New Therapies for Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA), which can cause irreversible joint deformities and functional impairment, affects approximately 0.3% of our local population. The etiology of RA is unknown. The inciting antigen drives specific CD4+ T cells proliferation, which contributes to the production of the rheumatoid-factor autoantibody. Consequently, recruited inflammatory cells produce cytokines such as tumour necrosis factor α (TNF-α) and interleukin-1 (IL-1) within the synovial cavity. These cytokines trigger the production of matrix metalloproteinases and osteoclasts, which results in irreversible joint damage. B-lymphocyte dysregulation mediates further damage through complement fixation.

Measuring Response to Drugs in RA

Methotrexate is considered the standard against which newer disease-modifying antirheumatic drugs should be evaluated. Efficacy and the toxic effects of new drugs are usually evaluated in clinical trials of 6 to 12 months’ duration. Improvement is often reported by an outcome measure of the American College of Rheumatology (ACR) called the ACR 20, which is defined as a reduction by 20 percent or more in the number of tender and swollen joints plus 20 percent improvement in at least three of the following five measures: pain, patient global assessment, physician global assessment, self-assessed physical disability, and concentrations of acute-phase reactant. The ACR 50 (improvement of 50 percent or more) and the ACR 70 (improvement of 70 percent or more) are also often reported.

Tumour Necrosis Factor Antagonists

The last few years have seen an expansion of therapeutic options for the treatment of patients with RA. TNF-α is a cytokine released by activated monocytes, macrophages, and T lymphocytes, which promotes inflammatory responses. A high concentration of TNF-α in the synovial fluid of RA patients is associated with bone erosion. Studies in RA patients indicate that blocking TNF improves symptom and retards radiographic erosions. Currently, there are three TNF-blocking drugs available for clinical use, namely, etanercept, infliximab, and adalimumab.

Etanercept

Etanercept, a soluble TNF-receptor fusion protein, binds to TNF and prevents TNF from interacting with its receptors. The half-life is generally four days. The usual dose is 25 mg twice/week or 50 mg once/week by subcutaneous injection. In a double-blind, randomised study in 632 patients with early RA, patients who received etanercept had a more rapid response than methotrexate recipients within the first two weeks, but after 12 months, the ACR 20 response rates were similar—72 percent in etanercept group and 65 percent in the methotrexate group (P=0.16). Other study has shown that patients with inadequate response to methotrexate receive benefit when etanercept is added to their regimen rather than placebo.

Infliximab

Infliximab, first approved for the treatment of Crohn’s disease, is a chimeric IgG1 anti-TNF-α antibody that binds to soluble and membrane-bound TNF-α with high affinity, impairing the binding of TNF-α to its receptor. Its half-life is nine days. The usual dose is 3 mg/kg of body weight given by intravenous infusion at 0, 2, and 6 weeks, then every 8 weeks. Frequent development of anti-infliximab antibodies led to its use in combination with methotrexate rather than as monotherapy. In a study involving 428 patients who had active RA despite methotrexate therapy, infliximab plus methotrexate was significantly more efficacious than methotrexate plus placebo.

After 54 weeks, the ACR 20 response ranged from 42 percent (with 3 mg/kg every 8 weeks) to 59 percent (with 10 mg/kg every 4 weeks). Radiographs of the hand and feet at 30 and 54 weeks showed marked inhibition of total erosion scores. Patients who have suboptimal response or who have relapse following an initial response may improve either if the interval between infusions is decreased or if the dose is increased.

Adalimumab

Adalimumab is a recombinant human IgG1 monoclonal antibody that is specific for human TNF-α. Its half-life is 2 weeks. The recommended dose of adalimumab in adults with RA is 40 mg administered as a single dose by subcutaneous injection. In a randomised, double-blind study, the ACR 20 response rate for adalimumab (46 to 53 percent) was significantly higher than the rate with placebo (19 percent). For suboptimal clinical responses, a weekly 40 mg dose may be beneficial in some patients. Adalimumab appears to have additive effects when used with methotrexate.

Adverse Effects of TNF Antagonists

Although initial studies reported no serious adverse effects, wider use of TNF antagonists had resulted in reports that link TNF-antagonists use with a wide range of adverse events.

Infection

Since TNF is an important regulator of host responses to microbial challenge, infection is a primary concern when using TNF inhibitors. Serious bacterial infections, tuberculosis,
atypical mycobacterial infection, aspergillosis, histoplasmosis, and other opportunistic infections have occurred, and such infections may be more common among patients 65 years of age or older than among younger patients. Tuberculosis has been reported in association with all TNF antagonists. The rate of tuberculosis among patients with RA who had been treated with infliximab was about four times higher than the background rate. Tuberculosis, which usually occurs within the first two to five months of treatment, often arises from reactivation of latent infection. Atypical presentations due to extrapulmonary and disseminated disease may lead to delayed diagnosis and increased morbidity.

