Rheumatoid arthritis (RA) is a disease characterized by joint destruction, leading to major disability, personal and societal economic burdens and reduced life expectancy. Evidence is accumulating that joint damage is an early phenomenon, and progresses relentlessly over the years. There is, moreover, a direct causal link between synovitis, anatomical damage and disability.\(^1\)

A consensus has thus emerged over the years that the key goals of therapy in RA are early, rapid control of joint inflammation and prevention of joint destruction. To achieve these goals, disease-modifying antirheumatic drugs (DMARDs) are now being used in higher doses or in combination.

Recently, a better understanding of the pathogenesis of RA led to the development of a new class of DMARDs called “biologic agents.” These new drugs are capable of selectively targeting pathogenic elements of disease. Several of these agents, for example, have been developed to target tumour-necrosis factor α (TNFα), a pivotal cytokine in the disease process.

Based on the above premises and developments, an effective therapeutic regimen in clinical trials must demonstrate: clinical improvement (defined by the American College of Rheumatology [ACR] response criteria)\(^2\) and retardation of radiographic progression assessed by standardized x-ray scoring methods (the most widely used being the Sharp or the Modified Sharp techniques).\(^3\)

Using data from well-designed, randomized controlled trials—and information gained from its wide pragmatic use—methotrexate (MTX) has emerged as the most widely used first-line DMARD. MTX is not only shown to improve the signs and symptoms of RA, but also to slow its radiographic progression.

Unfortunately, remission on MTX is achieved in few patients only, although a majority exhibit some clinical improvement (the so-called “partial responders”).

The most significant unmet rheumatological need, therefore, is currently an effective agent to provide additional benefit to patients whose arthritis is only partially responsive to MTX.

**SINGLE DMARD THERAPY**

Two compounds will be considered worth reviewing here, of the few agents shown to have significant clinical efficacy and ability to retard disease progression:

**Leflunomide** (Arava\(^{TM}\)) is a novel immunosuppressive compound recently approved by the Health Protection Branch (HPB) of Health Canada for the treatment of RA. The principal mechanism of action of leflunomide is the inhibition of pyrimidine synthesis, thus reducing T lymphocyte proliferation and clonal expansion. Leflunomide was demonstrated to have comparable efficacy to MTX (average dose 13.5mg/week) in two separate trials, with an ACR 20 response around 40%\(^4\). Interestingly, the ACR 50 and 70 responses were both superior to those found with MTX, demonstrating substantial clinical improvement in responders. Leflunomide also slowed disease progression in a fashion similar to that of MTX; moreover, when cases of MTX failure were treated with leflunomide in an open-label uncontrolled study, 50% fulfilled the ACR 20 response criteria. Controlled trials of leflunomide in combination with MTX are currently underway.

**Etanercept** (Enbrel\(^{TM}\)) is the soluble TNF-receptor fusion protein. This agent was the first to bring substantial improvement to patients with severe RA who failed to respond to several DMARDs, including MTX.\(^5\)

In a head-to-head comparison to high-dose MTX in the treatment of early RA (less than three years duration), etanercept showed an earlier onset of action, with a trend to achieve a better ACR response rate.\(^6\) Both agents slowed structural damage in a conclusive fashion when compared to the predicted x-ray progression.

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COMBINATION DMARD THERAPY

Two articles in the medical literature recently reviewed the different DMARD combinations.\(^7,8\) The excellent safety profile of MTX makes it the cornerstone of the five best combinations. In three of these combinations, the second DMARD was an add-on for patients with partial response to MTX.

**MTX plus cyclosporine A (CsA).**\(^9,10\) In a six-month placebo-controlled trial, the addition of CsA achieved a clinically significant response; in the extension phase, patients on placebo were switched to CsA and achieved the same rate of response after six months. Based on a previous placebo-controlled trial and an open-label cohort, CsA was shown to be capable of slowing radiographic progression.\(^11,12\) Thus although the MTX/CsA combination may be considered as a second step for partial responders to MTX, long-term toxicity (hypertension, increased serum creatinine) may limit its use.

