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REVIEW ARTICLE

Infliximab in paediatric inflammatory bowel disease

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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.

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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

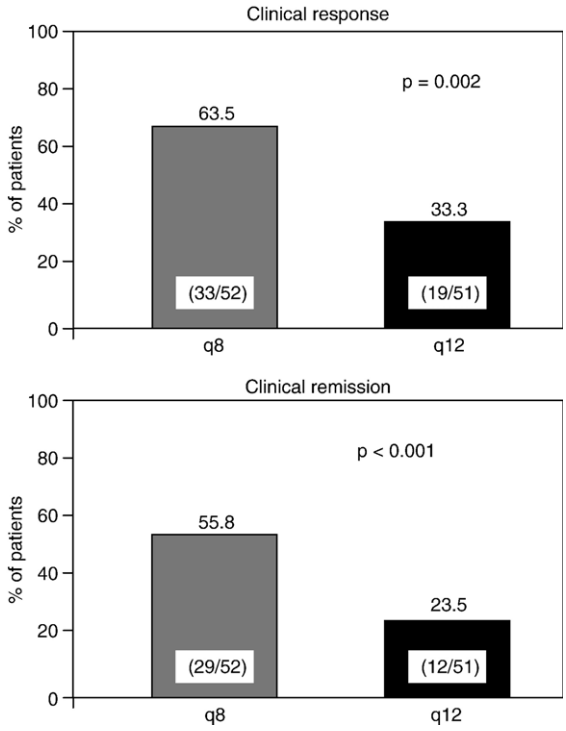

Figure 1 Clinical response and remission rates at week 54 in the REACH trial.[15]

receive maintenance therapy every 8 weeks (q8, $n=52$) or every 12 weeks (q12, $n=51$) at the same dose, until week 46. The clinical response/remission was evaluated at week 54. Patients who lost response (PCDAI >30 or 15 or more points increase above the week 10 value) were eligible to cross over one time during the study to receive treatment more frequently and/or at a higher dose, depending on the length of time between the previous infusion and the loss of response. If response was lost prior to 8 weeks from the previous infliximab infusion, for both q8 and q12 groups, patients were eligible to cross over to infliximab 10 mg/kg every 8 weeks. Patients of the group q12 who lost response within the period from week 8 to week 12 following the previous infusion were eligible to cross over to infliximab 5 mg/kg every 8 weeks. Assessment of clinical efficacy was made on an intention-to-treat basis.

At week 10, the clinical response rate was 88.4% (91/112), and clinical remission occurred in 58.9% of the cases (66/112). At week 54, response and remission rates were 63.5% (33/52) and 55.8% (29/52) in the q8 groups, and 33,3% (17/51) and 23.5% (12/51) in the q12 group ($p=0.002$, and $p<0.001$, respectively) (Fig. 1).[15] For this analysis, those patients who crossed over or escalated dose were considered as non-responders. About 50% of patients in the group q12 lost response (25/51) vs. only 19% in the group q8 (10/52). Seventy-five per cent of patients who crossed over or escalated dose re-gained response.[15]

The proportion of paediatric patients achieving clinical response or remission at week 10 in the REACH trial was higher that those observed in adults in the ACCENT I trial[16] (Fig. 2). Some characteristics of both trials could account for these differences: a) All patients in the REACH trial were on immunomodulators for at least 8 weeks, whereas only about 27% fulfilled this criterion in the ACCENT I trial, b) In the paediatric study smoking consumption is not relevant (although there is no evaluation of passive smoking), and c) the mean duration of the disease was shorter in the REACH study (1,6 vs. 7.0 years).

Taken together, the results of the REACH trial suggest that the clinical response to infliximab, in paediatric patients with moderate-to-severe Crohn's disease unresponsive to conventional therapies, is quite similar to that in adult patients. Infliximab is effective for both inducing and maintaining remission or response, and for sparing steroids as well. Maintenance infusions every 8 weeks appear superior than an every 12-week schedule.

