarizes the relative advantages and disadvantages of composite indices. The ACR response measures the percentage of change in clinical status relative to baseline but not disease status at a given point in time, making it a better tool for clinical trials than clinical practice. The DAS measures disease activity at a given timepoint change over time[30,31]. Due to time constraints, the complexity of calculating the score, and the need for an ESR level at the time of examination, few rheumatologists use the DAS routinely[29]. The SDAI measures the same variables as the DAS but is calculated by simple addition. The CDAI is a further simplification of the SDAI and omits the CRP level[28,32]. The Global Arthritis Score (GAS) has recently been developed as an additional quantitative disease assessment tool that is simple to calculate and does not require measuring acute-phase reactants[29].

In addition to clinical and functional outcome measures, numerous methods of visualizing and scoring joint damage are currently available to evaluate disease status and response to therapy. Although the ACR guidelines advocate baseline and periodic radiographic examinations of involved joints, deliberation continues about the role of standard radiography, ultrasound, and MRI in diagnosing and managing RA and the different methods used to score them[11]. In several small studies, ultrasound has demonstrated greater sensitivity and accuracy than conventional radiography in detecting changes in joint structure and may be predictive of future damage[33-35]. MRI may have sensitivity comparable to ultrasound[34] and may allow detection of new bone erosions at least one year earlier than conventional radiography[36]. The clinical relevance of improved sensitivity of the MRI and ultrasound, however, remains unclear. In a recent report, the ACR Extremity MRI Task Force concluded that the benefit of extremity MRI in the diagnosis and management of

RA needs to be determined[11]. Issues noted included the low specificity of extremity MRI for erosion detection, questions about the correlation of MRI-detected erosions with functional decline, and lack of consensus on appropriate timing of MRI for diagnosis and management of RA.

Further confounding the role of structural measures in evaluating response to therapy is the disparity that exists between structural change seen on radiography and correlation with clinical measures. In the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO), patients treated with etanercept alone and MTX alone showed similar ACR response rates, yet significantly less radiographic progression was seen in the etanercept group[16]. Similarly, in the Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) and Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trials, clinical assessments did not correlate with radiographic changes[37]. Radiologic progression has also been demonstrated in patients in clinical remission[38]. The growth in the number of instruments developed to quantitate change in RA disease activity confirms the utility of this approach. Consensus on a tool easily used in clinical practice is presently lacking, but continued research and interest in this arena should lead to greater utilization in daily clinical practice.

What are the effects on patient outcomes when routine care is provided without the benefit of quantitative assessments versus outcomes measured and used to guide RA management?

Several studies and registries reporting outcome data on patients in conventional care versus intensive treatment that systematically assesses disease activity and response to therapy show that using outcome measures to guide treatment decisions significantly improves patients' outcomes.

In the Study of New-Onset Rheumatoid Arthritis (SONORA), which evaluated treatment patterns and clinical and health-related outcomes among 1012 patients with early RA, outcome data were collected, but physicians were free to treat routinely without a mandate to use the outcome data to inform their therapy decisions. At 2 years, only 41%, 21%, and 7% of patients achieved ACR 20/50/70, respectively[1]. As shown in Figure 2, the percentage of patients achieving ACR response in the Rheumatoid Arthritis DMARD Intervention and Utilization Study (RADIUS) registry was similarly low[39,40]. A national, prospective, observational clinical database, RADIUS, like SONORA, enrolled patients who were subsequently managed at the discretion of the treating rheumatologist based on clinical status. In addition to showing that fewer than half of patients achieved ACR20 at one year, data from RADIUS revealed that many patients were maintained on RA therapies for > 6 months despite persistence of disease activity and failure to achieve meaningful improvement in function. Of the 9873 patients in the database, 5137 (52%) remained on the same DMARD or biologic agent at 6 months and 3797 (39%) at 12 months. Of patients with > 5 TJC and > 5 SJC after 6 months of therapy, 68% continued on that same therapy for at least 6 more months (> 1 year total); mean duration on that therapy was 18 months. After 12 months of therapy, 75% remained on that treatment for another 6 months; mean duration was 23 months[2,39]. Disappointing ACR response rates and delays in changing therapies seen in routine practice may result from not using objective measures to drive treatment changes.

In a prospective cohort study of 568 patients with moderate or severe RA who received routine care, rates of change in DMARD and/or systemic corticosteroid drug or dose were also low. Over 12 months, the proportions of 377 patients with severe disease activity observed for 1-month, 2-month, and 3-month time blocks who had a change in DMARD drug or dose were 36%, 57%, and 74%, respectively. Figure 3 shows that in patients with severe disease, a change in DMARD (drug or dose) was observed in 44%, 50%, and 68% of patients within 3, 6, and 12 months, respectively. Patients with moderate synovitis had a change in DMARD in 21%, 23%, and 34% of 149 patients within 3, 6, and 12 months, respectively[41].

In contrast to the poor responses and slow rate of change in therapy observed in routine care, the use

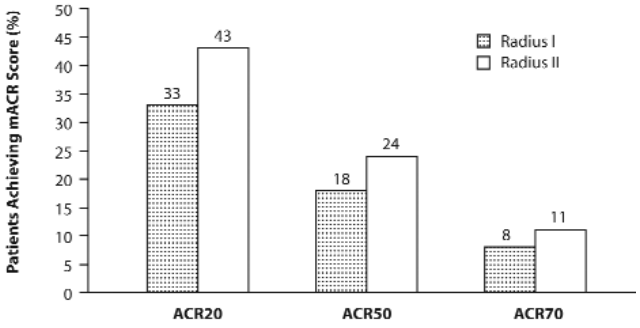


Figure 2. ACR response in RADIUS I and II[39,40].

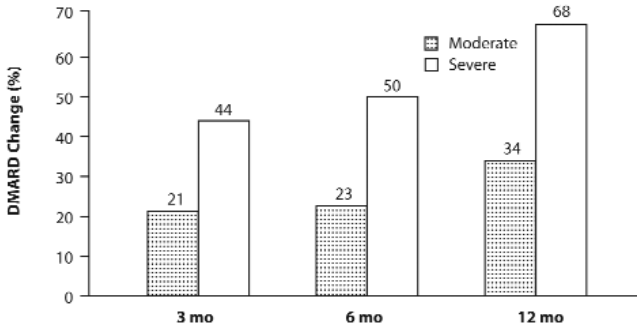
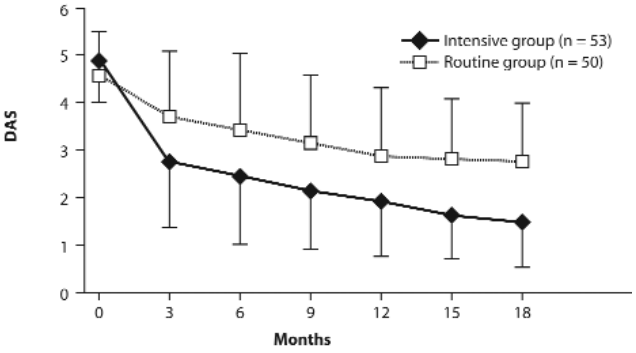


Figure 3. Pattern of DMARD change in routine practice[41].



$P < 0.0001$, intensive vs routine after 3 months.

Figure 4. Mean DAS scores in the TICORA study[26]. From Grigor, et al. Lancet 2004;364:263-9, with permission.

of composite measures to achieve tight control of disease status in RA results in better outcomes, as demonstrated in the BeSt and TICORA studies. In the BeSt trial, 32% of all patients allocated to one of 4 treatment strategies achieved remission (DAS < 1.6) during year 1, and 42% of patients in all groups were in remission during year 2. Response to therapy and corresponding treatment adjustments were made every 3 months, with a preset goal of low disease activity defined by a DAS44 of < 2.4[24,25]. In the TICORA study, patients assigned to an intensive regimen were seen monthly by the same rheumatologist versus every 3 months in the routine care group. Change in treatment for the intensive group was assessed by DAS, whereas no formal composite measure was used to assess disease activity in the routine-care group. Results demonstrated significantly greater improvement in the response-driven group as assessed by DAS than in the routine-care group both in clinical assessment and in radiographic progression (Figure 4)[26].

Verstappen and colleagues compared intensive versus conventional treatment with MTX in 301 patients with early-onset RA. In the intensive-strategy group, patients were evaluated once per month. Treatment was tailored to the individual patient, and response to therapy, aimed at remission and based on predefined criteria, was monitored using a computer program. In the conventional-strategy group, patients were evaluated once per 3 months, and treatment adjustment was based on daily practice. Forty-one percent of patients in the intensive-strategy group achieved remission for at least 6 months, compared to only 24% of patients in the conventional-strategy group[42]. While rheumatologists debate the appropriate use of outcome measures, these studies provide compelling evidence that "remission" is an achievable objective and that more patients achieve remission and low disease activity with therapy driven by preset goals and systematic monitoring of outcomes than by routine care based on standard practice.

PREDICTORS OF PROGNOSIS AND RESPONSE

Michael H. Schiff, MD

As the number of effective therapeutic options for RA increases and evidence mounts that early aggressive treatment improves outcomes, predictors of prognosis and response play an increasingly important role in improving clinicians' ability to provide timely intervention and thwart disease progression and joint damage. The following case study describes a common scenario where prognostic factors and response predictors may help determine who will benefit from therapy, how aggressively to treat, and what therapeutic approaches will result in the greatest response.

A 33-year-old Hispanic woman with early-onset RA returns to her rheumatologist for followup 5 months after starting treatment with MTX (initially taking MTX 15 mg per week for 3 mo then increased to 20 mg per week). She is feeling better and has returned to work part-time but is easily fatigued and continues to have morning stiffness that lasts about 45 minutes. Her physical examination and laboratory results reveal TJC 10, SJC 8, visual analog pain scale 31 mm, ESR 35 mm/h, DAS28 5.49, RF 175, and anti-CCP 72. The rheumatologist recommends adding a biologic response modifier (BRM). In talking with her doctor, the patient expresses concern about her prognosis and her response to the new therapy.

What factors have been shown to predict a poor prognosis?

