

# Pediatric Pharmacotherapy

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## Infliximab: a new therapy for Crohn's disease

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Crohn's disease (CD) is a transmural inflammatory process of the gastrointestinal tract that can occur from the mouth to the anus. Almost all cases involve the small bowel, primarily the distal ileum, and are manifested by mucosal damage, noncaseating granulomas, and fistula formation. The incidence of CD is approximately 3.5 new cases per 100,000 people per year.<sup>1</sup> CD can occur at any age, but tends to have a bimodal age distribution with peaks during the late teens and between the second and third decades of life. Caucasians develop CD two to five times more often than nonwhites. Females are affected slightly more often than males. CD is three to five times more prevalent in the Jewish population.<sup>2</sup>

Historically, exacerbations of CD have been treated with immunosuppressants such as cyclosporine, 6-mercaptopurine, and corticosteroids. The use of these drugs does not seem to alter long-term outcomes. In addition, many patients continue to have CD refractory to these therapies. Infliximab, commonly referred to as anti-tumor necrosis factor  $\alpha$  antibody, is a monoclonal antibody developed for the treatment of refractory CD. This new agent has the potential to make a significant impact on the long-term effects of CD. It has also shown efficacy in the treatment of fistulizing CD. Infliximab is expected to have a significant impact on the treatment of acute exacerbations of CD.

## **Mechanism of action**

Infliximab is a chimeric monoclonal antibody which neutralizes the biological activity of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) by binding to the soluble transmembrane forms of TNF $\alpha$  and inhibiting the binding of TNF $\alpha$  with its receptors.<sup>3</sup> Some of the systemic effects of TNF $\alpha$  which link it to CD include the induction of pro-inflammatory cytokines such as Interleukin-1 and Interleukin-6, enhancement of leukocyte migration and activation of neutrophil and eosinophil functional activity.<sup>4</sup> The cumulative results of these effects are inflammation, induction of edema and granuloma formation.<sup>1-2,4</sup> *In vitro* bioassays have demonstrated the ability of infliximab to inhibit functional activity of TNF $\alpha$ .<sup>3</sup>

## **Current Indication**

Infliximab is currently indicated for the treatment of moderately to severely active CD for the reduction of signs and symptoms in patients who have an inadequate response to conventional therapy. Infliximab is also indicated for the treatment of patients with fistulizing CD for the reduction in the number of draining enterocutaneous fistulas.<sup>3</sup> It has also recently been approved by the Food and Drug Administration for the treatment of rheumatoid arthritis.

## **Clinical Trials**

There are many clinical trials demonstrating the efficacy of infliximab in CD. Unfortunately, most of the studies have enrolled only adult patients. We must extrapolate from these data how infliximab might be used in adolescents.

In 1995, Van Dulleman and colleagues<sup>5</sup> reported the successful use of infliximab in patients who had failed standard prednisone therapy. In an open-label, single center trial, ten patients with active CD who had failed prednisone therapy of at least 20 mg per day for 2 weeks or more received either 10 mg/kg (n=8) of infliximab intravenously or 20 mg/kg (n=2). Each patient was admitted for 24 hours and followed for 2 months after infliximab infusion. Patients remained on all baseline medications. A baseline Crohn's Disease Activity Index (CDAI) score (remission  $\leq$  150) was performed to show efficacy for nine of the ten patients. The mean CDAI baseline score was 257. The mean decreased to 114 two weeks after infliximab treatment, to 79 after four weeks, to 61 after six weeks, and remained at 69 in the eighth week (p<0.0001). Eight of these nine

patients reported improvement in subjective symptoms after one week. Endoscopic exam after four weeks showed the healing of nearly all ulcerations observed at the baseline exam. Seven of the eight patients showing improvement remained in remission, with relapses ranging from three to six months. It was concluded that infliximab may be useful in the treatment of CD when steroid therapy had not alleviated symptoms.

In 1997, Targan et al<sup>6</sup> conducted a twelve week multicenter, double-blind, placebo-controlled trial of infliximab in 108 patients (average age  $8.5 \pm 11.0$  years) with moderate to severe CD that was resistant to standard treatment. Using the same scale described above, the baseline CDAI scores for these patients ranged from 220 to 400. CDAI scores were evaluated at 0, 2, 4, and 12 weeks. In addition to CDAI scores, quality of life was measured with the Inflammatory Bowel Disease Questionnaire (IBDQ) at baseline and four weeks after infliximab treatment. In this questionnaire, scores may range from 32 to 224, with higher scores reflecting a better quality of life.