Although there are no conclusive data, one can speculate with the possibility of using infliximab as first line therapy, at the onset of the disease, in children. It is conceivable that the early use of infliximab, with its ability for healing mucosal damage, might be a "curative" treatment able to revert the chronic inflammatory reaction in the bowel before it auto-perpetuates.[17]

3. Efficacy of infliximab in paediatric ulcerative colitis

The experience with infliximab in the treatment of paediatric patients with ulcerative colitis is quite limited, since all published studies are retrospective, non-controlled, and include a small number of patients.[18–26] Moreover, there is no homogeneity either in the inclusion criteria for treatment (although most patients had a steroid-refractory or steroid-

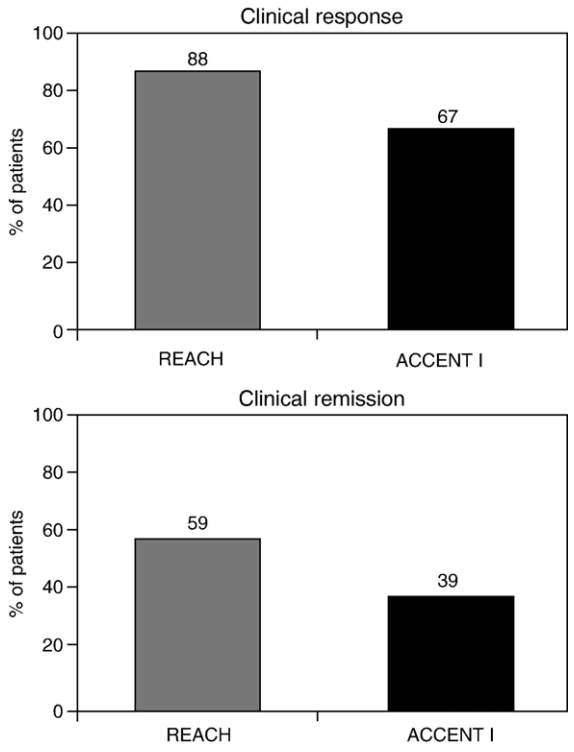

Figure 2 Clinical response and remission rates at week 10 in the REACH[15] and ACCENT I[16] trials.

dependent moderate-to-severe disease), or the definition of short- and long-term response. There is also a lack of consensus regarding the induction and maintenance dose as well as in the concomitant use of immunomodulators.

The recently published ACT1 and ACT2 trials show a clear benefit of infliximab in adult patients with moderate/severe ulcerative colitis.[27] The clinical response at 8 weeks ranges from 29% to 37% in the placebo groups as compared to 64%–69% in the therapeutic groups ($p<0.001$).[27] At weeks 30 and 54, the clinical response was still better with infliximab than with placebo. A recent systematic review on the efficacy and safety of infliximab in ulcerative colitis includes 92 children (Table 1). The short-term (mean 2.2 weeks) response and remission rates were 75% (95%CI: 64%–83%), and 63% (95%CI: 47%–76%), respectively. Long-term response (mean 7.9 months) reached 43% (95%CI: 33%–55%). Long-term remission was only assessed in one series of only 14 patients[24] (Table 1).

As in Crohn's disease, it would be nice to identify predictive factors for response to infliximab. In a recent study, Ferrante et al.[29] assessed the response to infliximab in 100 adult patients with ulcerative colitis (84 patients received a single dose of 5 mg/kg, and the remaining 37 cases were treated with a three-dose induction schedule). Sixty-five per cent of patients achieved a short-term response (either complete or partial) as evaluated at week 4 in those treated with a single dose, or at week 10 in those treated with three induction doses. Response was worse in those patients bearing a serotype pANCA(+)/ASCA(−), and in older patients as well.[29] The age at diagnosis, the duration of the disease, the concomitant use of immunomodulators, and the therapeutic schedule used did not influence the short-term response to infliximab.[29]

In spite of the limitations inherent to the above-mentioned paediatric series, one can speculate that infliximab would be particularly useful in acute steroid-refractory ulcerative colitis receiving concomitant immunomodulator treatment than in patients with steroid-dependent disease[18,24] (Table 1).

