Issue 16
May 2001

Issues in Emerging Health Technologies

Anakinra: Interleukin-1 Receptor Antagonist Therapy for Rheumatoid Arthritis

Summary

- **Anakinra is an interleukin-1 receptor antagonist (IL-1ra), which blocks interleukin-1 (IL-1), a protein involved in the inflammation and the joint destruction associated with rheumatoid arthritis (RA).**
- **The manufacturer's submission for drug approval is currently under review by Health Canada and the FDA.**
- **In randomized controlled trials, patients with severe RA were treated with anakinra. Significant improvement was demonstrated in several clinical, radiologic and health-related quality of life measures in patients treated with anakinra versus placebo.**
- **Minimal adverse effects, mainly injection site reactions, were reported.**

The Technology

Several inflammatory substances are involved in the natural course of RA. Interleukin-1 (IL-1) has been identified as one of them.[1-3] IL-1 receptors are found on various cell types and when activated, secondary substances are released that mediate inflammation and tissue remodeling. IL-1 stimulates the production of prostaglandins and nitric oxide, both of which are highly inflammatory. Also, IL-1 binding causes the synthesis of chemokines, small proteins that facilitate the entry of neutrophils, macrophages and lymphocytes into tissues. When IL-1 occupies its receptor, these inflammatory processes are initiated, but when IL-1ra occupies the receptor, these events are blocked, because IL-1 cannot bind to the cells.[2] The insufficient production of IL-1ra is thought to modulate the inflammatory effects of IL-1 in RA patients.[1]

Anakinra is the first biologic agent of this type designed specifically to modify the biological immune response by blocking the IL-1 receptor.[4] For this reason, it is called an IL-1ra. Amgen Canada Inc. located in Mississauga, Ontario, manufactures the IL-1ra, anakinra.

Regulatory Status

Amgen Canada Inc. filed for drug approval for anakinra with Health Canada and the submission is currently under review. As of May 2001, anakinra had not been approved for use in Canada. Amgen Inc. has also filed with the Food and Drug Administration (FDA) in the United States and has yet to receive approval. Amgen has applied for regulatory approval in Europe and Australia.[5]

Patient Group

In Canada, RA affects an estimated 300,000 people, or one person in 100.[6] It can affect people of all ages; however, it is mainly diagnosed in patients between the ages of 25 to 50 years. It is twice as common in females as compared to males. RA is a chronic autoimmune disorder that affects the entire body and is one of the most common forms of arthritis. It is characterized by inflammation of the synovium, the membrane lining the joint, causing pain, stiffness, warmth, redness and swelling.[7] The course of RA is variable. Some patients may experience mild intermittent symptoms, while others experience a sudden onset of symptoms, followed by prolonged clinical remission. In some patients, the disease may progress uninterrupted, which can result in characteristic disabling joint deformities. Activities of daily living become difficult or impossible and a patient's quality of life (QOL) is affected. Ultimately, it may lead to significant impairment, handicap and disability. Furthermore, statistical analysis has shown increased mortality in RA patients compared to the average population.[8]

Amgen Inc. is seeking approval for anakinra's use in moderate to severe RA patients who respond inadequately to disease modifying anti-rheumatic drug (DMARD) treatment, either alone or in combination with other therapy. (David Macarios, Amgen Canada Inc., Mississauga (ON): personal communication, 2001 Mar).

Dosage and Potential Cost

Anakinra will be packaged in a prefilled syringe (David Macarios, Amgen Canada Inc., Mississauga, Ontario : personal communication, 2001), and is administered by a subcutaneous injection once daily. An optimal dosing regimen for anakinra has not been identified; however, one study using 30 mg, 75 mg and 150 mg/day of anakinra and another study using 0.04-2.0 mg/kg/day, suggest that the higher dosage is the most effective regimen.[4] Patients must be able to self-administer the drug daily or arrange for administration. There is currently no information available about the potential cost of anakinra in Canada. (David Macarios, Amgen Canada Inc., Mississauga (ON): personal communication, 2001 Mar); however, the cost of the drug is expected to be higher than the cost of traditional RA therapies..