Patients were randomized to receive a single two hour infusion of either placebo (n=25) or infliximab at doses of 5 mg/kg (n=27), 10 mg/kg (n=28), or 20 mg/kg (n=28). Baseline medications were continued. Clinical response was defined as a 70 point decrease in CDAI. At four weeks, 81% of patients treated with 5 mg/kg, 50% treated with 10 mg/kg and 64% treated with 20 mg/kg had a clinical response. Thirty-two percent of the total patients achieved remission. In comparison, only 17% of patients receiving placebo had a positive clinical response ( $p < 0.001$ ). At 12 weeks, 41% of infliximab-treated patients had a clinical response compared to only 12% of placebo patients ( $p = 0.008$ ). IBDQ scores increased by an average of 36 points in the infliximab group compared to a mean increase of 5 in the placebo group ( $p = 0.001$ ). It was concluded that a single infusion of infliximab was effective in the short-term treatment of moderate to severe refractory CD and significantly improved the patients' quality of life.

Later in 1997, the first study demonstrating efficacy in retreatment with infliximab was published. A multicenter placebo-controlled, double-blinded, randomized trial was conducted by Rutgeerts et al<sup>7</sup> using the 73 patients from the previous study by Targan et al<sup>6</sup> who had shown a clinical response eight weeks after infliximab. The patients were randomized at 12 weeks, the end of the initial study period, to receive four blinded treatments of either placebo or 10 mg/kg of infliximab at weeks 12 (baseline), 20, 28, and 36. CDAI and IBDQ were evaluated at weeks 12 and 44.

At 44 weeks, 66% of patients receiving infliximab achieved a clinical response versus 35% receiving placebo ( $p < 0.1$ ). However, 51% of the infliximab achieved remission (mean CDAI=118) as opposed to 21% of placebo (mean CDAI=193,  $p < 0.05$ ). The IBDQ score was significantly higher in the infliximab group (175 vs 148,  $p < 0.05$ ). The authors concluded that retreatment with infliximab 10 mg/kg every eight weeks was effective in maintaining disease remission.

After these studies demonstrated the efficacy of infliximab in refractory CD, the same group of researchers performed a randomized, multicenter, double-blinded, placebo-controlled trial to evaluate the efficacy of infliximab in the treatment of fistulizing CD.<sup>8</sup>

Patients who suffer from CD now have hope for greater control of severe exacerbations of their disease. Ninety-four patients between 18 and 65 years of age with draining abdominal or perianal fistulas of at least 3 months duration secondary to CD were studied. Patients were randomized to three treatment groups: placebo (n=31), infliximab 5 mg/kg (n=31) and infliximab 10 mg/kg (n=32) to be administered at weeks 0, 2, and 6. The primary endpoint of the study was a 50% reduction in the number of draining fistulas observed during any two consecutive study visits at weeks 2, 6, 10, 14, and 18. Closure of all fistulas was a secondary endpoint. The primary endpoint was achieved in 68% of the 5 mg/kg infliximab group and 56% of the 10 mg/kg infliximab group as opposed to only 26% of the placebo group (p=0.002 5mg/kg vs. placebo, p=0.02 10 mg/kg vs. placebo). The median time to onset of a response was 2 weeks in the infliximab-treated patients versus 6 weeks in the controls. Fifty-five percent of the patients that received 5 mg/kg infliximab and 38% of those receiving 10 mg/kg had closure of all fistulas as compared with 13% of the placebo group (p=0.001 and p=0.04, respectively). The average time the fistulas remained closed was three months. The data from this study suggest that infliximab is also efficacious in the treatment of patients with fistulizing CD.

## **Pharmacokinetics**

Infliximab has a direct and linear relationship between dose and the maximum serum concentration ( $C_{max}$ ) and area under the concentration curve (AUC).<sup>3</sup> Volume of distribution ( $V_d$ ) and clearance are independent of dose. After a single dose of 5 mg/kg in adults, a median  $C_{max}$  of 118  $\mu\text{g/ml}$ ,  $V_d$  of 3.0 L, and terminal half-life of 9.5 days have been observed. Infliximab is primarily distributed within the vascular compartment. Differences in gender, age, weight, hepatic and renal function do not produce significant pharmacokinetic differences, although specific data in children are lacking. Accumulation of infliximab has not been observed in patients receiving repeated doses fistulizing disease<sup>8</sup> or in patients receiving 10mg/kg infliximab every 8 weeks for four doses for severe CD exacerbations. Corticosteroids have been found to significantly increase  $V_d$  from 2.8 to 3.3 L, possibly because of electrolyte imbalances and fluid retention. This increase in  $V_d$  was not associated with an increase in adverse effects.

## **Precautions**

Patients with hypersensitivity to murine proteins should not receive infliximab. Infliximab may also cause hypersensitivities manifested by urticaria, dyspnea, and hypotension. Epinephrine, acetaminophen, antihistamines, and corticosteroids should always be available in case of severe reactions. Patients should not be rechallenged with the medication after a severe reaction. Formation of autoimmune antibodies may result from infliximab therapy, resulting in a lupus-like syndrome. Because  $\text{TNF}\alpha$  mediates inflammation and immune responses, infliximab may alter normal immune response. During clinical trials, symptoms resolved after the discontinuation of infliximab.

