Acta Pædiatrica ISSN 0803–5253

SHORT COMMUNICATIONS

# Severe adverse reactions to Infliximab therapy are common in young children with inflammatory bowel disease

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**Keywords**
Adverse effect, Crohn´s disease, TNF-alpha antagonist, Ulcerative colitis

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**Received**
15 May 2006; revised 30 June 2006; accepted 11 July 2006

DOI:10.1111/j.1651-2227.2007.00042.x

**Abstract**

Since 2000 we have introduced 141 Infliximab infusions to 23 children with severe inflammatory bowel disease. A total of seven severe adverse reactions occurred in 26% (6 of 23) of the children. Four reactions were acute (anaphylaxis n = 2; allergic reaction n = 2) and 3/4 of these children were younger than 10 years of age. Two children developed an abscess and one child had septicaemia and brain lesions related to progressive multifocal leucoencephalopathy.

**Conclusion: adverse reactions to Infliximab infusions are common. Young children seem to be prone to severe allergic reactions although they are on azathioprine and conventional glucocorticoid therapy.**

Infliximab, a monoclonal human-murine chimeric antibody to tumour necrosis factor-α (TNF-α) has been a breakthrough in the therapy of severe inflammatory bowel disease (IBD) refractory to conventional treatment. Infliximab blocks both soluble and membrane-bound TNF-α thus reducing inflammation (1). In children with refractory Crohn's disease, Infliximab therapy benefits the majority but about one third of treated patients show no improvement (2). In those responsive, the effect of Infliximab is often transitory (3). Side effects are relatively common, ranging from 5% to 17% of paediatric patients (2–6) and hamper the use of this therapy in children.

We have used Infliximab infusions in our paediatric patients since year 2000 for treatment of severe Crohn's disease that is not responding to conventional treatment regimens with steroids, azathioprine, antibiotics or enteral feeding. We did a retrospective chart review in all our patients with IBD who had received one or more Infliximab infusions in Helsinki and Tampere university hospital that comprise the two major referral centres for the diagnostics and treatment of paediatric IBD with catchment area of 56% of the paediatric population in Finland (a population base of 2.9 million). We traced 23 children, 22 of them with Crohn's disease and 1 child with ulcerative colitis treated with Infliximab infusion.

The demographic data of the patients are presented in Table 1. Infliximab infusions were initiated with a regular dose of 5 mg/kg. Five children received infusion with lower dose of 3–4 mg/kg. The majority of patients were on azathioprine and on oral glucocorticoids (Prednisolone or Budesonide) at the time of their first infusion (Table 1).

The 23 children with IBD treated with Infliximab infusions received a total of 141 infusions during this 5-year period. Four children experienced a minor reaction (4 of 23; 17%; children no. 4–7 in Table 2) during infusion necessitating no medication. Five children (5 of 23; 22%) did not respond to the Infliximab infusion, and the therapy was discontinued soon. Six children had received 10 or more Infliximab infusions. The only child with UC experienced no adverse events during her seven Infliximab infusions.

Major adverse reactions occurred in 6 of 23 children (26%; children no. 1–4 and 8–9 in Table 2). The time interval to the preceding infusion was within 1–2 months in all children with an adverse reaction.

Severe acute reactions occurred in 4 children (4 of 23; 17%; children no. 1–3 and 8 in Table 2). The majority of these children were younger than 10 years of age (3 of 4; number of children $\leq$10 years of age in this study n = 3). All these children were on glucocorticoid therapy (Prednisolone 20 mg daily n = 1; 2.5 mg Prednisolone on alternate days n = 1; Budesonide 9 mg and 6 mg on alternate days n = 1; Budesonide 6 mg daily n = 1;) and two of these children were on azathioprine. The youngest child (2.7 years of age) had received 20 mg Prednisolone (2 mg/kg) 2–3 hour prior to infusion and she had been on azathioprine for 6 months.

The 2-year-old child, who had a severe acute reaction after her second infusion, had two abscesses necessitating revision under anaesthesia within 1 week after her first infusion. There was no bacterial growth. An 11-year-old boy had an abscess within 4 weeks in his buttock that needed surgical revision. None of the 23 children developed an opportunistic infection or tuberculosis.