Injection-site and Infusion Reactions
Minor redness and itching at the injection site are common among patients who receive etanercept and adalimumab. Drug discontinuation due to injection site reactions is uncommon. Infusion reactions, most often headache, nausea and urticaria, occur in 20 percent of patients during infliximab infusion. These symptoms are usually controllable with the use of anti-histamine or by slowing the infusion rate. Severe infusion reactions occur in 2 percent to 3 percent of patients and may lead to discontinuation of therapy.1

Lymphoma and Malignancy
Population studies have shown a two- to threefold increased rate of lymphoma in RA patients. Increased incidence of lymphoma among patients who receive TNF antagonists, which is estimated to be 2.3 to 6.4 times that in the general population, could be ascribed to either severe RA or its treatment. A causal relationship between lymphoma and TNF antagonists is debatable. Apart from lymphoma, the incidence of other malignancy is not significantly altered in patients receiving TNF antagonists.

Drug-induced Lupus
Antinuclear antibodies (ANA) were detected in approximately 60 percent of patients who were receiving infliximab and methotrexate, as compared with 26 percent of those who were treated with methotrexate alone. Anti-dsDNA antibodies developed after etanercept treatment (in 3 to 15 percent of patients), after treatment with infliximab plus methotrexate (in 8 to 15 percent), and after treatment with adalimumab plus methotrexate (in 5.6 percent). However, drug-induced systemic lupus erythematosus is rare.

Demyelinating Syndrome
Exacerbation of previously quiescent multiple sclerosis and new-onset demyelinating neurologic disease have been reported. Although a causal relationship has not been established, the fact that another TNF antagonist, lenerecept, worsens symptoms in patients with multiple sclerosis renders the association plausible.

Heart Failure
Studies of etanercept and infliximab in heart failure were stopped early because of lack of evidence of benefit and, in case of infliximab, increased mortality.

Pregnancy
There is little available information on the use of TNF inhibitors in women who are or may become pregnant. Infliximab, adalimumab, and etanercept are a category “B” pregnancy risk because there are no controlled studies in pregnant women.

Clinical Use of TNF Antagonists in RA
TNF antagonists appear to be among the most effective drugs available for RA. The response is generally rapid, often occurring within few weeks, although not all patients have a satisfactory response. Anti-TNF therapy should be withheld in patients with active infection and should be discontinued if a serious infection occurs. Chronic or recurrent infection is a relative contraindication. All patients should be screened for latent tuberculosis (history, physical examination, chest radiographs, tuberculin skin testing) before anti-TNF therapy is begun, and should be treated before starting such therapy if they test positive. TNF antagonists should also be avoided in patients with any demyelinating disorder or heart failure, and therapy should be discontinued if such an illness occurs.

Anakinra
Interleukin-1 (IL-1), produced by monocytes, macrophages, and some specialised cells in the synovial lining, has inflammatory effects. IL-1 receptor antagonists (IL-1Ra), a natural inhibitor, down regulates the action of IL-1. In patients with RA, the imbalance between IL-1 and IL-1 Ra is thought to contribute to the persistence of joint inflammation. Anakinra is a recombinant human IL-1 Ra that targets the type 1 IL-1 receptor expressed in many tissues. Since it has a short half-life (6 hour), daily administration (100 mg daily by subcutaneous injection) is recommended. Dose adjustment is required for patients with renal function impairment. Anakinra, alone or in combination with methotrexate, has been shown to be more effective than placebo in randomised, controlled trials involving approximately 900 patients with RA.6 The most common adverse event is dose-dependent injection site irritation, occurring in 50 to 80 percent of patients. The risk of infection, primarily bacterial, appears to be increased. Anakinra may benefit patients who have no response to or are unable to tolerate methotrexate, lefunomide, or TNF antagonists. Concomitant use of anakinra and a TNF antagonist may increase the risk of infections and should be avoided. However, combination of anakinra and methotrexate appears to be well tolerated.

Future Directions
The role of biologic agents in the treatment of diseases other than RA is evolving. TNF antagonists are finding a place in the treatment of many immune mediated inflammatory conditions, including ankylosing spondylitis, psoriasis, juvenile arthritis, Still’s disease, uveitis, and vasculitis. Other new drugs for treatment of RA that have shown promise in clinical trials include rituximab, tacrolimus, and CTLA-4-Ig. The introduction of additional effective therapies for RA will improve the outlook for patients that have poorly or incompletely controlled disease.

References