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# Safety of Infliximab in Children with IBD: The Experience of an Academic Center in WV

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## Abstract

**Background:** The immune-modulating drug, infliximab, is approved for Inflammatory Bowel Disease (IBD) treatment in children. Chronic therapy with infliximab is associated with the development of early and delayed infusion reactions. We reviewed our experience with infliximab treatment and its side effects in a cohort of children diagnosed with IBD who were treated in our clinic.

**Methods:** A retrospective analysis of all IBD children treated with infliximab in our center from 2006-2011 was performed. The demographic, chronological and clinical data were recorded. The infliximab infusion was given at 5mg/kg according to a standard protocol after pre-treatment with low dose steroid and diphenhydramine.

**Results:** Of 30 IBD patients (23 CD/7 UC) receiving 454 infusions (341 CD/113 UC), six (20%) patients experienced early infusion reactions. Two (6.7%) patients had a delayed reaction; of those, both required intestinal resection.

**Conclusion:** Our study is the first to address the safety of infliximab infusion reactions in children in the

state of WV. Our results lend support to the use and safety of infliximab in children with moderate to severe IBD.

## Introduction

Inflammatory Bowel disease (IBD) consists of ulcerative colitis (UC), Crohn's disease (CD), or intermediate colitis (IC). An estimated 1-1.5 million people in the US have ulcerative colitis or Crohn's disease.<sup>1</sup> The most common clinical symptoms of IBD in children include bloody stools, weight loss, fatigue, abdominal cramping, increased frequency of bowel movements, and fever.<sup>2</sup> Crohn's disease is histologically characterized by non-caseating granulomas, transmural inflammation, cobblestone-type mucosa, and bowel wall thickening.<sup>3</sup> The etiology of IBD is related to a combination of immune dysregulation and chronic inflammation, leading to bleeding of the mucosa.<sup>3</sup> TNF-alpha is an important cytokine central to the inflammatory process of IBD. Macrophages, mast cells, and activated T-helper cells (particularly T<sub>H</sub>1 cells) are responsible for the secretion of TNF-alpha.<sup>3</sup>

The treatment of IBD is based on the severity of the disease. For mild IBD, aminosalicylates and antibiotics are used.<sup>4,5</sup> For more severe cases, immuno-suppressive drugs, such as azathioprine or methotrexate, are utilized. For refractory cases, the biological drugs such as anti-TNF-alpha medications [infliximab (Remicade), adalimumab (Humira)] or other investigational drugs may be used.

Infliximab is an anti-TNF-alpha drug administered by IV for the treatment of children with moderate/severe IBD. It is a monoclonal

anti-TNF IgG molecule composed of part human and part mouse-derived TNF-alpha binding regions (chimeric).<sup>6</sup> Infliximab binds to TNF-alpha with high affinity and specificity and blocks free TNF-alpha in the serum.<sup>6</sup> The drug also affects TNF-alpha molecules that are attached to target cells such as the intestinal enterocytes.<sup>6</sup> Anti-TNF medications have been approved for the treatment of IBD in children. Furthermore, chronic therapy with these drugs is usually required and may be associated with the development of early or delayed infusion reactions.

In the present study, we reviewed the early and delayed adverse events associated with infliximab infusion in a cohort of IBD children followed in our medical center.

## Material and Methods

A cohort of children diagnosed with IBD, who were treated with infliximab at Marshall University Department of Pediatrics, Gastroenterology Division, between 2006-2011, was included in our study. Demographic, clinical symptoms, and infusion reaction data were recorded from the patients' charts. Per the recommended clinical guideline, all patients were screened negative to TB testing (Mantou test) before initiation of infliximab therapy. Infliximab infusion was given per written standard protocol that included pre-administration (IV) of low dose steroid and diphenhydramine. The recommended dose of infliximab for pediatric patients 6 years and older with moderately to severely active Crohn's disease or ulcerative colitis was given as follows: induction dose of 5 mg/kg given IV at 0, 2, and 6 weeks, followed by maintenance

**Table 1. Common reactions to infliximab infusion.**

Early infusion reactions (1-3 days post infusion)	Delayed Adverse events (3-12 days post infusion)
Hypersensitivity reactions and anaphylaxis associated with facial flushing, shortness of breath, chest tightness, pruritus, tachy/bradycardia, hives, nausea/vomiting/diarrhea, seizures	Tuberculosis, intra-abdominal abscesses, opportunistic infections, pseudo-membranous colitis, Hodgkin's lymphoma, upper respiratory infections, pharyngitis, neutropenia, thyroiditis, pancreatitis, seizures, psoriasis, bronchitis, pneumonia, bacterial infection, abnormal LFTs, appendicitis

regimen at 5 mg/kg. Patients initially received the infusion every 8 weeks, but the frequency was changed to every 6 weeks according to the clinical response of the patient.

