Rheumatoid Arthritis: Principles of Early Treatment

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ABSTRACT. Early diagnosis and effective treatment is considered to be important in the prevention of joint damage and disability in patients with rheumatoid arthritis (RA). This hypothesis has led to the establishment of special early arthritis clinics in many centers. The lag times between onset of symptoms of RA and diagnosis, and the introduction of disease modifying antirheumatic drugs, have been greatly reduced. Treatment strategies have become increasingly refined. Moreover, newer therapies have increased the options for limiting early joint damage and subsequent disability. (J Rheumatol 2002;29 Suppl 66:9–12)

Key Indexing Terms:
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INTRODUCTION

The potential importance of recognizing and treating rheumatoid arthritis (RA) in its earliest stages has been argued forcefully[1]. It is assumed intuitively by many that effective early suppression of synovial inflammation will directly prevent the progression of cartilage and bone degradation and associated functional impairment. In a longitudinal study over 19 years, an almost linear progression of joint damage was demonstrated[2]. There was a high correlation with measures of systemic inflammation, especially during the later phase of the study. Similarly, a significant correlation between the rate of progressive joint damage and the acute phase response was demonstrated in patients with early RA[3]. An important observation from the study of patients with early RA was that irreversible joint damage becomes established soon after the onset of disease. For example, in a cohort of patients with symptoms of RA for less than one year who were evaluated prospectively, 70% demonstrated evidence of radiographic joint damage after only 3 years' followup[4]. Moreover, the rate of progressive damage during the first year of followup was significantly more than in the second and third years.

EARLY DIAGNOSIS AND TREATMENT OF RA

Early diagnosis. There are some limitations to early diagnosis of RA. First, there are no early onset disease-specific features. Clinical assessment is operator dependent and, therefore, subject to bias. Often, the characteristic physical signs develop gradually over time. The overall sensitivity of the 1987 American College of Rheumatology (ACR) criteria for the classification of RA was 91%[5]. When applying the same criteria to patients with early RA (less than one year), the sensitivity was only 81%. Moreover, in a subsequent study of early RA, it was demonstrated that the 1987 ACR criteria were even less sensitive than the 1956 criteria[6]. In addition, the laboratory tests employed in diagnosis also lack sensitivity and specificity. For example, in patients with early RA, IgM rheumatoid factor demonstrated a specificity of 91% for the diagnosis of RA and a sensitivity of 54%, with positive and negative predictive values of 74% and 81%, respectively[7].

The introduction of dedicated early arthritis clinics over the past decade, with the emphasis on fast-track referral to a multidisciplinary rheumatology service, has resulted in much earlier diagnosis of RA. In a study reported from The Netherlands, 141 patients attending an early arthritis clinic were diagnosed with RA within 2 weeks of referral, 74 definite RA and 67 probable RA[8]. Only 4 of the patients diagnosed as definite RA required a change of diagnosis at one year. Thirty-two of the patients with a diagnosis of probable RA at 2 weeks were diagnosed as definite RA at one year, 16 remained probable RA, and 11 required a change of diagnosis. This study confirmed both the feasibility and the reliability of establishing a diagnosis of RA in dedicated early arthritis clinics.

Factors that may contribute to the delayed introduction of effective treatment to patients with early RA relate to the lag times between the onset of symptoms and the first referral to a rheumatologist, the diagnosis of RA, and the first use of disease modifying antirheumatic drug (DMARD) therapy. For example, in a study conducted in the UK, the median delay between the onset of symptoms and the first referral to a rheumatologist was 23 months during the period 1987 to 1989. This delay was reduced to 7 months between 1990 and 1993, and to 4 months between 1994 and 1997[9]. A similar improvement was observed in the median lag times between the first rheumatology encounter and the first use of a DMARD: before 1986, 32 months; 1987–1989, 21 months; 1990–1993, 8 months; 1994–1997, 1 month. In the US, the median total lag time between the onset of symptoms and the diagnosis of RA was approximately 9 months[10]. In this study, the median delay between the first medical encounter and diagnosis of RA was 4 months.

