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The effects of anti-TNF-α treatment with adalimumab on growth in children with Crohn's disease (CD)

S. Malik [a,b], S.F. Ahmed [a], M.L. Wilson [c], N. Shah [d], S. Loganathan [e], S. Naik [f], B. Bourke [g], A. Thomas [h], A.K. Akobeng [h], A. Fagbemi [h], D.C. Wilson [c], R.K. Russell [b,*]

[a] *Bone & Endocrine Research Group Royal Hospital for Sick Children, Yorkhill, Glasgow, UK*
[b] *Dept of Paediatric Gastroenterology & Nutrition, Royal Hospital for Sick Children, Yorkhill, Glasgow, UK*
[c] *University of Edinburgh, Child Life and Health, Edinburgh, UK*
[d] *Great Ormond Street Hospital, Paediatric Gastroenterology Department, London, UK*
[e] *Royal Aberdeen Children's Hospital, Department of Medical Pediatrics, Aberdeen, UK*
[f] *Bart's and the London Children's Hospital, London, UK*
[g] *Our Lady's Children's Hospital Crumlin, Children's Research Centre, Dublin, Ireland*
[h] *Royal Manchester Children's Hospital, Manchester, UK*

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KEYWORDS
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Abstract

Introduction: Adalimumab is used to treat children with Crohn's disease (CD), but the effects of adalimumab on growth in CD have not been studied.
Aim: To study growth and disease activity over 12 months (6 months prior to (T−6), baseline (T0) and for 6 months following (T+6) adalimumab).
Subjects and methods: Growth and treatment details of 36 children (M: 22) who started adalimumab at a median (10th, 90th) age of 14.7 years (11.3, 16.8) were reviewed.
Results: Of 36 cases, 28 (78%) went into remission. Overall 42% of children showed catch up growth, which was more likely in: (i) those who achieved remission (median change in height SDS (ΔHtSDS) increased from −0.2 (−0.9, 1.0) at T0 to 0.2 (−0.6, 1.6) at T+6, (p=0.007)), (ii) in those who were on immunosuppression ΔHtSDS increased from −0.2 (−0.9, 1.0) at T0 to 0.1 (−0.8, 1.3) at T+6, (p=0.03) and (iii) in those whose indication for using adalimumab therapy was an allergic reaction to infliximab, median ΔHtSDS increased significantly from −0.3 (−0.9, 1.0) at T0 to 0.3 (−0.5, 1.6) at T+6, (p=0.02). Median ΔHtSDS also increased from −0.4 (−0.8, 0.7) at T0 to 0.0 (−0.6, 1.6) at T+6, (p=0.04) in 15 children who were on prednisolone therapy when starting adalimumab.

* Corresponding author at: Department of Paediatric Gastroenterology, Yorkhill Hospital, Dalnair Street, Glasgow G3 8SJ, UK. Tel.: +44 141 201 0313; fax: +44 141 201 0303.
E-mail address: richardrussell@nhs.net (R.K. Russell).

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Conclusion: Clinical response to adalimumab therapy is associated with an improvement in linear growth in a proportion of children with CD. Improved growth is more likely in patients entering remission and on immunosuppression but is not solely due to a steroid sparing effect.

1. Introduction

Crohn's disease (CD) in children often results in malnutrition, growth retardation, pubertal delay and poor bone health.[1] Several interrelated factors contribute to linear growth retardation in children with CD, including poor nutrition, chronic use of glucocorticoids (GC) and lack of insulin like growth factor-1 (IGF-1); interdependent with these factors are the modulatory role of disease activity mediated via pro-inflammatory cytokines such as tumour necrosis factor (TNFα), interleukin (IL) 1β and IL6.[2] Conventional treatment of CD consists of enteral nutrition, corticosteroids, anti inflammatory agents and immunomodulators. However, these treatments have been largely unsuccessful in altering the natural course of the disease.[3] Growth is a vital outcome in intervention studies in paediatric IBD, yet is rarely reported as a secondary outcome let alone as the primary outcome.[4] Although the initial therapeutic strategy for CD has not been changed for a long time, the emergence of biological therapy, with its record of rapid efficacy and use as maintenance therapy has changed the management of severe paediatric CD dramatically.[5] Adalimumab (Humira®, Abbott UK) is a humanised anti-TNF therapy that has been shown to be efficacious for induction and maintenance of remission for adults with Crohn's disease.[6,7] Adalimumab is generally used in those patients who have an attenuated response or an adverse reaction to infliximab.[8–10]

Infliximab treatment has been shown to allow catch up growth and reduce steroid use in paediatric patients with CD in several studies.[11–19] Adalimumab, however, is not currently licenced for use in paediatric IBD patients (in the UK at least). The published clinical studies to date of adalimumab use in children are relatively limited[20–27] with no studies yet conducted to examine the effects of adalimumab on growth in children with CD. The aim of the present study was to assess the effect of adalimumab therapy on growth, puberty and disease activity over the 6 months prior to and 6 months after starting adalimumab treatment in children with CD.

