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Tumor Necrosis Factor Alfa (TNFα) Antagonists for Pediatric Immune-Mediated Diseases

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Over the past decade, the tumor necrosis factor alfa (TNFα) antagonists have had a profound impact on the management of immune-mediated diseases. These agents, infliximab, etanercept, and adalimumab, have been used in the treatment of adults and children with rheumatoid arthritis, Crohn's disease, and a variety of other related conditions.[1,2] They are effective in reducing inflammation and are typically well tolerated. Both infliximab and etanercept have been approved by the Food and Drug Administration (FDA) for use in children, and it is anticipated that adalimumab will also be approved. This issue of *Pediatric Pharmacotherapy* will review the pharmacology of the TNFα antagonists and recent studies supporting their use in the treatment of children with immune-mediated diseases.

Mechanism of Action

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine produced by T lymphocytes and macrophages. Its primary role in healthy individuals is to control infection by intracellular pathogens. In patients with immune-mediated diseases, TNFα levels are consistently elevated, leading to an abnormal sustained inflammatory response. The TNFα antagonists are monoclonal antibodies that bind to TNFα, forming a complex which inhibits its ability to bind to cell surface TNF receptors. Blocking TNFα activity prevents induction of proinflammatory cytokines, including interleukins (IL-1 and IL-6), as well as inhibiting expression of adhesion molecules responsible for leukocyte migration, activation of neutrophil and eosinophil functional activity, and induction of acute phase reactants.[2-8]

Infliximab is a chimeric monoclonal antibody, with a mouse variable region and a human constant region, that binds both soluble and transmembrane TNFα receptors. It does not bind TNFβ. Etanercept is a fully human, soluble fusion protein. It is formed from the linkage of two ligand-bearing regions of the p75 TNF receptor and the Fc portion of human IgG1. It binds both TNFα (soluble form only) and TNFβ. Adalimumab is a fully human monoclonal antibody to TNFα, produced by recombinant DNA technology. It does not bind to TNFβ.[3-5]

Clinical Experience

A number of studies and case reports have documented the efficacy of the TNFα antagonists in reducing the symptoms of immune-mediated diseases in children.[9-14] In addition, these agents may reduce the need for long-term corticosteroid therapy in these patients and minimize the adverse effects associated with corticosteroid use in children, such as impaired growth.[15]

Infliximab

Infliximab is currently approved by the FDA for use in the treatment of Crohn's disease in both children and adults, as well as ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis.[6] The approval for pediatric patients was based on the results of the REACH study, a randomized, open-label trial of 112 children (6-17 years of age) with moderately to severely active Crohn's disease.[9] All patients received an infliximab infusion of 5 mg/kg on weeks 0, 2, and 6. At week 10, 103 children were randomized to a regimen of 5 mg/kg given every 8 or every 12 weeks. Patients were monitored for clinical response and adverse effects for another 44 weeks. Clinical response was defined as a decrease $\geq$ 15 points from the patient's baseline Pediatric Crohn's Disease Activity Index (PCDAI) score or a score $\leq$ 30.

At week 10, 99 children (88%) had a clinical response and 66 (59%) were in remission. The average PCDAI score decreased by 31.3 points from baseline. At week 30, there were significantly more responders in the every 8 week treatment group than in the every 12 week group (73% versus 47%). Similar results were observed at week 54 (64% versus 33%). The proportion of children in remission was also significantly higher in the every 8 week group at both time points. Sixty percent of the every 8 week group was in remission at week 30 versus

35% in the every 12 week group. At week 54, 56% of the every 8 week group remained in remission versus 24% of the every 12 week group. Corticosteroid use also decreased, with 46% of the every 8 week and 33% of the every 12 week subjects able to stop steroids at week 30. The authors concluded that children were more likely to have a significant response to infliximab if treated every 8 weeks.[9]

Etanercept

Etanercept is currently approved for the treatment of rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis in adults. It is also approved for the treatment of refractory juvenile rheumatoid arthritis (JRA) in patients 2 years of age and older.[7] The FDA approval was based on a two-part clinical trial conducted by the Pediatric Rheumatology Collaborative Study Group in 69 children with polyarticular JRA.[10] In the first part of the trial, patients 4-17 years of age were treated with etanercept 0.4 mg/kg (up to 25 mg) subcutaneously twice weekly for 3 months. In the second part of the trial, patients with a clinical response during the first phase were randomized to remain on treatment or receive placebo for 4 months. Response was determined as a $\geq$ 30% improvement in three of six JRA core criteria (global assessment by a physician, assessment by patient or parent, active joint count, limitation of motion, functional assessment, and erythrocyte sedimentation rate). In the first part of the study, 51/69 (74%) had a clinical response. In the second part, six (24%) of the etanercept patients had a disease flare versus 20 (77%) of the controls (p=0.007). The average time to disease flare was 116 days for the etanercept patients and 28 days for the controls.