The optimal duration of infliximab therapy in ulcerative colitis is not defined yet. Fanjiang et al.[25] recommend to maintain the treatment every 8 weeks for one year, and then start with a progressive weaning, according to the clinical response, increasing the time between doses to 10 and 12 weeks, until discontinuation. Following this policy, with a mean follow-up of 10 months (range: 1–52) after the last infliximab infusion, remission was maintained in all patients who were able to discontinue the drug (80% of the initial responders).[25] At long-term, 75% of patients with either steroid-resistant or acute disease without steroid-dependence were able to maintain the clinical response, as compared to only 25% of steroid-dependent patients.[25] All patients received treatment with immunomodulators both during and after infliximab therapy. These results are in agreement with those obtained in adult ulcerative colitis, where only 33% of steroid-dependent patients improved, as compared to 83% in non-steroid-dependent cases.[30]

In summary, on the light of published data, it is conceivable that infliximab might be as effective in paediatric as in adult patients with ulcerative colitis, but large randomized controlled trials are needed in this particular group of patients to confirm such a suggestion.

4. Safety of infliximab in paediatric IBD

4.1. Reactions to infusion

The reported frequency of both acute and delayed reactions to infusion of infliximab in children with IBD is similar to that

Table 1 Summary of the series assessing the efficacy of infliximab in ulcerative colitis including only paediatric patients (modified from reference #[28])

Author (ref.)	*n*	Severity (mild/mod/severe)	Indication (SD/SR)	Previous IMM (*n*)	Induction doses	Repeated infusions	Short-term outcome	Time (wk)	Long-term outcome	Time (mo)
Eidelwein 18	12	0/6/6	8/4	8	6 (mean)	Yes	Response: 12/12 (100%) Remission: 9/12 (75%)	2	Response: 8/12 (67%) Remission: 9/12 (75%)	10.4
Mamula 20,21	17	1/10/6	0/17	12	1	Yes	Response: 14/17 (82%) Remission: 6/9 (66%)	0.3	Response: 10/16 (63%)	9.5
Russell 24	14	0/5/9	0/14	7	3	Yes	Remission: 8/14 (57%)	2.6	Remission: 8/14 (57%)	12
Serrano 26	3	–	–	3	1–6	–	Response: 3/3 (100%)	–	Response: 1/3 (33%)	1.5
McGinnis 22	29	0/0/29	0/29	–	–	–	Response: 18/29 (62%)	4	Response: 5/29 (17%)	12
Oliva–Hemker 23	5	–	–	3	1	Yes	Response: 5/5 (100%) Remission: 2/5 (40%)	2	–	–

All studies are retrospective and non-controlled series. Dose used in every study: 5 mg/kg.
SD: Steroid-dependent; SR: Steroid-refractory; IMM: immunomodulators.

reported in adult patients. A review of the paediatric literature yields a rate of reactions to infusion of about 17%, most of them being acute reactions (93%) defined as any event occurring during or in the immediate 2 h following the infusion. This frequency drops dramatically if one only takes into account those reactions needing medical care.[31] Most reactions to the infusion occur after the second or third dose of infliximab. Predictive factors for reactions to infusion in children include a) female gender, b) previous history of reactions to infusion, and c) less than four months on immunomodulator therapy.[31]

Most acute reactions to the infusion are easy to manage either with antihistaminic drugs or steroids.[32] Chronic (i.e. serum sickness-like) reactions require high-dose steroid therapy for 4–7 days, as well as prophylaxis with steroids (48 h before 5–7 days after the infusion) in further infusions.

Prophylactic pre-medication before infusions allows to decrease the frequency of reactions to infusion in those patients who had developed them previously. It has been also suggested that its use before the first infliximab infusion might prevent the development of these reactions. In adult patients, the number of reactions to infusion diminish with the concomitant use of immunomodulators, as well as with the scheduled use of infliximab (every 8 weeks) rather than administering it on demand. To our knowledge, there is only one study addressing this issue in paediatric patients with an adequate sample size ($n = 243$).[33] In this study, no benefit could be demonstrated from either administering pre-medication from the first infusion, using concomitant immunomodulators or administering infliximab on a scheduled sequence, in terms of reduction of the number of reactions to the infusion.[33] It is important to note that 7% of these reactions occurred after the first infliximab infusion, suggesting that a placebo effect could account for some of these events.

