Aggressive Treatment of Early Rheumatoid Arthritis: Recognizing the Window of Opportunity and Treating to Target Goals

Beth H. Resman-Targoff, PharmD, FCCP, and Marco P. Cicero, PhD

Abstract

Evidence supports the use of aggressive therapy for patients with early rheumatoid arthritis (RA). Clinical outcomes in patients with early RA can improve with a treat-to-target approach that sets the goal at disease remission. The current selection of antirheumatic therapies, including conventional and biologic disease-modifying antirheumatic drugs (DMARDs), has made disease remission a realistic target for patients with early RA. The challenge is selecting the optimal antirheumatic drug or combination of drugs for initial and subsequent therapy to balance the clinical benefits, risks, and economic considerations. In some cases, the use of biologic agents as part of the treatment regimen has shown superior results compared with conventional DMARDs alone in halting the progression of disease, especially in reducing radiographic damage. However, the use of biologic agents as initial therapy is challenged by cost-effectiveness analyses, which favor the use of conventional DMARDs. The use of biologic agents may be justified in certain patients with poor prognostic factors or those who experience an inadequate response to conventional DMARDs as a means to slow or halt disease progression and its associated disability. In these cases, the higher cost of treatment with biologic agents may be offset by decreased societal costs, such as lost work productivity, and increased health-related quality of life. Further research is needed to understand optimal strategies for balancing costs, benefits, and risks of antirheumatic drugs. Some key questions are (1) when biologic agents are appropriate for initial therapy, and (2) when to conclude that response to conventional DMARDs is inadequate and biologic agents should be initiated.

(Am J Manag Care. 2010;16:S249-S258)

For author information and disclosures, see end of text.

Introduction

The management of rheumatoid arthritis (RA) has undergone a paradigm shift in the past 15 to 20 years. Factors contributing to this include changes in treatment strategies and the development of antirheumatic biologic agents that down-regulate aspects of the host inflammatory response. In light of these advancements, recent updates have been made by leading organizations regarding clinical recommendations for the use of conventional and biologic agents for treating RA, and criteria for the classification of early RA.[1,2]

Contemporary approaches to the diagnosis and management of RA have made disease remission an attainable goal for some patients. Disease remission can prolong the health-related quality of life while reducing the long-term societal costs of RA. However, it is important for clinicians to incorporate economic considerations when deciding management approaches that can help optimize outcomes for patients with RA.

This review discusses the latest evidence-based approaches supporting aggressive treatment of early RA as a means to achieve optimal outcomes and reduce the clinical and economic burden of this disease.

Progression of RA

RA is a heterogeneous disease that can lead to severe joint damage and disability. Disease progression can vary greatly among patients, and predicting outcomes in patients with RA can be critical in selecting optimal management strategies. Studies have attempted to identify prognostic factors for progression of disease, with notable factors including the baseline radiographic score, erythrocyte sedimentation rate, C-reactive protein (CRP), and the presence of rheumatoid factor (RF) and anti-citrullinated protein antibody.[3-5] The presence of risk factors can aid clinical decision-making. For patients predicted to be at high risk for rapid radiographic progression of disease, the use of more aggressive initial therapy, followed by a more rapid advancement of their regimen, would be justified.[5] Conversely, for patients at lower risk, a less expensive, less rigorous treatment strategy could be considered.

A growing body of evidence is demonstrating that early therapeutic interventions can lead to greater improvement in clinical outcomes and greater reduction in joint damage and disability. Unfortunately, active therapy for early RA is often delayed, which can have long-term

consequences in disease progression. A report from the Early Rheumatoid Arthritis Network showed that the median time from onset of symptoms to the start of the first disease-modifying antirheumatic drug (DMARD) was 8 months.[6] This delay can have lasting consequences and hinder efforts to prevent permanent damage from RA.

The difficulty in identifying and treating patients with early RA has been a lack of uniform criteria that can differentiate patients who present with undifferentiated arthritis who are likely to progress to RA. In September 2010, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) jointly published RA classification criteria that focus on features at earlier stages of disease for a "definite RA" classification.[2] Although the goal of this classification scheme was primarily to aid recruitment of patients for clinical trials, these criteria can be an important guide to recognize patients who would benefit from early therapeutic intervention. Incorporating these criteria among other diagnostic approaches can be important in identifying patients at early stages of RA who would benefit most from aggressive treatment.

Evidence for a Therapeutic "Window"

The medical literature describes a "window of opportunity" to prevent permanent damage when managing patients with early RA.[7] Evidence suggests that remission is more likely in patients with early RA than in patients with long-standing disease. Aletaha and colleagues studied the effect of RA duration on reversibility of physical impairment. They compiled data from 6 clinical trials on patients who achieved remission (n = 2763) and compared the disability index of the Health Assessment Questionnaire (HAQ) score at study entry to time of remission and identified reversible and irreversible components of the HAQ score.[8] Decreases in HAQ score suggested response to therapy and represented a reversible component; continued elevations in HAQ score suggested irreversible damage. The percentage of the HAQ score that was reversible decreased as the duration of disease increased (**Figure 1**). Data suggest that early treatment of patients with RA may result in greater benefits than therapy started later in the disease course.

