Review
Unmet needs in rheumatoid arthritis
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Abstract

Until the pathophysiology/etiology of rheumatoid arthritis (RA) is better understood, treatment strategies must focus on disease management. Early diagnosis and treatment with disease-modifying antirheumatic drugs (DMARDs) are necessary to reduce early joint damage, functional loss, and mortality. Several clinical trials have now clearly shown that administering appropriate DMARDs early yields better therapeutic outcomes. However, RA is a heterogeneous disease in which responses to treatment vary considerably for any given patient. Thus, choosing which patients receive combination DMARDs, and which combinations, remains one of our major challenges in treating RA patients. In many well controlled clinical trials methotrexate and other DMARDs, including the tumor necrosis factor-α inhibitors, have shown considerable efficacy in controlling the inflammatory process, but many patients continue to have active disease. Optimizing clinical response requires the use of a full spectrum of clinical agents with different therapeutic targets. Newer therapies, such as rituximab, that specifically target B cells have emerged as viable treatment options for patients with RA.

Introduction

Current treatment guidelines suggest that early diagnosis and initial treatment with disease-modifying antirheumatic drugs (DMARDs) are necessary to limit early joint damage and functional loss and to reduce mortality associated with rheumatoid arthritis (RA) [1]. The earlier use of methotrexate alone and in combination with other DMARDs is now the standard of care and has yielded better outcomes for patients with RA.

However, RA is a heterogeneous disease, and patient responses to standard treatments are variable. Most recent clinical trials of newer DMARDs alone and in combination with methotrexate have shown that ACR50 response – which includes reducing the signs and symptoms of disease by 50%, according to criteria established by the American College of Rheumatology (ACR) – was achieved in less than two-thirds of the patients [2-5]. That leaves at least one-third of the most seriously affected patients with RA without an effective long-term treatment strategy. Until we are able to identify which patients will respond to which treatment, the availability of a variety of agents with different therapeutic targets offers the best opportunity to optimize clinical outcomes.

Rituximab, a chimeric anti-CD20 monoclonal antibody that has emerged as a potential treatment for RA via selective targeting of B lymphocytes, has been used extensively in the treatment of B cell malignancies. There is a growing body of evidence for the pathophysiologic role of B cells. Silverman and Carson [6] described that B lymphocytes can present immune-complexed antigens to autoreactive T cells; express adhesion and other co-stimulatory molecules that promote T cell activation; synthesize chemokines that induce leukocyte infiltration; produce factors that initiate and sustain angiogenesis and granulation tissue formation; and release autoantibodies that are directly or indirectly destructive to tissues and maintain a memory response to autoantigens. Apart from B cells and T cells, populations of monocytes, macrophages, endothelial cells, and fibroblasts have been implicated in the ongoing inflammatory process [7]. The availability of a broader spectrum of agents with different targeting mechanisms will provide more effective treatment options for diverse patient populations.

Overall picture of rheumatoid arthritis

RA affects almost 1% of the adult population worldwide [1]. Clinicians have reason to be concerned when they manage a chronic and debilitating condition that requires aggressive, life-long management. When one looks at large cohort populations, patients with RA exhibit increased morbidity and mortality, compounded by a dramatic impact on quality of life. Approximately 80% of affected patients are disabled after

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ACR = American College of Rheumatology; AE = adverse event; CTLA4–Ig = cytotoxic T lymphocyte-associated antigen 4–IgG$_1$; DMARD = disease-modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; IL = interleukin; RA = rheumatoid arthritis; SF-36 = Short Form 36-Item Health Survey; TNF = tumor necrosis factor.

20 years [8], and life expectancy is reduced by an average of 3–18 years [9].

The management of RA has a marked impact in terms not only of the financial burden to the health care system but also of the financial burden to individual patients and their families. It has been estimated that the disorder costs the average individual up to US$8500 annually [10], with time lost from work ranging from 2.7 to 30 days [11].

Treatment advances over the past decade

During the past 10 years or so, advances in the treatment of RA have underscored the role of methotrexate as a major cornerstone of therapy. However, many randomized controlled trials have demonstrated that methotrexate in combination with another DMARD is more effective than methotrexate monotherapy for many patient populations [3-5,12].