2. Subjects and methods

All members of the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) were approached by e-mail and invited to take part in the study. The full study methodology has been published previously.[28] Data collected included; patient demographics, anthropometry, drug treatments (including previous infliximab use) and details of any prior surgery.[28] No growth data were included in the initial publication.

Of the 70 cases in the original study cohort with CD, those included in this study were children who had sufficient growth data available at all 3 time points. Sufficient data on growth were available for the 6 months before starting adalimumab (T−6), at starting adalimumab (T0) and 6 months after starting adalimumab (T+6) in 36 children who were then studied further. Thirty four of 36 had previously received infliximab. The median (10th, 90th) ages at diagnosis and start of adalimumab were 10.3 years (6.5, 13.1) and 14.7 years (11.3, 16.8) respectively. CD was diagnosed using standard criteria.[29,30] In 28 of the 36 children, data on pubertal status was available at start of adalimumab therapy (T0). Additionally, in 11 children growth data were also collected at 12 months following adalimumab therapy.

Height was measured with a Harpenden stadiometer and Tanner pubertal stage was assigned using either clinical examination or self-estimation.[31,32] Height (Ht) data were converted into SDS (standard deviation scores) using 1990 British childhood standards.[33,34] T−6, T0, T+6 and T+12 HV (cm/year) were calculated from the prior 6 months of growth before time points with T0 representing the point of starting adalimumab therapy. Disease phenotype was assigned using the Montreal classification.[35] Adalimumab effect was assessed using the Paediatric Crohn's Disease Activity Index (PCDAI), where available, or Physicians Global Assessment (PGA) when PCDAI was not available.[36,37] Using this assessment, children were then categorised as either "Remission" or "No-remission". Standard definitions were used for PCDAI disease status and remission (remission, PCDAI $\leq$ 10).[36] Details of concomitant medications were recorded and are presented in Table 1. None of the children were on growth or puberty promoting treatments during the period of study.

3. Statistical analysis

All data are described as medians and 10th and 90th centiles and were analysed with 1-sample Wilcoxon non-parametric test by using Minitab software version 16. Statistical significance was set at $p<0.05$. To evaluate how growth was affected by adalimumab, change in height SDS (ΔHtSDS) was calculated as well as height velocity.

4. Results

4.1. General characteristics

Thirty-four (94%) had prior infliximab usage of whom 7 were primary non-responders, 16 had loss of clinical response and 11 had had an allergic reaction necessitating discontinuation. The induction dose of adalimumab most commonly used was 80 mg followed by 40 mg 2 weeks later in 18 patients (50%), 24 mg/m^2 in 9 patients (25%), 160 mg then 80 mg 2 weeks later in 2 patients (6%) and the 7 patients remaining received a combination of other dosing regimens

Table 1 Demographic details of children (n, 36) when starting adalimumab (T0) and at 6 months (T+6) after starting adalimumab. Continuous variables are presented as medians and 10th and 90th centiles.

	T+0 N, 36	T+6 N, 36	T+0 VS T+6 p-value
Age	14.7 (11.3, 16.8)	15.2 (11.9, 17.3)	
Concomitant medication			
Background immunosuppression (thiopurine or methotrexate)	23		
—Prednisolone	15		
—Previous Infliximab	34		
Anthropometry			
ΔHtSDS	−0.2 (−0.7, 0.2)	0.0 (−0.5, 0.8)	0.005
Height velocity (cm/year)	2.0 (0.0, 5.8)	4.0 (0.0, 11.2)	0.11
Pubertal status (n, 28)			
—I	7		
—II	5		
—III	5		
—IV	2		
—V	9		
PCDAI (n, 19)	25 (7.5, 65)	10 (0, 55)	0.0001

(19%). All 36 patients commenced maintenance adalimumab therapy at 40 mg (n=33, 92%) or 24 mg/m^2 (n=3, 8%); the maintenance regimen of adalimumab was fortnightly initially in all patients. One patient suffered an adverse reaction leading to withdrawal after adalimumab therapy. Of 36 cases, 2 had resectional surgery during the study period (removing these patients from analysis however had no impact on the overall growth results). Other previous medications included, 30 (83%) who had enteral nutrition, 32 (89%) who had glucocorticoids, 34 (94%) had prior azathioprine/6-mercaptopurine and 20 (56%) had previous methotrexate.