Further evidence for this "window of opportunity" was demonstrated in the FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) study (described in greater detail later in this paper).[9,10] The results from this study showed that early suppression of disease (by 6 months) was associated with maintenance of work capacity at 5 years.[11] More aggressive therapy (initial combination therapy with conventional DMARDs vs monotherapy) was associated with a better earlier response that was sustained long term (up to 11 years). Clinicians must be aware of the potential long-term consequences of delaying antirheumatic treatment while recognizing the benefits of early, aggressive approaches.

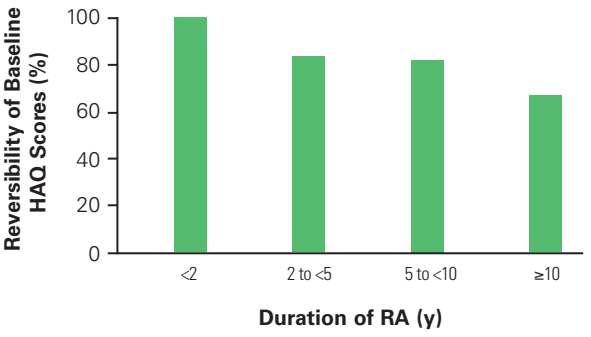
Contemporary Treatment Strategies

Early Aggressive Therapy

The large amount of data demonstrating the benefits of aggressive treatment of patients with early RA has garnered support for changing management strategies to maximize the possibility of achieving disease remission. A group of practicing rheumatologists in the United Kingdom published a set of treatment principles with the goal of reducing cumulative inflammation in patients with early RA.[12] The 4 core principles of management include: (1) detect and refer patients early, even if the diagnosis is uncertain; (2) treat RA immediately; (3) tight control of inflammation in RA improves outcome; and (4) consider the risk-benefit ratio and tailor treatment to each patient.

The latest ACR treatment guidelines (published in 2008) support the use of conventional DMARDs in patients at early stages of RA.[1] For patients with a disease duration less than 6 months, conventional DMARDs are favored and recommended, even for patients with low disease activity, and with or without features of poor prognosis. For patients with early RA (disease duration <6 months), biologic agents are recommended only for patients who experience high disease activity for 3 to 6 months, or those with high disease activity for less than 3 months and features of poor prognosis (depending on cost or insurance coverage limitations). Clearly, the use of antirheumatic agents in patients diagnosed with early RA can be important in optimizing patient outcomes, although the selection of an agent or combination of agents must be based on individual factors, such as the duration and severity

Figure 1. Median Reversibility of Baseline HAQ Scores Based on Duration of RA[8]



HAQ indicates Health Assessment Questionnaire; RA, rheumatoid arthritis. *P* across subgroups <.001.

of disease, the presence of prognostic factors for debilitating disease, and comorbidities.

Treat to Target

Treating to target means using specific parameters to decide whether or not treatment needs to be modified to meet treatment goals (such as remission or low disease activity). It has also been demonstrated that structured patient management that aims to meet defined targets leads to better outcomes than traditional care strategies.[13,14] To promote optimal management tactics for treatment and follow-up, an international task force developed a set of recommendations to improve the management of RA by emphasizing treating to target.[15] This set of 10 recommendations was developed with the goal of informing patients, rheumatologists, and other stakeholders about strategies to reach desired outcomes in patients with RA (**Table 1**).

These recommendations do not focus on particular therapeutic choices or take into account the potential for financial constraints and access to therapy. However, it is noted that clinical outcomes for patients with RA can be significantly improved with adherence to treatments that are normally easily accessible and affordable. Remission is the ultimate goal, particularly for patients with early RA. Yet, it is important to note that remission does not mean cure; patients may relapse and some definitions of remission allow residual disease activity. To reach this target of remission, frequent follow-up with the rheumatologist (sometimes every month) and therapy adjustment (at least every 3 months) is recommended until the target goal is reached. In addition to patients and clinicians, these recommendations can be an important reference for payers to assess success of patients being treated for RA and recognize the steps needed to reach this target.

The TICORA (TIght COntrol for Rheumatoid Arthritis) study demonstrated the benefits of using a treat-to-target approach in early RA.[14] This single-blind, 18-month study compared the effectiveness of routine care (n = 55) with intensive management (n = 55) in patients who had RA for less than 5 years. Intensive management included monthly assessment of disease progression and a protocol-based escalation of DMARDs—monotherapy or combination therapy with sulfasalazine, methotrexate, and/or hydroxychloroquine. Other DMARDs and corticosteroids were used when needed. Patients in routine care were reviewed every 3 months and DMARD monotherapy was given to patients with active synovitis. Failure of treatment in these patients resulted in a change to an alternative monotherapy or combination therapy (2 or 3 agents) at the discretion of the rheumatologist. The mean fall in Disease Activity Score (DAS) was greater in the intensive management group than in the routine care group (-3.5 vs -1.9; P <.0001). Patients in the intensive management group were more likely to attain remission (65% vs 16%; P <.0001). Despite the 65% remission rate in the intensive management group, radiographic analysis of these patients showed a median increase in total Sharp Score of 4.5, which, while significantly better than the routine care group (median increase of 8.5; P = .02), still indicated progression of joint damage. (Scoring was performed by 2 radiologists who compared the radiographs of hands and feet from 0 month and 18 months.)

