Current and future management approaches for rheumatoid arthritis

Ferdinand C Breedveld

Leiden University Medical Center, Leiden, The Netherlands

Correspondence: Professor Ferdinand C Breedveld, MD, Leids Universitair Medisch Centrum, Stafcentrum Reumatologie, Albinusdreef 2, Leiden 2333 ZA, The Netherlands. Tel: +31 71 526 3598; fax: +31 71 526 6752; e-mail: f.c.breedveld@lumc.nl

Abstract

With the introduction of new disease-modifying antirheumatic drugs (DMARDs) and other therapeutic agents, the management of rheumatoid arthritis (RA) has shifted toward earlier, more aggressive therapy. The ultimate goal is to prevent structural joint damage that leads to pain and functional disability. Early diagnosis of RA is therefore essential, and early DMARD treatment combined with nonsteroidal anti-inflammatory drugs is recommended. Combination DMARD regimens and new biologic agents (anti-tumor necrosis factor [TNF] therapies [infliximab, etanercept] and the interleukin [IL]-1 antagonist [anakinra]) have emerged as viable options for early treatment of RA patients. These new biologic agents and future nonbiologic agents that target proteins in signaling cascades are likely to change the landscape of RA treatments.

Keywords: rheumatoid arthritis, disease-modifying antirheumatic drugs, emerging therapies, infliximab

Introduction

The management of patients with RA has changed considerably over the past several years. The introduction of new DMARDs prompted the emerging trend among rheumatologists to treat RA patients earlier and more aggressively.

The ultimate goal in managing RA is to prevent structural joint damage and loss of function. Recent evidence suggests that early intervention is important in achieving this goal. In this new management setting, more attention is given to the differentiation between RA and other types of arthritis, particularly osteoarthritis. Initial evaluation of RA patients should include the risk of developing self-limiting arthritis, persistent nonerosive arthritis, and persistent erosive arthritis. In addition, strategies aimed at providing access to optimal medical care for this patient population need to be addressed.

To reduce the progression of RA, the vast majority of RA patients should be treated with DMARD therapy shortly after the diagnosis. An accurate method of monitoring disease activity is needed to assess the effect of this therapy. Rapid and sufficient control of disease activity is needed to prevent joint damage, loss of function, and to maintain quality of life. Combination DMARD therapy may, in this respect, provide additive effects or allow dose reductions to avoid toxicity. Optimal management also includes patient education and the involvement of a multidisciplinary team of health care providers to minimize the impact of the disease on the individual's functional activity. The following is a discussion of these issues in the treatment of RA patients.

Early RA

Because DMARD treatment is justified only when the risk benefit is favorable, it is mandatory to differentiate between

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ACR = American College of Rheumatology; ACR20 = ACR 20% response criteria; DMARD = disease-modifying antirheumatic drug; IL = interleukin; MTX = methotrexate; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

RA and other forms of arthritis as early as possible after the development of symptoms [1]. The 1987 American College of Rheumatology (ACR) criteria for RA have often been used as a diagnostic tool in patients with recent-onset arthritis. However, these criteria were not developed in patient populations in need of a diagnosis, and therefore the diagnostic ability in early RA is likely to be suboptimal.

In a collaborative effort, several groups involving data sets of patients with early arthritis are developing diagnostic criteria [2]. In these studies, the gold standard for diagnostic indicators will be defined by the clinical outcome after years of follow-up. This activity will provide a set of criteria that will allow discrimination between self-limiting, persisting nonerosive, and persistent erosive arthritis early in the course of the disease. An internationally accepted diagnostic model will allow construction of a therapeutic algorithm in which levels of probability for persistent arthritis are linked with choices for DMARD treatment.

Poor prognosis with respect to joint destruction is suggested by early age of RA onset, high titer of rheumatoid factor, high levels of acute-phase proteins, high numbers of involved joints, and early occurrence of joint erosions [3,4]. The presence of these factors indicates a 75% probability that clinically significant joint damage will occur. The ability to predict joint damage can be improved; however, current predictors are already influencing therapeutic choices.