4.2. Infections

As in adult patients, infections associated to the use of infliximab have been reported in paediatric patients. Non-severe respiratory infections are the most common infectious complications associated to infliximab use in children, but cases of herpes zoster, *tinea corporis*, catheter sepsis, meningitis due to *Listeria* spp., or a fatal case due to sepsis in a malnourished and leukopenic patient undergoing multiple surgical procedures, have been reported. To date, there are no reports of tuberculosis or hepatitis B reactivation in paediatric patients treated with infliximab. However, a complete tuberculosis work-up – including anamnesis, Mantoux test and X-ray film of the thorax – as well as serologic test for hepatitis B virus must be performed in any patient candidate to be treated with infliximab.

4.3. Neoplasia

The long-term adverse consequences of the use of infliximab still are a controversial issue. The development of neoplastic disease is a major concern for doctors using this agent, mainly in paediatric patients. Apparently, there is no increased risk for developing lymphomas in patients with IBD, but the role of conventional immunomodulators in the development of these neoplasms is a matter of debate.

Hepatosplenic T-cell lymphoma (HSTCL) is a rare neoplasm with about 100 cases reported in world literature. However, eight of them have been described associated to the use of infliximab[34,35] suggesting an increasing risk of this kind of lymphoma in patients treated with this biological agent, particularly young individuals (all reported patients were younger than 31). Nevertheless a primary or unique pathogenic link between TNF blockade and the development of HSTCL in IBD patients cannot be established, since all reported cases were on concomitant azathioprine or 6-mercaptopurine therapy, and there are some report of HSTCL in patients treated only with these traditional immunomodulators.[36,37]

Some experts in the management of IBD – particularly those dealing with paediatric disease – recommend not to use immunomodulators concomitantly to infliximab for more than six months, on the basis of recent studies which suggest that concomitant immunomodulatory therapy adds little benefit to the long-term maintenance therapy with infliximab, in terms of prevention of relapse.[38,39]

4.4. Congestive heart failure

It is well known that infliximab can worsen congestive heart failure. Recently, the preliminary results of a study assessing the heart function (by means of electro- and echocardiogram) during infliximab therapy, in twelve paediatric IBD patients (9 Crohn's disease, 3 ulcerative colitis), have been published.[40] Seven out of 12 patients showed cardiac disturbances consisting of dilation of the cardiac cavities (5 cases) and septal hypertrophy (2 cases), with a direct correlation between the length of Q–T interval and the systolic and diastolic diameter of the left ventricle. These findings point out to an increased risk of developing arrhythmias in these patients. However, further and more complete studies should be done before recommendations about cardiologic work-up required prior infliximab therapy could be made.

4.5. Other adverse events in paediatric IBD

Recently, the case of a young Crohn's disease patient who developed a progressive multifocal leukoencephalopathy after infliximab therapy has been reported.[41] This was a 16-year-old male who presented with a sepsis following the second dose of infliximab. His clinical condition progressively deteriorated, and three months later showed MRI findings suggestive of progressive multifocal leukoencephalopathy. Neither histological specific findings nor any infectious agent could be documented. Neurological symptoms subsided, and cerebral damage disappeared six moths after infliximab discontinuation.[41]

5. The impact of infliximab on growth retardation in children with IBD

5.1. IBD and growth

Delay in growth and puberal development is very frequent in IBD – mainly in Crohn's disease – and constitutes one of the peculiarities of this disease during this period of life. Growth retardation may occur at the time of IBD diagnosis or later, as a result of protracted chronic inflammation or its treatment.[42,43] If not treated before puberty, growth delay may become irreversible. About 25% of Crohn's disease and 10% of

