

Advances in the Treatment of Rheumatoid Arthritis: Costs and Challenges

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Rheumatoid arthritis is the most common form of inflammatory arthritis. Because of advances in therapy, clinical outcomes have improved dramatically and remission is possible for many patients. These advances have come with many challenges, prompting consideration of strategies to improve diagnosis and treatment and implement more cost-effective care.

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by polyarticular joint involvement in association with extra-articular manifestations that include accelerated cardiovascular disease. This disease affects approximately 1% of the population and occurs in women 2 to 3 times more frequently than in men. RA is often considered an autoimmune condition because of the expression of certain characteristic autoantibodies, including rheumatoid factors (RFs) and antibodies to citrullinated proteins (ACPAs). If not treated adequately, RA can lead to persistent pain, deformity, and disability, causing major personal and societal costs [1].

Because of recent advances in pharmacologic therapy, the outcomes of RA have improved dramatically and remission is now possible for many patients. These advances derive from increased scientific understanding of the disease as well as the development of new therapeutic agents that more specifically target important disease mediators. Among these agents, the biologics have produced dramatic results in well-designed clinical trials. Biologics are protein molecules and include monoclonal antibodies (eg, infliximab) or soluble receptors (eg, etanercept). Real world clinical experience fully supports the results obtained in these trials [2].

The improvement in RA outcomes has come with significant financial costs, of which medication has been a major contributor. Balanced against these financial costs are the benefits that medication offers individual patients, including greater work participation as well as enjoyment of life. As a disease that affects primarily women, RA has a major impact on family life and child rearing; current therapy can reduce that impact in a way that extends the benefits beyond the patient herself.

While clinical outcomes have improved, the costs of care for RA and other forms of inflammatory disease demand consideration of strategies to allocate resources more efficiently and effectively. At present, there are several nodes or points in the care continuum of RA where new approaches can be considered to allow the benefits of new therapy to increase while moderating direct financial outlays. In some instances, these approaches focus on allocation of medical personnel and, in other instances, on refinement in medication use. Research is essential to make these adjustments in care.

Current Framework of Rheumatoid Arthritis Therapy

Two overriding concepts guide early RA treatment: early aggressive therapy and treat to target (T to T) [3, 4]. Early aggressive therapy is the prompt institution of agents to decrease inflammation and thereby prevent the joint destruction that leads to pain and disability. In general, agents to treat RA can reduce inflammation by blocking immune mediators or by modulating the number or functional properties of immune cells. Agents that can ameliorate the signs and symptoms of RA and reduce the progression of damage are known as disease modifying anti-rheumatic drugs (DMARDs). DMARDs can be synthetic small molecules or

TABLE 1.
Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Classes of DMARDs	
Conventional synthetic	Methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine
Biologic	TNF blockers (infliximab, etanercept, adalimumab, golimumab, certolizumab); T cell co-stimulatory blocker (abatacept); anti-IL-6 receptor (tocilizumab); anti-CD20 (rituximab)
Targeted synthetic	Tofacitinib

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biologics (see Table 1). Methotrexate and TNF blockers are 2 of the most commonly used agents. Many others targeting new mediators and pathways are in development [2].

For any disease, the administration of optimal therapy depends upon achieving a target. Frequently, the target is a laboratory value such as glucose or hemoglobin A1c, although a physiological measure can also be a target (eg, blood pressure). For RA, the target is disease activity. While a number of different indices for assessing disease activity has been developed (see Table 2), in general, they include only a few clinical or laboratory parameters. A sample of joints (eg, 28 or 44 joints) frequently suffices for assessing disease activity [5, 6].

Each of the indices has a defined target value for remission or for low disease activity. The goal of treatment is therefore to achieve that target as quickly and safely as possible, and continue therapy for as long as necessary to sustain remission or low disease activity. There has long been interest in the possibility that, at its earliest stages, RA is especially amenable to therapy, such that treatment in that period can have long-lasting benefits that permanently alter disease outcome. Such a hypothetical period has been called the “window of opportunity” [7].

From these considerations emerge 4 places where current care has features that both raise issues about resource allocation care and form the basis of future innovation.

Key Nodes in Rheumatoid Arthritis Care

Early Diagnosis and Treatment

The key to improving RA outcomes is early diagnosis and treatment, but this goal is frequently not achieved, reflecting patient, provider, and system issues. While RA is a common disease in the population, osteoarthritis (OA) is far more frequent and is the usual disease to which the term arthritis is used. Patients developing joint symptoms from RA often believe that they are experiencing the expected symptomatology that occurs with OA and aging. Patients may self-medicate, and time frequently passes before they seek medical attention. At that point, the disease may have progressed to the stage of damage. Education directed at the public is therefore essential to convey the messages that arthritis occurs in different forms and that joint pain is not an inevitable consequence of life.

Correspondingly, professional education is also important. Unfortunately, education for health care providers frequently lacks adequate instruction on musculoskeletal disease in general. When confronted by a patient with persistent joint pain and swelling, primary care providers may themselves not recognize the tell-tale evidence of RA. Furthermore, many patients with RA, depending on the pattern of joint involvement, may seek help from health care providers such as physical therapists to deal with a particularly painful or swollen knee, for example. Education on RA and related forms of inflammatory arthritis, as well as musculoskeletal disease in general, should therefore be

TABLE 2.
The Measurement of Rheumatoid Arthritis Disease Activity

Clinical and laboratory measures
Tender joint count
Swollen joint count
Measure of inflammation (sedimentation rate, C-reactive protein)
Patient global assessment
Provider global assessment

Note. Examples: CDAI (Clinical Disease Activity Index); DAS28 (Disease Activity Score); SDAI (Simplified Disease Activity Index).

increased, requiring funding to support teaching activities for health professionals.