Monitoring of RA
Accurate monitoring of disease progression is mandatory to assess therapeutic efficacy of agents that slow or inhibit structural joint damage and limit long-term disability. Because of the heterogeneity in disease progression between individual patients, a composite evaluation of a variety of clinical parameters is needed. The selection of an evaluation index should be governed by parameters sensitive to changes that are easy to obtain, are not redundant, and have high predictive attributes for long-term disease outcome [5].

Both the European League Against Rheumatism and the ACR have defined core sets of disease activity measures for RA with the goal of providing uniformity in the assessment of outcome in clinical trials [6,7]. These measures include tender and swollen joint counts, patient and physician global assessments of disease activity, acute-phase reactants, and pain and physical disability assessments. Each core set has proven viability and reliability, and has a high level of agreement.

However, these core sets have limitations. The ACR 20% response criteria (ACR20) are composed of a combination of ratios and do not provide an absolute measure of changes in activity. Additionally, the European League Against Rheumatism Disease Activity Score is complex. Because of these limitations, these indices have not been introduced into day-to-day clinical practice for the assessment of RA treatment.

To avoid these limitations, Smolen et al. [8] recently proposed a simplified disease activity score (DAS). Using the sum score of the tender and swollen joint counts (28 joints), patient and physician global assessments of disease activity, and the C-reactive protein level, high correlations are obtained with validated measures. This simplified index may be a viable supplement to the core sets and can be implemented in daily clinical practice. In addition, when used in clinical trials, this index would have an intuitive familiarity, thereby allowing the practitioner to compare the results of clinical trials with familiar clinical observations.

Pharmacologic treatment
The initial drug treatment for RA involves the use of salicylates, nonsteroidal anti-inflammatory drugs, or selective cyclooxygenase-2 inhibitors to reduce pain and improve motion. Low-dose oral glucocorticoids and local injections of glucocorticoids are highly effective for relieving symptoms in patients with active RA, and prolonged treatment appears to have disease-modifying properties [9]. However, because these agents do not affect disease progression, they should not be used as monotherapy in RA. All RA patients are therefore candidates for DMARD therapy to prevent structural joint damage and maintain function. Furthermore, referral from a primary care physician to a rheumatologist is recommended in the event of clinical suspicion, as delay induced by the desire for a confirmation of a diagnosis often results in disease progression before effective treatment is initiated.

Early initiation of DMARD therapy is advocated to prevent irreversible structural joint damage. van der Heijde reported that approximately 75% of RA patients with early disease have joint erosions or develop erosions within the first 2 years after the onset of symptoms [10]. Three studies have compared the use of early single-DMARD treatment with the delayed approach and reported that early introduction of DMARD therapy is associated with a better outcome after 1 or 2 years of treatment [11–13]. Furthermore, a recent evaluation of primary data from 14 randomized clinical trials in RA patients indicates that patients with a longer disease history do not respond to DMARD therapy as well as patients treated at earlier stages of the disease [14]. Importantly, major side effects of early DMARD treatment are manageable, which supports the conclusion that all early RA patients should be treated with DMARDs. The large majority of RA patients are eventually subjected to the potential side effect of DMARD therapy; it is thus pointless to delay early treatment that may improve long-term outcome. Early DMARD treatment may also result in reduced total health care costs.

The DMARDs most frequently used include methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide. The choice of a DMARD for an individual patient is based on many factors, including the efficacy/toxicity spectrum of a drug, monitoring requirements, costs, and patient variables such as prognosis, comorbidity, and preferences. MTX has a prominent place in the therapeutic armamentarium of many rheumatologists. A generally accepted guideline for MTX use is that the drug should be prescribed as monotherapy when initial treatment with another DMARD has not achieved disease control. On failure of MTX monotherapy, combination therapy with MTX and other DMARDs is considered for the next line of therapy [15].

The most recently approved DMARD is leflunomide (Arava™; Aventis Pharmaceuticals, Kansas City, MO, USA), a pyrimidine synthesis inhibitor that has both immunosuppressive and immunomodulatory effects. Leflunomide inhibits T-cell proliferation, autophosphorylation of epidermal growth factor receptors, and activation of nuclear factor-κB [16,17]. The efficacy of leflunomide was investigated in three large, phase II clinical trials [18–20]. Leflunomide significantly increased the proportion of patients who experienced an ACR20 score and significantly improved tender joint counts, swollen joint counts, and physician and patient global assessments compared with placebo. However, MTX and sulfasalazine were found to be as effective as leflunomide. Common adverse events associated with leflunomide included gastrointestinal disorders, alopecia, skin rash, and elevated liver enzymes. Nevertheless, given the comparable efficacy and the improved safety profile of leflunomide compared with MTX, many physicians regard leflunomide as a good alternative [20].