An important window of opportunity for preventing irreversible joint destruction exists during the early stages of RA before the inflammatory process, joint inflammation, and bone loss become too great. Prompt and aggressive treatment can limit damage and functional loss and decrease mortality, especially among those at high risk for progressive, severe disease. Several patient-specific, disease-specific, and genetic factors, as shown in Figure 5, can help clinicians predict which patients will have a poor prognosis and require aggressive therapy[43,44].

Outcome studies in RA have suggested that female gender and earlier age of onset are associated with a worse prognosis for radiographic damage and disability. Other accepted patient-specific predictors of poor prognosis in RA include poverty, nonadherence to therapy, comorbidities, and smoking[44,45]. Disease-specific and genetic prognostic factors, such as joint involvement, high levels of CRP, RF positivity, and shared epitope, predicted 40% to 83% of subsequent progression in studies of radiographic progression among 50 to 200 patients with RA followed for 1 to 9 years. In studies evaluating predictors of functional disability in 65 to 720 patients with RA followed for 2 to 15 years, poor functional status at presentation was one of the best predictors of subsequent

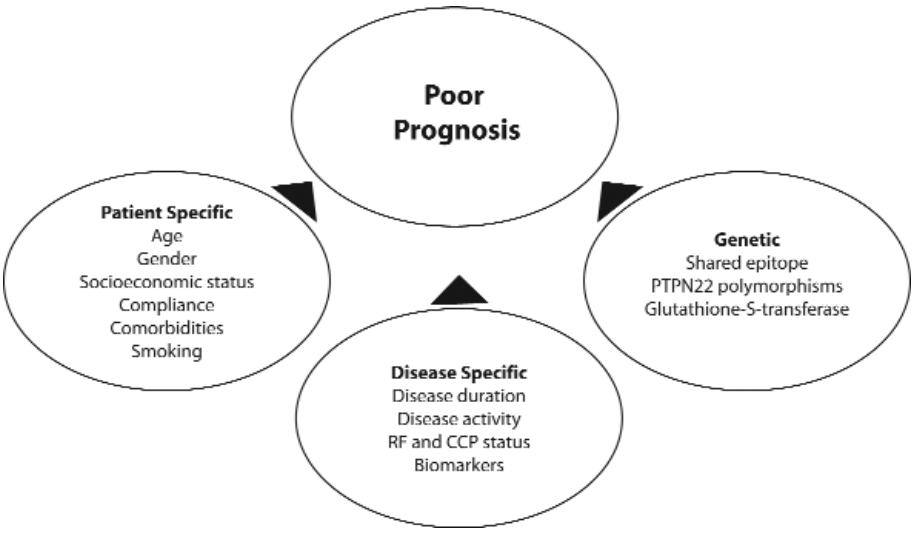


Figure 5. Predictors of poor prognosis[43,44].

outcome. RF positivity and levels of ESR and CRP predicted progression of functional disability; however, HLA-DRB and HLA-DBQ genes were not predictive of functional disability in these studies[44].

In small prospective cohort studies, high-field MRI scans performed in early RA predicted future radiographic damage. The degree of synovitis and tendinitis, as well as bone edema and erosion visible on MRI at baseline, closely correlated with the progression of joint erosions of the hands and feet as much as 6 years later. MRI scans performed at the initial presentation of RA can help predict future radiographic damage, allowing disease-modifying therapy to be targeted to patients with aggressive disease. Further, at followup, if no persistent clinical response is achieved, these imaging methods may help to predict future erosiveness and help in clinical therapeutic decision-making[46-48].

Table 6. Recent studies evaluating the prognostic value of anti-CCP[49-52].

Study	Description	Outcome
Van Gaalen, *et al* 2005[49]	467 patients with early RA; 4-year followup	CCP2 test had better diagnostic and prognostic ability than CCP1; both tests predictive of radiographic progression
Nielen, *et al* 2005[50]	379 patients with early inflammatory arthritis	Anti-CCP predictor for diagnosis of RA by ACR criteria at 1 year; predictor of radiographic progression at 2 years
Kastbom, *et al* 2004[51]	242 patients with early RA; 3-year followup	Anti-CCP and RF predictive of persistent disease; anti-CCP superior to RF
Rönnelid, *et al* 2005[52]	279 patients with RA; 1-year followup	Anti-CCP predictive of erosive disease

In recent years, the anti-CCP antibody assay has also emerged as a useful diagnostic and prognostic tool. Elevated anti-CCP antibody levels have been shown to be a highly specific marker of RA, with more sensitivity than RF in early disease, and to correlate with a worse prognosis, especially with more severe radiographic damage over time. A positive result prior to or at the onset of RA increases the likelihood of developing erosions and is associated with poorer radiographic outcome. Studies show that patients with levels greater than 50 U/ml are at increased risk for developing severe extraarticular manifestations[49-52]. Table 6 summarizes recent studies evaluating the prognostic value of anti-CCP.

What factors have been shown to predict response to therapy?

The reasons some patients respond to one treatment but not to another are not fully understood; however, heterogeneity in drug response likely results from a combination of individual patient factors (genetic and environmental) and disease-specific factors. The data on predictors of response to various RA therapies are limited but emerging. Potential predictors of response to therapy include both laboratory and clinical measures, many of which have overlapping diagnostic and prognostic value.

The role of pharmacogenomics in predicting prognosis and response to therapy represents a growing area of interest. The prognostic value of TNF polymorphism is an example of the clinically relevant information emerging from genomics research. Evaluating the association between TNF polymorphism and disease activity variables in 190 patients with early RA, researchers have determined that significantly higher progression rates in joint space narrowing score and total Sharp score occur in

patients with –308 TNFA AA+AG genotypes compared to patients with the TNFA GG genotype. Patients with the AA+AG genotypes compared to the GG genotype also show a trend for a higher erosion score progression rate[53]. Documentation of this observation in a larger patient cohort will be necessary before this finding has clinical application, but genetic biomarkers clearly hold great promise in enhancing targeted therapeutics in RA.

Another study of 457 patients with early RA treated with MTX or etanercept examined the roles of specific genetic polymorphisms of the shared epitope as predictors of therapeutic response. The presence of 2 HLA-DRB1 alleles encoding the shared epitope was associated with response to etanercept with an odds ratio of 4.3 (95% confidence interval, CI, 1.8 to 10.3)[54]. Genetic variation in TNF may be linked to response to TNF inhibitor therapy. In a study of 59 patients with refractory RA treated with infliximab, significant clinical improvement was associated with a specific phenotype of the TNF-308 SNP (single nucleotide polymorphism) region. Other genes in addition to those encoding TNF may be involved in response to therapy with TNF inhibitors[55].

In the ASPIRE study of patients with early RA, high CRP level, high ESR, or persistent disease activity predicted greater radiographic progression in the patients treated with MTX alone[56]. There was less radiographic progression in the group treated with MTX plus infliximab despite the abnormal level of these predictors. Thus, patients with an increased acute-phase response and/or greater radiographic evidence of joint damage may be candidates for early introduction of combination therapy with MTX and infliximab. In a study of patients with RA resistant to treatment who were started on infliximab, failure to suppress CRP at 2 weeks after initiation of therapy identified the majority of nonresponders at 12 weeks and also was associated with a good clinical response on switching to etanercept[57].

In addition to its role in predicting poor prognosis, studies have demonstrated that anti-CCP antibodies and the presence of RF may predict response to biologic therapy. In a study involving 90 patients with RA who failed treatment with DMARD, adding etanercept therapy led to a much greater decrease than DMARD alone in the serum levels of anti-CCP and RF, compatible with a reduction in clinical disease activity[58]. Several studies also have demonstrated an association between anti-CCP titer and response to infliximab therapy. A study of 30 patients with seropositive RA treated with infliximab showed significant correlation between clinical response to infliximab therapy and anti-CCP titer[59]. In contrast, anti-CCP titer remained stable, whereas RF significantly decreased in patients with refractory RA who were treated with infliximab plus MTX[60,61]. Preliminary information from the Randomized Evaluation of Long-Term Efficacy of Rituximab in RA (REFLEX) study shows that patients who were seronegative for RF and anti-CCP at baseline achieved lower ACR responses than seropositive patients[8]. Ongoing studies involving larger numbers of patients are necessary to confirm this observation.

Development of autoantibodies may herald loss of efficacy and thus serve as a predictor of response. In a prospective analysis of 26 consecutive patients with RA who were treated with infliximab, the appearance of ANA, anti-dsDNA, IgM and IgG anticentromere antibodies, and antihistone antibodies seemed to predict cessation of treatment[62]. In a prospective study of 42 patients followed for 12 months, "development of IgG and IgE antibodies against infliximab corresponded with inadequate response to treatment (IgG antibodies) and also with development of infusion reactions (IgG and IgE)" in patients with RA treated with infliximab[63]. Among 71 patients with active RA treated with adalimumab, human antihumanized antibodies (HAHA) to adalimumab were present in 8% and were related to a higher disease activity. To prevent the formation of antibodies it was important also to administer MTX[64]. A temporal relationship between clinical relapse and elevations in antidrug antibodies was observed with rituximab[65].

Although data continue to emerge on predictors of response, these factors along with prognostic factors serve an important function in individualizing pharmacologic therapy. Future advances in gene profiling should enhance the ability to properly target therapies. This approach to RA management will ensure a safer and more efficacious application of treatment options.

OVERCOMING INADEQUATE RESPONSE

RA remains an incurable disease; however, improving outcomes and inducing remission have become attainable goals for many patients. Biologic treatments that operate upstream of cytokine-targeted agents provide additional treatment alternatives to patients who have an inadequate response to existing DMARD and TNF inhibitors. The most recent additions to the armamentarium of RA therapies include abatacept, a costimulation modulator approved by the FDA in December 2005 for the treatment of moderately to severely active RA in adults who have had an inadequate response to one or more DMARD; and rituximab, a B cell-depleting therapy approved in February 2006 in combination with MTX for the treatment of moderately to severely active RA in adults who have had an inadequate response to one or more TNF inhibitor therapies[66,67]. The approval of rituximab and abatacept has led to a reevaluation of the previously used treatment strategies. In the past, when faced with a patient who did not respond to TNF inhibitor therapy as expected, such as the one described

in the case study below, the only options for rheumatologists were to increase the dose of the drug or to switch to another TNF inhibitor. This was done despite a lack of controlled studies on the efficacy and safety of dose escalation and switching. Now clinicians also must determine whether changing biologic therapy is an appropriate option and which agent will be safest and most efficacious. Treatment decisions depend on carefully weighing the therapy's indications, mechanism of action, effects on immune system components, side effect profiles, and the risk-benefit of switching within a drug class.