The patients randomized to placebo were allowed to resume treatment after the study, and a total of 58 of the original 69 patients continued on therapy as part of an open-label extension study. A long-term follow-up of these patients was published in 2006.[11] Analysis of the 32 children with complete efficacy data for 4 years or more revealed a 94% response rate, using the American College of Rheumatology Pediatric 30 criteria. Etanercept was well tolerated, with serious adverse effects occurring at a rate of 0.13 per patient-year. The authors concluded that etanercept produced a significant, sustained improvement in disease symptoms with an acceptable safety profile.

Adalimumab

Adalimumab is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease in adults. Although it does not yet have FDA approval for use in children, adalimumab has been used to treat children with rheumatoid arthritis, Crohn's disease, psoriasis, and childhood uveitis (immune-mediated intraocular inflammation).[12-14] In a retrospective study of 18 children with uveitis treated with adalimumab doses of 2 to 40 mg every 1-2 weeks, 16 (88%) achieved a reduction in the number of relapses.[14] Ten of the 16 children (81%) who also had arthritis showed improvement. Three patients had a mild response and one did not improve. Infliximab and etanercept have also been used in treatment of uveitis, with mixed results.

Pharmacokinetics

All of the TNFα antagonists are administered parenterally. Infliximab is administered as an infusion, reaching mean serum concentrations of 0.5-6 mcg/mL.[6] The pharmacokinetic profile in children is similar to that of adults, with a terminal half-life of 8-10 days. Etanercept reaches a maximum concentration of 1-3 mcg/mL 60-70 hours after a subcutaneous dose. The average half-life of etanercept is 102$\pm$30 hours.[7] A pharmacokinetic analysis was performed in the 69 children enrolled in the pediatric etanercept study described previously.[10] Using non-linear mixed effects modeling, the predicted mean trough concentration was 1.58$\pm$1.07 mcg/mL for 0.8 mg/kg once weekly dosing and 1.92$\pm$1.09 mcg/mL for 0.4 mg/kg twice weekly dosing, suggesting that the regimens were equivalent.[16]

In a study of adults receiving adalimumab, maximum concentrations of 4.7$\pm$1.6 mcg/mL were reached 131$\pm$56 hours following a single 40 mg dose.[8] The volume of distribution ranged from 4.7 to 6 L, with a systemic clearance rate of 12 mL/hr. The mean elimination half-life was 14 days (range 10-20 days). Administration with methotrexate reduces the clearance of adalimumab, but no adjustment is necessary in patients on combination therapy. The pharmacokinetic profile of adalimumab has not been assessed in children.

Drug Interactions

The TNFα antagonists should not be administered with anakinra, an interleukin-1 antagonist.[3-8] In a 24-week clinical trial, the combination of etanercept and anakinra resulted in a 7% rate of serious infections, compared to 0 in the group receiving etanercept alone. Based on the results of this trial, the combination is not recommended.[7] The use of etanercept with cyclophosphamide has been linked with a higher incidence of solid tumors and is not recommended. Concomitant use of etanercept and sulfasalazine may cause mild neutropenia.[7]

The safety and efficacy of live vaccines have not been studied in patients receiving TNFα antagonists. Because of the potential risk for infection, it is recommended that patients taking these drugs not receive live vaccines. Children should be brought up to date with all immunizations prior to initiating therapy. Patients with a significant varicella exposure should temporarily discontinue therapy. Treatment with varicella immune globulin may be beneficial if infection occurs.[3-8]

Contraindications and Precautions

All three TNFα antagonists are contraindicated in patients with known hypersensitivity reactions to the drug or murine proteins. Patients on TNFα antagonists are at risk for serious infections, including sepsis, pneumonia, opportunistic and invasive fungal infections, and tuberculosis. Patients should be assessed for potential infections prior to initiating therapy, including documentation of a negative tuberculosis skin test. Continued monitoring is necessary, and families should be aware of the need to report signs of infection to medical personnel.[3-8]

A higher rate of malignancies has been reported in patients receiving TNFα antagonists. In open-label infliximab studies, the rate of lymphoma was 3 to 5-fold higher than expected in the general population.[6] In clinical trials with etanercept, the rate of lymphomas was 3-fold higher, and in adalimumab trials, the rate was 3.5-fold higher.[7,8] The risk for malignancy may be increased in patients receiving other immunosuppressive agents. Hepatosplenic T-cell lymphoma, a rare and usually fatal disease, has been reported in adolescents and adults with Crohn's disease being treated with infliximab and azathioprine or 6-mercaptopurine.[6] As described previously, an increased rate of solid tumors was observed in patients with Wegener granulomatosis who were receiving etanercept and cyclophosphamide, methotrexate, and corticosteroids.[7] In addition to these restrictions and warnings, the use of infliximab is contraindicated in patients with severe heart failure.[6] Etanercept and adalimumab should be used with caution in patients with heart failure.[7,8]