In a 2002 study, Kremer and colleagues [12] tested the hypothesis that adding leflunomide to the regimen of patients taking methotrexate alone would strengthen the clinical response. The team assigned 263 patients with RA to leflunomide plus methotrexate or methotrexate alone. At 24 weeks, 46.2% (60 of 130) of patients receiving the leflunomide–methotrexate combination had achieved an ACR20 clinical response, as compared with 19.5% of the patients who had been maintained on a methotrexate–placebo regimen ($P < 0.001$). In addition, they reported that 26.2% of the leflunomide patients achieved an ACR50 response, as compared with 6.0% of the patients in the methotrexate–placebo arm ($P < 0.001$). This study was one of the first to show that the combination of the two biologic agents produced statistically significant and clinically meaningful improvement in patients with active RA.

In a 2-year, randomized, double-blind, placebo-controlled trial, O'Dell and colleagues [13] compared the effectiveness of methotrexate in combination with either hydroxychloroquine or sulfasalazine, as well as a combination of all three drugs. After 2 years, 55% of the 58 patients in the triple therapy arm achieved an ACR50 response; 40% of patients on hydroxychloroquine and methotrexate achieved an ACR50 response; and 29% of those on sulfasalazine and methotrexate achieved an ACR50 response. The differences between triple therapy and double therapy with sulfasalazine reached statistical significance ($P = 0.005$).

Biologic response modifiers

Efforts to develop safer and more effective treatments for RA, based on an improved understanding of the role of inflammatory mediators, have been realized through the development of the biologic response modifiers. Some biologics have been approved for use in RA by the US Food and Drug Administration and the European Medicine Evaluation Agency, including etanercept (a soluble tumor necrosis factor [TNF]-α type II receptor–IgG$_1$ fusion protein

administered subcutaneously), infliximab (a chimeric [human and mouse] monoclonal antibody against TNF-α), and adalimumab (a human anti-TNF monoclonal antibody). These therapies have shown the ability to change dramatically the outcomes of the disease in some RA patients.

Researchers have observed that interleukin (IL)-1, IL-6, and TNF-α are important mediators that initiate and maintain inflammation in RA, resulting in cellular infiltration of synovium and damage, and the destruction of cartilage and bone [14]. TNF-α, a potent cytokine that exerts diverse stimulatory effects, is produced mainly by monocytes and macrophages, but also by B cells, T cells, and fibroblasts. Newly synthesized TNF-α is expressed on the cell membrane and subsequently released through the cleavage of its membrane-anchoring domain by a serine metalloproteinase. Thus, inhibition of TNF-α secretion may represent a therapeutic target.

RA is believed to be initiated by CD4^{+} T cells, which amplify the immune response by stimulating other mononuclear cells, synovial fibroblasts, chondrocytes, and osteoclasts. Activated CD4^{+} T cells contribute to stimulation of osteoclastogenesis and activation of metalloproteinases responsible for the degradation of connective tissue, resulting in joint damage.
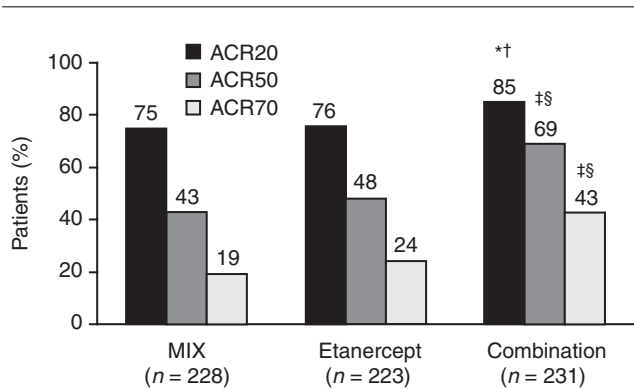
Clearly, there are many possible therapeutic targets, but inhibition of cytokines appears to offer an especially efficient approach to suppressing inflammation and preventing joint damage [14]. There are four biological therapies currently approved for RA: three TNF-α inhibitors (infliximab, etanercept, and adalimumab) and one IL-1 inhibitor (anakinra).

Abatacept, a cytotoxic T lymphocyte-associated antigen 4–IgG$_1$ (CTLA4–Ig) fusion protein, known as a co-stimulation blocker, is administered in a 30 min infusion. Recent clinical trial data show that the combination of abatacept and methotrexate improves the signs and symptoms, physical functioning, and quality of life of patients with active RA [15].