The most severe adverse reactions occurred in a 16-year-old boy who after the second Infliximab infusion developed severe septicaemia necessitating treatment in the intensive care unit. His clinical condition deteriorated, and 3 months later, MRI examination revealed changes related to progressive multifocal leucoenkephalopathy. There were no specific findings in biopsy and no infective agent was found. The neurological symptoms vanished and brain lesions disappeared

**Table 1** Demographic data on the paediatric patients with inflammatory bowel disease treated with Infliximab infusions at our hospitals

| Number of patients | n = 23 |
|---|---|
| Age (median, range) | 14 years (2.7–18) |
| Sex (male/female) | 10/13 |
| Diagnosis | Crohn's disease n = 22<br>Ulcerative colitis n =1 |
| Therapy at the time of first infusion (no. of patients) | |
| Mesalazine | n = 13 |
| Azathioprine | n = 17 |
| Oral glucocortioid | n = 18 |
| Antibiotics | n = 5 |

completely within 6 months after discontinuation of the Infliximab therapy.

Acute infusion reactions during Infliximab infusion are relatively common, the frequency estimated from 4–5% (5,7) to 12–16% (2,6,8) and 23% (8) per number of patients treated. A total of 35% of our patients experienced an acute reaction during Infliximab infusion, and 50% of these acute events were anaphylaxis or severe urticaria, the majority of them (3 of 4) occurring in children under 10 years of age. It is remarkable that each child under 10 years of age experienced an acute adverse reaction. To our knowledge, there are no reports addressing the safety of Infliximab infusion in the very young children. In paediatric studies on Infliximab, the age of children has been over 10 years (2,8,10). In the large recent multi-centre study in paediatric patients (6), severe reactions were rare (anaphylaxis 2 of 243) but the age of the patients with adverse reactions was not commented.

Infliximab is a recombinant chimeric antibody including antigens originating from mouse. Infusion reactions are considered secondary to the formation of antibodies directed against Infliximab (11). In the study by Miele et al. (9), more than one third of the child patients developed human antichimeric antibodies (HACA) during the course of repeated infusions (9). To avoid the development of HACA, azathioprine on regular doses may show a preventive effect and is thus recommended in patients receiving Infliximab (11). The majority of allergic reactions occur during the first four infusions (6,10). Among our patients, the most severe anaphylaxis occurred during the seventh infusion (a girl of 6 years of age). It is remarkable that anaphylaxis and severe urticaria occurred although the children were concomitantly on glucocorticoids. One child had received a Prednisolone dose of 2 mg/kg 2–3 h before infusion, but this did not prevent the development of severe urticaria during infusion. This particular patient had received immunosuppressive medication for more than 4 months, a time interval considered to reduce the risk for infusions reactions (10). Others have reported that immunosuppressive therapy does not exclude severe infusion reactions (3,6).

The incidence of serious infections in all patients treated with Infliximab is estimated to reach 8% in adults (7). In this study, 8.7% of the children (2 children) developed sterile abscesses within 2–4 weeks of the infusion and 1 child presented with severe septicaemia. No other infections were detected.

Infliximab may cause neural changes suggestive of multiple sclerosis or other demyelinating processes as described in a 19-year-old girl with Crohn's disease. Fortunately, these changes seem to recover after the Infliximab therapy is discontinued (12). Our patient was a 16-year-old boy with extremely aggressive Crohn's disease not responding to any of the treatments. His brain lesions related to progressive multifocal leucoenkephalopathy with corresponding neural

