Is There a Need for New Therapies for Rheumatoid Arthritis?

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ABSTRACT. Although traditional disease modifying and biological response modifying agents are very useful in controlling disease activity, limiting disease progression, and improving function in patients with rheumatoid arthritis (RA), very few patients achieve full remission from treatment with these medications either when given alone or in combination. The combination of methotrexate (MTX) and the biologic agents appears to provide the highest level of response that is presently achievable. A contributory factor to the limited benefit from such regimens in some patients is that patients are unable to continue these medications, either because of lack of efficacy or adverse events. As even the most effective currently available interventions are not ideal in all patients, the search for new therapies — which may be able to improve on the best possible clinical effect achievable to date — is therefore necessary, desirable, and justified. One approach to new treatment paradigms for RA is to evaluate the role of B cells in RA and the effect of targeted B cell therapy on clinical outcome, based on a sound rationale and encouraging emerging clinical evidence. This approach will be examined in this and the following articles. (J Rheumatol 2005;32 Suppl 73:3-7)

Key Indexing Terms:
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DISEASE MODIFYING ANTIRHEUMATIC DRUGS
BIOLOGICAL RESPONSE MODIFIERS
ANTIRHEUMATIC AGENTS
TREATMENT EFFICACY
ADVERSE EFFECTS

INTRODUCTION

In addressing the question about the need for new therapies for rheumatoid arthritis (RA), we need first to consider current expectations of treatment and how closely current therapies meet our expectations. Ideal outcomes of the treatment of RA include the abolition of constitutional symptoms, minimization of the impact of RA on the activities of daily living (including a return to a normal work schedule), and a fundamental change in the course of the illness. This can only be achieved by controlling signs and symptoms, slowing radiographic progression and improving patient function, and ideally by stopping the progression or even reversing the damage done before treatment was initiated.

Although modern treatments for RA are effective, none currently meets these exacting goals in all patients. Therefore, if we are to raise our expectations, we need to continue the search for new therapies that close the gap between reality and expectations. In this regard, the call for new treatments for RA is both desirable and necessary. In this brief overview, I will summarize the current state of our knowledge about the treatment of RA and future directions that aim to improve the current situation.

RATIONALE FOR AGGRESSIVE THERAPY IN RA

The course of untreated RA is one of rapid progression, especially in the first few years after onset. This results in significant joint damage, functional detriments, disability, and premature death. Leaving the patient untreated, therefore, constitutes the most significant risk to well being because the consequences of RA are generally considerably greater than the side effects of the medications used to treat it.

A modern treatment paradigm for RA is to start aggressive treatment as early as possible in the disease process, using effective doses of medications and either switching or adding further therapy in a timely fashion according to clinical response. It is clear, however, that the empiric control of inflammatory symptoms of RA, such as joint pain, swelling, and tenderness, with analgesic and nonsteroidal antiinflammatory drugs at any stage of the illness is unlikely to prevent longterm joint damage. For this reason, the use of disease modifying antirheumatic drugs (DMARD) has evolved through several important historical milestones. These milestones are the use of injectable gold since the 1930s, antimalarial drugs and steroids since the 1950s, penicillamine and sulfasalazine from the 1960s, MTX, oral

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gold, and azathioprine since the 1980s, and cyclosporine, leflunomide, and the biological response modifiers (BRM) since the 1990s.

Of the traditional DMARD, hydroxychloroquine, sulfasalazine, MTX, and leflunomide are most frequently used in the 21st century; however, it is the BRM — the tumor necrosis factor-alpha (TNF-α) blockers etanercept, infliximab, and adalimumab, and the interleukin 1 receptor antagonist anakinra — that have resulted in increased expectations that effective limitation of disease progression is an achievable goal. This has driven the search for more effective BRM, and several candidates, such as rituximab, CTLA4Ig, CDP870, and BLys (B lymphocyte stimulator)/BAFF (B cell-activating factor from the TNF family), are in clinical development. Of these, rituximab has the most defined clinical profile, derived from its approved use in the treatment of non-Hodgkin's lymphoma.

DMARD IN RA

There is little doubt that the optimal use of several of the traditional DMARD, particularly sulfasalazine, MTX, and leflunomide, is effective in limiting disease progression in RA, but an overview of the evidence regarding the outcome of treatment of RA with traditional DMARD either alone or in combination does not provide a clear picture of how effective they are. Using the American College of Rheumatology (ACR) criteria of response, many traditional DMARD are moderately effective in achieving ACR20% response level (a fairly low baseline measure of treatment outcome, but which essentially separates an effective from an ineffective medication), but few are effective in enabling the patient to achieve an ACR70 response. Indeed, some combinations of these drugs might offer little additional benefit over the drugs used alone (Figure 1). Further, although traditional DMARD can be effective, their adverse effects often limit their longterm use in the treatment of RA (Table 1), and many need to be discontinued in the event of a serious infection.