Infliximab is classified as a pregnancy category C drug. It is not known whether infliximab causes fetal harm or affects reproduction. Because infliximab only cross-reacts with the TNF $\alpha$  of humans and chimpanzees, animal models to study teratogenicity have not been developed. It is not known whether infliximab crosses into breastmilk, but it is recommended that mothers not nurse while receiving therapy, due to the potential for hypersensitivity reactions.

## **Adverse Reactions**

Infliximab is generally well tolerated. In clinical trials, therapy was discontinued in approximately 5% of patients because of adverse reactions.<sup>3,10</sup> Infusion reactions and infections were the most common adverse reactions reported with infliximab.<sup>3,10</sup> When data from the early clinical trials were combined, headache occurred in 22.6% of the patients treated with infliximab, but also in 21.4% of placebo patients (p=NS). Nausea (16.6%), upper respiratory infections (16.1%), abdominal pain (12.1%), fever (10.1%), fatigue (10.6%), and vomiting (8.5%) were also commonly reported. Rash, pruritis, chest pain, coughing, sinusitis and myalgias occurred in approximately 5% of treated patients.<sup>10</sup> Other adverse events noted in less than 5% of the patients included hot flashes, hypotension or hypertension, paresthesias, myoclonic jerks, conjunctivitis, tachycardia, dyspepsia, dysuria, and anxiety.

## **Dosing**

The recommended dose of infliximab for the treatment of severe active CD in refractory patients is 5 mg/kg intravenously as a single dose. In patients with fistula involvement, an initial dose of 5 mg/kg followed by additional 5 mg/kg doses at weeks 2 and 6 is recommended.

## **Conclusion**

The treatment of refractory CD is taking a new shape. Infliximab has been found to be safe and, more importantly, efficacious in the treatment of severe CD and fistulizing CD. Patients who suffer from CD now have hope for greater control of severe exacerbations of their disease. More clinical trials are needed to show the long-term efficacy of infliximab, but enough data exist to support the development of new studies using this drug for other patient populations. It is hoped that clinical trials enrolling adolescents will soon be available.

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## Literature Review

### Antibiotic Therapy for Neonates

This extensive review covers the spectrum of antibiotic choices for treating presumed sepsis in the neonate. The major focus of the article is the on the usual empiric antibiotic choices: penicillins, aminoglycosides, cephalosporins, and vancomycin. In addition to these agents, the authors also include a number of less widely used therapies, including the macrolides, clindamycin, quinolones, and trimethoprim-sulfamethoxazole. The potential role of these agents is addressed, as well as the factors which limit their use in the neonatal population. Fanos V, Dall'Agnola A. Antibiotics in neonatal infections: a review. *Drugs* 1999;58:405-27.

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### Felbamate revisited

The author of this article, Dr. John Pellock of the Medical College of Virginia, provides an interesting commentary on the relative risks of felbamate use and the potential for its revival as a viable choice for antiepileptic agent. The two most concerning toxicities with felbamate have been aplastic anemia and hepatic failure. Although many of the cases reported have been inconclusive due to the presence of confounding variables, the severity of these adverse reactions has prompted a decrease in use of the drug in the

United States. The mechanisms for these reactions are unclear, but new research points to the formation of a toxic intermediate metabolite in some patients. Dr. Pellock argues for the safety of felbamate in the majority of patients treated and the need for further research to isolate a method of identifying those patients at risk for metabolite accumulation. Pellock JM. Felbamate in epilepsy therapy: evaluating the risks. **Drug Safety 1999;21:225-39.**

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## **Medication Compliance**

This brief review addresses the prevalence of medication noncompliance in the pediatric population, factors that affect compliance, and includes recommendations for improving compliance. The authors suggest that the FDA Modernization Act of 1997 will provide significant incentives for pharmaceutical manufacturers to create new pediatric dosage formulations which may improve compliance by reducing dose frequency, improving taste, or decreasing toxicity. Blanchard N, Primovic J, Leff RD. **J Pediatr Pharm Pract 1999;4:181-5.**

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## **Formulary Update**

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 10/22/99:

1. Epoprostenol (Flolan<sup>®</sup>), also known as PGI<sub>2</sub> or prostacyclin, was added to the Formulary. Prescribing is restricted to the treatment of primary pulmonary hypertension.
2. Candesartan (Atacand<sup>®</sup>), an angiotensin II receptor antagonist, was added to the Formulary.
3. Naratriptan (Amerge<sup>®</sup>) also was added the Formulary. This agent is a serotonin receptor agonist used in the acute treatment of migraines. It is available in tablet form and offers a longer half-life than other agents in this class, including sumatriptan (6 versus 2-3 hours).
4. Rosiglitazone (Avandia<sup>®</sup>), a thiazolidinedione antidiabetic agent, was added for the management of Type II diabetes.
5. The following agents were rejected: pioglitazone (Actos<sup>®</sup>), irbesartan (Avapro<sup>®</sup>), telmisartan (Micardis<sup>®</sup>), valsartan (Diovan<sup>®</sup>), rizatriptan (Maxalt<sup>®</sup>), and zolmitriptan (Zomig<sup>®</sup>).

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