Etanercept

In the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO), Klareskog and coworkers [16] enrolled 685 patients with active RA in a double-blind, randomized trial to determine the safety and efficacy of treatment with etanercept or methotrexate alone or in combination versus placebo for up to 52 weeks. Patients were randomly assigned to treatment with etanercept 25 mg subcutaneously twice a week, oral methotrexate monotherapy up to 20 mg every week, or a combination of the two agents.

The researchers found that the proportions of patients achieving ACR50 and ACR70 responses were consistently higher for the combination group than either the etanercept or methotrexate treatment arms throughout the study (Fig. 1). At week 52, 69% of the patients in the combination protocol achieved an ACR50 response, as compared with 43% and

Figure 1

Etanercept in active rheumatoid arthritis (TEMPO trial): ACR responses at 52 weeks. *$P < 0.01$, ‡$P < 0.0001$, versus placebo; †$P < 0.05$, §$P < 0.0001$, versus etanercept. ACR, American College of Rheumatology; MTX, methotrexate; TEMPO, Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes. Reprinted with permission [16].

48% in the methotrexate and etanercept monotherapy groups, respectively ($P < 0.0001$). Moreover, after a 1-year period, 43% of the patients in the combination group had an ACR70 response, as compared with 19% and 24% in the methotrexate and etanercept monotherapy patients, respectively ($P < 0.0001$). Additionally, more than one-third of patients treated with the methotrexate–etanercept combination protocol were in remission at 52 weeks.

The number of patients reporting infection or adverse events (AEs) was similar in all groups. Overall, Klareskog and colleagues reported that the combination of etanercept and methotrexate was significantly better in reducing disease activity, improving functional disability, and retarding radiographic progression compared with methotrexate or etanercept alone.

A comparison of therapy with methotrexate and therapy with etanercept was also conducted by Bathon and colleagues [17]. They evaluated 632 patients with early RA who were given either twice weekly subcutaneous etanercept (10 mg or 25 mg) or weekly oral methotrexate (mean 19 mg/week) for 12 months.

Compared with patients who received methotrexate, patients taking the 25 mg dose of etanercept exhibited a more rapid rate of improvement, with significantly more patients having ACR20, ACR50, and ACR70 response improvement in disease activity during the first 6 months ($P < 0.05$). The mean increase in the erosion score during the first 6 months was 0.30 in the group assigned to receive 25 mg etanercept and 0.68 in the methotrexate group ($P = 0.001$). The respective increases during the first 12 months were 0.47 and 1.03 ($P = 0.002$).
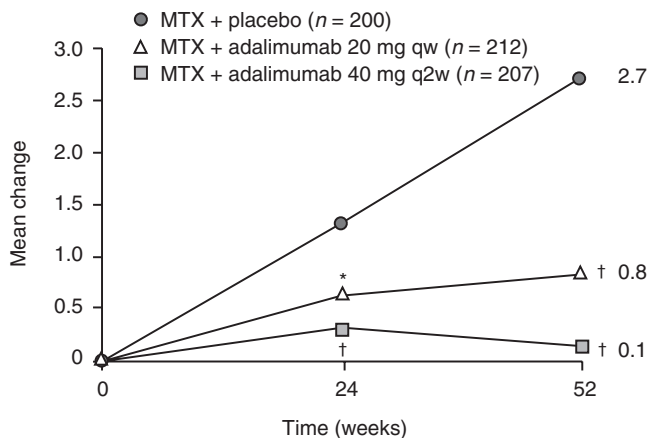
Among patients who received the 25 mg dose of etanercept, 72% had no increase in the erosion score, as compared with 60% of patients in the methotrexate group ($P = 0.007$). This group of patients also had fewer AEs ($P = 0.02$) and fewer infections ($P = 0.006$) than did the group treated with methotrexate. Compared with oral methotrexate, subcutaneous etanercept acted more rapidly to decrease symptoms and slow joint damage in patients with early active RA.

