

Treatment Options for Rheumatoid Arthritis

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Presentation Summary

Over the last several decades, approaches to the management of rheumatoid arthritis (RA) have been empirical. Subsets of RA patients respond well to traditional disease-modifying antirheumatic drugs (DMARDs), either as single therapy or in combination. However, a significant population remains untreated or undertreated. The lessons learned from DMARD strategies have led to stratification of patients based on observed or expected disease progression. At the same time, clinicians have gained a better understanding of the immunology and immunopathophysiology of RA. The advent of monoclonal antibody technology and other advances in

biotechnology have resulted in the development of agents that target specific components of the immune response. Recent trials with 2 anti-tumor necrosis factor (anti-TNF) alpha chimeric antibody agents, etanercept and infliximab, have shown promising results, both as proof of concept and in more rigorous clinical trial populations (eg, patients who are refractory to DMARDs). Future directions include combination DMARD/biologic agent therapy, and other molecular strategies targeted to parts of the immune response that appear to be dysregulated in RA patients. Stratifying patients will hopefully lead to more tailored and targeted therapies and a more cost-effective approach to RA management.

The goal of treating rheumatoid arthritis (RA) patients is to keep them functional—by whatever means. Maintaining function has a significant positive impact on quality of life. The famous painter Pierre Auguste Renoir suffered profoundly with RA and spent many of his later years in a wheelchair, yet he painted nearly until his death with the help of family members who tied the paintbrush to his hand and dipped the brushes in the paint. Renoir remained “functional” despite the pain but only through sheer force of will and the social support of family members.

The History of RA Treatments

New therapies for treating RA are imminent, and they are causing much excitement in the rheumatology community. This anticipation is partly due to the pattern of successes and failures in RA management. The evolution of treatment strategies has been a “long and winding road,” with many of the treatments introduced erroneously into RA management or borrowed from other diseases. Table 1 lists the agents considered to be the standard treatments for RA—disease-modifying antirheumatic drugs (DMARDs). Although these have been beneficial to many patients, many

clinicians are frustrated because these treatments are not able to accomplish all that was hoped for in RA. Clearly, the presence of so many treatments indicates that no one of them is a cure.

One of the most significant problems with DMARDs has been that patients are unable to continue therapy for long periods of time (ie, not more than 1 to 2 years), either due to inefficacy or adverse events. Patients

need a treatment that will be well tolerated and effective over the disease course (ie, 20 to 30 years).

The “therapeutic pyramid” was developed as a means of standardizing RA management; the pyramid typically began with nonpharmacologic treatments, then moved on to several nonsteroidal agents. Only after failing those treatments were DMARDs such as gold and hydroxychloroquine used, with the aggressive therapies used as a last resort (at the very top of the pyramid).

The frustration with suboptimal efficacy was coupled with a paradigm shift of what RA actually was. In the late 1990s, there is a much deeper understanding of the immunology and immunopathophysiology surrounding RA. In the 1970s, clinicians felt that RA was mostly benign with many patients going into remission after a few years of the disease. By the 1980s, the full impact of RA disease progression was appreciated. Clinicians realized that RA can be an aggressive disease. The malignment and erosion of joints observed in X-ray images and counts of swollen, deformed, or limited-motion joints ultimately affect functional status (ie, the ability to work).¹ Even if patients are working, they are not advancing in their jobs, and many are unable to work at all.

Functional status also correlates with survival.² Patients with the most severe functional impairment (including the inability to perform activities of daily living) show significant decreases in survival rates, comparable to other diseases such as advanced atherosclerotic disease and some neoplastic diseases. So, the new paradigm of RA as an aggressive disease that can affect function and survival, coupled with the suboptimal results observed with DMARDs, spurred the change in RA management.

Understanding RA as an Aggressive Disease

Early studies with large populations supported this new treatment

Table 1. DMARDs for Rheumatoid Arthritis*

■ Azathioprine	■ Hydroxychloroquine
■ Cyclosporine	■ Leflunomide
■ D-Penicillamine	■ Methotrexate
■ Gold (injectable)	■ Sulfasalazine
■ Gold (oral)	

*Appearing alphabetically.

Table 2. Rheumatoid Arthritis: Patient Evaluation

Clinical Manifestations	Slowly Progressive	Aggressive
Swollen joints	Few	Many
ESR or CRP	Normal or modestly elevated	Markedly elevated
Radiographic erosions	Absent	May be present
Rheumatoid nodules	Absent	May be present
Extra-articular manifestations	Absent	May be present
Serum rheumatoid factor	Normal or modestly elevated	Markedly elevated
Functional status	Preserved	Impaired

ESR = erythrocyte sedimentation rate. CRP = C-reactive protein. Patients can be stratified into 2 groups based on clinical parameters. Stratification helps to predict which patients will have more aggressive disease and therefore affects treatment approaches.

paradigm. Rheumatoid arthritis patients treated early in the disease course with DMARDs showed good results in decreased pain, decreased disability, fewer tender and swollen joints, and a decrease in the acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate).³ Given these results, what prompted the need for new treatments?