With respect to disease remission, it is important to note that patients can fall in and out of remission, and the percentages reported in clinical trials typically refer to a particular time point (in this case, at the 18-month assessment). The study concluded that intensive outpatient management of RA can

Table 1. Ten Recommendations on Treating RA to Target Based on Evidence and Expert Opinion[15]

1.	The primary target for treatment of RA should be a state of clinical remission.
2.	Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
3.	While remission should be a clear target, based on available evidence, low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.
4.	Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.
5.	Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3-6 months) for patients in sustained, low disease activity or remission.
6.	The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.
7.	Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.
8.	The desired treatment target should be maintained throughout the remaining course of the disease.
9.	The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of comorbidities, patient factors, and drug-related risks.
10.	The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.

RA indicates rheumatoid arthritis.

Adapted from Smolen JS, Aletaha D, Bijlsma JW, et al. *Ann Rheum Dis*. 2010;69(4):631-637.

substantially decrease disease activity while improving physical function and quality of life. This study also demonstrated that patients who experience clinical benefits from antirheumatic therapy do not necessarily experience comparable radiographic benefits. A more recent study confirmed the clinical and radiographic benefits of a systematic DAS-driven therapy compared with routine care when treatment is at the discretion of the physician.[16]

Therapeutic Options for Early RA

Conventional DMARDs

A good response, including remission, can be achieved in some patients treated with conventional DMARDs. As described earlier, results from the TICORA study demonstrated that an intensive step-up DMARD treatment strategy was superior to routine care for patients with early RA.[14] A follow-up study compared step-up therapy (n = 47; sulfasalazine monotherapy for 3 months, followed by addition of methotrexate, followed by addition of hydroxychloroquine) with parallel triple therapy (n = 49; therapy initiated with the 3-drug combination).[17] Both groups showed significant improvement in disease activity and functional outcome with no significant differences observed between the 2 treatment groups. A separate pilot study of 21 patients with active early RA showed that intensified and tightly controlled COBRA treatment (sulfasalazine, methotrexate, and high-dose step-down prednisolone, intensified by adding hydroxychloroquine and continued low-dose prednisolone) resulted in a remission rate of 90% (19 of 21 patients) after 40 weeks.[18] These studies demonstrate that remission can be achieved with conventional DMARDs when part of an intensive and tightly controlled management plan.

In addition to the potential for a good response with conventional DMARDs, remission is often sustained over the long term. The FIN-RACo study compared patients treated with triple DMARD therapy plus prednisolone with those treated with monotherapy for the first 2 years (before unrestricting treatment strategy while still targeting remission).[9,10] Better outcomes were observed with initial combination therapy than with monotherapy, including remission at 2 years and sustained remission (defined as remission at 6, 12, and 24 months) (Table 2). At the 11-year follow-up, a higher percentage of patients who received combination therapy experienced minimal disease activity and disease remission.

Although it is generally accepted that combination DMARD therapy is more effective than monotherapy (and triple therapy is more effective than dual combinations), further research is needed to determine the most effective regimens and approaches to utilize these combinations during the course of disease progression.[19] Guidelines for the use of methotrexate for rheumatic disorders recommend the use of methotrexate monotherapy for DMARD-naïve patients. Methotrexate should also be considered the anchor for combination therapy when methotrexate monotherapy does not achieve adequate disease control.[20] When used concomitantly with biologic drugs, methotrexate decreases the formation of antibodies against biologics, particularly chimeric drugs.

Glucocorticoids

Glucocorticoids, such as prednisone, are often used in the United States as an adjunct to DMARDs for early and advanced RA to help induce remission or delay progression of disease.[21] Often, glucocorticoids are used as "bridge" therapy to rapidly control inflammation while awaiting the effects of slower-acting agents. A recent systematic review evaluated the efficacy of glucocorticoids in the management of RA.[22] Eleven studies were included in the assessment and the data suggested that the addition of glucocorticoids to conventional DMARD monotherapy or combination therapy produced clinical benefits and inhibited radiographic progression of disease, which may extend for several years. BeSt study results (discussed later in this paper) showed that combination therapy with prednisone was comparable to initial combination therapy with a biologic agent (infliximab) in achieving low disease activity and radiographic progression over 6 years.[23]

Additional studies are clearly needed to fully understand the role of glucocorticoids in the management of early RA.

Table 2. Two- and Eleven-Year Outcomes Results From the FIN-RACo Trial[9,10]

	Combination Therapy	Monotherapy
Two-Year Results[9]	**n = 79**	**n = 90**
Modified ACR remission	42%	20%
Sustained	14%	3%
DAS28 remission	68%	41%
Sustained	51%	16%
11-Year Results[10]	**n = 68**	**n = 70**
Modified MDA	63%	43%
Modified ACR remission	37%	19%

ACR indicates American College of Rheumatology; DAS28, Disease Activity Score in 28 joints; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; MDA, minimal disease activity.

