Review Article

Treatment of Rheumatoid Arthritis in the New Millennium

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Abstract: Rheumatoid arthritis is a major cause of disability. The prognosis is poor despite treatment by disease modifying anti-rheumatic drugs. Their main drawbacks are limited efficacy, high toxicity and failure to arrest joint damage. Researches over the last 20 years have shed greater insight into the immunopathogenesis of rheumatoid arthritis. Allied with advance biotechnology, targeted therapy with biological agents is now used in routine clinical practice. In the new millennium, leflunomide and the cytokine inhibitors, etanercept, infliximab and anakinra provide rheumatologists with more effective treatment that could improve the prognosis and outcome of rheumatoid arthritis.

Keywords: Biologics, leflunomide, outcome, prognosis, rheumatoid

Introduction

The new millennium heralds a new era in the treatment of rheumatoid arthritis (RA). Although a "permanent cure" still eludes us, new treatments are safer and more effective. They promise to improve the life of RA patients by reducing pain and disability.

RA is the common with a prevalence of approximately 0.5-2% world-wide. The overall prognosis of chronic established RA is poor. Life expectancy is reduced with a Standardised Mortality Ratio over 1.5. Chronic synovial inflammation leads to progressive joint damage and consequently functional disability. Thirty percent of RA patients develop radiological joint damage after 1 year and 70% after the second year. After 20 years, most RA patients are disabled. In 1996, the total medical cost in US was over $8501/patient/year.

Traditionally, the main treatment strategy for RA has been monotherapy with slow-acting anti-rheumatic drugs (SAARDs). Although these drugs suppress inflammation and ameliorate symptoms, they do not improve the long-term disease outcome significantly. This is due to their failure to completely abolish inflammation and halt joint damage. Furthermore, they are associated with a high incidence of side effects and 50% of the patients have to discontinue treatment after two years. The long-term prognosis of RA can be improved by changing the traditional treatment approach and introducing new and more effective therapies. Hitherto, the mechanisms of action of many current conventional treatments remains unknown as their entry into rheumatological practice was by serendipity rather than through rational drug research. In contrast, new treatments for RA such as etanercept® (Immunex) and infliximab® (Centocor Inc) were developed based on increased understanding in the pathogenesis of synovitis in RA.

Pathogenesis of RA

RA is characterized by an intense mononuclear cell infiltrate in the hypertrophied synovium. CD4+ lymphocytes, the main orchestrator of cell-mediated immune responses, are present in abundance. RA is also strongly linked to the class II human leucocyte antigens (HLA) DRB1*0404 and DRB1*0401. Since the main function of HLA class II molecules is to present antigenic peptides to CD4+ lymphocytes, this strongly
suggests that RA is caused by an, as yet, unidentified arthritogenic antigen. The antigen could be either an exogenous antigen such as a viral protein or an endogenous protein i.e. an autoantigen such as the cartilage antigen Hc-gp39.

Upon activation by an antigen, CD4+ lymphocytes release lymphokines such as interferon gamma (IFNγ) and interleukin (IL)-2 and increase cell surface expression of IL-2 receptors (IL-2R), leucocyte activation antigen-1 (LFA-1), HLA molecules and CD69. These activated CD4 lymphocytes amplify the inflammatory reaction through their effects on monocytes/macrophages and mesenchymal cells. Cell surface contact via LFA-1 and CD69 as well as IFNγ,9 stimulates monocytes/macrophages and mesenchymal cells to produce IL-1, tumour necrosis factor alpha (TNFα) and matrix metalloproteinases (MMP). Both IL-1 and TNFα are potent pro-inflammatory cytokines.10 They stimulate synoviocytes to produce IL-6, GM-CSF and IL-8.11-13 IL-6 induces hepatocytes to release acute phase proteins such as C-reactive proteins (CRP). IL-1 and TNFα also upregulate the expression of adhesion molecules including intercellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) on endothelial cells. These adhesion molecules act in concert with chemokines, such as IL-8, to enhance recruitment of inflammatory cells into the synovial joints and thereby perpetuate inflammation. IL-1 and TNFα also stimulate synoviocytes to release MMPs that degrade tissue matrix and therefore lead to joint damage.