4.2. Disease characteristics

Disease location was most commonly panenteric (ileocolonic and upper GI tract, L3+L4) in 15 (42%); 15 (42%) children had perianal disease. Of the 36 children, 28 (78%) achieved remission on adalimumab therapy in this cohort.

A PCDAI score was available in 19 children at baseline (T0) and at 6 months (T+6) after adalimumab therapy. Median PCDAI score decreased significantly from 25 (7.5, 65) at T0 to 10 (0, 55) at T+6, (p=0.0001). Of 19 patients with PCDAI data, 14 achieved clinical remission as assessed by the PCDAI. Twelve of the 19 children had a PCDAI score available at 6 months and 12 months after starting adalimumab therapy. In this group median PCDAI score also was reduced significantly from 27.5 (7.5, 65) at T0 to 6.25 (0, 55) at T+6, (p=0.001) and 5 (0, 37.5) at T+12, (p=0.0005) (Fig. 1a and b).

4.3. Linear growth in the whole cohort

The median change in height SDS (ΔHtSDS) in the whole group increased from −0.2 (−0.7, 0.2) at T0 to 0.0 (−0.5, 0.8) at T+6, (p=0.005) (Fig. 2a). Dividing patients by gender showed improvement of linear growth in both genders (data available on request). The median HV of the whole group also increased significantly from 2.0 cm/year (0.0, 5.8) at T0 to 4.0 cm/year (0.0, 11.2) at T+6, (p=0.02). Of the 36 children, 15 (42%) demonstrated catch-up growth with median ΔHtSDS of this group increasing from −0.3 at T0 to 0.3 at T+6, in 6 (14%) children median ΔHtSDS was 0 (before and after adalimumab therapy), 1 (2.7%) had a reduction in ΔHtSDS from 0.1 to 0.0 and 14 (39%) had ongoing growth deterioration with median ΔHtSDS of this group decreasing

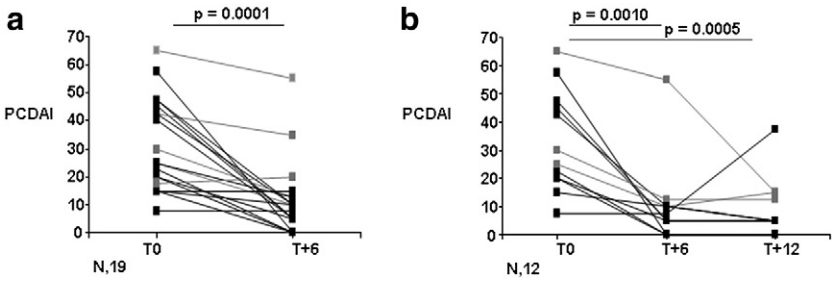

Figure 1 PCDAI values in children with CD at baseline (T0) and in the 6 months (T+6) and 12 months (T+12) following start of adalimumab therapy. a — PCDAI in overall of 19 children at baseline (T0) and 6 months following adalimumab therapy; b — PCDAI in overall group of 12 children at baseline (T0) and 6 months (T0) and 12 months (T+12) following adalimumab therapy. (■) and (■) indicate remission and no-remission.