A 55-year-old retired college professor with RA for 9 years was poorly controlled taking DMARD monotherapy until starting MTX and infliximab 2 years ago. Over the past 2 visits, his RA has worsened. At this visit, he reports morning stiffness that lasts about 90 minutes, and has a TJC of 8, SJC 5, ESR 44 mm/h, and DAS 5.1. His history is significant for hypertension, gastroesophageal reflux, and carpal tunnel syndrome. He is currently taking MTX 20 mg per week, infliximab 400 mg every 8 weeks (4.1 mg/kg), folate 1 mg daily, and metoprolol 50 mg daily.

This case study raises the following important questions:

- At what point should this patient's therapy have been considered inadequate?
- How is inadequate response defined?
- What percentage of patients experience a primary or secondary inadequate response to TNF inhibitors, abatacept, or rituximab or discontinue therapy as a result of toxicity?
- What are his treatment options following an inadequate response to a single TNF inhibitor?
- Should the physician increase the infliximab dose or frequency, switch to a therapy with another TNF inhibitor, such as etanercept or adalimumab, or change to another BRM, such as rituximab or abatacept?
- What is the rationale for rituximab or rituximab therapy in patients who are resistant to DMARD and other biologic therapies (e.g., mechanism of action, advantages over other biologics)?
- What are the effects of abatacept in patients who have an inadequate response to MTX or TNF inhibitors?

Primary and Secondary Response Failures and Withdrawal due to Toxicity

Arthur L. Weaver, MD

How is inadequate response defined?

Defining an inadequate response to therapy remains an open and difficult dilemma. Where best to draw the line on inadequate response along the spectrum of potential treatment responses, from complete disease remission to total treatment failure, is difficult to establish, especially given the absence of a clear criterion and definition for remission.

An inadequate response can be defined as any response that falls short of remission (i.e., failure to achieve low disease activity by clinical measurements, failure to stop radiographic progression despite low disease activity) or more broadly defined as any response that leads to a change in or the discontinuation of a treatment. Three scenarios that can lead to termination of therapy include (1) the absence or unacceptable level of any therapeutic benefit once a treatment is initiated (primary inadequate response), (2) diminution of efficacy over time upon initial success of treatment (secondary inadequate response), and (3) development of toxicities or adverse events that necessitate termination of therapy. The term "inadequate" response or "incomplete" response is preferable to treatment "failure," as very few patients demonstrate no response to therapy. Due to the increased potential for achieving remission afforded by the current treatments for RA, many regard the threshold for inadequate response as a response that falls short of remission or good response as defined by various composite indices.

Adding to the complexity of defining an inadequate response to therapy is the disconnection between clinical and radiographic responses. As the TICORA study demonstrated, radiographic progression can occur despite significant clinical improvement with conventional DMARD (Figure 6). Patients allocated to intensive therapy in the TICORA study had a reduction in erosion score progression and total Sharp scores, but there was no difference in joint space narrowing progression[26].

What percentages of patients experience a primary or secondary nonresponse to TNF inhibitors, abatacept, or rituximab or discontinue therapy as a result of toxicity?

Although treatment options for RA have expanded considerably over the past few decades, making remission a realistic goal for many, RA remains an incurable disease with a significant number of patients who experience an inadequate response to available therapies. The percentage of patients who do not have an adequate response to RA therapy varies depending upon the definition of inadequate response used; however, it is significantly higher in the "real world" clinical practice setting, where composite indices are seldom measured and rheumatologists tend to misjudge the magnitude of response to therapy and undertreat, compared to the backdrop of highly structured clinical trials. As previously described, the SONORA study showed that only 7% of patients who received routine care achieved an ACR70 response at 2 years. Using failure to achieve ACR70 as a surrogate for inadequate response,

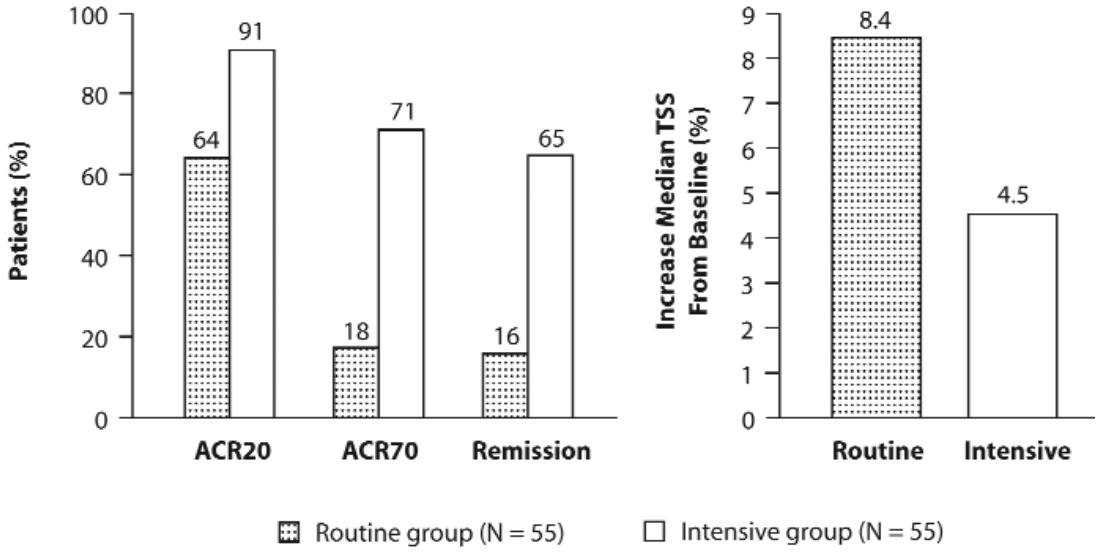


Figure 6. Radiographic progression despite clinical improvement in the TICORA study[26]. TSS: total Sharp score.

93% of these patients would be considered inadequate responders. The percentages of patients receiving traditional DMARD versus biologic DMARD in the SONORA study were 78% and 20%, respectively[1]. Similarly, in RADIUS I and II, 92% and 89% of patients failed to achieve modified ACR70 response, respectively[39,40]. In the DANBIO registry, which includes data from 417 consecutive patients with RA who received TNF inhibitor therapy, primarily infliximab, only 15% to 20% of patients at each visit, from 6 weeks onward, were in clinical remission, and 10% to 15% had low disease activity, based on DAS28 scores[68]. Overall, using an ACR70 as a surrogate measure, about 80% to 90% of patients who received routine care in the SONORA and RADIUS studies and 70% of patients receiving TNF inhibitors in the DANBIO registry experienced a primary inadequate response to therapy[1,39,40,68].

Based on RCT data, response rates of ACR20, 50, and 70 for TNF inhibitors + MTX and abatacept + MTX are about 40% to 77%, 21% to 55%, and 8% to 29%, respectively, in patients naïve to biologic therapies. Thus, 71% to 92% of patients failed to achieve remission defined as ACR70 as above (Figure 7)[21,69-72]. In the TICORA study, tight control resulted in ACR70 or EULAR remission in 65% to 71% of patients, which translates into an inadequate response in 29% to 35% of patients[26]. Among patients treated with rituximab + MTX and abatacept + MTX following an inadequate response to TNF inhibitor therapy, ACR20, 50, 70 response rates are about 50%, 20%, 10%, respectively[7,8].

Data on the rate of primary versus secondary inadequate response to BRM and termination of therapy due to toxicity are limited, as RCT often do not delineate between patients who have never displayed a response to treatment versus those who lost their initial response. Moreover, while safety findings are discussed, data on the number of patients who terminate therapy as a result of toxicity are often omitted. Information from treatment registries and studies evaluating switching between TNF inhibitors (also discussed in the subsequent section on cycling and dose escalation) has provided some insight. In the Dutch Rheumatoid Arthritis Anti-TNF-α Monitoring (DREAM) registry, one-year survival rates of TNF inhibitor therapy ranged from 59% to 80% and 2-year survival percentages were 49% to 74%. Lack of efficacy was the reason for discontinuation of treatment for 35% of all patients (percentages of primary vs secondary nonresponse were not noted) and the occurrence of adverse events was the reason in 42% of patients. No significant differences were noted between the different TNF inhibitors concerning the reasons for stopping treatment[73]. In a study of the longterm, survival, effectiveness, and safety of TNF inhibitor therapy in 501 patients with RA, overall drug survival rates were 64%, 42%, and 34% after 1, 2, and 3 years. Drug survival was best for adalimumab, whereas infliximab showed a higher discontinuation rate due to adverse events, and etanercept tended to have a higher discontinuation rate due to ineffectiveness[74]. Among 84 patients with an inadequate response to infliximab enrolled in the EMBARK study, 19% had a primary inadequate response and 81% had a secondary loss of response[75]. Buch and colleagues reported a secondary nonresponse and toxicity to infliximab therapy in 38 and 23 patients, respectively, among 95 consecutive patients who experienced an inadequate response to infliximab therapy[76].