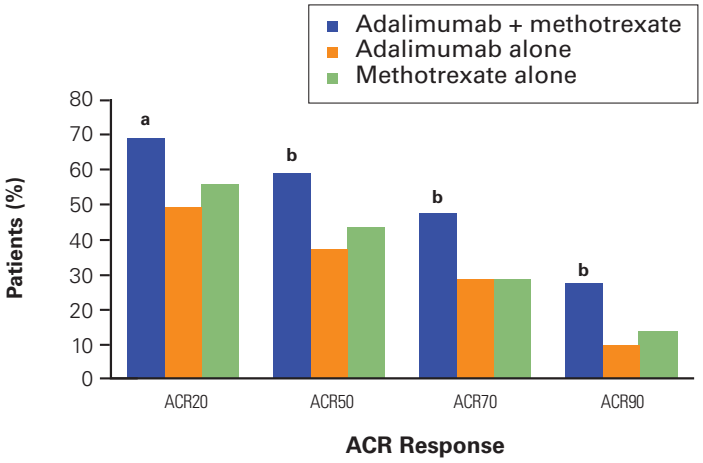
Biologic Agents: Tumor Necrosis Factor Antagonists

Antirheumatic biologic agents are the latest addition to the armamentarium to treat RA and have made disease remission a possibility for a significant percentage of patients. However, because the use of these agents is often limited due to cost constraints, it is important to recognize when a biologic agent offers clear advantages to conventional DMARDs in the management of RA. The first biologic agents were tumor necrosis factor (TNF) antagonists; these include etanercept, infliximab, adalimumab, golimumab, and certolizumab.

The BeSt study demonstrated that biologic agents can play an important role in the treatment of early RA.[24,25] It compared the clinical and radiographic efficacy of 4 treatment strategies: sequential monotherapy (n = 126); step-up combination therapy (n = 121); initial combination therapy with methotrexate, sulfasalazine, and tapered high-dose prednisone (n = 133); and initial combination therapy with methotrexate and infliximab (n = 128). Therapy in all groups was frequently monitored and adjusted as needed. Initial combination therapy with either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year when compared with sequential monotherapy or step-up combination therapy. However, all 4 groups were comparable for several other assessments over time, suggesting that the initial therapeutic approach may not be as important as ensuring that prompt adjustments to therapy are performed when needed.[23] Some patients in each group were eventually able to achieve drug-free remission.

The SWEFOT trial compared triple DMARD therapy with methotrexate plus infliximab in patients with early RA (symptom duration <1 year) who were not previously treated with a DMARD and had moderate disease activity as determined by the DAS in 28 joints ([DAS28] >3.2).[26] Patients were first treated with methotrexate (20 mg/week) for 3 to 4 months. Patients who did not achieve a DAS28 less than 3.2 at the end of this period were randomized to additionally receive sulfasalazine plus hydroxychloroquine (n = 130) or infliximab (n = 128). The use of methotrexate as initial therapy was found to be sufficient in approximately one third of the patients. At month 12, 25% of the patients in the triple DMARD group achieved a EULAR good response compared with 39% in the infliximab plus methotrexate group (P = .0160). These results suggest that although a large portion of patients responded well without biologic therapy, the addition of an anti-TNF agent was superior to the addition of conventional DMARDs in patients who fail to respond to methotrexate therapy.

Figure 2. ACR20/ACR50/ACR70/ACR90 Response at Year 2 by Treatment Groups (PREMIER Study)[27]



[a]P <.001 versus adalimumab alone, and P = .002 versus methotrexate alone.
[b]P <.001 versus adalimumab alone and methotrexate alone.
ACR indicates American College of Rheumatology; ACR20, ACR50, ACR70, and ACR90, at least 20%, 50%, 70%, and 90% improvement, respectively.

Adapted from Breedveld FC, Weisman MH, Kavanaugh AF, et al. *Arthritis Rheum.* 2006;54(1):26-37.

Several studies have compared the use of anti-TNF agents (with or without methotrexate) with methotrexate therapy for early RA. The PREMIER study, a randomized, double-blind trial, compared adalimumab and methotrexate combination therapy (n = 268) with adalimumab monotherapy (n = 274) or methotrexate monotherapy (n = 257).[27,28] Patients included in the study had active disease (duration <3 years) and were not previously treated with methotrexate. After 2 years, a greater percentage of patients in the combination therapy group achieved ACR20/ACR50/ACR70/ACR90 than those in either monotherapy group (**Figure 2**). (ACR20/ACR50/ACR70/ACR90 responses were defined as at least 20%, 50%, 70%, and 90% improvement in tender and swollen joint counts and 3 of 5 parameters [CRP, HAQ Disability Index, pain score, and assessors' and patients' global assessment].) Combination therapy was also associated with significantly less radiographic progression of disease (1.9 increase in Sharp units) compared with methotrexate monotherapy (10.4 increase in Sharp units) and adalimumab monotherapy (5.5 increase in Sharp units).

The COMET study—COmbination of Methotrexate and ETanercept in active early rheumatoid arthritis—compared methotrexate plus etanercept combination therapy with methotrexate monotherapy in treatment-naïve patients with confirmed RA.[29,30] Patients in the combination therapy group who completed year 1 of the study were randomized to receive either the same combination therapy or etanercept monotherapy. Patients initially in the methotrexate monotherapy group were randomized to receive either the same monotherapy or combination therapy. After 1 year, combination therapy was associated with significantly better DAS28 remission rates (50% vs 28%; P <.0001). After 2 years, clinical remission rates were significantly higher with both continued and delayed combination therapy compared with continued methotrexate monotherapy (Table 3). Radiographic nonprogression was significantly better with continued combination therapy (P <.01).