Given that RA is an illness requiring lifetime treatment, it is disappointing that the probability of discontinuing a particular DMARD treatment at 2 years is high, either because of inefficacy, toxicity, or both. The exception is MTX. In a retrospective audit of records of RA patients, conducted over the period spanning January 1985 to June 1994, the only DMARD that was continued for > 2 years in the majority of treatments was MTX (Figure 2)[10]. It is, however, possible that one reason for this apparent benefit of MTX is that there was no better alternative than MTX at that time, as this audit was conducted prior to the availability of the BRM.

BRM IN RA

The efficacy of BRM, particularly in combination with MTX, has been shown to have a clinically important effect on the signs and symptoms of RA in patients who have had an inadequate response to DMARD given alone or in combination (Figure 3). Because a higher proportion of patients treated with BRM achieve responses at the ACR20, ACR50, and ACR70 levels compared with both clinical trial and historical DMARD controls, and because BRM treatment can result in clinically and statistically significant decreases in the rate of radiographic progression in addition to improvements in patient function measured by the Health Assessment Questionnaire[2,16], it is unsurprising that the "biologic" approach with BRM has received so much clinical and research attention in recent years.

However, although the current BRM are effective, they are not a panacea because approximately 30% of patients do not respond at all to these agents, and less than 50% achieve an ACR70 level of response[11,12,14,18,19]. This is one reason why the continued research into new agents is both desirable and justifiable. A further reason is that although the safety profile of the BRM is probably superior to that of the DMARD, and they are generally safe and effective in clinical practice, BRM are associated with their own spectrum of unwanted effects that also limit their longterm use (Table 2).

As with many traditional DMARD, the occurrence of a significant infection during treatment with BRM is a signal to stop treatment with these agents until the infection is fully treated and resolves. Further, rare reports of tuberculosis during treatment with etanercept, infliximab, and adalimumab have made it imperative to screen candidate patients for latent tuberculosis before starting treatment with these agents. Lymphoma has been reported in patients treated with BRM. Although the occurrence of lymphoma during treatment with BRM falls within the elevated inherent risk rate in RA patients, the establishment of a possible link between lymphoma and BRM will only become clearer as population studies monitor this risk in patients treated with BRM over the coming 10–15 years. In the meantime, we need to remain vigilant about this potential risk when considering initiating therapy with BRM in our patients. Other signals about the potential risks of treatment with BRM have been seen. There are rare reports of demyelination with some of the BRM; consequently, these drugs should not be used in patients with multiple sclerosis. There have been rare reports of increased mortality with the use of TNF-α blockers in patients with Class III and IV congestive heart failure, and for this reason these agents are contraindicated in these patients. In addition, because these drugs are administered parenterally, all the BRM are associated with injection site or infusion reac-

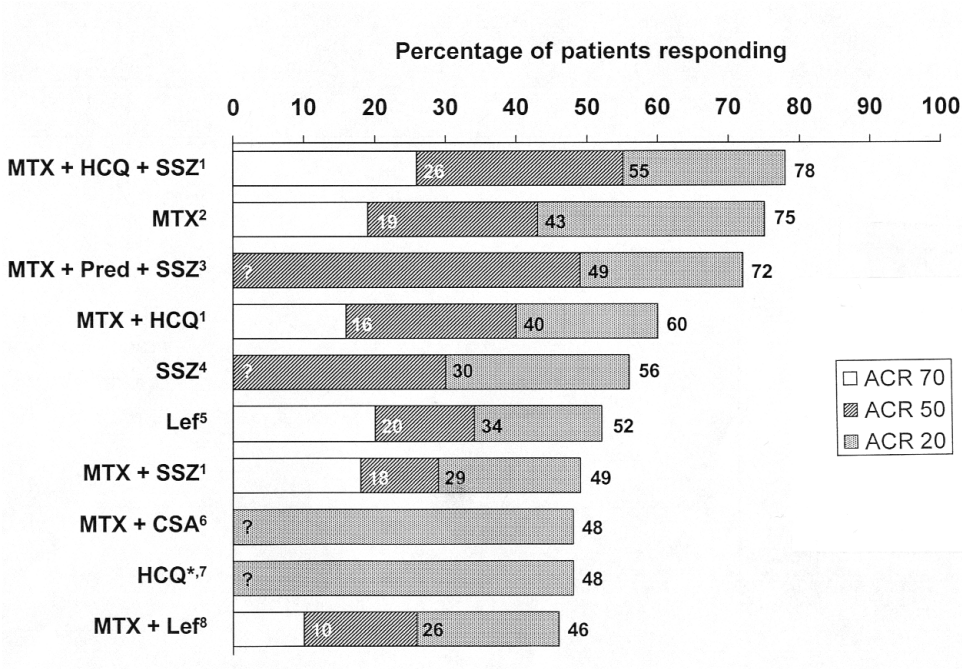

Figure 1. Clinical efficacy of traditional DMARD in RA[1-8]. *Paulus criteria; ?: ACR70/50 not reported/available/ achieved; CSA: cyclosporin A; HCQ: hydroxychloroquine; Lef: leflunomide; MTX: methotrexate; Pred: prednisone; SSZ: sulfasalazine.