Current Treatments

Non-drug therapy aimed at reducing joint pain and inflammation, preserving joint function and preventing joint deformity is important in the management of RA. These may include rest, exercise and heat. Physical and articular rest (achieved by splinting the affected joints) may reduce inflammation markedly. Passive exercises can minimize muscle atrophy and maintain joint function without increasing inflammation. The external application of heat may reduce joint stiffness and allow greater benefit from passive exercise programs.[9]

Non-steroidal anti-inflammatory drugs (NSAIDs) can be used for the symptomatic treatment of mild to moderate RA.[10,11] They provide analgesic and anti-inflammatory effects; however, they do not slow disease progression, or prevent bony erosions or joint deformity.[10] Long-term use of NSAIDs has been associated with adverse drug reactions including gastrointestinal (GI) ulceration.[10] Thus, gastro-protective agents may be indicated in some patients or a switch to COX-2 inhibiting NSAIDs may be considered.[11] DMARDs, such as methotrexate and gold preparations, are often started when NSAIDs do not provide an adequate response. However, since these drugs offer the added advantage of reducing or preventing joint damage and preserving joint function,[11] they may be considered early in RA therapy.[10,12] DMARDs generally have a slow onset and have been associated with severe toxicities that require frequent monitoring.[9-12] Corticosteroids, given orally or intra-articularly, can be used to decrease inflammation associated with RA and represent an important component of treatment during the course of unremitting disease. Long-term use of corticosteroids may however lead to potentially serious adverse effects such as adrenal gland suppression, increased risk of infections, weight gain, fat redistribution and osteoporosis.[9-11]

Concurrent Developments

Etanercept (Enbrel™, Immunex Corporation and Wyeth-Ayerst Laboratories) and infliximab (Remicade™, Schering Canada Inc.) are new biological agents being used for severe RA. They target tumor necrosis factor (TNF), a chemical mediator also involved in RA pathogenesis. Etanercept is given by subcutaneous injection twice weekly.[13] Infliximab is an intravenous infusion given every two weeks for a total of three doses over a four-week period, then every eight weeks thereafter.[14]

Presently, anakinra is being investigated for expanded use in juvenile rheumatoid arthritis,[15] as well as other conditions such as acute stroke[16] and multiple sclerosis.[17]

Projected Rate of Diffusion

In order to accurately identify anakinra's potential rate of diffusion, its cost and place in therapy with respect to existing traditional therapy and other biological agents, must be identified. As anakinra has not yet been approved, information on the possible selling price is not available; therefore, it is difficult to make predictions about the potential financial impact and application of anakinra in relation to other therapies.

The Evidence

A 24-week, double blind, randomized, placebo controlled, multi-centered trial conducted by Bresnihan et al., enrolled 472 patients with active a nd severe RA.[18] Patients were permitted to continue current NSAIDs and oral corticosteroids; however, all DMARDs were discontinued at least six weeks prior to the study. The patients were randomized into four groups to receive a single, self-administered

subcutaneous injection of either placebo or anakinra at a daily dose of 30 mg, 75 mg, or 150 mg. The primary efficacy measure was the American College of Rheumatology (ACR) composite score. All groups demonstrated improvement in ACR20 at 24 weeks; however, only the 150 mg treatment group demonstrated statistically significant improvement (43%) vs. placebo (27%) (P=0.014). Nine secondary clinical measures were also assessed.

The ACR score is a core set of outcome measures for RA clinical trials. ACR20 is a 20% improvement in tender joint count, swollen joint count, and three of the following five criteria: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function and an acute-phase reactant value. An acute phase reactant value may be assessed according to the laboratory tests Westergren erythrocyte sedimentation rate (ESR) or a C-reactive protein level (CRP), both of which can measure changes in disease activity.[19,20] The ACR scoring can include radiographic changes or other imaging techniques which may be included for trials lasting greater than one year.[20]

The nine secondary clinical efficacy measures assessed by Bresnihan et al. in the same study included the number of swollen joints, number of tender/painful joints, patient's assessment of disease activity, patient's assessment of pain, investigator's assessment of disease activity, duration of morning stiffness, Health Assessment Questionnaire (HAQ), CRP levels, and ESR. The 150 mg treatment group demonstrated significant improvement in all nine criteria at 24 weeks. Patients receiving 30 mg and 75 mg demonstrated improvement in five of the nine criteria.[18]