Many rheumatologists already prescribe combination therapy even though evidence to support combination therapy was limited until recently [21]. Three main strategies are often used in combining DMARDs, and include parallel, step-up, and step-down regimens. Data from an increasing number of trials that support combination therapy have recently been completed. Step-down bridge therapies that include corticosteroids have been shown to provide enhanced efficacy with low toxicity [22–24]. In patients with a long history of disease, leflunomide [25,26] improved a suboptimal response to MTX, and the triple combination of MTX, sulfasalazine, and hydroxychloroquine appears to be clinically superior compared with the agents used in monotherapy [27].

Because of the immunosuppressive properties of DMARDs, the combination of leflunomide with MTX or any other immunosuppressive agent needs to be closely monitored. Indeed, most of the rare reports of pancytopenia in patients receiving leflunomide occurred in patients who had recently discontinued or were receiving concomitant immunosuppressive agents. Further studies are required to determine whether any combination of DMARD therapy provides improved efficacy. Many new therapeutic strategies are being investigated for RA. The most advanced product under development is the IL-1 receptor antagonist (anakinra), a biologic agent that has to be administered by daily subcutaneous injections.

Nonpharmacologic treatment
Reconstructive surgery can provide great improvement for patients with end-stage joint damage that is causing unacceptable pain or limitation [28]. However, despite the achievements of pharmacologic and surgical treatment, many patients are left with residual disability. Regular participation in conditioning exercise programs improves mobility, strength, and well-being, and does not increase arthritis activity [29]. RA patients may therefore benefit from a variety of rehabilitation programs.

Recent evaluations suggest that physical therapy, occupational therapy, psychosocial support, and the care of nurse practitioners and orthopedic surgeons is more effective when given by a multidisciplinary team [30]. The additional value of team care may be explained by enhanced communication, the specific mix of professional expertise, and the increased attention provided to the patient.

Emerging therapies
Dynamic and fast-growing insights into cell biology and the understanding of inflammation have resulted in a new appreciation of the pathophysiology of RA. It is now believed that RA is mediated by a vast array of cells and soluble factors that recruit immune cells and perpetuate inflammation [31]. Although the primary antigen is unknown, the initial autoimmune response is associated with an infiltration of T lymphocytes that secrete chemotactic agents, particularly TNF-α and IL-1. These chemotactic agents recruit lymphocytes, macrophages, and B cells to the synovial interstitium of the joint. Extracellular signals also activate complex intracellular signaling pathways, alter messenger RNA synthesis, and increase the production of pro-inflammatory cytokines. Increases in pro-inflammatory cytokines lead to further cell recruitment of macrophages and the activation of synovial fibroblasts, chondrocytes, and endothelial cells in a synovial capsule [32]. Activation of these cell types further increases cell migration to the area, and leads to more inflammation, cartilage degradation, and increased bone resorption.

Developments in molecular biology and computational chemistry have allowed the design of agents that specifically target pro-inflammatory cytokines. IL-1 is elevated in the synovial fluid of RA patients and is thought to contribute to the pathophysiology of the disease [33]. IL-1

receptor antagonist is a naturally occurring cytokine that competes with IL-1 for binding to the IL-1 type 1 receptor, but does not initiate the IL-1 signaling transduction cascade on binding to the IL-1 type 1 receptor [34]. Fujikawa et al. [35] demonstrated that IL-1 receptor antagonist production is reduced in synovial cells isolated from RA patients.

Anakinra (Kineret™; Amgen, Thousand Oaks, CA, USA), a recombinant nonglycosylated form of IL-1 receptor antagonist, is an approved therapy for RA patients. The efficacy and safety of anakinra was demonstrated in three double-blind trials. In those studies, patients treated with anakinra experienced significant improvements in tender and swollen joint counts, pain scores, morning stiffness, and radiographic progression [36–39]. Anakinra treatment was associated with injection-site reactions, a higher incidence of neutropenia compared with placebo, and an increased risk of infection. Interestingly, neutralizing concentrations of IL-1 receptor antagonist reduced the production of IL-6 and IL-8, but not TNF-α, in rheumatoid synovial membrane cultures [40]. In contrast, anti-TNF-α antibodies neutralized not only TNF-α levels, but also IL-6, IL-8, and IL-1 levels, suggesting that TNF-α may play a more central role in the pathophysiology of RA.