Table 1. Adverse effects of traditional disease-modifying antirheumatic drugs (DMARD) limiting their longterm use in rheumatoid arthritis. Adapted with permission from Paget. Rheumatoid arthritis. The Arthritis Foundation; 1997 [9].

	Adverse Effects						
	Hematologic	Hepatic	Lung	Renal	Infection	Lymphoma	Other Events
DMARD							
Gold salts	+++	–	+	+++	*	?	Skin
Hydroxychloroquine	+	–	–	–	–	?	Eye, skin
Sulfasalazine	++	++	+	–	*	?	GI, skin
Methotrexate	+++	+++	+++	–	*	?	Malaise
Azathioprine	+++	+	+	–	*	?	Pancreas, cancer
Leflunomide	++	++	++	–	*	?	HTN, skin
Penicillamine	+++	+	+	+++	*	?	SLE, MG
Cyclosporin A	+++	++	–	+++	*	?	HTN, skin

+++: high risk; ++: moderate risk; +: low risk; –: no known risk; ?: risk unclear; *hold in face of infection; GI: gastrointestinal; HTN: hypertension; SLE: systemic lupus erythematosus; MG: myasthenia gravis.

tions, although these are generally mild and self-limiting.

CONCLUSIONS AND FOREWORD TO THE SYMPOSIUM

In conclusion, although the introduction of BRM into clinical practice has heralded a new treatment paradigm in the treatment of RA, a role remains for new therapies that – through a different mechanism of action – may overcome the limitations of the currently available agents. In the first instance, such agents would need to show that they can elicit a clinically meaningful response in patients with active RA who have had an inadequate response to current therapies. They would also need to exhibit good tolerability and safety in patients who are unable to tolerate current agents. If such agents are successful in this scenario, we would be justified in expecting improved symptomatic response over current therapies in RA patients who are DMARD- and/or BRM-naive.

Table 2. Safety comparisons of biological response modifiers.

	Etanercept	Infliximab	Adalimumab	Anakinra
Serious infectious episode	Warning	Warning	Warning	Warning
Tuberulosis	Rare	Rare	Rare	None
Sepsis	Warning	Warning	Warning	Warning
Malignancies	SEER	SEER	SEER	SEER
Lymphoma	? RA	? RA	? RA	? RA
Demyelination	Rare	Rare	Rare	None
Hematologic	? Rare	? Rare	? Rare	? Rare
Congestive heart failure (III/IV)	Caution	10 mg/kg contraindicated	? Contraindicated	No reports
Injection/infusion reaction	Yes	Yes	Yes	Yes

Source: U.S. Food and Drug Administration labeling. SEER: Surveillanace, Epidemiology, and End Results Program: no difference from national cancer database, ? RA: difference from inherent elevated risk of lymphoma in RA patients unclear, Rare: < 0.1% of the treated population.