An early infusion reaction was defined as either hypersensitivity or an anaphylactic reaction occurring during the infusion, immediately post-infusion, or up to three days post-infusion. Early infusion reactions consisted of facial flushing, fevers and chills, pruritus, heart rate changes and other symptoms as outlined in Table 1. A delayed adverse event was defined as a

reaction that occurred 3-12 days after the infusion.<sup>7</sup> Those events may include respiratory infections (i.e. TB) and/or other serious infections (intra-abdominal abscesses, opportunistic infections), pseudo-membranous colitis, gastroenteritis, thyroiditis, pancreatitis, seizures, psoriasis, pneumonia, or appendicitis.<sup>7</sup>

**Results**

Thirty patients were included in the study, of whom 23 had CD and 7 had UC. A total of 454 infusions were given during the

study period; 341 infusions were given to the CD patients and 113 were given to the UC patients. Experimental data and infusion data are described in Table 2. In 26 of the 454 total infusions, a total of six patients experienced early infusion reactions and two experienced delayed adverse events. Six IBD patients experienced early infusion reactions associated with hypersensitivity (itching, facial flushing, chest tightness and/or shortness of breath). All responded to decreased infusion rate and completed their therapy uneventfully.

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**Table 2. Infliximab infusions and reactions for Crohn's disease and ulcerative colitis patients.**

Diagnosis	<u>Crohn's Disease</u>	<u>Ulcerative Colitis</u>
No. pts (M/F)	23 (13/10)	7 (6/1)
Age of patients at conclusion of study (mean)	16.7	16.3
No. infusion (total)	341	113
No. infusion/ pt (Mean $\pm$ SD)	14.7 $\pm$ 11	14.1 $\pm$ 9.5
No. infusion/ pt [Median (range)]	15 (1-35)	11 (3-27)
Early infusion reaction	5	1
Delayed adverse event	2	0

A delayed adverse event (intra-abdominal abscess) was seen in 2 CD patients; in both cases an intestinal resection was needed.

## Discussion

Anti-biological drugs, such as infliximab and adalimumab, are very potent medications for children with IBD. Results have shown that since these drugs were approved for this disease by the Food and Drug Administration (FDA), the entire prognosis of IBD patients has dramatically improved; the remission rate has increased and the hospitalization rate and number of operations have decreased.<sup>8,9,10</sup> As with all potent medications, the side effects of these drugs are significant, including: immune suppression, secondary infection (viral, TB and more), autoimmune disease (arthritis and psoriasis), and cancer development (lymphoma and hepato-splenic T cell lymphoma).<sup>7</sup> In addition to these effects, there is increasing evidence of the reactions associated with the infusion itself. In a recent multicenter registry, the infusion-related side effects were described in 533 pediatric patients who had a total of 6914 infusions.<sup>11</sup> In that report, 72 (13.5%) patients experienced early infusion reactions associated with facial flushing and shortness of breath. In the same study, delayed adverse events

occurred in 38 patients, including 7 (1.3%) with pancreatitis, 13 (2.4%) with psoriasis, 4 with abnormal LFT's, 10 with opportunistic infections, 1 with neutropenia, and 2 with seizures.<sup>11</sup> One patient developed Hodgkin's lymphoma of the bowel. No intra-abdominal abscesses were reported. Hyams et al studied 60 patients receiving 670 infusions, of which 14 patients (23%) developed early infusion reactions.<sup>7</sup> Delayed adverse events developed in 46 (77%) patients, including upper respiratory infections, pharyngitis, bronchitis or pneumonia. Severe adverse events were noted in 20 (33.3%) patients, which included an intra-abdominal abscess, appendicitis, pneumonia, gastroenteritis, pseudomembranous colitis, and/or bacterial infection.<sup>7</sup> In our small cohort, only six (20%) patients developed early infusion reactions and two (6.7%) experienced delayed adverse events (Table 1). The rate of early infusion reaction was higher in our study compared to Markowitz et al (20% vs. 13.5%, respectively), but the latter study was a collection of data from a registry list collected from multiple clinical centers, while our data was derived from a single center from WV. When we compared our data to a single center report (i.e. the study from a center in Connecticut),

our early infusion reaction rate was lower (20% vs. 33%).<sup>7</sup> Additionally, it has been documented that approximately 10-30% of patients suffering from Crohn's disease can expect an abdominal or pelvic abscess to develop spontaneously during the course of their disease without ever receiving an infusion of infliximab.<sup>12</sup> Thus, it is possible that the abscesses reported in our patients were developed as a result of the illness itself. Nonetheless, no patients in our study developed abscesses before starting the treatment with infliximab suggesting that the drug was a major contributor to the abscess development. Additionally, the low rate of overall adverse events (26/454 infusions, 5.7%) noted in our study may partially be related to the pre-treatment infusion of steroid and diphenhydramine. A pre-medication regimen was not described in the previously cited multicenter study, but other reports have supported this practice.<sup>13,14</sup> In addition, to reduce complications, it is important to follow the infusion protocol closely to include gradual increase/decrease of the infusion rate followed by a close monitoring of the patients.

Our pilot study is limited by the small number of patients and the retrospective nature of the investigation. Further research could include a multi-center study in

the state. Nevertheless, our study demonstrated encouraging results that lend support to the safety of infliximab in children diagnosed with IBD. Our data support the notion that infliximab treatment for children in WV is safe and feasible. To our knowledge, this is the first report of infliximab infusion adverse events in children from West Virginia.

In conclusion, we find the infusion of infliximab to be safe in children with moderate to severe IBD, particularly when preventive measures are taken to minimize or stop the progression of infusion reactions. Our data suggest that our patient population should not seek out-of-state medical services for intravenous infliximab therapy, and that such therapy is available at various GI centers within the state.

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