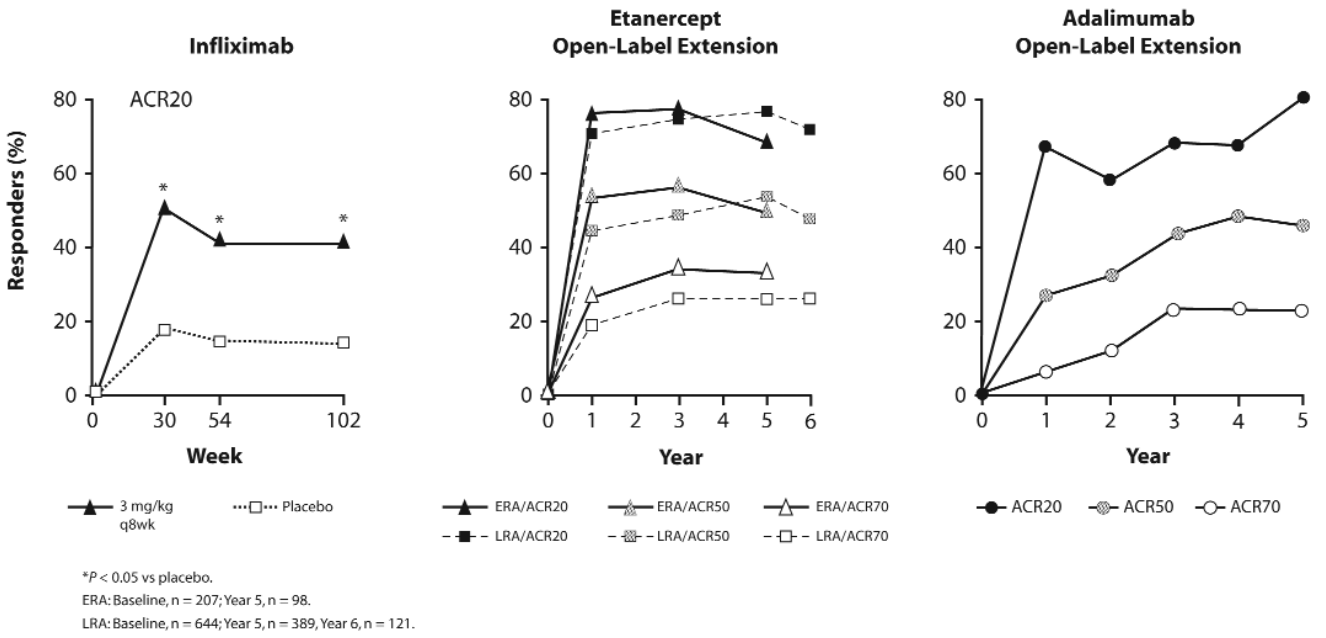


Figure 7. ACR responses in randomized controlled trials[21, 69-72]. ERA: early RA; LRA: late-stage RA.

What are the treatment options for patients who experience an inadequate response to BRM?

Additionally, one could recycle DMARD as monotherapy or combination therapy, utilize nonapproved immunomodulators such as cyclosporine, or if available, experimental therapies.

A recent report suggested that a switch to rituximab in patients failing TNF inhibitors was more effective than switching to another TNF inhibitor. This prospective cohort study by Finckh and colleagues involved 116 patients with RA[77]. Among these, 50 patients received one cycle of rituximab, and 66 patients received a second or a third TNF inhibitor. Evolution of the DAS28 was more favorable in the group that received rituximab compared with the group that received an alternative TNF inhibitor. At 6 months, the mean decrease in the DAS28 was 1.61 among patients receiving rituximab and 0.98 among those receiving subsequent TNF inhibitor therapy. Corroborating this report from an observational registry with other independent studies may change present treatment strategies[77].

The efficacy of these treatment options is discussed in the subsequent sections.

Cycling and Dose Escalation

Marc D. Cohen, MD

What is the safety and efficacy of switching to a second or third TNF inhibitor in patients who experience a primary or secondary response failure or toxicity to treatment with etanercept, infliximab, or adalimumab?

It is difficult to draw conclusions based on the currently available data on switching within class. To date, no large prospective randomized studies have been conducted to guide switching within class or to elucidate a specific order for using available treatments that will improve efficacy and safety when switching. Several small, uncontrolled studies have examined switching among the 3 currently approved TNF inhibitors[78-82]. In these studies, switching was initiated either because of inadequate response to therapy or occurrence of side effects. In a study assessing switching between etanercept and infliximab, improvement was more marked when the reason for switching was secondary failure or side effects rather than primary treatment failure[83]. Information from the Stockholm Tumor Necrosis Factor-α Follow-up Registry database (STURE) shows that patients with inadequate response to etanercept achieve considerable gain upon switching to infliximab[78]. Patients with secondary loss of efficacy to infliximab or etanercept benefited from switching to adalimumab as measured by DAS[81]. Solau-Gervais and colleagues assessed the potential benefits of switching to a third TNF inhibitor[84]. In this 364-patient cohort study, 28% of patients failed the first TNF inhibitor. Upon switching to a second TNF inhibitor, almost half achieved a good response as measured by DAS28. Among those who failed a second TNF inhibitor, 35% discontinued the third TNF inhibitor due to lack of efficacy. Data from

Table 7. Small open-label studies evaluating the efficacy of switching TNF inhibitors[75,76,87,88].

Name/Study Design	Number of Biologic Patients	Duration of Study	Reason for Switch	Response	Abstract
EMBARK/ Prospective open label observational	84 infliximab switched to etanercept	8 wks	Primary NR and secondary NR/LOE	"Preliminary results suggest that some infliximab failures may respond to etanercept"	Bingham, *et al*, Ann Rheum Dis 2005; 64 Suppl 3:172.
Prospective open label observational	95 infliximab switched to etanercept	12 wks	Primary NR and secondary NR/LOE	• 42% ACR20, 30% ACR50, 15% ACR70 (primary infliximab failures) • 34% ACR20, 21% ACR50, 14% ACR70 (secondary infliximab failures)	Buch, *et al*, Arthritis Rheum 2007;57:448-53.
ReACT/ Prospective open label observational	71 infliximab switched to adalimumab, 32 etanercept switched to adalimumab	12 wks	Secondary NR or LOE	• 63% ACR20, 35% ACR50, 12% ACR70 (prior biologic—infliximab) • 52% ACR20, 30% ACR50, 11% ACR70 (prior biologic—etanercept)	Burmester, *et al*, Ann Rheum Dis 2005; 64 Suppl 3:423.
Prospective open label observational	25 infliximab switched to etanercept	22 patients completed 3 mo	LOE	• 64% ACR20, 23% ACR50, 5% ACR70	Haraoui, *et al*, J Rheumatol 2004;31:2356-9.

the Swiss Clinical Quality Management of RA system follow all patients with RA who are treated with TNF inhibitors. The data show that previous failure of the first TNF inhibitor increases the rate of drug discontinuation of the second agent by 77%. Interestingly, this study also suggests a differential acquired drug-resistance among TNF inhibitors in RA. Infliximab was associated with a higher risk of intensification of DMARD therapy than other TNF inhibitors and a significant dose escalation over time[85]. A retrospective review of pharmacy and medical records at infusion centers of the US Brigham and Women's Hospital found that 48% of patients treated with infliximab discontinued therapy during the first year and 67% of patients treated with infliximab withdrew overall[86]. Table 7 shows information about additional small open-label studies evaluating the efficacy of switching TNF inhibitors[75,76,87,88]; however, more controlled trials are needed to determine which patients would benefit from switching and which clinical situations would warrant switching. The data demonstrate that patients failing TNF inhibitors may respond to a switch to a different TNF inhibitor. There are no mechanistic data to explain this phenomenon to date. Additionally, survival on subsequent TNF inhibitors seems less than the initial therapy, which suggests these patients may represent a more resistant population.

Does treatment escalation, via a decrease in the interval between infusions and/or an increase in the dose at each infusion, result in a better clinical outcome for patients treated with TNF inhibitors, abatacept, or rituximab?

A recent systematic review of 15 studies including 8483 patients evaluated the frequency and effectiveness of dose escalation (Table 8). Among infliximab patients, 53.2% underwent dose escalation. Forty-four percent of the

Table 8. Dose escalation in patients treated with infliximab or etanercept (from Ariza-Ariza, *et al*[89]. Rheumatology Oxford 2007;46:529-32, with permission).

	Patients, n	Dose Escalation/*n* % (95% CI)	Days to Dose Escalation	Dose Increase/*n* % (95% CI)	Decreased Interval/*n* % (95% CI)	Effectiveness
Infliximab	5862	2716/5099 53.2 (51.9–54)	128–254	1957/4445 44 (42.6–45.5)	175/2106 8.3 (7.2–9.6)	ACR20: 27%–36% ACR20: 13% DAS28:–0.46, –0.66
Etanercept	2621	435/2493 17.4 (16–19)	123	435/2493 17.5 (16–19)	—	—

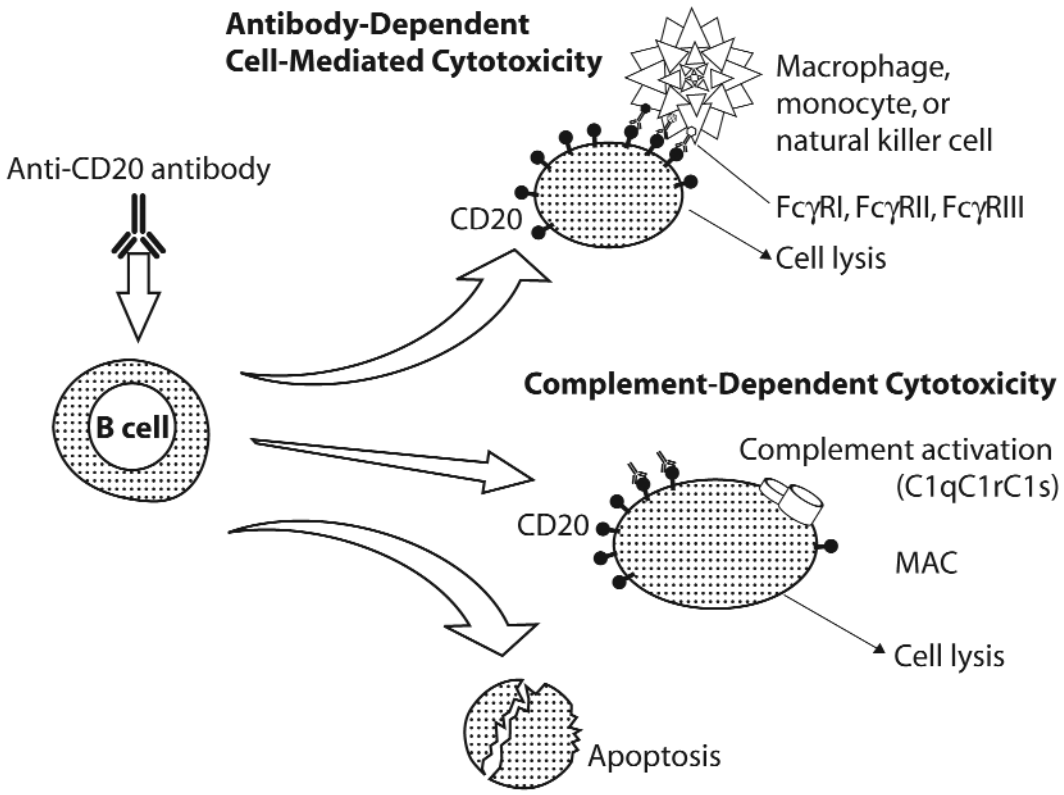


Figure 8. Mechanism of action of rituximab[93-98].

infliximab patients experienced dose increase and 8.3% experienced frequency increase. The ACR20 response to dose escalation range was 27% to 36%, and DAS28 improvement was 5.2 to 4.5 in one study and 4.1 to 3.7 in another study. Of the etanercept patients, 17.5% experienced a dose increase, but changes in the mean dose were not statistically significant. The study concluded that dose escalation was common in patients treated with infliximab and less frequent with etanercept. In a proportion of patients, the dose escalation seemed effective[89].

