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How Safe and Effective is Infliximab in the Treatment of Children with Moderate to Severe Crohn's disease?

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Abstract

Objective: The objective of this systematic review is to determine whether or not "how safe and effective is infliximab in treatment of children with moderate to severe Crohn's disease?"

Study Design: Review of three English language primary studies published in 2007, 2009 and 2009.

Data Sources: Two randomized control trials and a cohort study measuring the safety and efficacy of infliximab therapy in children with Crohn's disease were found by using PubMed and Cochrane databases

Outcome(s) Measured: The outcomes measured in the studies were clinical response and clinical remission. The Hyams et al 2007 study determined clinical response and remission by the Pediatric Crohn's Disease Activity Index (PCDAI). The Ruemmele et al study measured clinical remission by Harvey Bradshaw Index (HBI) and Erythrocyte Sedimentation Rate (ESR). In the Hyams et al 2009 study, the Physician Global Assessment (PGA) was used to measure clinical response and clinical remission.

Results: All three studies showed that infliximab is safe and effective against Crohn's disease in the pediatric population. The Ruemmele et al study demonstrated that a scheduled 2-month therapy was better than an on demand therapy in the number of clinical responses and remissions. The Hyams et al 2007 study showed that more patients were more likely to be in clinical response and remission if therapy was given every 8 weeks rather than every 12 weeks.

Conclusions: Infliximab is a safe and effective treatment in the treatment of children with moderate to severe Crohn's disease according to the results of the three studies in this review

Key words: pediatric Crohn's disease, infliximab

Introduction:

Crohn's disease is a chronic inflammatory bowel disease (IBD), which is characterized by transmural inflammation skip lesions with a cobblestone appearance that can affect any part of the GI tract, but commonly the terminal ileum. Crohn's disease has no known cause, but may have some genetic link such as first-degree relatives and environmental factors including smoking. Crohn's disease has a higher rate in Caucasians and Ashkenazi Jews. Its peak incidence is between the age of 15-35 and 50-70.[1]

Signs and symptoms depend on the severity and location of the disease. Symptoms can include malaise, fatigue, abdominal pain, nonbloody diarrhea, and fecal urgency. Signs include fever, weight loss, abdominal tenderness/distention, hepatospleenomegaly, hyperactive bowel sounds, perianal fistulas, and abscess. There can be extraintestinal signs and symptoms such as oral aphthous ulcers, erythema nodosum, pyoderma gangrenosum, iritis, uvetitis, and arthrithis.[1,2]

Crohn's disease is typically treated non-pharmacologically and/or pharmacologically. Surgery is another option, but it does not cure the disease. A well-balanced diet with high fiber, low fat, and low roughage may be beneficial to patients. Analgesics such as acetaminophen and anti-diarrheals can provide symptomatic relief. Antibiotics such as metronidazole can be given to treat bacterial overgrowth in the intestines. Corticosteroids and 5-Aminosalicyclic acid (5-ASA) are used to treat inflammation. When patients do not receive relief with corticosteroids or 5-ASA, immunomodulator drugs are used such as azathioprine and mercaptopurine, which blocks the reaction that cause inflammation in the body.[1] Infliximab, which is a monoclonal antibody against tumor necrosis factor alpha, is used when conventional therapy fails or in refractory cases usually in moderate to severe Crohn's disease.[1,2] Research suggests infliximab may provide

satisfactory treatment and maintenance for moderate to severe Crohn's disease in children., which is essential since Crohn's disease is incurable.

It is estimated that IBD affects about 1 million people in the United States, and an estimated 500,000 of those Americans has Crohn's disease, with 10% of this population affecting people under the age of 18.[3,4] It is estimated that 25% of new diagnoses of inflammatory bowel disease occur in patients younger than 20 years of age.[5] Depending on the severity of the disease and the treatments, it is estimated to an annual cost of $19,000 for a Crohn's disease patient.[6] Crohn's disease patients contribute to 716,000 ambulatory care visits and 82,000 hospitalizations in 2004.[4] Physician assistants nationwide can encounter patients with Crohn's disease not only in primary care but also in the emergency room and operation room depending on the severity of the disease. Physician assistants in primary care, such as pediatrics, internal medicine, and family medicine, play an important role in educating the patient about the disease, its treatment, management, and complications.