**Leflunomide: A New Disease Modifying Drug for Rheumatoid Arthritis**

Leflunomide belongs to a new group of immunosuppressants known as malonitrilamides. It is a pro-drug that is rapidly converted by the liver into A771726 which is the active compound.14 A771726 has a long half-life as it is excreted in the bile and reabsorbed from the intestine. It prevents transplant rejection in animal models.15 Randomised controlled trials in RA showed that leflunomide is a disease modifying drug with a rapid onset of action. In a European double blind placebo controlled trial, it was as efficacious as sulphasalazine16 and superior to placebo. Approximately 50% of the leflunomide treated patients achieved the American College of Rheumatology 20% (ACR20) response criteria of clinical improvement. In a similar trial in the US, leflunomide has similar efficacy as methotrexate.17 In both studies, statistically significant disease improvement occurred after 4 weeks of therapy. Leflunomide also improves quality of life as measured by the short form 36 and modified health assessment questionnaire.18 In both the US and European studies, leflunomide reduced progression of radiological joint damage.19

Side effects of leflunomide include diarrhoea, raised hepatic transaminases, leukopenia, reversible alopecia, hypertension, dizziness, abdominal pain and dyspepsia. Fatal but rare pancytopenia and liver necrosis had been reported. Therefore, patients should have regular full blood count and liver function tests to monitor these possible side effects. Leflunomide is teratogenic and should not be used in women who have childbearing potential and are not taking effective contraception precautions. The half-life of leflunomide is long and may take several months before it is completed eliminated from the body after cessation of treatment. Elimination can be accelerated by treatment with cholestyramine.

Leflunomide inhibits T and B cell proliferation20,21 by inhibiting an important enzyme, dihydroorotate dehydrogenase in the pyrimidine pathway.22 Consequently, there is a reduction in uridine triphosphate level although there is a savage pathway that could bypass such inhibition. However, rapidly dividing cells require the savage pathway to generate the necessary quantity of uridine triphosphate. Therefore, pyrimidine synthesis by lymphocytes and other rapidly developing cells is reduced, leading to reduction in DNA and RNA synthesis and cell proliferation.20 Furthermore, leflunomide treated T cells stimulate monocytes to increase the release of IL-1ra & TIMP and decrease the production of IL-1 & MMP.23 This may account for the disease modifying property of leflunomide.

**Biologics**

With new advances in biotechnology, there are many new therapeutic tools, such as monoclonal antibodies (mAbs), recombinant human proteins and soluble cytokine receptors/human immunoglobulin (Ig) constructs, that can modulate the immune response. Monoclonal antibodies are made by hybridomas and are the commonest used biological treatment. They are attractive therapeutic tools because mAbs bind to their target antigens with high affinity and specificity. Furthermore, mAb with different isotypes can mediate
various functions such as complement-mediated cytotoxicity. Initially, their use in human disease was hampered by the development of human anti-mouse antibody which occurred in all patients because most mAbs were murine in origin. Retreatment was therefore less efficacious and was associated with anaphylaxis. This problem has been partially circumvented by the use of chimeric and humanised mAbs. These are generated usually by transfection of the selected variable and constant region genes of immunoglobulin into a myeloma cell line. Chimeric antibodies are murine Ig with their Fc substituted by human sequences. When the framework region of the Fab is also replaced by the human sequences, it is then known as a humanised antibody. Recently, the phage display library technique has allowed us to generate mAbs that are completely made up of human sequences. These "man-made" mAbs are less antigenic and made their use as therapeutic agents in human diseases feasible.