Remission is a realistic therapeutic goal when combination therapy is initiated during early stages of RA. Etanercept in combination with methotrexate was superior to methotrexate monotherapy in providing clinical remission and radiographic nonprogression of disease. However, methotrexate monotherapy was effective in more than one third of patients (producing disease remission) and halted radiographic progression in two thirds of patients. Delaying the use of etanercept did not seem to reduce the incidence of clinical remission, although an advantage was observed in radiographic nonprogression with early etanercept therapy (comparing etanercept–methotrexate/etanercept–methotrexate vs methotrexate/etanercept–methotrexate). Whether this difference justifies initial use of a biologic agent in early RA must be based on clinical and cost-effectiveness analyses.

Higher remission rates with biologic agents were also observed in the ASPIRE study—Active-controlled Study of Patients receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset. This study compared infliximab plus methotrexate combination therapy with methotrexate monotherapy in patients with early RA (duration ≤3 years) who had not previously received methotrexate.[31] At week 54, clinical remission, as defined by the simplified disease activity index, occurred more frequently in the combination therapy group—21.3% versus 12.3% (P <.001). This study also showed that with methotrexate monotherapy, joint damage progressed even with low disease activity. Infliximab plus methotrexate more effectively inhibited radiographic progression across all disease activity states.

The approval of golimumab and certolizumab provides additional options for clinicians in the management of RA. Golimumab plus methotrexate showed positive results compared with methotrexate alone in patients with early-onset RA.[32] Certolizumab also showed rapid and sustained improvements in clinical efficacy and patient-reported outcomes.[33,34]

Biologic Agents: Others

Other biologic agents approved for the treatment of RA inhibit different pathways of inflammation and include abatacept (inhibits T-lymphocyte activation), rituximab (causes depletion of B-lymphocytes), and tocilizumab (inhibits interleukin-6 receptor). Westhovens and colleagues assessed the efficacy of abatacept in methotrexate-naïve patients with early RA and poor prognostic factors in a randomized, double-blind, placebo-controlled study.[35] Patients with RA (duration <2 years) were randomized to receive abatacept and methotrexate combination therapy or placebo and methotrexate. Patients were required to be seropositive for RF or anti-cyclic citrullinated peptide antibodies, and have radiographic evidence of joint erosions. After 1 year of therapy, combination therapy with abatacept was associated with a significantly higher percentage of patients achieving disease remission by DAS28 (CRP) criteria (41.4% vs 23.3%; P <.001) and less radiographic progression of disease (as measured by Genant-modified total Sharp Score; mean change = 0.63 vs 1.06; P = .04) than methotrexate and placebo.

The authors concluded that in methotrexate-naïve patients with early RA, abatacept and methotrexate combination therapy results in significantly better clinical and radiographic outcomes compared with methotrexate monotherapy.

Published studies with rituximab generally involve patients who had an inadequate response to prior antirheumatic therapy. The SERENE study—Study Evaluating Rituximab's Efficacy in methotrexate iNadequate

Table 3. Clinical Remission and Radiographic Response in the COMET Study at 2 Years[29]

	EM/EM	EM/E	M/EM	M/M
DAS28 Remission	57%[a] (n = 108)	50% (n = 108)	58%[a] (n = 88)	35% (n = 94)
Radiographic Nonprogression	90%[b] (n = 99)	75% (n = 99)	75% (n = 79)	67% (n = 83)

[a]P <.01 versus M/M ; [b]P <.01 versus all other groups.
COMET indicates COmbination of Methotrexate and ETanercept in active early rheumatoid arthritis; DAS28, Disease Activity Score in 28 joints; EM/E, etanercept plus methotrexate (year 1), etanercept monotherapy (year 2); EM/EM, etanercept plus methotrexate (year 1), etanercept plus methotrexate (year 2); M/EM, methotrexate monotherapy (year 1), etanercept plus methotrexate (year 2); M/M, methotrexate monotherapy (year 1), methotrexate monotherapy (year 2).

rEsponders—compared 2 doses of rituximab (2×500 mg and 2×1000 mg) with placebo in patients with inadequate response to methotrexate.[36] Patients in all groups continued to receive methotrexate. Both doses of rituximab resulted in a higher percentage of patients achieving ACR20, ACR50, and ACR70 after 24 and 48 weeks (Table 4). Rituximab has also been shown to reduce radiographic progression of disease in patients who do not respond to anti-TNF therapy.[37]

In the AMBITION study, tocilizumab monotherapy was compared with methotrexate monotherapy in patients with moderate to severe RA who had not previously failed methotrexate or biologic therapy.[38] Tocilizumab was superior to methotrexate at achieving ACR20 (69.9% vs 52.5%; P <.001) and DAS28 remission (DAS28 <2.6) (33.6% vs 12.1%).

Table 4. ACR20/ACR50/ACR70 Responses with Rituximab Treatment (SERENE Study)[36]

	Rituximab 2×500 mg (n = 167)	Rituximab 2×1000 mg (n = 170)	Placebo (n = 172)
Week 24			
ACR20	54.5%[a]	50.6%[a]	23.3%
ACR50	26.3%[a]	25.9%[a]	9.3%
ACR70	9.0%	10.0%	5.2%
Week 48			
ACR20	55.7%	57.6%	—
ACR50	32.9%	34.1%	—
ACR70	12.6%	13.5%	—

[a] $P \leq .0001$ versus placebo.
ACR indicates American College of Rheumatology; ACR20, ACR50, and ACR70, at least 20%, 50%, and 70% improvement, repectively; SERENE, Study Evaluating Rituximab's Efficacy in methotrexate iNadequate rEsponders.

