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REVIEW ARTICLE

Infliximab in paediatric inflammatory bowel disease

Pere Vilar [a,*], Javier Martín de Carpi [a], Claudia E. Acuña [b], Mª Luisa Masiques [c]

[a] *Paediatric Gastroenterology Section, Hospital Universitari Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain*
[b] *Paediatric Gastroenterology Unit, Department of Paediatrics, Hospital General de Catalunya, Sant Cugat del Vallés, Barcelona, Spain*
[c] *Paediatric Gastroenterology Unit, Department of Paediatrics, Hospital General de Granollers, Granollers, Barcelona, Spain*

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Abstract Infliximab has been widely used in paediatric Crohn's disease, mainly in luminal and fistulous disease refractory to standard treatment and for extraintestinal manifestations. Moreover, there is growing experience with its use in refractory ulcerative colitis. Infliximab has shown similar efficacy and safety in children as in adult population. It is postulated that its early use in paediatric inflammatory bowel disease, as a bridging treatment until the onset of action of other immunomodulators, could reduce the use of steroids and change the natural history of the disease as well. The effect of infliximab on mucosal healing could also contribute to the normal growth and sexual maturation in these patients.

Contents

Abbreviations: CDAI, Crohn's disease activity index; GH, growth hormone; HSTCL, hepatosplenic T-cell lymphoma; IBD, inflammatory bowel disease; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; IL, Interleukin; PCDAI, paediatric Crohn's disease activity index; TNF, tumour necrosis factor.

* Corresponding author. Paediatric Gastroenterology Section, Hospital Universitari de Sant Joan de Déu, Passeig de Sant Joan de Déu, 2, 08950 Esplugues de Llobregat, Barcelona, Spain. Tel.: +34 639 53 8226; fax: +34 93 203 3959.
E-mail address: pvilar@hsjdbcn.org (P. Vilar).

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1. Introduction

The onset of inflammatory bowel disease (IBD) in paediatric age is associated to a high rate of complications, sometimes more severe than those occurring in adult patients. In children and adolescents, the chronic maintenance of mucosal inflammation (either with or without symptoms) has deleterious effects upon their growth and development, and increases the likelihood of a torpid evolution of the disease itself. In the last years, there is a growing trend to prefer therapies able to achieve mucosal healing – enteral nutrition,[1,2] azathioprine, infliximab[3] – rather than treatments that merely ameliorate symptoms with no improvement in mucosal damage, such as steroids[4] or mesalazine.

Protracted mucosal inflammation should result in a greater probability of irreversible damage. Therefore, the early use of able to heal the mucosa appears to be of utmost importance. In children with Crohn's disease, the response to infliximab appears to be better and persist for a longer time when this biological agent is used earlier in the course of the disease.[5–7] On the other hand, adults receiving infliximab therapy associated to azathioprine have long-term (two years) rate of mucosal healing as high as 75%, in comparison to only 25% in those patients receiving classical treatment with steroids.[8] These data are viewed as an indirect evidence that early "aggressive" therapy may result in a more complete remission, thus avoiding the need for other therapies.[9] Indeed, maintained mucosal healing with infliximab therapy has been reported to be associated to lower complication and hospitalisation rates in adult Crohn's disease patients,[10] thus suggesting that this agent would be able to alter the natural course of the disease.

In the present article, available data on the efficacy and safety of infliximab in paediatric Crohn's disease and ulcerative colitis are reviewed. In addition, the impact of this therapy on the catch-up growth of these patients is also discussed.

2. Efficacy of infliximab in paediatric Crohn's disease

In spite that the first reported IBD patient treated with the anti-tumour necrosis factor (TNF) monoclonal antibody infliximab – in 1993 – was a 13-year-old girl suffering from severe Crohn's disease,[11] the first trial of the use of this agent in paediatric Crohn's disease patients was published as late as in 2000.[6] In fact, most published papers on the paediatric use of infliximab are retrospective and uncontrolled series. Most of these studies use the paediatric Crohn's disease activity index (PCDAI), a validated index for children and adolescents that, in contrast to the adult Crohn's disease activity index (CDAI) includes parameters of growth retardation as well as laboratory markers of inflammation, rather than subjective symptoms.[12,13] PCDAI scores from 0 to 100 points. Scoring $\leq$10 points are considered as inactive disease, mild disease scores from 11 to 30 points whereas scoring >30 points denote moderate/severe disease. In most papers, clinical remission is defined as a PCDAI $\leq$10, and clinical response as a decrease in PCDAI of at least 15 points (and below 30 points) from pre-treatment value.

As in adult patients, paediatric use of infliximab has been mostly restricted to patients with moderate/severe or fistulising disease who were refractory or dependent to steroid and who also failed to respond to traditional immunomodulators. However, the possibility of using this agent as a bridging therapy to long-term immunomodulatory maintenance therapy or even as a first line treatment to avoid the sue of steroids should be considered, particularly in children and adolescents. In this respect, it has been suggested that infliximab would be more potent in children than in adults, since many paediatric patients respond well to an early short-scheduled administration of the agent, remaining thereafter in remission for years.[14]

There are data suggesting that the effectiveness of infliximab in children and adolescent depends on how early is this agent used. Kugathasan et al.[6] prospectively assessed the short- and long-term response to a single infusion of infliximab in 15 paediatric patients (mean age 12.8 years, range 6–18) with refractory Crohn's disease. A rapid and dramatic response was obtained in 14 out of 15 patients. Of these, six patients had an "early" (<2 years) and eight had a "late" (>2 years) disease. At 10th week, 10 of these patients remained and remission without differences between those with "early" or "late" disease. However, at week 32, all patients with "late" disease had lost their response to infliximab, as compared to those with "early" disease in whom remission was maintained in 3/6 patients at week 52. In a similar paper, Lionetti et al.[5] report on the outcome of 22 patients with refractory and/or fistulising Crohn's disease treated with infliximab "on demand". Six and 16 patients were classified as having "early" (<1 year), and "late" (>1 year) disease, respectively. After 16 weeks of therapy the PCDAI was significantly lower in those patients with "early" than in those with "late" disease. Moreover, fistulising disease also had a better evolution in patients with "early" disease: 5/6 in this group had complete fistula closure, as compared to 2/7 in the "late" disease group. These data suggest that therapeutic response of infliximab is more sustained in patients with shorter lived disease, so that the early use of infliximab in paediatric Crohn's disease might be of benefit.

Very recently the REACH trial has been published.[15] This is an open, multicentric and randomized trial designed to assess the efficacy and safety of infliximab in paediatric patients suffering from moderate-to-severe Crohn's disease refractory to steroids and/or immunomodulators. One-hundred and twelve patients (mean age: 13 years, range 6–17) with Crohn's disease diagnosed at least 3 months before, PCDAI higher than 30, and at least 8 weeks on immunomodulators, were treated with three induction infusions (5 mg/Kg each) of infliximab at weeks 0, 2 and 6. Those patients who responded to the induction schedule were then randomized (1:1) at week 10 to