In addition to mAbs, natural cytokine antagonists, immunosuppressive cytokines or soluble cytokine receptors can be used to suppress inflammation. The latter are cell surface receptors that have been cleaved off and act as competitive inhibitors to membrane bound receptors for cytokines. Unfortunately, soluble cytokine receptors have a very short half-life but this can be prolonged by engrafting them to human Ig Fc. The resultant construct also has the advantage of being completely made up of human sequences and therefore is less antigenic.

**TNFα Inhibitors in Rheumatoid Arthritis**

TNFα, is a potent pro-inflammatory cytokine that is produced mainly by activated monocyte/macrophages. Its pathogenic role in RA is supported by evidence from in vitro experiments and animal models. The TNFα transgenic mice, which produce high levels of TNFα, develop a spontaneous inflammatory and destructive polyarthritis resembling RA. Furthermore, in collagen-induced arthritis, disease can be treated effectively by anti-TNFα mAb. In RA patients, increased level of TNFα is found both in the synovial joints and peripheral blood.

**Infliximab**

Infliximab (cA2) is a chimeric anti-TNFα mAb that has been tested in randomised placebo controlled trials in RA. High doses of infliximab (10 mg/kg) produced rapid suppression of inflammation with clinical improvement detectable within one week of therapy. The therapeutic effect of infliximab was dose related and correlated with serum antibody concentration. Both erythrocyte sedimentation rate (ESR) and CRP, dropped rapidly after treatment in parallel with clinical improvement. Furthermore, decrease in plasma IL-6 also correlated with changes in ESR and CRP, therefore confirming the role of TNFα and IL-6 in mediating the acute phase response in RA. After treatment there was a transient increase in circulating lymphocyte numbers akin to that observed with anti-ICAM-1 mAb. This is probably secondary to reduction in the expression of vascular adhesion molecules which is induced by TNFα which has been demonstrated by synovial immunohistology.

Although infliximab suppress synovitis in RA, clinical improvement was transient and lasted 4-8 weeks after a single 10 mg/kg dose. Re-treatments were also effective but the duration of clinical improvement shortened with repeated therapies. This may be due to the development of human anti-chimeric antibody response. The latter could be reduced by concomitant methotrexate therapy. In a randomised, placebo-controlled trial of 101 patients with RA, infliximab or placebo was given repeatedly with or without methotrexate. Many patients developed anti-infliximab antibodies after repeated treatment, but this was reduced by concomitant treatment with methotrexate. Furthermore, 3 mg/kg of infliximab plus methotrexate was as efficacious as 10 mg/kg of infliximab with or without methotrexate. This was confirmed by a larger phase III randomised, placebo-controlled trial in 428 patients with RA. Infusions of the 3 or 10 mg/kg of infliximab were given every 4 or 8 weeks for 30 weeks in patients who were receiving a stable dose of methotrexate. At 30 weeks, the ACR20 response criteria were achieved in 50-58% in patients receiving different doses of infliximab plus methotrexate compared with 20% in patients receiving placebo plus methotrexate. Anti-DNA antibodies were positive in 16% of the infliximab groups compared with 0% in the placebo group. Drug-induced lupus was diagnosed in one patient. Radiological damage was significantly reduced in the infliximab treated groups compared with the placebo group. Physical and mental function as assessed by short form 36 also improved.

The main concern with long term TNFα blockage is immunosuppression. Repeated treatments with infliximab
were associated with increased incidence of infection. A few patients developed or suffered reactivation of tuberculosis. Another worry is the theoretical risk of developing malignancies after chronic TNFα blockade as TNFα is known to kill malignant cells in vitro and is important in tumour immunosurveillance. An unexpected side effect was the development of anti-dDNA auto-antibodies in some patients after repeated treatments. The mechanism for the latter remains unknown.

**Etanercept (Wyeth)**

Although chimeric and humanised mAbs are less immunogenic, they still provoke an immune response especially after repeated treatments. An alternative to mAbs is soluble cytokine receptors-human Ig Fc constructs.