Rituximab

Philip J. Mease, MD

What is the rationale for rituximab therapy in patients who are resistant to DMARD and other biologic therapies (e.g., mechanism of action, advantages over other biologics)?

Rituximab is a chimeric IgG1 monoclonal antibody that specifically targets the CD20 surface antigen expressed on the cell surface of certain preplasma cell stages of B cell development. Selective B cell depletion through antibody-dependent and complement-dependent cell lysis occurs as a result of binding to CD20[90,91]. B cell depletion is believed to disrupt the many B cell functions that contribute to the pathogenesis of RA (Figure 8)[92-98].

Preclinical studies have helped elucidate the role of B cells in RA. Lund and colleagues have shown that B cells regulate antibody-independent mechanisms of RA pathogenesis, such as the production of proinflammatory cytokines[92]. B cells are also present in antigens and produce autoantibodies required for the induction of severe autoimmune arthritis in mice[99]. Takemura and other researchers have shown that B cell depletion results in disruption of germinal center architecture (with implication for less efficient antigen presentation), decreased overall inflammatory cellularity, decreased T cell number and activation, and reduction of proinflammatory cytokines in a severe combined immunodeficiency (SCID) mouse/human RA synovial tissue model[100].

What are the effects of rituximab in patients who have an inadequate response to MTX or TNF inhibitors?

Table 9. Rituximab clinical trials.

Study	N	Population	Treatment	Duration
Phase IIa study Edwards, *et al* 2004[101]	161	Active RA and failed ≥ 1 but < 5 DMARD (other than MTX)	Oral MTX (control) or RTX (1000 mg on days 1 and 15) or RTX + CTX (750 mg on days 3 and 17) or RTX + MTX	11 mo
DANCER (Phase IIb study) Emery, *et al* 2006[102]	465	Active RA and inadequate response to MTX	9 treatment arms in multifactorial 3 × 3 configuration: RTX (placebo, 500 mg, 1000 mg) given on days 1 and 15 with 1 of 3 glucocorticoid options: placebo, methylprednisolone 100 mg IV × 2 or 100 mg IV × 2 + 60 mg/day oral prednisone on days 2–7 + 30 mg/day oral prednisone on days 8–14	6 mo
REFLEX Cohen, *et al* 2006[8]	520	Active RA and inadequate response to one or more TNF inhibitors	RTX 1000 mg or placebo on days 1 and 15 plus background MTX	6 mo

Three randomized controlled clinical trials, a Phase II study of rituximab alone or added to cyclophosphamide or MTX, and the Dose-Ranging Assessment International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) and REFLEX studies evaluated the efficacy of rituximab (Table 9)[8,101-103].

The phase II study was a one-year trial evaluating the safety and efficacy of rituximab in patients with active RA who had failed at least one but less than 5 DMARD (other than MTX)[101]. One hundred sixty-one patients were randomly assigned to one of 4 treatment regimens: oral MTX (> 10 mg per week; control); rituximab (1000 mg on days 1 and 15); rituximab plus cyclophosphamide (rituximab 1000 mg and cyclophosphamide 750 mg on days 3 and 17); or rituximab plus MTX. At baseline, participants had long-standing (9–12 mean yrs) and highly active disease as shown by a high number of mean swollen and tender joints (19–23 and 32–34, respectively), elevated levels of acute-phase reactants, and a high mean DAS28 score (6.8–6.9). At week 24, rituximab plus MTX and rituximab plus cyclophosphamide treatment resulted in a significantly greater proportion of patients who reached the primary endpoint of the study, ACR50 (43%, $p = 0.005$; 41%, $p = 0.005$, respectively). All ACR responses were maintained at week 48 in the rituximab plus MTX group. In addition, 83% to 85% of patients treated with rituximab had a moderate or good response according to EULAR criteria, compared with 50% in the control group ($p < 0.004$). The results from this study show that significant and longterm improvement in disease symptoms can be achieved with a single short course of 2 infusions of rituximab given either alone or in combination with continuing MTX or cyclophosphamide.

By showing significant efficacy of rituximab in treating patients with moderate to severe RA who had failed prior treatment with one or more DMARD (including biologics) and were inadequately responding to MTX, the DANCER trial further confirmed the results of the phase II study[102]. This dose-ranging trial, the largest trial of rituximab in RA to date, randomly assigned 465 patients to 9 treatment arms in a multifactorial 3×3 configuration. Patients received rituximab (500 mg or 1000 mg) or placebo on days 1 and 15 plus one of 3 glucocorticoid options. Patients also received one of 3 glucocorticoid treatments in addition to the study drug: placebo, methylprednisolone 100 mg IV ×2, or 100 mg IV ×2 + prednisone 60 mg/day orally on days 2 to 7 + 30 mg/day on days 8 to 14.

Of the 376 RF-positive patients who comprised the primary intention-to-treat (ITT) efficacy population, significant improvement in ACR20/50/70, EULAR "good" responses, and change in DAS28 scores were observed at week 24 in those who received rituximab along with background MTX compared to placebo. Overall, both doses of rituximab provided rapid relief to approximately twice as many patients or more compared to placebo and showed a trend, albeit not statistically different, toward greater frequency of achievement of ACR70 or EULAR "good" responses in the 1000-mg dose arm. Thus both doses of rituximab demonstrated similar efficacy[102]. Based on a logistic regression model with rituximab and glucocorticoids as the main-effect factors, analysis of ACR20 response rate at week 24 showed that rituximab was highly effective ($p < 0.0001$)

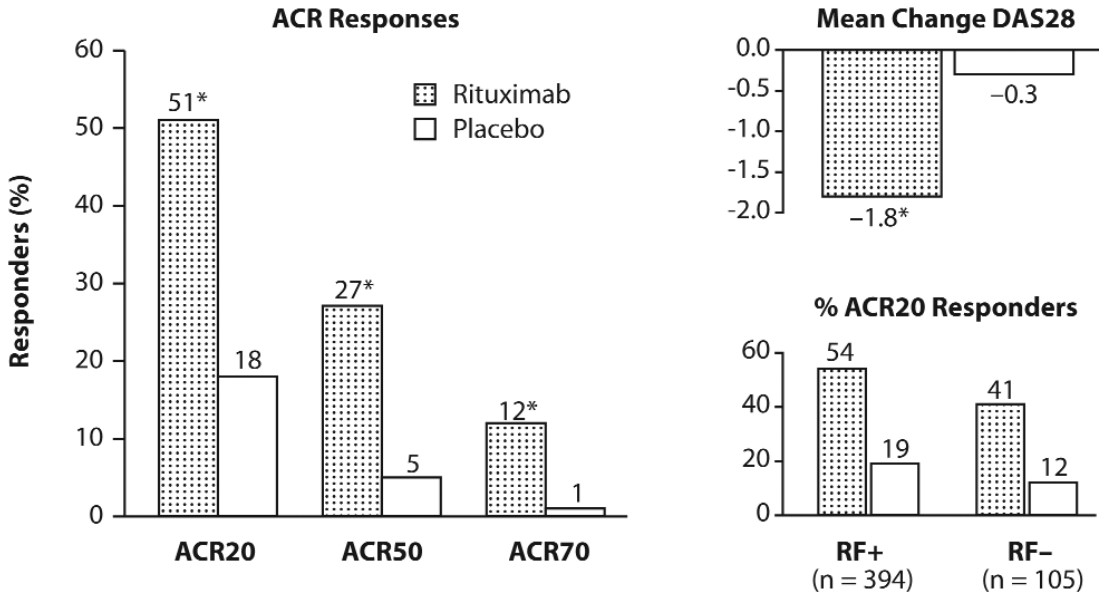


Figure 9. Clinical response at 24 weeks[8,105]. *P<0.0001.

and, further, that the addition of glucocorticoids conferred no additional efficacy benefit (p = 0.17)[103].

The REFLEX study provides additional evidence to support the efficacy of rituximab in providing statistically significant and clinically meaningful improvement in the signs and symptoms of RA[8]. The study enrolled 520 patients with long-standing and highly active RA who experienced an inadequate response to one or more TNF inhibitors and had active disease despite ongoing treatment with MTX and a TNF inhibitor. Two hundred one patients were randomly assigned to placebo and 298 to rituximab 1000 mg (given by intravenous infusion on days 1 and 15), among the 499 patients included in the ITT analysis. All patients were maintained on background MTX (10–25 mg/wk)[8,104].

Analysis of the primary efficacy parameter showed that a significantly higher proportion of patients achieved an ACR20 response at week 24 following treatment with rituximab in combination with MTX than with MTX monotherapy (51% vs 18%; p < 0.0001). ACR50/70, EULAR responses, and change in DAS28 were also achieved by a greater proportion of patients in the rituximab cohort. Figure 9 shows the ACR and DAS28 responses at week 24. These efficacy results correlated with improvements in patient-reported outcomes, as measured by HAQ Disability Index (HAQ-DI), Medical Outcome Study Short-Form 36 (SF-36), and Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F)[8,104,105].