This apparent central role of TNF-α has led to the development of a new class of agents (anti-TNF antagonists) that includes infliximab (Remicade®; Centocor, Malvern, PA, USA), a chimeric monoclonal antibody specific for TNF-α, and etanercept (Enbrel; Immunex, Seattle, WA, USA), a fusion protein of the p75 TNF receptor and immunoglobulin G1. Anti-TNF antagonists have been shown to inhibit the development of polyarthritic disease in collagen-induced arthritic mice [41,42] and in mice that constitutively express human TNF-α [43].

Etanercept exhibits a lower specificity than infliximab and binds to both TNF-α and lymphotoxin-α. Nevertheless, the efficacy of etanercept in the treatment of RA patients was demonstrated in several phase II/III studies. Moreland et al. [44] reported that, at 3 months, patients treated with etanercept achieved significant improvement in swollen and tender joint counts, morning stiffness, physician and patient assessment scores, erythrocyte sedimentation rate, and quality of life.

Further evidence to support the use of etanercept in the treatment of RA has been reported by Weinblatt et al. [45]. In that study, 71% of patients treated with 25 mg/week etanercept achieved an ACR20 score at week 24 compared with 27% of patients treated with placebo (P < 0.001). Bathon et al. [46] also reported a significant increase in the number of etanercept-treated patients achieving an ACR20 compared with MTX.

However, no advantage was seen for etanercept at 6 months. Nevertheless, etanercept slowed joint damage in patients with early RA by significantly reducing joint erosion, although no benefit on joint space narrowing was observed.

Infliximab has also been shown to be effective in the treatment of RA patients. In a phase II trial (ATTRACT study), 428 patients with active RA despite MTX were treated with or without infliximab. Significant improvements in swollen and tender joint counts and rheumatoid factor and C-reactive protein levels occurred at 30 weeks, and were maintained through week 54 [47,48]. In addition, response to treatment occurred rapidly, with approximately 90% of the ultimate responders achieving an ACR20 after only two treatments (6 weeks). This improvement in clinical score was maintained through week 54 [48]. Importantly, infliximab significantly inhibited joint erosion, joint space narrowing, and total radiographic score progression at 54 weeks and through week 102 (P < 0.001) [48,49].

Clearly, anti-TNF therapy provides significant benefit to patients with RA. However, because TNF is a normal component of the immune system, some investigators have questioned whether blockade of TNF could lead to an elevated risk of infection. Although infections are more common in the RA population relative to the general public, there is a concern that anti-TNF therapy may increase serious infections. Indeed, serious infections and sepsis have been reported in postmarketing reports in patients treated with etanercept and infliximab. Furthermore, rare cases of tuberculosis have been reported in patients treated with TNF antagonists. Nevertheless, with proper screening and care in observing patients susceptible to infections, anti-TNF therapy can provide the benefits of reduced structural joint damage and improved quality of life for the majority of RA patients.

According to international consensus, patients are candidates for treatment with biologic agents if DMARD treatment fails to achieve disease control [50]. Nevertheless, studies in selected areas of efficacy, toxicity, and the general use of TNF antagonists are still needed to help further define the most appropriate use of these agents. The success of TNF inhibitors in treating RA suggests that inhibition of other upstream and downstream members of extracellular and/or intracellular signaling cascades may also prove to be of therapeutic benefit.

At present, biologic agents have been shown to be effective and have the advantage of specificity over other agents, such as DMARDs. However, the development of nonbiologic inhibitors with improved safety profiles compared with current DMARDS may lead to improved outcomes and reduced costs.

Conclusion

Earlier DMARD treatment and the use of new biologic agents such as the TNF and IL-1 antagonists have begun to alter the treatment practices of rheumatologists. Further experience in the use of these, and of agents not yet developed, alone and in combination with DMARDs, is likely to lead to further changes in the manner in which rheumatologists treat this debilitating disease.

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