Conventional treatment. Most clinicians choose the thera-

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peutic approach for RA that is most likely to rapidly alleviate the symptoms of joint inflammation. Nonsteroidal antiinflammatory drugs (NSAID) and low dose corticosteroids can often provide satisfactory rapid relief of pain and stiffness. The slow acting antirheumatic drugs (SAARD) usually provide more sustained relief of symptoms. However, in choosing which therapeutic agent to prescribe first to patients with early RA, the physician needs an understanding of its capacity to slow the rate of progressive structural damage. Unfortunately, the classification of SAARD as agents that effectively decrease the rate of progressive structural damage remains controversial, as many of the earlier randomized clinical trials of drugs such as gold salts, D-penicillamine, and azathioprine were not designed to evaluate this aspect adequately, or they utilized radiologic outcome measures that were not validated. Therefore, the attempted classification of drugs into categories such as symptom modifying antirheumatic drugs (SMARD), DMARD, and disease controlling antirheumatic treatments (D-CART) was based on limited evidence to support the inclusion of some conventional non-targeted drugs.

There are several historic approaches to the treatment of RA. These include the "pyramid," the "step-down," the "sawtooth," and the "graduated step-up" approaches. The pyramid approach involves a gradual escalation of the potency of prescribed treatments. In this approach, DMARD were invariably prescribed after joint damage was established. This approach is now considered obsolete.

An example of the step-down approach that was previously proposed included early prescription of 10–20 mg/day prednisolone, followed by the introduction of a DMARD if prednisolone could not be successfully tapered after one month[11]. This scheme was never validated by randomized clinical trials. A successful example of the step-down approach was the COBRA trial, which evaluated efficacy in patients with RA for < 2 years[12]. Prednisolone 60 mg/day was combined with methotrexate (MTX) 7.5 mg/day, and sulfsalazine (SSZ) 2 g/day. Prednisolone was gradually tapered to 7.5 mg/day, and discontinued after 28 weeks. The combination regime was compared to SSZ given alone. It was concluded that the combination step-down protocol was superior to monotherapy, with additional disease control and slowing of structural damage for up to 2 years after discontinuation of prednisolone.

The sawtooth strategy has also been evaluated in early RA. The principle behind this approach requires the measurement of variables at diagnosis and, subsequently, at regular intervals. Therapeutic decisions to control disease progression are made according to preset clinical criteria. The application of this strategy suggested an improved outcome[13].

The graduated step-up approach involves initial staging of RA into mild, moderate, and severe. Patients with mild disease might receive an NSAID in combination with a DMARD such as hydroxychloroquine (HCQ) or SSZ. Patients with moderate RA might receive gradually escalating doses of MTX and, sequentially, combinations of HCQ, SSZ, or both. Patients with more severe RA are now likely to receive up to 25 to 30 mg MTX per week followed, in some countries, by targeted biologic agents that inhibit either tumor necrosis factor (TNF) or interleukin 1 (IL-1).

Combination therapy. MTX is considered by most rheumatologists to be the drug of choice in RA because of its safety profile and its potential to reduce symptoms and signs, and prevent progressive structural damage[14]. However, a significant number of patients treated with MTX in monotherapeutic regimes fail to achieve optimal disease control. This failure has resulted in the development of several DMARD combination regimes, both in Europe and the US, that usually include MTX. As reported, combining 2 or more DMARD with different modes of action has the potential to produce a range of outcomes in relation to both efficacy and toxicity[15]. The ideal outcome of combination DMARD therapeutic strategies is one that is synergistic for efficacy, and lacking any additive effects on toxicity.

Much consideration has been given to the indications for use of combination DMARD regimes in RA. Some studies have evaluated the role of combination therapy as the initial approach to treatment in early RA. Others have examined the effects of introducing combination regimes to patients who have failed to respond adequately to maximal doses of MTX. One protocol that successfully demonstrated significant longterm symptomatic and radiographic benefits from the early introduction of combination therapy was the COBRA trial[12]. Studies that compared the combination of MTX and SSZ to monotherapy regimes of the same compounds failed to demonstrate significant differences[16,17]. A study that evaluated the early introduction of triple combination DMARD therapy in RA compared MTX, SSZ, HCQ, and low dose prednisolone to SSZ with or without prednisolone. The triple combination regime was associated with a superior rate of remission after 2 years[18].