Bathon and colleagues observed that the patients in the study were at risk for rapidly progressive joint damage. Their disease was predicted to progress without treatment at an estimated rate of four to five points per year on the Sharp erosion subscale, and four points per year on the Sharp joint-space narrowing subscale. The rates of progression for joint-space narrowing were low. Both etanercept and methotrexate prevented joint-space narrowing. The overall rates of erosion were also low, equivalent to the occurrence of one new erosion or the erosion of 20% of one joint every year in the methotrexate group and every 2 years in the group assigned to receive 25 mg etanercept. The effects of this dose of etanercept were evident sooner than were the effects of methotrexate, but the rates of change were similar in the two groups during the latter half of the study. Over a 1-year period, treatment with etanercept halted erosions in 72% of patients, whereas treatment with methotrexate halted erosions in 60% of patients [17].

Adalimumab
In a pivotal study [18], the combination of the biologic adalimumab and methotrexate, particularly at a higher dose of 40 mg every other week, yielded a statistically significant improvement compared with methotrexate plus placebo. In that multicenter, 52-week, double-blind, placebo-controlled study, 619 patients with active RA who had an inadequate response to methotrexate alone were randomly assigned to receive adalimumab 40 mg subcutaneously every other week ($n = 207$), adalimumab 20 mg subcutaneously every week ($n = 212$), or placebo ($n = 200$) plus concomitant treatment with methotrexate. The primary efficacy end-points were radiographic progression at week 52 (total Sharp score by a modified method); clinical response at week 24, defined as improvements that achieved at least an ACR20 response; and improvement in physical function at week 52, based on the disability index of the Health Assessment Questionnaire (HAQ). At week 52 there was statistically significantly less radiographic progression (Fig. 2), as measured by change in total Sharp score, in the patients receiving adalimumab either 40 mg every other week (change [mean ± standard deviation] 0.1 ± 4.8) or 20 mg weekly (0.8 ± 4.9), as compared with that in the placebo group (2.7 ± 6.8; $P < 0.001$).

At week 52, ACR50 responses were achieved by 42% and 38% of patients taking adalimumab 40 mg every other week and 20 mg weekly, respectively, but by 10% of patients taking placebo ($P < 0.001$). In terms of physical function at

Figure 2

Adalimumab plus methotrexate in active rheumatoid arthritis: mean change from baseline in total Sharp score. *$P < 0.01$, †$P \leq 0.001$, versus placebo. MTX, methotrexate. Reproduced with permission [18]. Copyright © 2004 by John Wiley & Sons, Inc.

week 52, patients on combination therapy with adalimumab and methotrexate experienced statistically significant improvement (mean change in HAQ score −0.59 and −0.61, respectively, versus −0.25; $P < 0.001$).

Adalimumab was generally well tolerated. Discontinuations occurred in 22% of adalimumab treated patients and in 30% of placebo treated patients. The rate of both serious AEs and nonserious AEs was similar between adalimumab and placebo groups. The proportion of patients reporting serious infections was higher in patients receiving adalimumab (3.8%) than in those receiving placebo (0.5%; $P < 0.02$) and was highest in the patients receiving 40 mg every other week.

The benefits of early treatment of RA with adalimumab, either alone or in combination with methotrexate, were supported more recently by the results of the PREMIER study [19]. In an analysis of almost 800 patients with a disease duration of less than 3 years, adalimumab 40 mg every other week plus methotrexate (escalated rapidly to 20 mg/week) exhibited statistically significant improvement in ACR50 clinical response and amelioration of disease progression compared with either adalimumab or methotrexate alone. Of patients in the combination therapy group, 61% and 46% achieved ACR50 and ACR70 responses, respectively, as compared with 46% and 28% in the methotrexate group ($P < 0.001$) – a statistically significant difference that was sustained for up to 2 years. The difference in clinical response was also comparable between the combination arm of the trial and patients taking adalimumab alone. Moreover, at 2 years radiographic remission (as indicated by a Disease Activity Scale [DAS28] score <2.6) was achieved by 50% of patients receiving combination therapy.

Infliximab

Much of the recent knowledge regarding the safety and efficacy of infliximab in combination with methotrexate emerged from analysis of data from the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial [20,21], the pivotal study that led to approval of the TNF-α inhibitor infliximab in the USA and worldwide. ATTRACT demonstrated that the combination of methotrexate and infliximab, in particular, with highest doses given every 4–8 weeks, resulted in better clinical responses than methotrexate plus placebo.

In that study the investigators established that infliximab not only provided significant improvements in physical function and quality of life, but also succeeded in slowing or halting progressive joint damage and signs and symptoms of RA in patients who previously had an incomplete response to methotrexate alone.