The DMARDs clearly were effective for a subset of patients, but there remained another subset for whom these agents were not effective.⁴ In one market analysis, patients who were treatment failures with DMARDs constituted almost one third of those on drug therapy. It is possible that this group of patients might have the most aggressive disease requiring new therapeutic strategies.

Identifying Patients with Aggressive RA

Certain genetic alleles predispose patients to a more aggressive disease course.⁵ However, clinical definitions or parameters may also be used to stratify patients and they are more readily available and less expensive than genetic testing. In addition, genetic predispositions are not uniformly noted in racially distinct groups of patients.

Clinical practice calls for the stratification of patients so those likely to have an aggressive disease course can be identified. Combinations of risk factors for such serious or severe disease have been found to correlate with outcomes such as functional disability and accelerated mortality. Other characteristics that are sometimes used to label patients as having refractory disease include steroid dependency and failure to respond to DMARD therapy.

A number of clinical parameters can be measured that, along with genetic testing, can act as surrogates (Table 2). A patient with 8 swollen or tender joints would be expected to have a better prognosis than someone

with 30 or 40 swollen joints. Persistently elevated acute-phase reactants are also a bad sign, indicating joint destruction. Those with rheumatoid nodules on the arms or

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on other places, or rheumatoid lung involvement, are more likely to have aggressive disease. Functional status is also an important issue as it correlates directly with disease progression, as discussed earlier.

By identifying refractory patients and measuring these clinical parameters, patients can be stratified, which affects the treatment approach. Patients with aggressive RA have traditionally been treated in a stepwise fashion, ie, they were given one DMARD, then others in sequence to find one that worked. Today, combination therapies are used, much like treatment strategies for oncology. The hope is that together they will have an additive or synergistic effect, without incurring excess toxicity. Several studies have shown that the combination of methotrexate/sulfasalazine/hydroxychloroquine is more effective than single therapy.^{6,7} Methotrexate, in particular, is an important agent and is the foundation of current approaches to treating people with RA, either as single therapy for milder disease or in combination as more aggressive therapy. One approach to the treatment of patients with aggressive disease would be to use optimal doses of methotrexate initially. If this is insufficient, the next step could include the addition of anti-TNF

agents, or the use of other DMARDs or combinations of DMARDs.

Biotechnology and RA

Despite the documented success of combination DMARD therapy, there remains a subset of patients who do not respond to these treatment approaches. For them, the new classes of biologic agents under development offer hope.

The advent of biotechnology in the 1970s introduced the monoclonal antibody (a murine antibody produced from the fusion of a myeloma cell that no longer produces antibodies and a murine B cell). Murine antibodies offer specificity to human antigens but, unfortunately, are immunogenic over time in humans. Chimeric antibodies, in which the antigen-binding region is murine but the rest of the antibody is human, address some of those problems.

A deeper understanding of the immunology of RA has enabled the development of specific biologic agents using monoclonal antibody technology. These agents target specific points in the immune cascade, which is thought to have become dysregulated in the RA patient. Normally, cytokines play a key role in keeping the inflammatory immune response in homeostasis. The effects of proinflammatory cytokines such as tumor necrosis factor alpha (TNF α) and interleukin-1 (IL-1) are usually kept in balance by anti-inflammatory mediators such as soluble TNF receptors and IL-10 and IL-1 receptor antagonists.⁸ This balance of stimulatory and inhibitory factors is typical of other processes in the body, such as the clotting/fibrinolytic cascade. The activities of TNF α include upregulating the immune response, inducing other inflammatory mediators, and directly causing bone and cartilage damage.⁹ It is at the center of many immune processes and is a pivotal molecule in RA.

Several studies have confirmed the

value of targeting TNF α . The initial studies were “proof of concept” trials. In a study evaluating the effect of single doses of a chimeric anti-TNF α antibody, infliximab (1 or 10 mg/kg), patients showed significant improvement in tender and swollen joint count, pain scores, and patients’ assessment of disease severity, as well as decreases in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) after 4 weeks.¹⁰ While the results were encouraging, the data clearly showed that the parameters of RA activity returned to baseline or near baseline, especially in the lower-dose group. This study was especially exciting, however, because previous T-cell directed agents (eg, anti-CD4, anti-CD5) gave promising results in open trials but did not stand up to rigorous analysis against placebo.

Etanercept, a similar agent—the soluble form of the TNF receptor (2 TNF receptors attached via an immunoglobulin piece)—was evaluated in a similarly designed study. Etanercept functions much like an antibody by soaking up excess TNF α .¹¹ At 3 different doses (0.25, 2, and 16 mg/m²), etanercept was given twice a week for 3 months and then stopped. Again, the results showed dramatic, dose-dependent decreases in swollen joint counts, but the disease activity returned when treatment was stopped. A Phase III trial has examined the effects over 6 months with similar positive results compared with placebo. The trial has moved to open label for up to 2 years.