Objective:

The objective of this systematic review is to determine "how safe and effective is infliximab in the treatment of children with moderate to severe Crohn's disease?"

Methods:

All three studies, two randomized controlled trials and one cohort study, used in this selective review included the population of patients diagnosed with moderate to severe Crohn's disease under the age of 18. The intervention used in the studies was IV infliximab 5mg/kg. The demographics and characteristics of each study are displayed in Table 1. For the study by Ruemmele et al, the comparison groups were patients who received infliximab on a fixed schedule of 2 months and patients who received infliximab on an on demand basis where there

were signs of relapse. Patients were given infliximab infusions at week 0, 2, 6, and then only the patients who had a clinical remission at week 10 where they were randomized into the group with scheduled therapy every 2 months or the on demand group.[7] In the Hyams et al 2007 study, the comparison groups were patients who received infliximab every 8 weeks and patients who received infliximab every 12 weeks.[5] Patients were given infliximab infusions at week 0, 2, 6, and then only the patients who responded to treatment at week 10 were randomized to infliximab every 8 or 12 weeks. There was no comparison group for the Hyams et al 2009 study. The outcomes measured were clinical response and clinical remission in the Hyams et al 2007 and 2009 studies, and the outcome measured was only clinical remission in the Ruemmele et al study. Clinical response and clinical remission qualify as patient orientated evidence that matters (POEM).

Key words used in the searches were "pediatric Crohn's disease and infliximab." All articles searched were published in peer-reviewed journals in the English language. The author searched the articles through PubMed and Cochrane databases. The articles were selected based on the importance to patient (POEM). Inclusion criteria for this review were randomized controlled trials and cohort studies based outcomes relevant to the patient (POEM) and patients <18 years old diagnosed with moderate to severe Crohn's disease. Exclusion criteria for this review were individuals over the age of 18 and articles written before the year 2004 due to a student in the 2004 with a similar topic. The statistics reported in the studies were *p*-values, relative risk reduction (RRR), absolute risk reduction (ARR), numbers needed to treat (NNT), and numbers needed to harm (NNH).

Table 1-Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Ruemmele, 2009 (1)	Randomized multicenter open-label trial	40	7-17	Diagnosis of Crohn's disease 6 mos prior to trial; mod to severe Crohn's disease; non-stricturing non-penetrating and penetrating disease; prior resistance to a combo therapy of an immunosuppression	Previous treatment of infliximab or any other anti-tumor necrosis factor	9	Infliximab 5mg/kg at week 0, 2, 6; those who had a clinical remission and steroid withdrawal were randomized to either subsequent infliximab every 2 mos or a on demand basis
Hyams, 2007 (2)	RCT	112	6-17	Pts 9-17 y/o with a PCDAI score >30 at baseline; initiated tx with an immunomodulator at least 8 weeks before screening, and were to have been receiving a stable dose for at least the previous 2 weeks	Pts who had received previous treatment of infliximab or any other agent aimed at lowering TNF	24	Infliximab 5 mg/kg at weeks 0, 2, and 6; those who had a clinical response at week 10 were randomized to receive either subsequent infliximab every 8 or 12 weeks
Hyams, 2009 (3)	Cohort study	202	<16	Children under the age of 16 who are newly diagnosed with Crohn's disease	N/A	N/A	Infliximab maintenance therapy defined as either an increased dose or a decreased interval between 2 doses

Outcomes Measured:

The outcomes measured in all three studies were based on POEMS, which were clinical response and clinical remission. The Hyams et al 2007 study determined clinical response and remission by the Pediatric Crohn's Disease Activity Index (PCDAI). Clinical response is a decrease from baseline of $\geq$15 points and a total score of $\leq$30 points. Clinical remission is a PCDAI score of $\leq$10 points.[5] The Ruemmele et al study measured clinical remission by the Harvey Bradshaw Index (HBI) <5 and Erythrocyte Sedimentation Rate (ESR) <20 mm/h.[7] In the Hyams et al 2009 study, the Physician Global Assessment (PGA) was used to measure clinical response and clinical remission. Clinical response was defined as mild or inactive disease at every assessment while receiving infliximab without associated corticosteroid use or surgery. Clinical remission was defined as inactive disease at every assessment while receiving infliximab without associated corticosteroid use or surgery.[9]

Results:

The Hyams et al 2007 was a multi-center randomized open-label study with outcomes that were presented as dichotomous data. All analyses were based on the intent-to-treat principle. The 112 patients in this study were given infliximab 5mg/kg at week 0, 2, and 6 and then were evaluated at week 10 if there was a clinical response. At week 10, the study showed at 95% CI between 82.5% and 94.3% that 99 out of the 112 patients (88.4%) were in clinical response, and at 95% CI between 49.8% and 68% 66 of the 112 patients (63.5%) were in clinical remission. Of the 112 patients, 103 patients showed clinical response; 52 patients were randomized to the group (A) that will be receiving infliximab every 8 weeks and 51 patients were randomized to the group (B) that will be receiving infliximab every 12 weeks. The 9 patients that were not in clinical response received no further treatment with infliximab and were discontinued from the

study. The number of patients either in clinical response or clinical remission for Group A and B along with p-values at week 54 is displayed in Table 2. More patients were in clinical response and clinical remission in Group A than the patients in Group B (Table 2). Patients in Group A trended towards a clinical response and clinical remission compared to patients in Group B based on the p-value=0.002 and p<0.001, respectively, which are both statistically significant. In Table 3, the NNT for clinical response and remission was calculated to be 4, which means we must treat 4 pediatric patients with Crohn's disease with infliximab for 54 weeks in order to have 1 patient in clinical response or clinical remission.

Table 2: Results of infliximab for the group receiving infliximab every 8 weeks and the group receiving infliximab every 12 weeks

	Number of patients in clinical response at week 54	Number of patients in clinical remission at week 54
Infliximab every 8 weeks (Group A)	33 (63.5%)	29 (55.8%)
Infliximab every 12 weeks (Group B)	17 (33.3%)	12 (23.5%)
p-value	p=0.002	P<0.001

Table 3: Clinical Response and Remission-NNT

	CER	EER	RRR	ARR	NNT
Clinical Response	23.5%	55.8%	137%	32.3%	4
Clinical Remission	33.3%	63.5%	90.6%	30.2%	4

Twenty-four out of the 112 patients discontinued from the study; nine patients discontinued the study before week 10 and 15 patients discontinued the study after week 10. Table 4 shows the safety findings for Group A and Group B. Patients in Group B had more patients who discontinued the study from adverse effects than patients in Group A, 4 (8.0%) and 2 (3.8%), respectively. The most occurring safety parameter for both groups was infection; Group A has a higher incidence than Group B, 39 (73.6%) and 19 (38.0%), respectively; mostly

upper respiratory infections. However, the incidence of serious infections between Group A and Group B were similar. The NNH was calculated to be -44, shown in Table 5, meaning the control condition is more likely to harm than the treatment condition, in this case the control group being Group B.

Table 4: Summary of safety findings for all (112) patients through week 54

Safety parameter	Patients not randomized at week 10	Infliximab every 8 weeks (Group A)	Infliximab every 12 weeks (Group B)
Adverse event	9 (100%)	51 (96.2%)	46 (92.0%)
Adverse events leading to discontinuation	6 (66.7%)	2 (3.8%)	4 (8.0%)
Serious adverse events	7 (77.8%)	8 (15.1%)	7 (14.0%)
Infection	3 (33.3%)	39 (73.6%)	19 (38.0%)
Serious infection	2 (22.2%)	3 (5.7%)	4 (8.0%)
Intestinal stenosis	2 (22.2%)	1 (1.9%)	0 (0.0%)
Infusion reactions	1 (11.1%)	9 (17.0%)	9 (18.0%)
Pneumonia	0 (0.0%)	2 (3.8%)	1 (2.0%)
Herpes Zoster	0 (0.0%)	2 (3.8%)	0 (0.0%)