Biologic Agents: Head-to-Head Studies

Because of a general lack of randomized clinical trials that compare the efficacy of biologic agents, head-to-head comparisons are largely based on placebo-controlled studies, chart-based retrospective analyses, and registry studies. In the ATTEST study—Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy, and Safety in Treating rheumatoid arthritis—the addition of abatacept or infliximab therapy to methotrexate was compared with the addition of placebo to methotrexate in patients with RA who failed to respond to methotrexate therapy.[39] At month 6, the mean change in DAS28 scores was significantly greater for both abatacept and infliximab compared with placebo. At month 12, significantly more patients achieved an ACR20 response with abatacept than infliximab (Table 5).

A nationwide Danish registry study compared the use of and response to anti-TNF agents as the initial biologic treatment for RA.[40] In the study, 29% received adalimumab, 22% received etanercept, and 49% received infliximab. Treatment with adalimumab was found to have the highest rates for treatment response and disease remission whereas infliximab had the lowest rates. The drug survival rate was greatest for etanercept and lowest for infliximab. However, in the absence of prospective head-to-head randomized studies, it is difficult to judge whether one agent offers clear advantages over others.

Cost-Effective Approaches to Care

In general, the efficacy of biologic agents is largely comparable when considering broad patient populations, although individual response to treatment can vary greatly. This can be a challenge for payers trying to identify the most cost-effective approaches to managing RA. The 2008 ACR guidelines recommend initiating therapy with conventional DMARDs, which can be more cost-effective than starting therapy with biologic agents.[1] As described previously, although clinical trial results tend to favor biologic agents over conventional DMARDs, a significant portion of patients with early RA (typically ≥30%) will respond to conventional DMARD therapy. Therefore, initial treatment with 1 or more conventional DMARDs may be appropriate, while reserving biologic agents for patients with an inadequate response or with high disease activity.

When a biologic agent is needed, the guidelines recommend concomitant use with a conventional DMARD, such as methotrexate, as evidence suggests better clinical and radiographic results. However, evidence for step-up therapy versus initial combination therapy remains conflicting. As described earlier with the BeST study, an initial combination containing infliximab or prednisone results in earlier functional improvement and less radiographic progression of disease compared with sequential monotherapy or step-up combination therapy with conventional DMARDs.[24] However, after 6 years of DAS-steered therapy, the rates of low disease activity and remission were comparable in all 4 treatment groups, and radiographic progression had stabilized during this time.[23] Given these results, choosing a treatment strategy may be more critical than specific choice of drugs in achieving optimal outcomes, as long as an intensive management program is followed with frequent follow-up and therapeutic adjustments. From an economic standpoint, this may lead to fewer hospital-

Table 5. ACR Response at Month 12 in the ATTEST Trial[39]

Response	Abatacept Plus Methotrexate (n = 156)	Infliximab Plus Methotrexate (n = 165)	Difference (95% CI)
ACR20	72.4%	55.8%	16.7 (5.5, 27.8)
ACR50	45.5%	36.4%	9.1 (-2.2, 20.5)
ACR70	26.3%	20.6%	5.7 (-4.2, 15.6)

ACR indicates American College of Rheumatology; ACR20, ACR50, and ACR70, at least 20%, 50%, and 70% improvement, respectively; ATTEST, Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy, and Safety in Treating rheumatoid arthritis.

izations and office visits, better quality of life, and maintained work productivity, leading to lower long-term costs.[41]

Loss of work productivity can contribute greatly to the overall costs of RA. A cohort from the FIN-RACo study was followed for 5 years to estimate work absence from sickness and income losses due to RA.[42] An estimated 75% of patients lost work days, and the mean loss of productivity per patient-year was €7217 (2002 euros). There was an inverse correlation with lost productivity and clinical improvement, while lost productivity was directly associated with the number of erosions. Other studies have confirmed the benefits of DMARD therapy, particularly biologic agents, on work productivity, prevention of job loss, work absenteeism, quality of life, and household productivity.[11,43-49]

It remains to be seen whether reducing the loss of work productivity can outweigh the higher acquisition costs of biologic agents. The BeSt study showed that initial combination therapy with infliximab resulted in significantly better quality of life at 2 years compared with other less costly treatment strategies.[50] The results may be different after a longer time period. However, a cost-utility analysis demonstrated that the cost to achieve this difference is generally too high to be considered, especially since the clinical and radiographic benefits with infliximab were not much different from combination therapy with prednisone at various timepoints.[50]

This result was confirmed in a cost-effectiveness analysis model that compared 3 treatment strategies: (1) a "pyramid" strategy with initial nonsteroidal anti-inflammatory drugs, patient education, pain management, and low-dose corticosteroids, with DMARDs given at 1 year for nonresponders; (2) early methotrexate therapy; and (3) early biologic agents plus methotrexate therapy.[51] The model showed that both of the early therapy strategies increased quality-adjusted life-years (QALYs) more than the pyramid strategy and saved long-term costs. The cost of early DMARD therapy versus the pyramid strategy was $4849 per QALY, while the cost for biologic therapy versus the pyramid strategy was substantially higher ($727,894 per QALY). The authors concluded that the use of biologic agents should be reserved for patients with more treatment-resistant disease of longer duration. However, the cost-effectiveness of biologic therapy can be improved if (1) drug prices are lower; (2) the risk of death is permanently reduced with biologic therapy; (3) patients experience drug-free remission; (4) responders can be selected prior to therapy initiation; and (5) effective alternative treatments are available for patients in whom several biologic agents have failed.