The strategy for optimal treatment approach emerged from these exciting results. Combination therapy, using a biologic agent and a DMARD, has been under consideration. Also, the measure of success has expanded from singular clinical parameters (eg, ESR, numbers of swollen/tender joints) to composite indices, or a responder index, where several parameters are measured and weighted. For example, some patients may have

less tender joints, yet the disease itself does not improve. So one of the ways to really separate active treatments from a placebo response is to demand that several parameters of disease improve.

The most common responder index is the ACR 20, developed by the American College of Rheumatology (ACR).¹² Patients must experience at least 20% improvement in tender and swollen joint counts, as well as a minimum of 20% improvement in 3 of the 5 core set measures: patient and physician global assessments, pain (visual analog scale, VAS), disability (MHAQ/ HAQ, Modified Health Assessment Questionnaire/Health Assessment Questionnaire), and an acute-phase reactant (ESR or CRP). This is a more stringent way of evaluating disease in RA patients.

Using the responder indices, a new trial was performed using infliximab. One of the intentions of using TNF inhibitors as a class was to be able to use them long term and have sustained efficacy, and to use them in RA patients who still have active disease despite the use of methotrexate. In this study, patients had used a median of 3 previous DMARDs, including methotrexate; 37% had already had joint surgery. This was a population of patients who could clearly benefit from this treatment approach. The anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial studied 2 doses of infliximab (3 or 10 mg/kg) in 2 dosing schedules (either every 4 or 8 weeks) compared with placebo. All patients, including those in the placebo group, took methotrexate.¹³

The results indicated that the different doses are comparable, as were the different dosing regimens. At least 50% of patients from each treatment group had an ACR 20 response.¹³ However, since it was not clear that patients with 20% fewer swollen joints or a 20% lower sedimentation rate actually feel significantly better, it

seemed that more stringent criteria were needed.

The results were analyzed again in terms of an ACR 50 and ACR 70. (For the ACR 50 and ACR 70, a minimum of 50% and 70% improvement, respectively, is required for the parameters as described in the ACR 20.) An ACR 70 response may be considered as "approaching remission." Approximately one third of each treatment group showed an ACR 50 response, and up to 18% showed an ACR 70 response in the higher dose (10 mg/kg every 8 weeks).¹³ Given that this population had very severe disease with no response to methotrexate, these data are impressive.

In a similar etanercept/methotrexate trial, the ACR 20, 50, and 70 data were similar (71%, 39%, and 15% of each treatment group, respectively), indicating that both therapies are effective at inhibiting the effects of TNF α .¹⁴ Why do we not see this response in 100% of the study participants? The data raise interesting questions regarding the immune systems of these patients. It is possible that the disease may be heterogeneous, and that TNF may play a less important role for some patients.

Table 3. Costs of Therapies for Rheumatoid Arthritis: Approximate Medication Costs for 6 Months

Agent	Cost (\$)*
Methotrexate	600
Sulfasalazine	600
MTX/HCQ/SSZ	600-1750
Cyclosporine	2400
Leflunomide	1500
Infliximab [†]	3000
Etanercept	5700

*In US dollars.

[†]Based on a dose of 3 mg/kg administered every 8 weeks for a 65-kg patient. HCQ = hydroxychloroquine; MTX = methotrexate; SSZ = sulfasalazine.

Future Directions

Despite the promising results with biologic agents and combination therapies, we live in an era of cost containment. The costs for current standard and newer therapies for 6 months can elicit “sticker shock” (Table 3). While the acquisition costs may be higher or lower than expected, depending on the treatment, a more global view of “cost” is required to properly evaluate each treatment. Issues such as monitoring and treating toxicity, and the cost of untreated RA, need to be considered. To date, many of the medications used for treating RA have been inexpensive and rheumatologists have normally managed the therapy of RA patients without substantial influence (eg, guidelines) from payers. The higher price tag for biologic agents may change that.

Current approaches are focusing on identifying the most appropriate treatment strategy for each particular patient, which means stratifying patient populations so treatment can begin earlier for those with the most aggressive disease. The better responses with a tailored approach are, in turn, expected to be more cost effective (where “cost” is defined by clinical and societal parameters).

Conclusion

Paradigm changes in RA patient management have led to the stratification of patients based on disease progression, both measured and projected. Future interventions are focusing on biologic agents (targeted at cytokines, cell surface receptors, chemokines, and immune mediators) in combination with DMARDs. The goal, however, has not changed—disease modification and optimizing outcomes.

Future goals may include tolerance induction and specific immunomodulation as advances in biotechnology provide the opportunity for very targeted therapies. Promising interven-

tions may include human monoclonal antibodies, orally available TNF α inhibitors, molecular approaches such as antisense DNA, other combinations of agents, and other antigen/immune response-specific therapies.

The long and empirical history of RA management appears to be narrowing in on its target, resulting in more appropriate therapies for specific subsets of patients. More efficacious and potentially cost-effective therapies (overall) can improve quality of life, thus keeping RA patients more functional for longer than ever before.

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