Table 5: Number needed to harm

CER	EER	RRI	ARI	NNH
8%	5.7%	-28.7%	-2.3%	-44

The Ruemmele et al study was a multi-center randomized open-label trial with outcomes that were presented as dichotomous data. Forty patients were given infliximab 5mg/kg at week 0, 2, 6, and at week 10 patients who were in clinical remission and steroid withdrawal were randomized to either Group A, scheduled 2 week therapy, or Group B, an on demand basis with signs of relapse. At week 10, after the induction phase, 34 out of 40 patients (85%) were in clinical remission with a HBI mean drop of 6.7 ± 2.5 to 1.1 ± 1.5, with a p-value of <0.001. Nine out of the 40 patients did not reach clinical remission and/or had ESR >20mm/h at week 10, so 18 patients were randomized to Group A and 13 patients were randomized to Group B. Patients in Group A had fewer patients experiencing a relapse than Group B, which is statistically

significant with a p-value<0.003 (Table 6). Group A also had more patients in clinical remission and a lower mean HBI than Group B, which is statistically significant with p<0.01 and p=0.011, respectively (Table 6). The NNT was calculated to be 5, shown in Table 7, which means we must treat 5 pediatric patients with Crohn's disease with infliximab for 60 weeks in order to have 1 patient in clinical remission. A total of 12 adverse events were reported during the study (Table 8), but there were no serious adverse reactions or serious infectious complications that caused any patients to discontinue the study. The study also reported no difference in the number of adverse events between Group A and Group B.

Table 6: Results of children receiving a 2week schedule and an on demand schedule

	Number of children experiencing a relapse between week 10 and 60	Number of patients in clinical remission at week 60	Mean HBI at week 60
Schedule 2 week therapy (Group A)	3 (23.1%)	15 (83%)	0.5
On demand schedule with signs of relapse	11 (92%)	8 (61%)	3.2
p-value	p<0.003	P<0.01	p=0.011

Table 7: Number needed to treat-clinical remission

CER	EER	RRR	ARR	NNT
61.0%	83.0%	36.0%	22.0%	5

Table 8: Adverse events

Adverse Event	Mild Headache	Fever	Rash	Increased liver enzymes	Neutropenia	Joint/muscle pain
# of patients	3	3	3	1	1	1

The Hyams et al 2009 is a prospective, multi-center cohort study with outcomes that were presented as continuous data, but can be converted to dichotomous data. Disease severity by physician global assessment (PGA) was divided into inactive, mild, moderate, or severe. The

study included 729 patients, with 202 patients receiving infliximab categorized into maintenance, episodic or episodic converted into maintenance therapy. The percentage of patients in clinical response increased over 3 years, and the percentage of patients in clinical remission increased then decreased over 3 years (Table 9). The percentage of patients needed corticosteroids decreased over 2 years but increased slightly during the third year, which is statistically significant to baseline since $p<0.001$. The use of 6-MP/azathiopurine and immunomodulator decreased over 3 years, which is statistically significant with $p<0.02$ and $p<0.01$, respectively. The study reported no serious infections, but one patient had bowel associated Hodgkin's lymphoma who was on 6-mercaptopurine and received 8 does of infliximab.

Table 9: Results of infliximab therapy from year 0-3

	6 months	First Year	Second Year	Third Year	p-value
% of patients in clinical response		64%	70%	83%	
% of patients in clinical remission		26%	44%	33%	
% of patients receiving corticosteroids	14%	8%	7%	9%	P<0.001
% of patients using 6-MP/azathiopurine		74%	69%	58%	P<0.02
% of patients using immunomodulator	87%	84%	82%%	75%	P<0.01

Discussion:

Crohn's Disease is a chronic disease, so treating relapses and maintaining remission is extremely important. When Crohn's disease is not treated properly, it can lead to serious complications such as small bowel obstruction, hemorrhage, abscess, and fistulas, which in turn can lead to more treatments and procedures and increasing the already high costs for patients. Infliximab, a monoclonal immunoglobulin antibody can alleviate the symptoms and assist in the

management of Crohn's disease. Infliximab, which can also be used in rheumatoid arthritis, plaque psoriasis, and ulcerative colitis, was FDA approved for pediatric patients with Crohn's disease in May 2006.[2] There are still studies being conducted on this drug especially in children and its long term affects. Infliximab can increase a patient's risk for serious infections especially if the patient is also receiving other immunosuppressive drugs. Infections were reported in the Hyams et al 2007 study, but the number of people who decided to discontinue the study because of an adverse event was significantly lower. Malignancy is also a concern, because there have been some reports of T-cell lymphoma in children receiving infliximab and azathioprine.[7] The Hyams et al 2007 and Ruemmele et al study reported no malignancy in the patients, but the Hyams et al 2009 study reported one patient with bowel associated Hodgkin's lymphoma. According to the results of Hyams et al 2007, Hyams et al 2009, and Ruemmele et al studies, there is evidence that infliximab is effective and safe for pediatric Crohn's disease by the significant number of patients in either clinical response or clinical remission with a small percentage of serious adverse events in long term use.

There were some limitations among the three studies in this review. In the Ruemmele et al study, the sample size was small with 40 patients, which may not have represented the study population well enough. The Hyams et al 2007 study required patients to be on immunomodulator at least 8 weeks before the screening and at least on a stable dose for at the 2 previous weeks. The results of this study such as clinical remission and clinical response may differ between patients that were not taking the same immunomodulator. The limitation in the Hyams et al study 2009 was that the inclusion criteria may have been too broad, children under the age of 16 who were newly diagnosed with Crohn's disease, the results of the study may not be as specific to infliximab.

Conclusion:

Infliximab is a safe and effective treatment in children with moderate to severe Crohn's disease according to the results demonstrated in the three studies in this review. Further study is needed to evaluate whether dependency and/or resistance can develop with the treatment of infliximab associated with treatment duration.

References

1. Auth PC, Kerstein MD. *Physician Review*. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2009: 84-85.

2. Hyams, J.; Lerer, T; Griffiths, A.; Pfefferkorn, M; Kugathasan, S.; Evans, J.; Otley, A.; Carvalho, R; Mack, D.; Bousvaros, A; Rosh, J.; Mamula, K; Crandall, W; Oliva-Hemker, M; Keljo, D; LeLeiko, N. Long term outcome of maintenance infliximab therapy in children with Crohn's Disease. Inflamm Bowel Dis. 2009;15(6):816-822.

3. Digestive Diseases Statistics for the United States website. 2010. http://digestive.niddk.nih.gov/statistics/statistics.htm. Accessed October 1, 2010.

4. Crohn's and Colitis Foundation of America website. 2009. http://www.ccfa.org/info/about/crohns. Accessed October 1, 2010.

5. Hyams, J.; Crandall, W.; Kugathasan, S.; Griffiths, A.; Olson, A.; Johanns, J.; Liu, G.; Travers, S.; Heuschkel, R.; Markowitz, J.; Cohen, S.; Winter, H.; Veer-Wauters, G.; Ferry, G.; Baldassano, R. Induction and maintenance infliximab therapy for the treatment of moderate to severe Crohn's disease in children. Gastroenterology. 2007;132(3):863-873.

6. Crohn's Disease Center website. 2010. http://www.everydayhealth.com/crohns-disease/managing-crohns-treatmenr-costs.aspx. Accessed October 1, 2010.

7. Ruemmele, FM.; Lachaux, A.; Cezard, JP.; Morali, A.; Maurage, C.; Ginies, JL.; Viola, S.; Goulet, O.; Lamireau, T.; Scaillon, M.; Breton, A.; Sarles, J. Efficacy of infliximab in pediatric Crohn's disease: A randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. Inflamm Bowel Dis. 2009;15(3):388-394.