When a biologic agent is needed, it is important to recognize if there are differences in the cost-effectiveness among available drugs. One modeling study evaluated the cost-effectiveness of sequential therapy with anti-TNF agents for early RA.[52] The use of anti-TNF agents as part of the sequential therapy produced a greater number of QALYs gained compared with using conventional DMARDs alone. The use of sequential therapy initiated with adalimumab plus methotrexate resulted in a cost of $47,157 per QALY gained, which was more cost-effective compared with infliximab and etanercept sequences.

Based on available health economic evidence, a systematic review was performed to evaluate economic aspects of treatment options for RA.[53] The use of conventional DMARDs at the onset of disease was found to be cost-effective. If therapy fails, escalation with anti-TNF agents is recommended and it is cost-effective when standard dosing regimens are used. If anti-TNF agents fail, rituximab or abatacept are cost-effective options. It is important to note that the authors emphasize that intensive escalation of treatment is justified in patients with RA due to the costly consequences of uncontrolled disease. Tocilizumab, golimumab, and certolizumab were likely too new in the marketplace for evaluation, although tocilizumab was included as a search term. A goal of treatment must include keeping patients productive in the work environment, thus decreasing indirect costs.

It will be important to continue to evaluate the cost-effectiveness of antirheumatic agents as conditions change, including acquisition cost fluctuations, new agent availability, and new clinical trial results with head-to-head comparisons of biologic agents. When choosing among biologic agents, it is also important to consider drug administration, such as the need for intravenous infusion in a clinic versus self-administration of subcutaneous injections at home. The availability of oral biologic agents will also have an impact on management approach-

es, although it is uncertain whether they will provide any cost advantages over currently available agents. Finally, although not reviewed in this article, it is important to mention that all antirheumatic agents have the potential for adverse events, and it is important to consider patient characteristics and comorbidities when selecting an appropriate agent. Although clinical trials have yet to distinguish differences in efficacy among biologic agents across populations, individual patients will respond differently to each agent. Therefore, treatment must be individualized for each patient and the response must be regularly monitored to determine if therapeutic adjustment is needed. Nonetheless, managed care professionals must make use of the available data to recognize today's environment in RA management and find a balance between achieving clinical targets and minimizing costs.

Author Affiliations: University of Oklahoma College of Pharmacy (BHR-T), Oklahoma City, OK; Vemco MedEd, LLC (MPC), Bridgewater, NJ.

Funding Source: Supported by an educational grant from Genentech and Biogen Idec.

Author Disclosures: The authors (BHR-T, MPC) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (BHR-T, MPC); acquisition of data (BHR-T); analysis and interpretation of data (BHR-T, MPC); drafting of the manuscript (BHR-T, MPC); and critical revision of the manuscript for important intellectual content (BHR-T, MPC).

Address correspondence to: Beth H. Resman-Targoff, PharmD, FCCP, University of Oklahoma College of Pharmacy, 1110 N Stonewall Ave, Oklahoma City, OK 73117. E-mail: beth-resman-targoff@ouhsc.edu.

REFERENCES

1. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59(6):762-784.

2. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis.* 2010;69(9):1580-1588.

3. Courvoisier N, Dougados M, Cantagrel A, et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. *Arthritis Res Ther.* 2008;10(5):R106.

4. Markatseli TE, Papagoras C, Drosos AA. Prognostic factors for erosive rheumatoid arthritis. *Clin Exp Rheumatol.* 2010;28(1):114-123.

5. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. *Ann Rheum Dis.* 2010;69(7):1333-1337.

6. Kiely P, Williams R, Walsh D, Young A; Early Rheumatoid Arthritis Network. Contemporary patterns of care and disease activity outcome in early rheumatoid arthritis: the ERAN cohort. *Rheumatology (Oxford).* 2009;48(1):57-60.

7. Cush JJ. Early rheumatoid arthritis: is there a window of opportunity? *J Rheumatol Suppl.* 2007;80:1-7.

8. Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: identifying reversible and irreversible components. *Arthritis Rheum.* 2006;54(9):2784-2792.

9. Makinen H, Kautiainen H, Hannonen P, et al. Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. *J Rheumatol.* 2007;34(2):316-321.

10. Rantalaiho V, Korpela M, Hannonen P, et al; FIN-RACo Trial Group. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. *Arthritis Rheum.* 2009;60(5):1222-1231.

11. Puolakka K, Kautiainen H, Mottonen T, et al; FIN-RACo Trial Group. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. *Arthritis Rheum.* 2005;52(1):36-41.

12. Kiely PD, Brown AK, Edwards CJ, et al. Contemporary treatment principles for early rheumatoid arthritis: a consensus statement. *Rheumatology (Oxford).* 2009;48(7):765-772.

13. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med.* 2007;146(6):406-415.

14. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet.* 2004;364(9430):263-269.