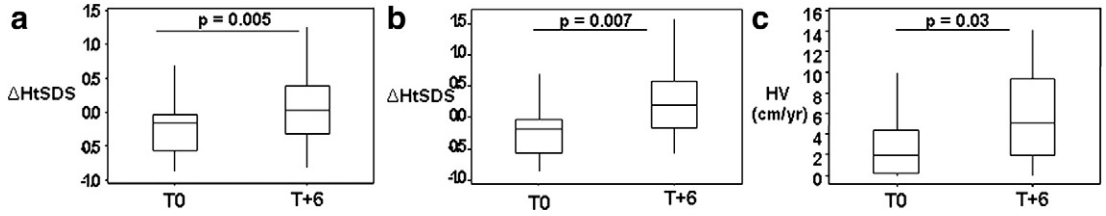

Figure 2 Growth in children with CD during the 6 months prior to adalimumab therapy (T0) and in the 6 months following start of therapy (T+6); a — change in height standard deviation scores (ΔHtSDS) in overall group of 36 children; b — change in height standard deviation scores (ΔHtSDS) in overall group of 28 children who had remission after adalimumab therapy; c — height velocity (HV, cm/year) in overall group of 28 children who had remission — box and whisker plots represent median, 10th, 25th, 75th, and 90th centiles.

from −0.4 to −0.3 after starting adalimumab therapy (Fig. 3).

In 11 children growth data were available over the 12 month period following adalimumab therapy. The median ΔHtSDS in the overall group changed from −0.2 (−0.9, 0.7) at T0 to 0.0 (−0.6, 0.7) at T+12, (p=0.10).The median HV of this group changed from 2.6 cm/year (0.0, 8.9) at T0 to 4.2 cm/year (0.0, 10.3) at T+12, (p=0.30).

4.4. Growth in those achieving remission

Median ΔHtSDS increased from −0.2 (−0.7, 0.2) at T0 to 0.03 (−0.5, 0.8) at T+6, (p=0.007) in children who achieved remission. Median HV of this group increased significantly from 2.0 cm/year (0.0, 9.9) to 5.1 cm/year (0.0, 14.1) at T+6, (p=0.03) (Fig. 2b and c). In those who had no remission, median ΔHtSDS did not show any significant change; −0.1 (−0.7, 0.1) at T0 and −0.3 (−0.8, 0.2) at T+6, (p=0.87) and likewise median HV also did not show any improvement being 2.6 cm/year (0.3, 6.1) at T0 and 1.5 cm/year (0.0, 4.5) at T+6, (p=0.36).

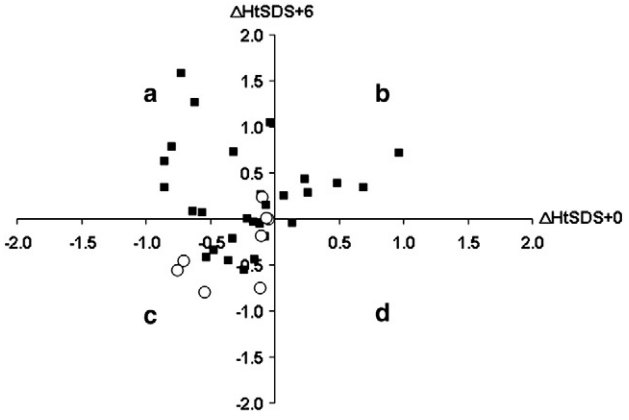

Figure 3 The relationship between change in height standard deviation scores over the 6 months before (ΔHtSDS0, x-axis) and the 6 months after (ΔHtSDS+6, y-axis) starting adalimumab therapy in children with CD. The children in quadrant a — had slow growth before starting adalimumab therapy but had improved growth after treatment. The children in quadrant b — had normal growth both before and after adalimumab therapy. The children in quadrant c — had normal growth before but had slow growth after starting adalimumab therapy. The children in quadrant d — had slow growth before and after starting adalimumab therapy. (■) and (o) indicate remission and no-remission.

Growth response was also examined based upon the indication for using adalimumab therapy as (i) allergic reaction to infliximab (ii), loss-of-response to infliximab and (iii) primary non-responder to infliximab (Fig. 4a, b and c). Of thirty four patients 11 had an allergic reaction, 16 had a loss of response and 7 were primary nonresponders. Median ΔHtSDS increased from −0.3 (−0.9, 1.0) at T0 to 0.3 (−0.5, 1.6) at T+6, (p=0.02) in children who had an allergic reaction; median HV changed from 0.2 cm/year (0.0, 8.6) to 5.3 cm/year (0.0, 14.1) at T+6, (p=0.058). Median ΔHtSDS did not show any significant change from −0.1 (−0.7, 1.0) at T0 to −0.1 (−0.8, 0.7) at T+6, (p=0.73) in children who had loss of response nor in children who were primary non-responders −0.1 (−0.5, 0.1) at T0 to 0.0 (−0.8, 0.2) at T+6, (p=0.93).

