New Therapies for Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is an autoimmune disorder which affects 0.5-1% of the adult population [1-3]. It is characterized by symmetrical, erosive synovitis, and in some cases, extra-articular involvement. In the fifties and early sixties, the treatment of RA revolved around the use of high-dose aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. These drugs provided symptomatic relief but did not have any significant effect on the underlying disease process. In addition, they caused a fair degree of side-effects. Subsequently, disease modifying anti-rheumatic drugs (DMARDs) were added to the existing armamentarium. These included gold, D-penicillamine, chloroquine and hydroxychloroquine. These drugs had their limitations. Sulphasalazine was designed for the treatment of RA but failed in its initial trials to produce benefit. The drug was rediscovered about 30 years later and became an important addition to the other DMARDs. Methotrexate, sulfasalazine, hydroxychloroquine and cyclosporine, either alone, or in combination, have been the principal therapies for RA in the last decade [4-8]. It is now well established that early therapy with DMARDs is critical for better long term outcome in RA [9,10]. Also, combinations of DMARDs are well tolerated and result in better outcome than monotherapy. It is well recognized that erosive changes occur early in the disease, often in the first year [11]. In addition, mortality among RA patients who present early is lower than those who present later in the course of the disease [12]. Early and aggressive therapy is the current standard of care for RA.

The last 4 years or so have seen the advent of several new therapeutic agents for RA. Firstly, safer NSAIDs or 'Coxibs' have become available. The list which began with celecoxib seems to be expanding fast with the addition of rofecoxib, valdecoxib and etoricoxib etc. Secondly, interventions designed specifically to target pathogenic cytokines have reached the clinic. These include most notably, anti-TNF antibody or 'infliximab', soluble TNF- α receptor or 'etanercept' and interleukin-1 receptor antagonist or 'anakinra'. The other very important new agent is, leflunomide.

Specific Cox-2 inhibitors were introduced into clinical practice recently. They reduce the incidence of serious gastro-intestinal events by about 80% of that observed with conventional NSAIDs. Patients likely to benefit most with Cox-2 inhibitors include, elderly, those taking steroids or anticoagulants and those with past history of peptic ulcers. However, these agents lack antiplatelet effect. This has important implications in the context of RA. Recent work has shown that increased mortality in RA is because of higher incidence of atherosclerosis. At present there is uncertainty about the efficacy of even conventional NSAIDs as substitutes for low dose aspirin in coronary artery disease (CAD) prophylaxis. Patients taking low dose aspirin for CAD or stroke must not discontinue it. Coxibs have renal adverse effects similar to those of conventional NSAIDs [13].

Leflunomide is an oral antimetabolite which has shown efficacy in the treatment of RA. It is a pro-drug which is rapidly converted to its active form, which inhibits dihydro-orotate dehydrogenase, the rate limiting enzyme for de novo synthesis of pyrimidine nucleotides. Three large clinical trials [14-16] showed the clinical efficacy and safety of this drug as equivalent to that of methotrexate and sulfasalazine. Currently, the drug merits the status of a very good alternative to methotrexate. Combination of leflunomide with methotrexate has been found to be superior to methotrexate alone [17]. The side effects of the drug in general include nausea, diarrhoea, drug rash, reversible alopecia, transient mild transaminitis and hypertension. It is advisable to monitor the blood pressure and liver functions periodically. Leflunomide is teratogenic and thus contraindicated in pregnant women and those contemplating pregnancy. Similarly, it is also not recommended in men who wish to father children [14].

Advances in the pathogenesis of RA have led to the use of a number of biological agents in the last 2 decades. Recognition of the central role of proinflammatory cytokines (TNF- α and IL-1)

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culminated in the successful use of TNF antagonists and IL-1 receptor antagonist for the treatment of RA. However, the present cost of these drugs is prohibitive, especially, for developing countries. Etanercept was the first of these agents introduced for the treatment of RA. It consists of high affinity type II TNF- α receptors covalently linked to the Fc portion of IgG1. Etanercept has high affinity for TNF- α . The other TNF antagonist is infliximab. It is a chimeric mouse/human anti-TNF- α monoclonal antibody (mAb) developed using recombinant technologies. It binds and inactivates soluble TNF- α . Human IL-1 Ra (Anakinra) is a cloned replica of the human cytokine from which it is derived. All the 3 agents have been shown to be effective in management of RA refractory to multiple DMARDs. Methotrexate is usually combined with these agents [18,19]. This serves the dual purpose of enhanced efficacy and reduced immune response to murine component in the molecule. Significant improvement occurs in 40-60% of patients with truly refractory RA. Joint erosions have been shown to be not only retarded but also healed with anti-TNF agents. This is indeed a remarkable achievement in the context of RA.

The downside of biological agents merits a critical comment. Propensity for infections, particularly tuberculosis is significantly increased [20]. In countries like India, with high prevalence of tuberculosis the estimated risk of reactivation is to the tune of 10%. Often, this is in the form of a disseminated disease with high mortality. Anti-dsDNA antibody may develop in about 15% cases, but frank SLE is rarely observed. TNF antagonists should be avoided in patients with CHF because of risk of deterioration and even death. Pancytopenia and demyelinating neurological disease have also been reported. Last but not the least, their exorbitant cost makes them inaccessible to the vast majority of patients in developing countries.

Extracorporeal immunoadsorption of plasma against a staphylococcal protein A column (Proisorba) was reported to be efficacious in a proportion of patients with severe refractory RA [21]. Keeping in mind, the cost, the method of administration, limited duration of response and high frequency of side effects, this treatment should be considered only for patients with refractory RA.

Randomized double-blind, placebo-controlled trials have shown the efficacy of minocycline in RA [22,23]. Other agents currently under evaluation for potential use in RA include mycophenolate mofetil [24] and B-cell ablative therapy with rituximab (anti-CD20 antibody) [25].

The future for patients with RA looks promising.

Leflunomide represents a true advance in this treatment of RA in recent years. It is orally administered, safe and effective. Biological agents do hold promise, but their scope in the Indian setting is quite limited for reasons stated above. In the end, it must be admitted that cure for RA still eludes us! Treating the disease early and aggressively with DMARDs to prevent joint damage, using NSAIDs judiciously, making full use of various physiotherapy measures and employing joint replacement surgery when appropriate, sums up the present philosophy of treatment. Improving the quality of life should be a major goal of treatment.

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