Patients who fail to achieve an adequate response to MTX treatment, usually given orally in escalating doses that reach a maximum of 15 to 25 mg/week, or who relapse after an initial satisfactory response, may benefit from weekly subcutaneous administration of MTX, because gastrointestinal absorption can be highly variable. Unfortunately, a considerable number of patients who receive adequate doses of MTX fail to demonstrate acceptable relief of symptoms or retardation of structural damage. Several studies have evaluated the effects of combining other DMARD to maintenance MTX treatment in patients exhibiting a partial response to MTX alone. The first of these studies used a cyclosporine/MTX combination protocol[19]. The combination of cyclosporine and MTX was significantly superior to maintenance MTX monotherapy after 6 months, but cyclosporine dosage adjustments due to elevations in serum creatinine levels were necessary in some. Moreover, continued use of cyclosporine was associated with

a high rate of withdrawal, most commonly due to elevated creatinine levels, hypertension, and lack of sustained efficacy. MTX has also been studied in combination regimes with SSZ and HCQ in patients with established RA. In one study, 3 therapeutic strategies were compared: the triple combination, SSZ and HCQ, and MTX monotherapy[20]. The triple combination demonstrated significantly greater efficacy, as well as fewer withdrawals.

The combination of MTX and leflunomide has also been studied in patients demonstrating an inadequate clinical response to MTX monotherapy (mean dose 17 mg/week)[21]. Seventy-seven percent of the patients completed one year of combination therapy. Fifty-three percent met the ACR 20% response criteria. In general, treatment was well tolerated, with the exception of raised liver enzyme levels. Ten percent of the patients withdrew because of persistently elevated serum transaminases.

Finally, the use of MTX in combination with targeted cytokine inhibition has been associated with impressive clinical and radiographic benefits that are discussed below. An exciting possibility for future therapeutic advancement is the combination of targeted treatments that modulate the biologic effects of more than one cytokine, or other critical mediators, in the complex pathophysiologic pathways associated with RA. Liver enzyme levels should be monitored at monthly intervals.

Low dose corticosteroids. The effects of low dose corticosteroid therapy (prednisolone ≤ 7.5 mg/day) on the symptoms and signs of RA can be immediate and dramatic. In current clinical practice, low dose corticosteroids are frequently prescribed in early RA to provide adequate relief of symptoms while awaiting full expression of the beneficial effects of MTX or other DMARD. The prednisolone dosage may then be reduced, or even discontinued, depending on the clinical course. In addition to the effects on the symptoms and signs of RA, low dose prednisolone may have important beneficial effects in the prevention joint damage[22]. High dose prednisolone is commonly prescribed for vasculitis, mononeuritis multiplex, and for acute pericarditis and pleurisy.

The following is a reasonable approach to prescribing low dose prednisolone for some patients with RA[23]. In patients with active disease for less than 2 years, low dose prednisolone may reduce the rate of articular damage, whether or not erosions are already established. In patients with active RA for 3 to 5 years, it may be prudent to add low dose prednisolone to reduce the risk of developing further erosions, but prednisolone should not be added if erosions are not present, as the likelihood of new erosions developing in those patients is extremely small. There are few indications for prescribing low dose prednisolone to patients with RA for more than 5 years. Low dose prednisolone may be prescribed to pregnant women who have had to discontinue an effective DMARD, those with persistent active disease, or those who suffer a disease flare during or immediately after pregnancy.

Patients with worse RA are likely to receive higher cumulative doses of corticosteroids. The combination of more severe disease and greater corticosteroid exposure increases the risk of progressive loss of bone density. Therefore, monitoring of bone density and effective prevention of osteoporosis is essential.

CONCLUSION

Current recommendations for the treatment of RA may be considered in the context of both initial treatment of early disease and treatment of established disease when MTX fails to provide an adequate response[15]. In most circumstances, the optimal treatment of early disease is MTX, commencing with a dose of 7.5 to 10 mg/week, and escalating in doses of 2.5 to 5 mg/week at monthly intervals, until maintenance of 15 to 25 mg/week is achieved. Prednisolone 5 to 10 mg/day is sometimes added in order to achieve rapid symptom relief while awaiting final expression of the MTX effect. Prednisolone should be reduced to a minimal maintenance dose, or discontinued if possible, after 4 to 6 months. An incomplete therapeutic effect should be followed by aggressive step-up to a combination DMARD regime, which could include HCQ, SSZ, or leflunomide. In the more severe disease categories, or when combination DMARD treatment is unsatisfactory, the introduction of targeted treatments that inhibit TNF-α or IL-1 should be considered in appropriate patients. Similarly, in patients with established RA who fail to respond to oral and/or subcutaneous MTX, an aggressive step-up to combination DMARD therapy, or a switch to targeted therapy in combination with MTX is advised.

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