4.5. Pubertal status and growth

In 28 of the 36 children, data on pubertal status were available at start of adalimumab therapy (T0). On the basis of pubertal stage patients were categorised into two groups according to the method previously published by Walters et al[15] i.e. Tanner stages I–III and Tanner stages IV–V patient groups. Of 28 patients 17 were at Tanner stages I–III with a median age of 13.5 years (6.8, 6.5) and 11 were at Tanner IV–V with a median age 16.6 years (14.2, 17.3). In Tanner stages I–III patient group, median change in height SDS (ΔHtSDS) increased significantly from −0.4 (−0.8, 0.6) at T0 to 0.2 (−0.8, 1.3) at T+6, (p=0.02). Median HV of this group also increased from 2.0 cm/year (0.2, 8.8) at T0 and 5.3 cm/year (0.1, 14.1) at T+6, (p=0.03). In Tanner stages IV–V patient group, median change in height SDS (ΔHtSDS) did not change significantly from −0.0 (−0.8, 0.2) at T0 to −0.0 (−0.2, 1.5) at T+6, (p=0.10). Median HV of this group also showed an increase from 0.0 cm/year (0.0, 8.6) at T0 to 2.0 cm/year (0.0, 13.6) at T+6, (p=0.34) but the difference was not significant (Fig. 5a).

4.6. Glucocorticoids

The cohort of children was divided into two groups based on whether they were on glucocorticoids (prednisolone) or not when adalimumab was commenced. Of the 36 children,

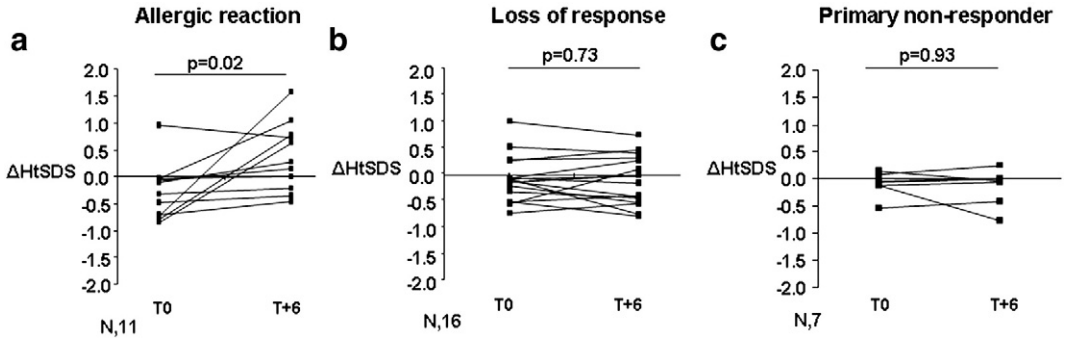

Figure 4 Growth response based upon the indication for using adalimumab therapy as (i) allergic reaction to infliximab (ii) loss-of-response to infliximab and (iii) primary nonresponder to infliximab. a — Change in height standard deviation scores (ΔHtSDS) in 11 children who had an allergic reaction. b — Change in height standard deviation scores (ΔHtSDS) in 16 children who had a loss of response. c — Change in height standard deviation scores (ΔHtSDS) in 7 children who were primary nonresponders.

15 (42%) were receiving prednisolone therapy when starting adalimumab and 21 (58%) were not. In the prednisolone group, median ΔHtSDS increased from −0.4 (−0.8, 0.7) at T0 to −0.0 (−0.6, 1.6) at T+6, (p=0.04). Median HV of this group also changed, but not significantly, from 1.4 cm/year (0.0, 9.9) at T0 to 4.0 cm/year (0.0, 14.1) at T+6, (p=0.22); in the prednisolone-free group, median ΔHtSDS increased from −0.1 (−0.9, 1.0) at T0 to 0.1 (−0.8, 1.0) at T+6, (p=0.02). Median HV of this group also increased from 2.7 cm/year (0.0, 8.6) at T0 to 4.0 cm/year (0.0, 12.0) at T+6 but the difference did not reach statistical significance (p=0.28) (Fig. 5b).