**Table 2** Adverse reactions to Infliximab infusions in 23 children with inflammatory bowel disease

| No. | Age (years) | Sex | Diagnosis | Therapy at the time of adverse reaction | No. of infusions (5 mg/kg) | Adverse reactions |
|---|---|---|---|---|---|---|
| 1 | 2.7 | Female | Crohn | Prednisolone 20 mg | 2 | Abscess at the infusion site and in the leg (2 weeks after 1st infusion) |
| | | | | Azathioprine 12.5 mg × 2 | | Severe urticaria (during 2nd infusion) |
| 2 | 6.5 | Female | Crohn | Mesalazine 500 mg × 2 Budesonide 6 mg* | 7 | Anaphylaxis (during 7th infusion) |
| 3 | 9 | Male | Crohn | Mesalazine 500 mg × 3 Azathioprine 25 mg × 2 Budesonide 6 mg | 3<br>3 | Severe urticaria (during 3rd infusion) |
| 4 | 11 | Male | Crohn | Prednisolone 20/5 mg on alternate days | 4** | Dizziness and nausea (2nd infusion)<br>Abscess in the buttock (4 weeks after 2nd infusion) |
| 5 | 12 | Female | Crohn | Azathioprine 25 mg × 2 | 12 | Flu mild (1st infusion)<br>Vertigo (2nd infusion) tiredness (3rd infusion) |
| 6 | 13 | Male | Crohn | Azathioprine 25 mg × 2 Mesalazine 500 mg × 3 Budesonide 9 mg/week | 12 | Low blood pressure (3rd infusion) with no subjective symptoms |
| 7 | 14 | Female | Crohn | Prednisolone 20 mg × 1 Azathioprine 50 mg × 2 Mesalazine 500 mg × 6 | 1 | Difficulties to breath, chest pain (1st infusion) |
| 8 | 14 | Female | Crohn | Prednisolone 2.5 mg on alternate days Azathioprine 25 mg + 12.5 mg | 5 | Anaphylaxis (during 5th infusion) |
| 9 | 16 | Male | Crohn | Azathioprine 50 mg × 2 | 5 | Severe septicaemia (after 2nd infusion)<br>Multifocal leucoencephalopathy |

*Azathioprine not tolerated.

**Infliximab dose 3.5 mg/kg.

symptoms developed within 3 months after introduction of Infliximab therapy. Within 6 months after discontinuation of Infliximab therapy, his brain MRI was completely normal and he presented no neurological symptoms.

In conclusion, adverse reactions to Infliximab infusions are common. The majority of reactions are mild and enable continuation of the therapy. However, young children seem to be prone to severe adverse reactions although they are on azathioprine and conventional glucocorticoid therapy. It is advisable that this therapy should be limited to specialized paediatric centres.

Ms Sari Honkanen is thanked for her excellent assistance in gathering the data. The Finnish Cultural Foundation and the Finnish Pediatric Research Foundation supported this study.

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# Identification of a novel compound heterozygote SCO2 mutation in cytochrome c oxidase deficient fatal infantile cardioencephalomyopathy

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**Keywords**
Cardioencephalomyopathy, Mitochondrial disorder, Respiratory chain deficiency, SCO2

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**Received**
15 February 2006; accepted 14 June 2006

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DOI: 10.1111/j.1651-2227.2007.00008.x

**Abstract**

*Fatal infantile cardioencephalomyopathy* (OMIM No. 604377) is a disorder of the mitochondrial respiratory chain and is characterised by neonatal progressive muscular hypotonia and cardiomyopathy because of severe Cytochrome c oxidase deficiency. Here we report a novel mutation in the Cytochrome c oxidase assembly gene SCO2 in an infant with fatal infantile cardioencephalomyopathy despite normal initial metabolic screening.

**Conclusion: In newborns with unexplained muscular hypotonia and cardiomyopathy genetic testing of mitochondrial respiratory chain disorders might be helpful to establish a final diagnosis and guide treatment decisions.**

Cytochrome c oxidase (COX) is a multimeric enzyme of the inner mitochondrial membrane and catalyses the reduction of molecular oxygen by reduced cytochrome c, the terminal step in the respiratory chain. The incidence of respiratory chain disorders is 1 in 10 000 newborns of which isolated COX deficiency constitutes around 1/3 (1). COX deficiency presents with a wide range of multi-system symptoms. Several pathogenic mutations have been reported in the three mitochondrial-encoded COX subunits and in genes involved in the assembly of the COX holoenzyme (2).

 