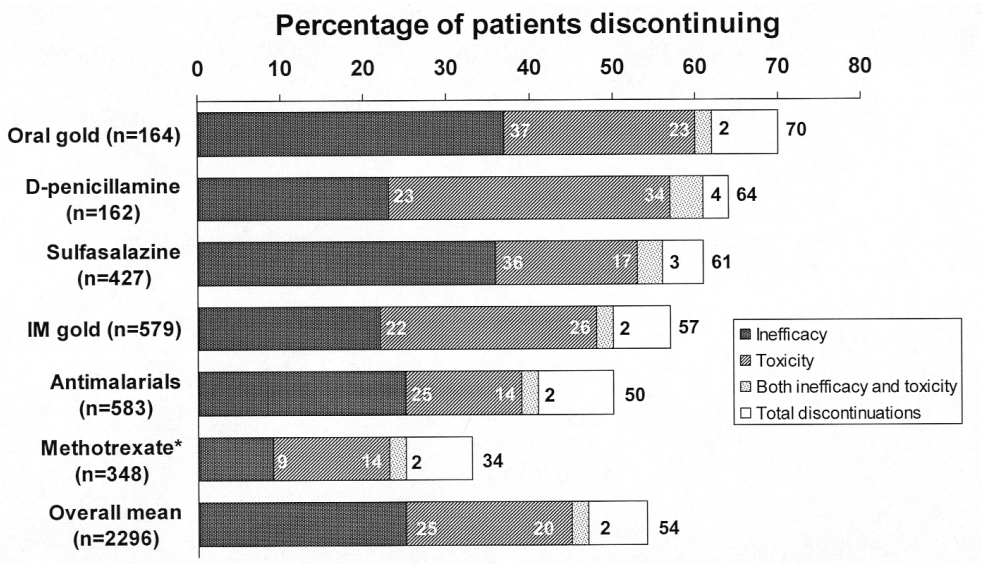

Figure 2. Reasons for discontinuation of traditional DMARD in patients with RA. IM: intramuscular; *study completed in 1994 — no other choices available at that time for those with inadequate effect requiring alternative therapy after MTX. Source: Retrospective audit of records of patients with onset of RA between January 1985 and June 1994[10].

One of the alternative approaches being investigated is B cell-targeted therapy. There has been a resurgence of interest in recent years concerning the role of B cells in the pathophysiology of RA, and emerging evidence has given increased impetus to the contention that therapeutic agents that selectively deplete target B cells may be of therapeutic value in the treatment of RA. The following articles by distinguished experts in this field of study will explore the mechanisms in immune-mediated inflammatory disease, the evidence for the role of B cells in the pathophysiology of RA, and the effect of B cell-targeted therapy in patients with active RA and other immune-mediated conditions.

It is only by seeking new ways to treat an old disease and asking questions that are often difficult to answer that we can make progress towards the ideal but elusive goal — a cure.

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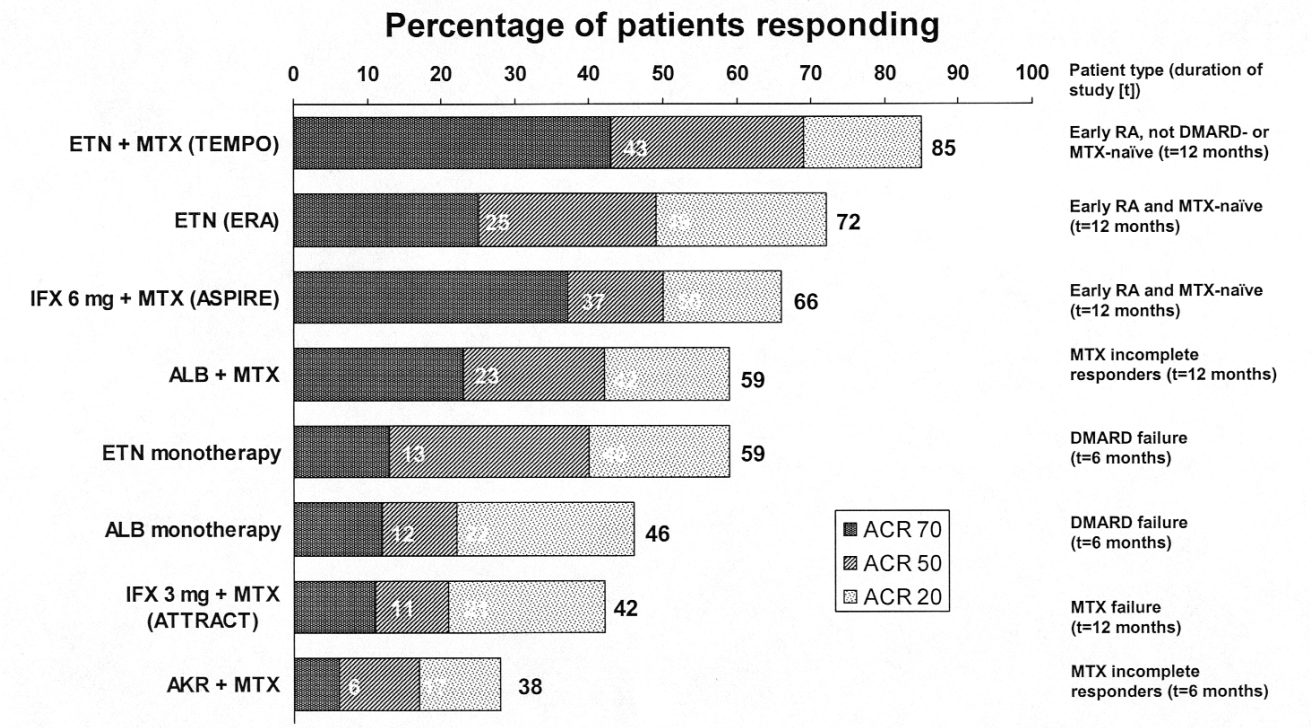

Figure 3. Clinical efficacy of biological response modifiers in RA. AKR: anakinra; ALB: adalimumab; ETN: etanercept; IFX: infliximab; MTX: methotrexate; DMARD: disease modifying antirheumatic drug[11-18].

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