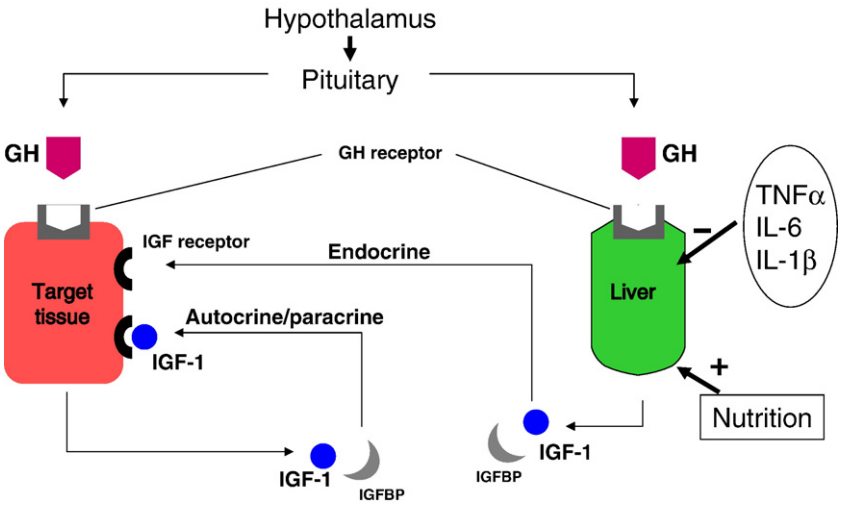

Figure 3 The GH/IGF-I axis (see text for details).

ulcerative colitis adult patients with disease onset during childhood have a height below the 5th percentile of the healthy population.[44]

At the time of diagnosis, 88% of children with Crohn's disease have a delayed growth velocity,[45] and about 33% have a height below the 5th percentile.[46] In this clinical setting, the deleterious role of steroid therapy on growth is of utmost relevance. Puberty is also delayed,[47] and persists for a longer time, in those patients with Crohn's disease with continuous activity or frequent relapses in the pre-puberal period. In 73% of a series of girls with Crohn's disease starting in the pre-puberal period, menarche occurred at 16 or later.[48] Induction of clinical remission in these cases is usually followed by menarche.

5.2. The growth hormone/insulin-like growth factor-I axis

Growth hormone (GH) exerts its somatotropic actions either directly or by means of other growth factors known as insulin-like growth factor-I and II (IGF-I, IGF-II). IGFs are synthesized upon GH stimulation, mainly in the liver (thus resulting in systemic endocrine effects) but also at local level (producing paracrine/autocrine effects). IGFs circulate bound to six different IGF binding proteins (IGFBP-1 to 6) (Fig. 4). IGF tissue bioavailability mostly depends on the concentrations of the different IGFBP. In general, IGFBP-3 increases the action of the IGFs, whereas it is inhibited by IGFBP-1 and 2.[49] Increased serum levels of IGFBP-2 are associated to growth retardation.[50] GH up-regulates serum IGF-1 and IGFBP-3, and down-regulates IGFBP-2. The integrity of the GH/IGF-I axis is of utmost importance for a normal growth.

Both malnutrition and pro-inflammatory cytokines negatively influence the GH/IGF-I axis (Fig. 3). Malnourished children show low serum concentrations of IGF-1 which do not normalize with the administration of exogenous GH. Interleukin (IL)-1β, IL-6 and TNF-α decrease the IGF-I synthesis by blocking the GH hepatic receptors, with independence of the nutritional status.[51] Indeed serum IGF-I levels inversely correlate with the ESR, and the C-reactive protein levels, whereas IGFBP-2 are directly related to ESR, IL-1β, and IL-6.[52]

In adults, it has been demonstrated that gastrointestinal inflammation – no matter what is the cause – results in decreased serum IGF-I and IGFBP-3 concentrations, as well as increased IGFBP-1 and IGFBP-2, in the presence of normal GH levels,[53] indicating the existence of peripheral resistance to GH. Similar results have been obtained in paediatric patients with active IBD.[54,55] These disturbances normalize upon remission.