The efficacy and safety of retreatment with rituximab after disease recurrence following initial response has been evaluated in patients from the phase IIa and phase IIb DANCER and phase III REFLEX trials of rituximab who were retreated after 24 weeks. In general, response to a second course of treatment was as good as or better than response to the first course. ACR responses for the first course were ACR20 65%, ACR50 33%, ACR70 12%, and for the second course of treatment, ACR20 72%, ACR50 42%, ACR70 21%. The median time to subsequent treatment course was 30.9 weeks between the first and second treatment course and 30.1 weeks between the second and third course[106]. Infusion reactions decreased in subsequent treatment courses, and the incidence of serious infections per 100 patient-years did not significantly increase through course 3. This study suggests that patients with initial response to rituximab are likely to respond again after disease activity returns and have a similar safety experience through course 3[106-108].

Abatacept

Lee S. Simon, MD

What is the rationale for abatacept therapy in patients who are resistant to DMARD and other biologic therapies (e.g., mechanisms of action, advantages over other biologics)?

Abatacept, the first in a new class of agents known as costimulation modulators, binds to CD80 and CD86 on antigen-presenting cells (APC; e.g., B cells, dendritic cells, and macrophages) to prevent them from joining with CD28 on T lymphocytes. In the process of blocking CD28 engagement, abatacept prevents positive costimulation signals required for full T cell activation. This is

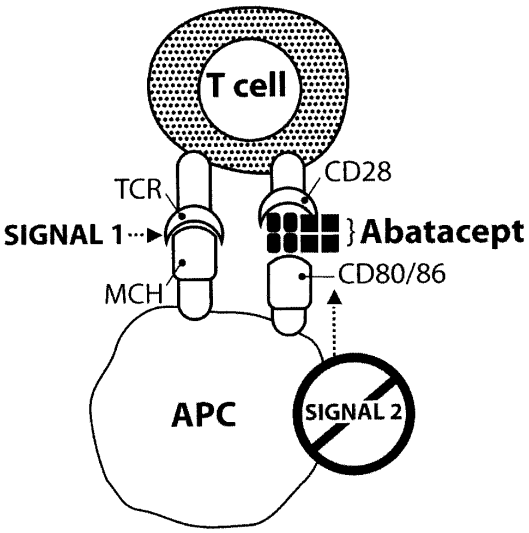


Figure 10. Mechanism of action of the costimulation-modulating agent abatacept[109,110]. Abatacept prevents CD28 from binding to CD80 and CD86, resulting in suppression of T-cell proliferation and cytokine production. TCR: T cell receptor.

thought to prevent the stimulation of T cell effector functions in response to autoantigen exposure and inhibit proliferation of autoreactive T cells in RA[66] (Figure 10) illustrates the mechanism of action of abatacept[109-110].

Animal studies of T cell-mediated diseases, including RA, have demonstrated that modulating T cell activation reduces disease severity[111-113]. An *in vitro* lymphocyte activation model in which human T cells were stimulated with APC and antigen also demonstrated that abatacept exposure suppresses T cell proliferation and significantly reduces the release of interleukin 2 (IL-2), TNF-α, and interferon-γ (IFN-γ) by T cells[66,109].

What are the effects of abatacept in patients who have an inadequate response to MTX or TNF inhibitor therapy?

In addition to the Abatacept Study of Safety in Use with Other RA Therapies (ASSURE), which evaluated the longterm safety of abatacept, 4 double-blind, placebo-controlled trials have been conducted to study the safety and efficacy of abatacept in patients with RA[7,114-118]. The approved indication of abatacept for the treatment of adults with moderately to severely active RA who have had an inadequate response to one or more DMARD is primarily supported by studies conducted in inadequate responders to MTX and inadequate responders to TNF inhibitor therapy[66]. Table 10 summarizes these studies.

Initial evidence of the efficacy of abatacept in RA came from a pilot study of abatacept versus placebo, which was primarily designed to evaluate safety and tolerability[115]. Patients with active disease who were refractory to treatment with at least one DMARD (N = 214) were randomly assigned to one of 3 doses of abatacept (0.5, 2, or 10 mg/kg) or placebo. Evaluation at 3 months revealed a clear, dose-dependent increase in the ACR20 response (23%, 44%, and 53% of abatacept-treated patients at 0.5, 2, and 10 mg/kg, respectively, vs 31% of placebo-treated patients).

A phase IIb study of the efficacy of abatacept versus placebo was subsequently conducted to evaluate the safety and efficacy of abatacept in 339 patients with active RA who had an inadequate response to MTX[116-119]. Baseline characteristics of the participants included a mean duration of disease activity of 9 to 10 years, approximately 28 to 30 tender and 20 to 22 swollen joints, and RF positivity in the majority of patients (76%–86%). During the 12-month study, patients were randomly assigned to receive abatacept (2 mg/kg or 10 mg/kg) or placebo while continuing to take background MTX. The study reported significantly greater achievement of ACR20 response in patients allocated to abatacept 10 mg/kg (n = 115) compared with patients receiving placebo (n = 119) [$p < 0.001$ at 6 months (primary efficacy endpoint) and $p < 0.001$ at 12 months]. This response became significant by day 60 and was maintained through 1 year. Patients who received abatacept 2 mg/kg (n = 105) showed an increased likelihood of achieving ACR20 response; however, the difference between the low-dose and placebo groups did not reach statistical significance. A significantly great proportion of patients achieved ACR50 (42% vs 20%; $p < 0.001$) and ACR70 responses (21% vs 8%; $p < 0.003$), disease remission (defined as a DAS28 < 2.6; 35% vs 10%; $p < 0.001$), and improvement in physical function assessed by the Modified HAQ (50% vs 28%; $p < 0.001$). Overall, the phase IIb study established the efficacy of the 10 mg/kg abatacept dose and showed that abatacept and background MTX resulted in significant reductions in disease activity, and improvements in physical function that were maintained over the course of the study.

The AIM trial further confirmed the efficacy of abatacept in inadequate responders to MTX[117-121]. Patients in the AIM study remained on background MTX and received either treatment with abatacept 10 mg/kg (n = 433) or placebo (n = 218). The study had 3 co-primary endpoints: ACR20 response at 6 months, HAQ response at 12 months, and change in joint erosion score at 12 months. Secondary endpoints included ACR50 and ACR70 response, change in DAS28, and improvement in health-related quality of life, as measured with the Medical Outcome Study Short-Form 36. Patients had a mean duration of RA of about 9 years and high degree of baseline disease activity based on the mean number of tender joints (31–32), swollen joints (21–22), and DAS28 (CRP) score (6.8). Baseline radiographic total scores for structural damage were also consistent with moderate disease (31.65–33.35) and 79% to 82% were RF-positive at baseline.

Table 10. Abatacept clinical trials.

Study	N	Population	Treatment	Duration
Phase IIa study Moreland, *et al* 2002[115]	214	Active RA and inadequate response to ≥ 1 DMARD	Abatacept (0.5, 2, or 10 mg/kg) vs placebo	3 mo
Phase IIb study Kremer, *et al* 2005[116]	339	Active RA and inadequate response to MTX	Abatacept 2 or 10 mg/kg + MTX vs placebo + MTX	12 mo
AIM Steinfeld, *et al* 2005[117] Westhovens, *et al* 2005[118]	652	Active RA and inadequate response to MTX	Abatacept 10 mg/kg + MTX vs placebo + MTX	12 mo
ATTAIN Genovese, *et al* 2005[7]	391	Active RA and inadequate response to TNF inhibitor therapy	Abatacept 10 mg/kg vs placebo	6 mo

Patients allocated to abatacept demonstrated significantly greater ACR20 (73% vs 40%; $p < 0.001$), ACR50 ($p < 0.001$), and ACR70 ($p < 0.001$) response rates and improvement in ACR components than placebo. More patients in the abatacept than in the placebo treatment group also maintained ACR70 response over a continuous 6-month period (14% vs 2%; $p < 0.001$) at 1 year. A greater proportion of patients in the abatacept cohort versus placebo had clinically meaningful improvement in physical function (> 0.3 units) in HAQ-DI compared with placebo (64% vs 39%; $p < 0.001$). Comparison of the mean change from baseline and distribution of changes in structural damage progression between the treatment groups was statistically significant in favor of abatacept for erosions ($p = 0.029$), joint space narrowing ($p = 0.009$), and total score ($p = 0.012$).

The ATTAIN study was conducted to determine whether abatacept could serve as a treatment alternative for patients with RA who have an inadequate or unsustained response to TNF inhibitor therapy[7,119]. Patients with active RA who had an inadequate response to infliximab or etanercept, despite at least 3 months of therapy, were randomly assigned to receive abatacept 10 mg/kg (n = 258) or placebo (n = 133) in addition to at least one DMARD. At baseline, most patients had long-standing (11 to 12 yrs' duration) RF-positive (73%) RA and a high level of disease activity as determined by a high mean number of tender joints (31–33), swollen joints (22), HAQ-DI scores of 1.8, CRP of 4.0 to 5.0 mg/dl, and DAS28 scores of 6.5. As shown in Figure 11, the proportion of patients achieving an ACR20 response at 6 months (primary endpoint) was 50.4% in the abatacept treatment group versus 19.5% in the placebo group ($p < 0.001$). Similarly, the ACR50 and ACR70 responses were significantly higher in the abatacept group compared with the placebo group (20.3% vs 3.8%, $p < 0.001$ and 10.2% vs 1.5%, $p = 0.003$, respectively). Consistent with improvements assessed by the ACR variables, more patients receiving abatacept had clinically meaningful improvement in DAS28 score (> 1.2) versus patients receiving placebo (65% vs 32%; $p < 0.001$). Improvement in physical function (HAQ-DI > 0.3 units) also was greater in the treatment group compared with the placebo group (47.3% vs 23.3%; $p < 0.001$), and abatacept was significantly more effective than placebo in improving all 8 domains of the SF-36.