The study included 428 patients who were randomly assigned to receive methotrexate plus placebo or infliximab at a dose of 3 mg/kg or 10 mg/kg plus methotrexate for 54 weeks, with an additional year of follow up. The protocol was later amended to allow for continued treatment during the second year.

Of 259 patients who entered the second year of treatment, 216 continued to receive infliximab plus methotrexate for 102 weeks. Ninety-four of these 259 patients experienced a gap in therapy of greater than 8 weeks before continuing therapy. Infusions were administered at baseline, week 2, and week 6, followed by treatment every 4 weeks or every 8 weeks – alternating with placebo infusions in the interim 4-week visits – at a dose of 3 mg/kg or 10 mg/kg for a total of 102 weeks, which included the gap in therapy.

The results of the study showed that the infliximab plus methotrexate regimens led to significantly greater improvement in HAQ scores ($P = 0.006$) and in the Short Form 36-Item Health Survey (SF-36) physical component summary scores ($P = 0.011$), compared with the group of patients receiving monotherapy with methotrexate. There also was stability in the SF-36 mental component summary score among patients who received the infliximab plus methotrexate regimens. The median changes from baseline to week 102 in the total radiographic score were 4.25 for patients who received the methotrexate-only regimen and 0.50 for patients who received the infliximab plus methotrexate regimen. The proportion of patients achieving an ACR50 response at week 102 varied from 20% to 21% for the infliximab plus methotrexate groups, as compared with 6% for the methotrexate-only group. These data emphasize that the combination of infliximab plus methotrexate conferred significant, clinically relevant improvement in physical function and quality of life, accompanied by inhibition of progressive joint damage and sustained improvement in the signs and symptoms of RA

among patients who previously had an incomplete response to methotrexate alone.

The ASPIRE (Active controlled Study of Patients receiving Infliximab for RA of Early onset) trial [5] randomly assigned patients with early RA to either methotrexate alone or methotrexate plus 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6, and every 8 weeks thereafter through week 46. It revealed improvement in ACR scores in both combination treatment groups compared with the methotrexate arm (38.9% and 46.7%, versus 26.4%, respectively; $P < 0.001$ for both comparisons), significantly less radiographic progression at 6 months and 12 months, and improvement in physical function.

Anakinra

Treatment with anakinra, the first IL-1 receptor antagonist, either alone or in combination with methotrexate, has emerged as an effective medication for patients with moderate-to-severe RA. In a study of 419 patients with active RA of duration greater than 6 months but less than 12 years [22], patients were randomly assigned to placebo or one of five doses of anakinra (0.04, 0.1, 0.4, 1.0 or 2.0 mg/kg) plus methotrexate. Those assigned to the five anakinra regimens exhibited statistically significant ($P = 0.001$), dose-escalating efficacy in ACR20 responses as compared with the placebo plus methotrexate group after 12 weeks. The ACR20 response rates in the anakinra 1.0 mg/kg (46%; $P = 0.001$) and 2.0 mg/kg (38%; $P = 0.007$) dose groups were significantly better than those in the placebo group (19%). ACR20 responses at 24 weeks were consistent with those at 12 weeks. Other researchers have reported similar 6-month ACR20 (and ACR50) responses, as well as in individual components (i.e. HAQ, pain, C-reactive protein level, and erythrocyte sedimentation rate) [23].

Abatacept

Abatacept (CTLA4–Ig), a cytotoxic T-lymphocyte-associated antigen 4–IgG$_1$ fusion protein, is the first in a new class of drugs known as co-stimulation blockers that are being evaluated for the treatment of RA. Abatacept selectively modulates the co-stimulatory signal required for full T cell activation. The agent, which binds to CD80 and CD86 on antigen-presenting cells, blocking the engagement of CD28 on T cells and thus preventing T cell activation, acts earlier in the inflammatory cascade than do other biologic therapies by directly inhibiting the activation of T cells and the secondary activation of macrophages and B cells.

The efficacy of this novel therapy was tested by Kremer and colleagues [24], who randomly assigned patients with active RA despite methotrexate therapy to receive 2 mg/kg CTLA4–Ig (105 patients), 10 mg/kg (115 patients), or placebo (119 patients) for 6 months. All patients also received methotrexate therapy during the study. Patients treated with 10 mg CTLA4–Ig were more likely to have an ACR20 response than

were patients who received placebo (60% versus 35%; $P < 0.001$). Significantly higher rates of ACR50 and ACR70 responses were seen in both CTLA4–Ig groups than in the placebo group [24]. The group given 10 mg CTLA4–Ig had clinically meaningful and statistically significant improvements in all eight subscales of the SF-36. CTLA4–Ig was well tolerated, with an overall safety profile similar to that of methotrexate [15].