5.3. Infliximab and the GH/IGF-I axis

The effect of infliximab on the GH/IGF-I axis has been recently assessed in a series of 14 adult IBD patients with low levels of IGF-I and IGFBP-3 treated with three induction doses (weeks 0, 2 and 6) plus two additional infusions every eight weeks.[56] Peripheral resistance to GH is apparently reversed after the second infusion of infliximab, as judged by the significant increase in the serum levels of IGF-I and IGFBP-3 as compared to baseline. However, this effect is not sustained since they return to baseline values between the first and second maintenance dose.[56] TNF blockade by infliximab could account for the initial improvement of GH

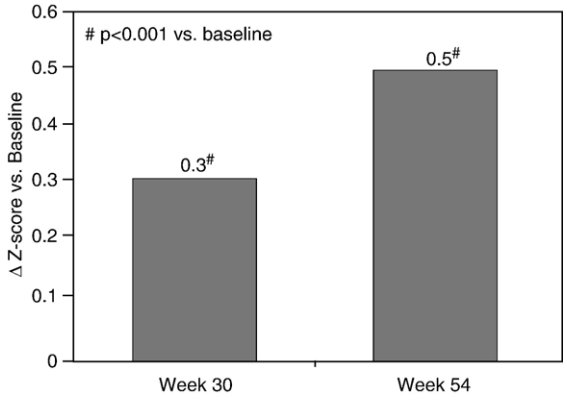

Figure 4 Changes in the mean *Z*-score for height in the REACH trial.[15] Mean baseline *Z*-score was −1.6.

sensitivity as increased TNF activity suppresses the GH/IGF-I axis in the liver. The late impairment of GH sensitivity during maintenance therapy is harder to explain, but one can speculate that during this period some degree of subclinical mucosal inflammation might persist.

5.4. Infliximab and growth catch-up in paediatric IBD

In the above-mentioned REACH trial,[15] the Z-score for height at weeks 0, 30 and 54 was assessed in those patients with more than one year retardation in their bone age (as judged by the wrist X-ray exam) ($n=38$). A significant improvement over the baseline Z-score for height was observed both at weeks 30 and 56 on infliximab therapy (Fig. 4).

Borrelli et al.[57] reported on a prospective series of 18 patients (mean age: 13 years, range 6–18) with moderate-to-severe Crohn's disease refractory to conventional treatments (azathioprine/steroids), who received 5 mg/kg infliximab at weeks 0, 2 and 6 (followed in 8 of them by maintenance doses every 8 weeks). At week 8 (after the three induction doses), the PCDAI improved significantly (from 34.1±5.1 to 14.8±4.8; $p<0.01$), as did the nutritional status and endoscopic/histological parameters. Ten patients were on clinical remission (PCDAI ≤10) and 12 were in endoscopic remission. All patients could discontinue steroids at week 4. At 6 months, the PCDAI was significantly lower in those patients on infliximab maintenance therapy (10.5±1.41 vs. 18.8±4.54 in those receiving only three induction doses; $p<0.05$). By this time, significant increases in both weight and height were also observed but, again, these were much more marked in those patients receiving infliximab on a long-term basis (Table 2).[57]

Improving the nutritional status and promoting catch-up growth are major end-points of the treatment of paediatric IBD (mainly Crohn's disease), particularly in the pre-puberal and puberal periods. Therefore, measures of growth and development should be routinely performed during the follow-up of these patients, and failure to improve them must be considered as lack of efficacy of IBD therapy.[58] Catch-up is conceivably easier to achieve with treatments able to control mucosal inflammation and restore the nutritional status. There are reasons to believe that the growth and development of these patients is less compromised when treated with infliximab.[59] Maintenance therapy may be important in this setting.

Table 2 Changes in Z-scores for weight and height in paediatric Crohn's disease patients on infliximab therapy (from reference #[57])

	Baseline	At 6 moths	*p*-value
Patients on maintenance therapy (n=8)			
Z-score for weight	−0.67±0.43	−0.26±0.49	<0.01
Z-score for height	−1.15±0.81	−0.62±0.99	<0.01
Patient receiving only three induction doses (n=10)			
Z-score for weight	−0.21±0.44	−0.19±0.42	NS
Z-score for height	−0.86±0.42	−0.86±0.40	NS

(NS: non-significant).

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