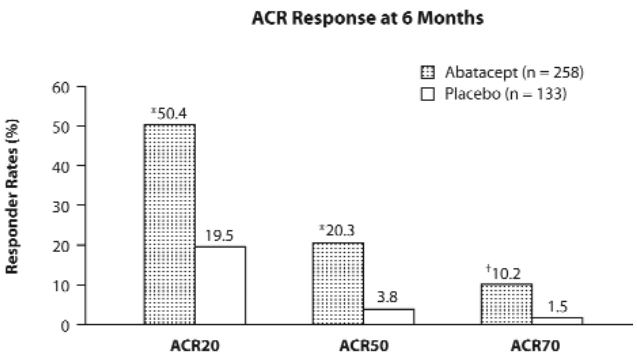


Figure 11. ATTAIN ACR results at 6 months. From Genovese, et al. N Engl J Med 2005;353;1114-23, with permission[7]. *p<0.001 vs placebo; †p=0.003.

The clinical trials of abatacept provide a substantial body of evidence to support the efficacy of the costimulation modulator in patients who inadequately respond to treatment with MTX or other biologics. In each of the 3 principal efficacy studies, abatacept demonstrated consistent and statistically significant effects on all primary and secondary endpoints. Clinicians must weigh the benefits of abatacept therapy against the potential risks as described in the safety section.

What are the effects of abatacept in patients concurrently treated with another biologic?

In an integrated safety analysis of abatacept that included 2944 patients, there was an increased frequency of infections in patients treated concurrently with abatacept and a biologic therapy[122]. Concurrent therapy of abatacept with a TNF inhibitor, therefore, is not recommended.

SAFETY OF BIOLOGICS

Roy M. Fleischmann, MD

When prescribing BRM, clinicians must weigh the benefits of therapy compared with the potential risks and consider the risks of progressive joint destruction, disability, and increased mortality associated with untreated RA versus the potential safety hazards of biologic therapies. The following case study emphasizes the types of safety considerations needed when choosing an appropriate treatment regimen.

A 28-year-old registered nurse who works in an acute care hospital has recently developed pain, stiffness, and swelling of multiple joints including her elbows, wrists, MCP, proximal interphalangeal joints, knees, ankles, and feet. She was in a motor vehicle accident at age 18 and received 4 units of blood. She also has a history of asthma and smokes 10 cigarettes per day. Her laboratory findings include a normal complete blood count, alanine aminotransferase (ALT) 64 IU/l (normal < 50 IU/l), aspartate aminotransferase (AST) 62 IU/l (normal < 50 IU/l), serum glucose 192 mg/dl, ESR 48 mm/h, RF 462 IU/ml, anti-CCP 342 IU/ml, and hepatitis C positive. A purified protein derivative (PPD) skin test shows > 20 mm induration, and her chest radiography reveals apical granulomas. She has a strong family history of breast and colon cancer as well as atherosclerotic heart disease. On physical examination she has a blood pressure of 144/100 mm Hg, extensive synovitis of the joints in which she has symptoms, wheezing on pulmonary auscultation, and an open ulcer on the plantar aspect of her right third MTP joint.

This case study raises the following questions:

- What safety considerations should be weighed in the decision to prescribe biologic therapies?
- Based on the safety profile of the different biologic therapies, which therapies should be avoided given the patient's history of presumed hepatitis C, asthma, probable diabetes, possible tuberculosis (TB), family history of cancer and hypertension, and an open skin wound?
- What are the differences in safety profile among TNF inhibitors, anakinra, abatacept, and rituximab?
- What screening tests should be performed before initiating treatment with a BRM?

What safety considerations should be weighed in the decision to prescribe biologic therapies, and what are the differences in safety profile among TNF inhibitors, anakinra, abatacept, and rituximab?

Cessation of therapy due to drug toxicity effectively constitutes an inadequate response necessitating change in treatment. The known risks of biologic therapies that can result in termination of therapy include infection, malignancy/lymphoma, skin or infusion reactions, lack of safety in pregnancy, cardiovascular risks, hepatotoxicity, and demyelination (Table 11). The literature suggests that patients with RA are also at a greater a priori risk of bacterial infections, independent of treatment, which may be increased by disease duration, disease severity, and the presence of inflammation[123-126]. The potential risks, however, do not increase over time, and the benefits of treatment generally outweigh the risks. Patients with RA need treatment in an evidence-based manner and in accordance with national guidelines, with vigilant monitoring for potential adverse events. Awareness of safety issues with biologic therapies, appropriate screening prior to initiating treatment, and individualized treatment based on the safety profile of different therapies

Table 11. Safety issues with biological response modifiers.

Infection
• Nonserious (regulatory-defined)
• Serious
• Opportunistic
• TB
• Opportunistic infections (pneumocystis, atypical TB, histoplasmosis, listeriosis, aspergillosis, coccidiomycosis, cytomegalovirus, candidiasis, cryptococcosis, nocardiosis, toxoplasmosis)
Reduced/delayed response to vaccinations (hepatitis C, influenza vaccine, pneumococcal vaccine)
Malignancy
• Lymphoma
• Lung cancer
• Melanoma and nonmelanoma skin cancers
• History of malignancy
Skin or infusion reaction
Safety in pregnancy
Cardiovascular effects
• Heart failure
• Reduced cardiovascular risk of myocardial infarction and stroke
Chronic obstructive pulmonary disease exacerbation
Hepatotoxicity
• Hepatitis B and C
• Reversible elevated liver enzymes
• Rare autoimmune hepatitis
Demyelination
Effect of antichimeric and antihuman antibodies
Immunoglobulin deficiency

and the patient's risk for developing adverse events can help to minimize the potential risks of therapy.

The effects of biologic therapies on the immune system raise the risk of infection. Table 12 summarizes data on infections and serious infectious events (SIE) observed in clinical trials[66,67,122,127-130]. While the overall risk of serious infections, defined as an infection requiring hospitalization or treatment with parenteral antibiotics, is low, there is a higher frequency in patients with comorbidities, disability, and concomitant medications, especially corticosteroids[123,131,132]. Similarly to TNF inhibitors, anakinra, and abatacept, the overall incidence of SIE in rituximab in RA clinical trials of this agent was 2% compared to 1% for placebo[102].

Opportunistic infections reported in clinical trials and postmarketing surveillance of biologic agents include atypical TB, pneumocystis, histoplasmosis, listeriosis, aspergillosis, coccidiomycosis, cytomegalovirus, candidiasis, cryptococcosis, nocardiosis, and toxoplasmosis[133]. Patients with RA have an estimated 2-fold increased risk for TB and a 4-fold magnification of this risk if treated with a TNF inhibitor. There are no reports about TB with anakinra, abatacept, or rituximab[134]. Infliximab has the greatest number of reported TB cases, attributed to a number of factors, including the use of infliximab in Europe, where the endemic TB rate is greater, as well as pharmacokinetic, pharmacodynamic, and structural differences among the TNF inhibitors that are not yet fully understood. The clinical presentation of TB in these patients is frequently atypical, in that 50% present with extrapulmonary disease and 25% with disseminated disease[135].

In patients with RA compared to the general population, an increased rate of lymphoma, skin cancer, and possibly lung cancer occurs. An analysis of incident cases of cancer among 13,001 subjects in a study of RA outcomes revealed that rates of melanoma and nonmelanoma skin cancers were higher in biologic users compared to nonbiologic users, but not in solid tumors and lymphoproliferative malignancies[136]. A recent metaanalysis of an RCT of infliximab and adalimumab cited a 3.3 odds ratio for malignancy (95% CI 1.2–9.1). The metaanalysis did not separate lymphomas from solid malignancies, however[137]. Overall, the rate of solid malignancies in patients treated with TNF inhibitor therapy is comparable to that of the general population, and lymphomas occur at the increased rate expected in patients with active, inflammatory RA. Information on malignancies with rituximab is not available, although lymphoma is not expected in patients treated with rituximab. The overall frequency of malignancies between abatacept and placebo is similar; however, there is an increased number of lung cancer cases in the clinical trials of patients treated with abatacept compared to the other biologics, but not compared to the overall population of patients with RA[66].

Infusion reactions have been reported with infliximab, abatacept, and rituximab, while skin reactions have been reported in association with the subcutaneous administration of anakinra, adalimumab, and etanercept. Table 13 lists the incidences of administration reactions and consequent withdrawal from therapy reported in clinical trials. In general, the majority of infusion reactions with rituximab and infliximab are mild to moderate in severity and are easily managed. Although the infusion reactions are clearly of more concern than the skin reactions observed with the subcutaneous injections, very few patients discontinue therapy as a result of reactions to drug administration[66,67,127-130,138].

Table 12. Infections and serious infectious events (SIE) observed in clinical trials[66,67,122,127-130].

	ETN	IFX	ADA	ANA	RTX	ABA
Infections*	38.0%	36.0%	51.9%	39.0%	39.0%	54.0%
SIE*	1.0%	5.3%	1.3%	1.8%	2.0%	3.0%
SIE per patient-year	0.04	0.06	0.04	0.06	0.05	0.05

* Incidence of infections and serious infections equal to placebo.

Table 13. The incidences of administration reactions and consequent withdrawal from therapy reported in randomized clinical trials[66,67,127-130].

	ETN	INF	ADA	ANA	RTX	ABA
Incidence, %	37	20	20	71	26 (1) 10 (2)	? (but low)
Withdrawn, %	?	3	?	6	1	? (but low)

During pregnancy, BRM are contraindicated[66,67,129-132]. The FDA classifies anticytokine therapies as pregnancy category B, meaning that animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies in pregnant women; however, there are limited postmarketing data available. A total of 35 pregnancies reported in the British Society for Rheumatology Biologics Register includes 11,473 patients using TNF inhibitors; three-quarters (72%) are women. All patients discontinued TNF inhibitor therapy after confirmation of pregnancy. Among patients directly exposed to treatment, there were no major congenital malformations or evidence of maternal harm, and the rate of miscarriages was consistent with the expected background population rate, estimated to approach 30%[139]. The Spanish registry for adverse events of biological therapies in rheumatic diseases (BIOBADASER) of patients treated with TNF inhibitors reported a total of 14 pregnancies in 13 women. Seven patients had RA, 4 had juvenile idiopathic arthritis, and 2 had psoriatic arthritis. Four patients were treated with infliximab, 8 with etanercept, and 2 with adalimumab. There were 7 live births without complications, 1 miscarriage, and 3 therapeutic abortions. Two pregnancies had no outcome data reported, and one was in the 20th week. The authors concluded that treatment with TNF inhibitors was not teratogenic[140]. The OTIS Autoimmune Diseases in Pregnancy Project reported a total of 6 pregnancies in patients with RA treated with adalimumab. All 6 pregnancies resulted in live births with no major structural abnormalities[141].