4.7. Immunosuppression

The cohort of children was divided into two groups based on whether or not they were on immunosuppression therapy (either thiopurine or methotrexate) at commencement of adalimumab. In the 23/36 (64%) children who were on immunosuppression therapy, median ΔHtSDS increased from −0.2 (−0.9, 1.0) at T0 to 0.1 (−0.8, 1.3) at T+6, (p=0.03). Median HV of this group changed from 2.0 cm/year (0.0,9.9) at T0 to 5.1 cm/year (0.0,12.1) at T+6 (p=0.23); in the other 13 children median ΔHtSDS did not change significantly at −0.1 (−0.8,0.1) at T0 to −0.0 (−0.6,1.6) at T+6, (p=0.12). Median HV of this group also remained similar at 2.0 cm/year (0.0, 5.6) at T0 to 3.0 cm/year (0.0, 14.1) at T+6, (p=0.32) (Fig. 5c).

5. Discussion

At present there are no published paediatric studies that adequately assess the effect of adalimumab on linear growth in children with CD. This study provides evidence that adalimumab is associated with improvement in short term linear growth in children with CD who enter remission but not in those who do not. It is also more likely to happen in children who are on immunosuppression and those in early puberty but seems to be relatively independent of steroid use. These findings suggest that growth improves as a result of several interrelated factors, including improved disease control.

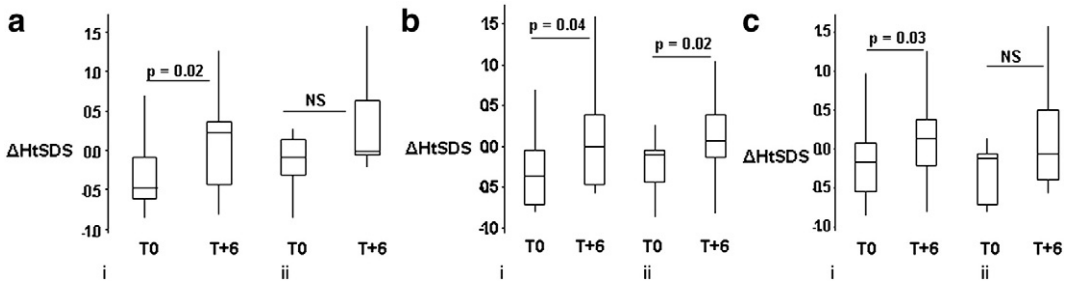

Figure 5 a. Growth in children with CD during the 6 months prior to adalimumab therapy (T0) and in the 6 months following start of therapy (T+6). (i) — Change in height standard deviation scores (ΔHtSDS) in 17 children who were at Tanner stages I–III at starting adalimumab. (ii) — Change in height standard deviation scores (ΔHtSDS) in 10 children who were at Tanner stages IV–V pubertal at starting adalimumab. b. Growth in children who were on prednisolone therapy at starting adalimumab; (i) — change in height standard deviation scores (ΔHtSDS) in 15 children who had received prednisolone therapy when starting adalimumab. (ii) — Change in height standard deviation scores (ΔHtSDS) in 21 children who did not receive prednisolone therapy when starting adalimumab. c. Growth in children who were on immunosuppression therapy when starting adalimumab; (i) — Change in height standard deviation scores (ΔHtSDS) in 23 children who had received immunosuppression therapy on starting adalimumab. (ii) — Change in height standard deviation scores (ΔHtSDS) in 13 children who did not had receive immunosuppression therapy when starting adalimumab. All box... Box and whisker plots represent median, 10th, 25th, 75th, and 90th centiles.

Use of co-immunosuppression therapy with biologics remains controversial.[38] Our study has shown significant improvement in growth in children who were on immunosuppression therapy (either thiopurine or methotrexate) at adalimumab commencement compared to those children who were not. This complements the findings in the larger cohort of children treated with adalimumab where higher response rates were seen in those patients who were on immunosuppression therapy when starting adalimumab.[28] There are no other published data on growth in children with CD receiving adalimumab, but there are in other groups of children, such as those with juvenile idiopathic arthritis, which have shown that the beneficial effect of biologic therapy on growth may be more likely when the patient is receiving background immunosuppression therapy using methotrexate.[39,40] Giannini et al.[39] conducted a 3-year, open label nonrandomised study to evaluate the effects of long-term anti-TNFα etanercept treatment with or without methotrexate on growth in children with selected categories of juvenile idiopathic arthritis. This study reported statistically significant increase in mean height percentiles from baseline for etanercept monotherapy at year 3 only and for etanercept in combination with the methotrexate group at 1, 2 and 3 years[39]. In a similar study Billiau et al.[40] also reported a significant improvement in growth velocity allowing catch-up growth in a combined etanercept and methotrexate group only.[40]