Recently released phase III results from the Abatacept in Inadequate responders to Methotrexate (AIM) trial [24] found that 48.3% of patients achieved an ACR50 response after 1 year of therapy compared with 18.2% of patients who were given methotrexate injections ($P < 0.001$). At 6 months, the number of patients on abatacept who achieved an ACR70 response was 19.8%, compared with 6.5% of patients on methotrexate. After 1 year, 28.8% of patients had reached an ACR70 response, compared with 6.1% of patients on methotrexate. Both differences were statistically significant ($P < 0.001$).

Tumor necrosis factor-α: potential safety issues

Although researchers, scientists, and clinicians are enthusiastic in their support of early intervention with TNF-α inhibitors for patients with RA, safety issues remain an important consideration. Although infusion reactions and other AEs are infrequent, they may be very serious in some patients, in particular when complications associated with opportunistic infections occur. There is a need to follow patients very closely and to work with primary care physicians to see that these issues are addressed first and foremost.

Rare and serious AEs include infections (bacterial, fungal, or tubercular), demyelination, infusion related events, hematologic/lymphoproliferative disorders, drug-induced systemic lupus erythematosus/vasculitis, hepatotoxicity (infliximab), and potential congestive heart failure. The development of neutralizing antibodies also can be an issue in some patients and needs further exploration. Further studies are needed to determine whether some of these reported side effects are truly related to the TNF-α inhibitor, or are a consequence of the disease itself and/or comorbid conditions and concomitant medications.

Challenges

Typically, clinicians have reserved biologics for those patients with severe disease who have failed other therapies. However, the emerging body of evidence suggests that practitioners should be moving toward treating earlier disease with these biologic agents in an effort to prevent structural damage. In addition, because of the costs associated with biologic therapy – often more than US$1000 per month [25] – and the potential risk for immune suppression, one of the key challenges that clinicians should address when considering the use of TNF-α inhibitor therapy for active RA is how to determine which

Table 1

Therapy for rheumatoid arthritis: unmet needs

Problem	Details
Heterogeneity of the disease	Some patients respond to DMARD monotherapy
	Not every patient responds to anti-TNF (mono or combination) therapy
	'Remission' rates
	What is the pathology/biologic process in each individual patient?
Toxicities	Infections, immunogenecity, congestive heart failure, drug-induced vasculitis, etc
Costs	Limits availability to may patients

DMARD, disease-modifying antirheumatic drug; TNF, tumor necrosis factor.

patients should be receiving which agents and in what combination. Importantly, the medical community must endeavor to identify those patients who will respond over the long term to these agents and weigh the risk/benefit. Is it possible to pick out which patients are most likely to have that long-term response? There are numerous challenges and opportunities, as well as many unmet needs for patients with RA.

Conclusion

RA is a hetereogeneous disease; there is substantial evidence that some patients respond adequately to a single DMARD, whereas others require a combination regimen. Reliable predictors of response are needed to guide therapeutic decision making, along with a firm definition of therapeutic goals. It is of equal importance to arrest the ongoing pre-existing damage or to intervene earlier to prevent damage. In addition, over the long term, as research and treatment become more aggressive, efficacy, toxicity, and costs must be balanced within the therapeutic equation to enhance the quality of life in patients with RA (Table 1).

The next generation of therapies for RA will provide considerable opportunities. These include next generation TNF-α inhibitors, anticytokines (anti-IL-6 receptor, anti-IL-15, and anti-IL-1), angiogenesis inhibitors, antiadhesion molecules, anti-T-cell co-stimulatory blockers (e.g. abatacept), anti-B-cell therapies (i.e. rituximab and belimumab), and many others.

Competing interests

LM has received research grant support, and consulting and speaking fees from several companies in the past, including Abbott, Amgen, Centocor, Wyeth, Immunex, Bristol-Myers Squibb, Regeneron, Genentech, Merck, Pfizer, Boehringer Ingelheim, Roche and others.

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