The recombinant human TNFR75-Fc fusion protein, etanercept, was tested in a large phase II placebo-controlled trial. Doses of 0.2 to 1.6 mg per metre$^2$ were administered subcutaneously twice weekly for 3 months. In the high dose group, 75% of the patients experienced at least ACR20 improvement in disease activity. Treatment was well tolerated with only minor side effects.

In two placebo-controlled trials in 168 and 234 patients with RA, respectively, subcutaneous injections of etanercept 25 mg twice weekly resulted in significant clinical improvement. The number of swollen joints decreased by approximately 50% from baseline after treatment for 6 months. Etanercept treatment was well tolerated, with only minor reactions at the site of injection. Synovial biopsies showed a statistically significant decrease in the number of T cells, plasma cells, vascular cell adhesion molecule 1, and IL-1 expression after one month of treatment. Long-term, open-label studies have indicated that the efficacy of etanercept is sustained for over 4 years with continuous treatment, and no major adverse events have developed. Furthermore, the combination of etanercept plus methotrexate was significantly more effective than methotrexate alone in a placebo-controlled trial of 89 patients with RA who had a partial response to methotrexate. Recent studies have also shown etanercept to be better tolerated and more clinically effective than methotrexate in early rheumatoid arthritis. Furthermore, etanercept treated patients had less radiographic joint damage 1 year after treatment than those receiving methotrexate.

**Anakinra, Recombinant Human IL-1ra (Amgen)**

IL-1 binds to two types of receptors: IL-1 receptor type I (IL-1RI) and IL-1 receptor type II (IL-1RII). However, only IL-1RI transmits signals intracellularly, leading to cell activation while IL-1RII does not. Both IL-1RI and IL-1RII exist as soluble forms. These soluble receptors and cell surface IL1-RII compete with cell bound IL-1RI for IL-1 and inhibit IL-1 mediated cell activation. In addition, there is also a naturally occurring antagonist: interleukin-1 receptor antagonist (IL-1ra) which binds to IL-1RI but does not deliver any signal. Therefore, it inhibits IL-1 by competing for IL-1RI. However, IL-1ra needs to be given in concentration 500 times in excess that of IL-1 in order to completely abolish the effects of the latter.

Recombinant human IL-1ra (Anakinra) was tested in RA in a 6-month double-blind placebo-controlled randomised multi-centre trial. Daily subcutaneous injections of either placebo or IL-1ra at doses of 30, 75 and 150 mg were given to 472 RA patients. Local injection site reactions were common and appeared to be dose related. Patients receiving 150 mg/day of IL-1ra (43%) showed a significant response compared with placebo (27%) using the ACR20 response criteria. The acute phase response dropped in parallel with clinical improvement. There was also a significant reduction in the rate of radiological joint damage measured by both the Larsen’s index and the number of erosions after 6 months. Clinical benefit persisted up to 12 months without any increase in toxicity. In a randomised controlled trial of 419 RA patients who had a partial response to methotrexate, IL-1ra or placebo were given by subcutaneous injection daily for 24 weeks. Forty-two percent of the IL-1ra treated patients achieved the ACR20 compared with 23% in the placebo group. Hence, IL-1ra may be used in combination with methotrexate in RA.

Etanercept is also effective in juvenile rheumatoid arthritis. In a randomised, placebo-controlled trial of 51 patients with juvenile polyarticular rheumatoid arthritis, etanercept 0.4 mg/kg of body weight or placebo was injected subcutaneously twice weekly for 4 months or until a flare of the disease occurred. The total number of active joints decreased by 58% from baseline, and joint motion was improved by 80%.
Conclusion

Through better understanding of the pathogenesis of RA, new treatments especially the anti-cytokine therapies have been developed that are safer and more effective. They suppress inflammation, improve symptoms and substantially reduce joint damage. Moreover, they may be used in combination with current SAARDs to achieve better control. These are major advances in the treatment for RA. The prognosis for RA should be much better in this millennium.

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