In our cohort there was a significant improvement in the change in height SDS (ΔHtSDS) of both children who received steroids and those who did not. There was no difference in both groups. Our data suggests that the growth-promoting effects of adalimumab therefore is not solely due to its "GC-sparing effect". This complements infliximab data where the improvement in growth was similarly not only due to its steroid sparing effect.[16]

Proinflammatory cytokines and chronic inflammation may be associated with altered gonadal function and reduced sex steroid synthesis, and affected children and adults may exhibit a combined picture of central and peripheral hypogonadism.[41] In adolescents, this may present as delayed onset of puberty, slow progression through puberty, and/or associated growth retardation. Improvement of the disease status would be expected to be associated with pubertal progression and improved growth. We observed significant improvement in ΔHtSDS of children who were at Tanner stages I–III as compared to those who were at Tanner stages IV–V at time of starting adalimumab. This suggests that the improvement in growth may in part be due to progression through puberty replicating similar observations made in children treated with infliximab.[15] Pfefferkorn et al. have suggested that growth is more likely to improve in those who were in early puberty at the introduction of infliximab therapy,[13] whilst this study (albeit smaller) implies that growth improvement may be *secondary* to progression in puberty.

Therapeutic interventions that have been reported to improve growth in children with CD include infliximab, enteral nutrition and growth targeting growth hormone therapy. Short-term improvement in growth has been observed by the use of infliximab in children with CD.[11–17] Substantial evidence suggests that nutritional therapy, both elemental and polymeric formulation, has growth-promoting effects.[42] Nutritional therapy has also been shown to improve height velocity[43,44] and accelerated linear development in growth in children with growth retardation.[45,46] Studies have also been conducted to examine the effects of recombinant growth hormone on linear growth in children with CD and short stature.[47,48] Most of these studies however that have been conducted so far have reported changes in growth over the short term only. A recent North American study observed changes in height z-scores at diagnosis, as well as 1 year and 2 years post diagnosis in children with CD and have reported that the distribution of height z-scores remained similar during the 2-year observation period despite improved disease activity plus the frequent use of immunomodulators and biologics.[13] A recent study has also shown that at maximum follow-up no treatment was significantly associated with height improvement.[49] Groups that have reported growth data in whole IBD patient cohorts including UK data from a Scottish cohort in the west of Scotland (Malik S, unpublished data) have shown that current therapies do not improve final height outcome; although current treatments improve short term height most children do not improve their final height.[13,49] Therefore although we are reporting short term improvement in growth, future studies need to look at final height as an outcome rather than the short term changes in height presented in most studies to date.

Improvement in linear growth after adalimumab was observed in children who enter remission but not in those who do not. This effect of adalimumab is similar to that of infliximab where responders improved growth and nonresponders did not.[15,16] Our data also suggest that the beneficial effect of adalimumab on growth is more likely when a child is receiving background immunosuppression therapy (either thiopurine or methotrexate) at adalimumab commencement. This effect of adalimumab with concurrent immunosuppression is also similar to the findings in the cohort of children treated with infliximab.[16] In a similar manner the growth promoting effect of adalimumab does also not seem solely due to the simple explanation of a steroid sparing effect.[16] It is also interesting to note that the growth response to adalimumab varied dependent on the reason for discontinuing infliximab; those who had an allergic reaction to infliximab fared best paralleling preliminary adalimumab clinical trial data suggesting that clinical response and remission are higher in patient who are anti-TNF naïve rather than those who have had no/lost response to infliximab previously.[50]

In summary, we have demonstrated that clinical response to adalimumab therapy is associated with an improvement in linear growth over the short term in children with CD most of whom have been treated with previous infliximab. Adalimumab continues to be mainly used at present as the second line biological agent in clinical paediatric IBD practice in the UK and elsewhere. Further prospective studies are required to clarify the effect of adalimumab on growth, including long term follow-up to final adult height.

Conflict of interest

RKR has received speaker's fees, travel support, or participated in medical board meetings with MSD Immunology, Abbott, Dr Falk, and Ferring Pharmaceuticals. DCW has received speaker's fees, travel support, or participated in medical board meetings with MSD Immunology, Abbott Laboratories, Dr Falk, Warner Chilcott UK and Ferring Pharmaceuticals.

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