**MTX plus etanercept.** The addition of etanercept \((25 \text{ mg sc } 2\times\text{wk})\) achieved an ACR response rate never seen in previous RA clinical trials.\(^13\) In the open-label extension, in fact, with some patients reaching more than 30 months of therapy, this response rate was sustained. Coupled with a very benign toxicity profile, this combination seems to constitute one of the most efficacious therapeutic alternatives available.

**MTX plus infliximab** (Remicade\(^\text{TM}\)). Infliximab is a chimeric anti-TNF monoclonal antibody administered in combination with MTX by intravenous infusion every eight weeks. In the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial, patients with long-standing, moderate-to-severe RA who had a partial clinical response to MTX were randomized to receive placebo or infliximab according to different dosing regimens.\(^14\) The four infliximab groups were statistically comparable to each other, and were superior to placebo; the retardation of radiographic progression in all four infliximab groups was even more impressive. Added to a good safety profile over one year, this combination appears to be one of the most efficacious therapies.

Two combinations were studied as first-line regimens in two separate clinical trials. The triple DMARD therapy—which, from the outset, combines MTX, hydroxychloroquine (HCQ) and sulfasalazine (SSZ)—was tested in a two-year study against HCQ + SSZ or MTX alone.\(^15\) The primary efficacy measure was a 50% improvement in the Paulus composite criteria by month nine of therapy, at which point nonresponders were dropped from the study. The triple DMARD group fared much better than the other two groups, with more than 75% of patients maintaining the 50% Paulus response by two years.

The big limitations of this study are the very small number of patients (31 for the triple DMARD and 36 for the MTX alone) and the lack of any radiographic evaluation. A second trial, with similarly small groups of patients, was presented in an abstract format,\(^16\) but failed to duplicate the same extent of clinical response; only 46% of patients achieved the ACR 50 clinical response, compared to 36% for the MTX+HCQ group.

In the COBRA trial (Combinatieetherapie Bij Reumatoide Artritis) of early RA patients, the combination of SSZ \((2 \text{ gm/day}) + \text{MTX} (7.5 \text{ mg/week}) + \text{prednisone} (60 \text{ mg/day and tapered over 28 weeks})\) was initially better than SSZ alone, but clinical efficacy was similar by week 58.\(^17\) The combination group, however, had a slower radiographic progression when evaluated at week 80. The lack of an “MTX alone” group (with increasing doses up to 17.5 mg to 20 mg) casts a serious shadow on the usefulness of such a combination.

In conclusion, there is ample evidence that if optimal benefit is not achieved with high-dose MTX \((17.5 \text{ mg/week to } 25 \text{ mg/week})\), the addition of TNF antagonists demonstrates a better benefit/risk profile and achieves the two-pronged goal of substantial clinical improvement and slowing of radiographic progression.
Appropriate Uses for Anti-TNF Therapy

The availability of existing treatments for RA demands that the use of new and more costly agents such as anti-TNF therapy be justified. Those therapies most commonly used (such as MTX) fail to prevent the high direct costs (e.g., frequent hospitalization, joint-replacement surgery) and indirect costs (e.g., disability, premature death) of this disease.

There is enough evidence to draw a consensus that it is appropriate to add anti-TNF therapy to an existing regimen of MTX and/or other DMARDs that have failed to achieve sufficient beneficial effect. One would not add anti-TNF therapy without first establishing lack of disease control through treatment with a DMARD—usually MTX at a minimum dosage of 15 mg/week for at least three months.

Anti-TNF therapy also could be considered as a first DMARD for patients whose comorbid conditions might contraindicate other agents, such as those with severe liver or renal diseases.

Recommendation

Given the high disability rate and shortened life expectancy of patients with RA, it is the strong consensus of the Canadian Rheumatology Association that effective therapy with TNF antagonists be made available as soon as possible, and be made readily accessible—through provincial drug plans and private insurers—to all patients for whom this therapy is deemed appropriate. It is expected that the early high cost of TNF antagonists will be offset by lowering the higher costs of morbidity, decreased productivity and earlier mortality.

References