15. Smolen JS, Aletaha D, Bijlsma JWJ, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis.* 2010;69(4):631-637.

16. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Kerstens PJ, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. *Ann Rheum Dis.* 2010;69(1):65-69.

17. Saunders SA, Capell HA, Stirling A, et al. Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. *Arthritis Rheum.* 2008;58(5):1310-1317.

18. van Tuyl LH, Lems WF, Voskuyl AE, et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. *Ann Rheum Dis.* 2008;67(11):1574-1577.

19. Dale J, Alcorn N, Capell H, Madhok R. Combination therapy for rheumatoid arthritis: methotrexate and sulfasalazine together or with other DMARDs. *Nat Clin Pract Rheumatol.* 2007;3(8):450-458.

20. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis.* 2009;68(7):1086-1093.

21. Kirwan J, Power L. Glucocorticoids: action and new therapeutic insights in rheumatoid arthritis. *Curr Opin Rheumatol.* 2007;19(3):233-237.

22. Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis.* 2010;69(6):1010-1014.

23. Klarenbeek NB, Dirvin L, Guler-Yuksel M, et al. Clinical and radiological outcomes of four DAS driven treatment strategies: 6-year results of the BeSt study. Paper presented at: American College of Rheumatology; October 19, 2009; Philadelphia, PA. Abstract 1019.

24. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum.* 2005;52(11):3381-3390.

25. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, et al. Clinical and radiological efficacy of initial versus delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. *Ann Rheum Dis.* 2009;68(7):1153-1158.

26. van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (SWEFOT trial): 1-year results of a randomised trial. *Lancet.* 2009;374(9688):459-466.

27. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum.* 2006;54(1):26-37.

28. Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. *J Rheumatol.* 2009;36(7):1429-1441.

29. Emery P, Breedveld F, van der Heijde D, et al; Combination of Methotrexate and Etanercept in Early Rheumatoid Arthritis Trial Group. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. *Arthritis Rheum.* 2010;62(3):674-682.

30. Kekow J, Moots RJ, Emery P, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. *Ann Rheum Dis.* 2010;69(1):222-225.

31. Smolen JS, Han C, van der Heijde DM, et al; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) Study Group. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Ann Rheum Dis.* 2009;68(6):823-827.

32. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum.* 2009;60(8):2272-2283.

33. Strand V, Mease P, Burmester GR, et al. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. *Arthritis Res Ther.* 2009;11(6):R170.

34. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis.* 2009;68(6):797-804.

35. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. *Ann Rheum Dis.* 2009;68(12):1870-1877.

36. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naïve with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis.* 2010;69(9):1629-1635.

37. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. *Ann Rheum Dis.* 2009;68(2):216-221.

38. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis.* 2010;69(1):88-96.

39. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis.* 2008;67(8):1096-1103.

40. Hetland ML, Christensen IJ, Tarp U, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum.* 2010;62(1):22-32.

41. Bansback N, Marra CA, Finckh A, Anis A. The economics of treatment in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol.* 2009;23(1):83-92.

42. Puolakka K, Kautiainen H, Pekurinen M, et al; FIN-RACo Trial Group. Monetary value of lost productivity over a five year follow up in early rheumatoid arthritis estimated on the basis of official register data on patients' sickness absence and gross income: experience from the FIN-RACo trial. *Ann Rheum Dis.* 2006;65(7):899-904.

43. Bejarano V, Quinn M, Conaghan PG, et al; Yorkshire Early Arthritis Register Consortium. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. *Arthritis Rheum.* 2008;59(10):1467-1474.

44. Globe D, Mazonson P, Santas C, et al. Impact of etanercept treatment on absenteeism and productivity: the Work Loss and Productivity survey. *Am Health Drug Benefit.* 2010;3(3):191-200.

45. Uutela T, Hannonen P, Kautiainen H, Hakala M, Paananen ML, Hakkinen A. Positive treatment response improves the health-related quality of life of patients with early rheumatoid arthritis. *Clin Exp Rheumatol.* 2009;27(1):108-111.

46. Puolakka K, Kautiainen H, Mottonen T, et al. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. *Arthritis Rheum.* 2004;50(1):55-62.

47. Kimel M, Cifaldi M, Chen N, Revicki D. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. *J Rheumatol.* 2008;35(2):206-215.

48. van Vollenhoven RF, Cifaldi MA, Ray S, Chen N, Weisman MH. Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical and radiographic measures from a randomized controlled trial companion study. *Arthritis Care Res (Hoboken).* 2010;62(2):226-234.

49. Kavanaugh A, Smolen JS, Emery P, et al. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. *Arthritis Rheum.* 2009;61(11):1592-1600.

50. van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. *Arthritis Rheum.* 2009;61(3):291-299.

51. Finckh A, Bansback N, Marra CA, et al. Treatment of very early rheumatoid arthritis with symptomatic therapy, disease-modifying antirheumatic drugs, or biologic agents: a cost-effectiveness analysis. *Ann Intern Med.* 2009;151(9):612-621.

52. Davies A, Cifaldi MA, Segurado OG, Weisman MH. Cost-effectiveness of sequential therapy with tumor necrosis factor antagonists in early rheumatoid arthritis. *J Rheumatol.* 2009;36(1):16-26.

53. Schoels M, Wong J, Scott DL, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis.* 2010;69(6):995-1003.