At present there is a severe shortage of rheumatologists, physicians with specialized training in RA [8, 9]. This shortage is likely worldwide, and even in locations where there are rheumatologists, access may be limited due to a variety of factors (eg, significant delays in obtaining a referral). The solution to this problem is the development of better systems for patient triage and the creation of early arthritis clinics. In Europe, early arthritis clinics have been in operation for many years because of the increased access to specialty care inherent in their health care systems. Not surprisingly, European investigators have been in the forefront of research on the diagnosis and treatment of early RA and the development of early aggressive therapy and T to T.

Treat to Target

Early aggressive therapy with T to T approaches is designed to reduce inflammation, prevent damage, and alter the course of disease to limit late complications. As shown in many clinical studies, numerous agents alone or in combination can achieve this goal. Indeed, there are likely too many possible approaches to obtain hard evidence as to whether there is a preferred way. In general, an agent to rapidly reduce inflammation is an important element in early aggressive therapy and provides a foundation for other DMARDs to act [10, 11], with methotrexate as the anchor drug for most patients. Glucocorticoids at high doses are frequently used in this setting, although these agents carry significant toxicity and often are not well tolerated by patients, especially those with coexistent illness such as diabetes or hypertension.

Another approach to early aggressive therapy involves the use of biologic therapy, specifically tumor necrosis factor (TNF) blockers, in association with methotrexate. Given the pleiotropic actions of TNF, blocking this cytokine has many immunological effects, including a prompt reduction in inflammation marked by almost instantaneous pain relief and increased patient energy and well-being. TNF blockers also have powerful DMARD actions and could be considered for monotherapy, although in general they are used in association with methotrexate. The major difference between glucocorticoids in combination with methotrexate and therapy with a TNF blocker and methotrexate is cost [12]. TNF

blockers are much more expensive and therefore payers try to limit their use to patients whose disease cannot otherwise be controlled.

Early aggressive therapy is therefore a junction point in RA treatment where cost considerations become very real. While biologic therapies are effective, they are expensive. The alternative approach of combination therapy with conventional DMARDs, such as hydroxychloroquine and sulfasalazine together with methotrexate (so-called “triple therapy”) and the use of glucocorticoids as bridge therapy, is also effective [12]. It is much less expensive, but it involves several agents and the inclusion of glucocorticoids and their associated side effects.

Many rheumatologists believe that initial therapy with a TNF blocker along with methotrexate represents one of the best current approaches to RA therapy. The side effect profile is also favorable. Nevertheless, cost considerations limit the use of this combination. The compromise is a more gradualist approach in which patients are treated with methotrexate first for a period of time (usually 3 months). For those patients who have not achieved a remission or low disease activity, an additional agent or agents, including a biologic, is added, with payers making judgments on the sequencing of agents or requesting justification for use of a biologic, as opposed to a less expensive combination.

This approach adds time and delay and incurs costs in communication and justification between a provider and payer; it also entails an administrative staff to navigate the system where there are multiple payers. As will be discussed later, the availability of biosimilars may change this situation and simplify the application of early aggressive therapy.

DMARD Withdrawal and Discontinuation

Fortunately, the treatment of RA with therapy has advanced to the point where many patients can achieve remission or a state of low disease activity. In the face of such attenuated and quiescent disease, patients and providers may both ask whether continuation of aggressive therapy is still necessary, or whether reduction in therapy is possible. This is a new situation, and data on the advisability of modifying DMARD therapy are just becoming available. These studies, which involve elimination of therapy or dose reduction, suggest that, at least for some patients, modification of the intensity of DMARD therapy is possible. While some patients may flare if a biological agent is eliminated, at least some may maintain their remission [13-15].

The elimination of an expensive agent and the obvious cost saving is an attractive approach for payers and pharmacy managers who wish to constrain expenditures. The future will undoubtedly see many studies to address this issue, and important questions will be asked, including: Do aggressive approaches differ in the likelihood of inducing remissions that can be maintained with the reduction or withdrawal of DMARDs? Do existing clinical measures give an accurate picture of ongoing inflammation or do they fail

to detect silent disease that will continue to cause damage and disability? Does elimination or reduction of DMARDs affect the occurrence of later complications such as cardiovascular disease [16]? Data on these questions are needed for system-wide planning, resource allocation, and determination of best practices.

Biosimilars

The current considerations of the cost of care reflect current pricing. Although the field is filled with agents displaying similar levels of efficacy (including 5 TNF blockers), competition has not yet significantly affected drug pricing. The advent of biosimilars for biologics may alter this equation. Biosimilars are analogous to generics for small molecule drugs, although the technology for producing a protein and synthetic small molecule are sufficiently different that an alternative terminology is appropriate. A biosimilar shares the protein sequence with the originator product, but the conditions of production and purification may introduce some differences. These products are thus similar, with the extent of identity more difficult to assess [17, 18].

Price competition will likely occur between the originators and the biosimilars, rather than between the originator products. Nevertheless, the cost savings can be large, although the magnitude will depend on the health care system and the nature of the price negotiation. For rheumatologists, an important question concerns the reallocation of money that will be saved by any switch to a biosimilar. Will these savings be used to allow treatment of more patients with RA with biologics? Will they be used to support the therapy of patients with other diseases? Will they be used to simply reduce costs?

Conclusion

Rheumatology is a dynamic field in the midst of a treatment revolution that is leading to dramatically improved outcomes for patients with RA. Along with all other providers, rheumatologists are well aware of cost issues and look forward to working with other stakeholders to assure that the benefits of modern treatment can extend to as many patients as possible in a way that meaningfully balances costs and outcomes. NCMJ

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