Jiang et al. continued the Bresnihan et al. study and measured radiologic progression.[21] At week 24 of the Bresnihan et al. study, the patients in the placebo group were randomized into one of the three existing treatment groups for an additional 24 weeks. The results of the three treatment groups were combined to give the anakinra-treated group. The combined result was compared to placebo. Radiologic scores of hand and wrist were recorded at baseline, 24 and 48 weeks and were rated according to two radiographic scoring methods : the Genant scoring method and Larsen scoring method. The Genant scoring method evaluates erosion, joint space narrowing (JSN) and a combination of erosion and JSN referred to as the total score. The Genant scoring method detected a statistically significant reduction of progression in erosion by 38% (P=0.0097), joint space narrowing (JSN) by 58% (P=0.0003) and total score by 47% (P=0.0004) in all anakinra-treated groups. The Larsen method includes a global score by examining 15 specific areas and ranking them according to abnormality. The anakinra-treated group demonstrated a significant reduction in Larsen erosion joint count (LEJC) of 45% vs. the placebo group (P=0.0005).

Another double blind, randomized, placebo controlled study involving 419 patients assessed two criteria: ACR20[22] and health related quality of life (HRQOL).[5] Patients with active RA, currently receiving methotrexate (MTX), were randomized to receive either placebo or 0.04-2.0 mg/kg of anakinra via daily subcutaneous injections. At 24 weeks, ACR20 was demonstrated in 23% of the placebo and 42% of the 1.0 mg/kg anakinra-treated group (p=0.021).[22] It is unclear whether a significant dose response was demonstrated. Additionally, the patients were assessed at baseline and every four weeks for 24 weeks using the health assessment questionnaire (HAQ). Patients receiving 1.0 and 2.0 mg/kg daily demonstrated the greatest improvement versus placebo at week 24. Improvement was -0.37 ($p<0.05$) at 1.0 mg/kg and -0.51 ($p<0.01$) at 2.0 mg/kg versus -0.15 for placebo.[5]

Adverse Effects

In general, anakinra was well tolerated. The most common adverse effect experienced was dose-related injection-site reactions, which were experienced by 25% of the patients in the placebo group, and by 50%, 73% and 81% of the patients in the 30 mg, 75 mg and 150 mg treatment groups, respectively.[18] These reactions were usually mild and transient, and often resolved in 2-3 weeks. However, more severe injection site reactions resulted in withdrawal from the study in less than 1-2% of patients in the placebo, 30 mg and 75 mg treatment groups and 5% of the 150 mg treatment group. Infections requiring antibiotic therapy occurred in 12% of the placebo treated patients and 15-17% of the anakinra-treated patients. Two patients were diagnosed with malignancy unrelated to the study, and withdrew. Neutropenia was observed in three patients who were receiving anakinra. The protocol required a patient to discontinue if the absolute neutrophil count fell below 2.0×10^3 /µl, as this may predispose patients to infection. None of these patients developed clinical symptoms of infection, and the neutrophil count returned to normal in each case. Twenty-four percent, 16%, 14% and 11% of patients withdrew from the

placebo, 30 mg, 75 mg and 150 mg groups, respectively, due to lack of efficacy. Overall, the greatest number of withdrawals due to any reason was from the placebo group (32%). It was not stated whether the adverse event or withdrawal rates of the patients in the treatment groups were significantly different from the placebo group.

Implementation Issues

As the new biological agents anakinra, etanercept and infliximab come to market, evidence will be needed to determine the respective roles of each of these agents in RA. Presently, there are no studies comparing their effectiveness. Since RA is a chronic disorder, long-term effectiveness and safety data is important. To date, anakinra has demonstrated an acceptable side effect profile in studies lasting 24-48 weeks;[18,21] however, long-term data is still pending.

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This brief was prepared by Ms. Kirsten Garces; CCOHTA and has been peer reviewed.
The contents are current as of May, 2001.

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ISSN 1488-6324