Researchers indicate that cardiovascular disease is an extraarticular complication of RA. One study with etanercept and one with infliximab demonstrated either no benefit (etanercept) or increased mortality in patients with class III and IV congestive heart failure. The FDA MedWatch has reported cases of heart failure (HF) after therapy with a TNF inhibitor (n = 47). Overall, the prevalence of HF and the number of persons exposed to TNF inhibitor therapy is 2% among those aged 40 to 59 and 5% among those aged 60 to 69[142]. In contrast to the risk of HF with TNF inhibitor therapies, differences in the rate of myocardial infarction and cerebrovascular accidents between patients taking traditional DMARD versus TNF inhibitors suggest that anti-TNF treatment reduces cardiovascular risk by lessening the inflammatory burden[143].

With regard to hepatotoxicity, clinical trial data suggest that mild and reversible elevation of liver enzymes is common with infliximab and less so with adalimumab but not with other agents in the same class. Postmarketing reports describe rare forms of serious hepatic toxicity with all agents, but most frequently with infliximab. While multiple confounders exist, there are reports of rare cases of serious and life-threatening autoimmune hepatitis[144]. Investigators have questioned the safety of using TNF inhibitor agents in patients with active hepatitis C. An open-label study evaluating the efficacy of etanercept in patients with RA and hepatitis C suggests that etanercept may be beneficial and, by implication, safe to use in treating patients with hepatitis C[144].

In some cases of immunosuppressed patients, hepatitis C reactivation has occurred, usually 15 to 60 days after stopping treatment. Rare cases of hepatitis have been reported in patients treated with infliximab. Possible clinical considerations for patients with active hepatitis B include pretreatment with lamivudine and frequent monitoring of hepatitis B virus-DNA (HBV-DNA) and ALT levels[144]. Because of reports of fatal reactivation of hepatitis B in patients with lymphoma treated with rituximab, patients with evidence of hepatitis B should not use rituximab[67].

Patients with RA treated with TNF inhibitors have experienced demyelinating diseases, including cases of new and relapsing multiple sclerosis and optic neuritis. Table 14 shows cases of demyelination reported in clinical trials and postmarketing surveillance of adalimumab, etanercept, and infliximab[133,145].

This brief review of the risks associated with BRM has discussed the safety profile of different classes of anticytokine therapies. Table 15 provides an additional overview of the differences in safety issues among the various biologic agents[66,67,129-132].

Human antichimeric antibodies (HACA) and HAHA had effects in patients who are treated for RA. In patients who develop HACA to infliximab, reduction in efficacy has been reported. Additionally, although few patients with HACA develop an infusion reaction, this is more likely to happen in patients who do develop HACA versus those who do not[146].

Table 14. Cases of demyelination reported in clinical trials and postmarketing surveillance of adalimumab, etanercept, and infliximab in RA[133,145].

Adalimumab 2334 in clinical trials	Etanercept 180,000 in clinical trials, extension, and postmarketing studies	Infliximab 170,000 in clinical trials, extension, and postmarketing studies
3 cases of demyelinating diseases	18 cases of demyelinating diseases	19 cases of demyelinating diseases
1 case of optic neuritis	14 cases of new definite/probable MS	3 relapses of existing MS
1 case of paresthesia with abnormal MRI	4 cases of MS relapse	3 cases of new MS
1 case of lower extremity numbness	7 cases of optic neuritis	5 optic neuritis
2 of 3 cases resolved completely	Other cases including myelitis, paresthesia	8 other
1 has residual leg numbness	4 cases resolved completely, 4 lost to followup	

Table 15. Overview of differences in safety issues among the various biologic response modifiers[66,67,127-130].

Issue	TNF Inhibitor	Anti-IL-1	Anti-CD80/86	Anti-CD20
Infection	✓	✓	✓	✓
SIE	✓	✓	✓	✓
Opportunistic infection	✓	✓	ND	ND
Increased malignancy	Skin	Skin	Skin Lung ND	ND
Lymphoma	ND	ND	ND	No
Skin/infusion reaction	✓	✓	✓	✓
Safety in pregnancy	ND	ND	ND	ND
CHF	✓	No	No	No
Hepatotoxicity	✓	No	No	No
Use in hepatitis C	✓	ND	ND	ND
Demyelination	Yes	No	No	No
Other issues*	No	No	No	✓
Can combine biologics	No	No	No	ND

* Decreased lg, PML, etc. ND: not determined.

With adalimumab, HAHA have developed in 12% of patients not treated with concomitant MTX and in 1% of patients who are treated with concomitant MTX. The development of HAHA in patients treated with adalimumab relates to a decreased efficacy but not with an increase in adverse events[66,147]. With rituximab, HACA occurred in 9.2% of patients. The development of HACA does not seem to affect either safety or efficacy[148]. Etanercept, anakinra, and abatacept show no association with the development of neutralizing antibodies.

Rituximab is the only currently approved biologic that affects B cells. Administration of rituximab results in virtual elimination of peripheral CD20 B cells. With repeated treatments (up to 7 courses), 24.7% of patients developed low IgM levels, and 6.3% developed low IgG levels, and the incidence of decreased immunoglobulins lessened with repeated therapy. Although the rate of SIE per 100 patient-years in patients with low IgG and IgM levels was comparable to that in patients with normal IgG and IgM levels, the percentage was higher in these patients (12.3% in patients with low IgM vs 9.9% in patients with normal IgM; and 17.9% in patients with low IgG vs 9.9% in patients with normal IgG). In patients in the lowest quartiles of IgG levels there were 109 infections per 100 patient-years versus 63 infections in patients in the highest quartile of IgG. The rate of SIE in patients in the lowest quartile per 100 patient-years was 6.8 versus 5.0 in patients in the highest quartile[149]. If there is continued decrease of IgG levels over repeated courses, SIE may be a serious concern in this group of patients. For this reason, the practicing rheumatologist may want to monitor immunoglobulin levels in patients who are treated with repeat courses of rituximab.

As there is a virtual elimination of peripheral CD20 cells that persists for months after therapy, the safety of treating a patient with another biologic, such as a TNF inhibitor, anakinra, or abatacept, in the face of B cell depletion is in question. To date, there is no complete answer. In a subanalysis of the clinical trials of rituximab, 78 patients who had withdrawn from rituximab studies and subsequently received one or more TNF inhibitors had a low overall incidence of adverse events. The rate of serious infections was consistent with the rate reported for *de novo* use of TNF inhibitors in patients with RA (6.39 events/100 patient-years) despite the fact that peripheral B cell levels were below the lower limit of normal[150]. This open-label, *post hoc* analysis needs many more patients who are treated for longer periods in a more structured study to answer this very important question.

What screening tests should clinicians perform before initiating biologic therapy?

In addition to a careful history and physical examination to assess a patient's risks or adverse effects, clinicians should consider the following screening tests prior to instituting treatment with a BRM. The ACR also advocates periodic evaluation for toxicity during treatment with all pharmacologic therapies[11], as follows.

Complete physical examination
Laboratory tests
- Complete blood count
- Liver function
- Renal function
- Screen for hepatitis B and C
- Screen for HIV
- Consider ANA, anti-DNA, antiphospholipid antibodies
- Pregnancy

Chest radiography
All necessary vaccinations

CONCLUSION

Stanley B. Cohen, MD

Significant advances in the treatment of RA over the past several years have made remission an achievable goal for a large number of patients. Widespread use of MTX, a cornerstone of treatment as monotherapy or in combination with other traditional DMARD, has yielded improved clinical outcomes in patients with RA. The use of biologic agents has further enhanced efficacy, although about 36% of patients treated with TNF inhibitors discontinue therapy after 1 year[74]. Rituximab and abatacept provide important treatment alternatives to patients who have an inadequate response to standard therapies, and these agents can induce subsequent remission in an additional 10% to 12% of patients[7,8]. To achieve the best possible outcomes with currently available therapies, rheumatologists must recognize deficiencies in RA care. The potential to attain remission or significantly ameliorate disease progression with tight control is not fully realized, due in part to the many unanswered questions surrounding identifying and overcoming inadequate response. This review of the evidence provided the following insights into the issues rheumatologists face in helping patients overcome inadequate response and achieve optimal outcomes:

- Treatment options for RA have expanded considerably and make remission and low disease activity an achievable goal for a large number of patients
- Depending on the definition of remission used, as many as 71% of patients have been shown to achieve remission in RCT. In prospective studies of patients managed with routine care, however, remission rates are significantly lower and physicians are considerably less likely to change patients' treatment regimens despite a high level of disease activity
- Routine use of outcome measures/tools to monitor attainment of predefined treatment objectives greatly improves patient outcomes compared to routine care
- Predictors of prognosis and response can further enhance individualization of care by helping to identify patients at greatest risk for severe progressive disease and may determine to which drugs individual patients will most or least likely respond
- Development of standardized definitions of remission and inadequate response is necessary to help physicians determine when a change in treatment regimen is required
- Limited but emerging support exists for the efficacy of cycling TNF inhibitor therapies and dose escalation. Patients who experience an inadequate response to therapy can subsequently achieve a good response by increasing the drug dose or frequency or by switching to a second or third TNF inhibitor
- A number of RCT have established the safety and efficacy of rituximab and abatacept. These agents have unique mechanisms of action that operate upstream of cytokine-targeted agents to provide additional treatment alternatives to patients who have an inadequate response to DMARD and TNF inhibitors
- It is important to weigh the benefits of biologics compared with the potential risks and to consider the competing risk of joint destruction, disability, and increased mortality associated with RA versus potential safety hazards of biologic therapies.

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