Adverse Effects

The most common adverse effects associated with infliximab administration are infusion-related reactions (in up to 20% of patients), upper respiratory infection (32%), nausea (21%), headache (18%), sinusitis (14%), coughing, pharyngitis, abdominal pain, and diarrhea (all 10-12%).[3,6] In patients receiving etanercept, the most common adverse effects have included infections (35-64%), injection site reactions (37%), headache (17-24%), rhinitis (12-16%), and nausea (9-15%). Response rates were similar in the pediatric patients studied to date. In the 69 children studied by the manufacturer, 19% of patients reported headache or abdominal pain, 13% experienced vomiting, and 9% had nausea.[4,7] Common adverse reactions to adalimumab include upper respiratory tract infection (17%), injection site pain, headache, and rash (12% each), and sinusitis (11%).[5,8]

While most patients tolerate the milder adverse effects to TNFα antagonists without needing to stop therapy, more serious reactions may require discontinuation. Severe blood dyscrasias (leukopenia, neutropenia, thrombocytopenia, and pancytopenia) have been reported in adults and children receiving TNFα antagonists. Hepatotoxicity, including acute liver failure, has also been linked to these therapies. Patients and family members should know to seek medical attention for bleeding, severe bruising, pallor, or unexplained fever. Rare neurologic adverse effects, including optic neuritis, seizures, multiple sclerosis, and central nervous system demyelinating disorders have also been reported. Hypersensitivity reactions have been reported in 1-2% of patients, ranging in severity from mild to severe reactions requiring hospitalization. Autoimmune reactions, including a lupus-like syndrome, have also been reported.[3-8]

Dosing Recommendations

Infliximab is administered as an IV infusion. Depending on the indication, a dose of 3 mg/kg (for rheumatoid arthritis) or 5 mg/kg (for other disease states) is given over a minimum of 2 hours. Therapy is initiated with infusions at 0, 2, and 6 weeks, followed by a maintenance dose every 8 weeks. The dose or frequency of administration may be adjusted for patients who fail to respond to therapy.[3,6]

Etanercept is administered subcutaneously at a dose of 50 mg weekly in adults and 0.8 mg/kg in children, up to a maximum of 50 mg. In adults with plaque psoriasis, a 50 mg dose is given twice weekly for three months as an induction, followed by a reduction to the standard 50 mg weekly dose. In patients unable to tolerate injection of the entire 50 mg dose, the dose may be split and given as two injections on the same day or up to 4 days apart. Instructions for administering the injections are available in the prescribing information, on the manufacturer's website, or by calling the manufacturer's support line at 1-888-436-2735.[4,7]

In adolescents and adults, adalimumab is typically initiated at a dose of 40 mg administered subcutaneously every other week. For patients who do not respond, the frequency

may be increased to every week. In patients with Crohn's disease, therapy should be initiated with a 160 mg dose, followed a week later by an 80 mg dose, then two weeks later with a maintenance dose of 40 mg every other week. The larger initial doses for patients with Crohn's disease may be divided into four separate injections to improve patient comfort.[5,8] Children with uveitis have been successfully treated with adalimumab doses ranging from 20 to 40 mg administered every week or every other week.[14]

Availability and Cost

Infliximab (Remicade®; Centocor) is available in 100 mg single-use vials. The contents must be reconstituted with sterile water and then diluted with normal saline to a final concentration between 0.4 and 4 mg/mL. Etanercept (Enbrel®; Immunex/Amgen) is available in pre-filled syringes and autoinjectors (50 mg/mL), as well as a 25 mg/mL multi-use vial. When reconstituted with sterile bacteriostatic water, the vial can be used for up to 14 days. Adalimumab (Humira®; Abbott) is available in 40 mg/0.8 mL pre-filled syringes and pens. All of these products must be refrigerated.[3-8]

As with other immunobiologic therapies, the TNFα antagonists cost substantially more than traditional therapies. The average wholesale price of a vial of infliximab is $670, while a one month supply of etanercept (4 doses) or adalimumab (2 doses) is approximately $1,500.[17]

Summary

The TNFα antagonists offer a highly effective alternative to traditional therapies for the management of immune-mediated diseases. While now established in the treatment of rheumatoid arthritis and Crohn's disease, it is likely that these agents will play a role in many other disease states as well. Continued research is needed to optimize their use in children and further define their adverse effect profiles.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 7/27/07:

1. Lansoprazole orally disintegrating tablets (Prevacid® SoluTab™) were added to the Inpatient and Outpatient Formularies for use in patients with enteral administration tubes who cannot take oral solids. The 15 and 30 mg tablets may be dissolved within the mouth or dissolved in water to make a suspension. Lansoprazole simple suspension is restricted to patients who require doses < 15 mg.
2. Ethacrynic acid (Edecrin®) was added to the Inpatient Formulary with restriction to use in patients with sulfa allergies or who do not respond appropriately to other diuretics.
3. Ampicillin capsules and oral suspension were deleted from the Formulary due to lack of use.

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