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**Disease status and pubertal stage predict improved growth in anti-TNF therapy for Pediatric Inflammatory Bowel Disease**

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## **Abstract**

### **Background**

Growth failure is well-recognised in paediatric Inflammatory Bowel Disease (PIBD; <18 years). We aimed to examine whether anti-Tumor Necrosis Factor (TNF) therapy improves growth in a PIBD population-based cohort.

### **Methods**

A retrospective review of all Scottish children receiving anti-TNF (infliximab (IFX) and adalimumab (ADA)) from 2000-2012 was performed; height was collected at: 12 months before anti-TNF (T-12), start (T0) and 12 (T+12) months after anti-TNF.

### **Results**

93/201 treated with IFX and 28/49 for ADA had satisfactory growth data; 66 had full pubertal data. Univariate analysis demonstrated early pubertal stages (Tanner 1-3 n=44 vs. T4-5 n=22), disease remission, disease duration  $\geq 2$  years and duration of IFX  $\geq 12$  months were associated with improved linear growth for IFX; for ADA only improvement was seen in Tanner 1-3. For IFX, Tanner 1-3 median  $\Delta$  ht SDS -0.3 (-0.7,0.2) at T0 changed to 0.04 (-0.5, 0.7) at T+12 (p<0.001) vs -0.01 (-0.5, 0.9) at T0 in T4-5 changed to -0.01 (-0.4, 0.2) at T+12 (p>0.05). For IFX disease duration  $\geq 2$  year, median  $\Delta$  ht SDS was -0.13 (-0.6, 0.3) at T0 then 0.07 (-0.3, 0.6) at T+12 (p<0.001). Remission improved  $\Delta$  ht SDS (median  $\Delta$  ht SDS -0.14 (-0.6, 0.3) at T0 to 0.17 (-0.2, 0.7) at T+12 (p<0.001)). Multiple regression analysis demonstrated corticosteroid usage at T0 predicted improved  $\Delta$  ht SDS at T+12 for IFX and ADA.

**Conclusions:** Anti-TNF therapy is more likely to be associated with growth improvement when used at earlier stages of puberty with remission a key growth-promoting strategy in Paediatric Crohn's disease.

**Keywords:** Inflammatory Bowel Disease, Infliximab, growth

### **What is known**

- Growth is adversely affected in active IBD especially Crohn's disease
- Infliximab and Adalimumab are associated with improvement in short term growth with most studies being multicentre and non-population based

### **What is new**

- Children who are treated with greater than 12 months of Infliximab, achieve remission post induction and are in the early stages of puberty demonstrate improved linear growth
- Children with disease duration at the start of Infliximab of greater than 2 years demonstrated improved linear growth compared to those with disease for less than 2 years
- Combination therapy with Infliximab and Azathioprine results in greater improvement in linear growth

## Introduction

The treatment of pediatric Inflammatory Bowel Disease (PIBD) has evolved significantly in recent years with the advent of anti-Tumor Necrosis Factor (TNF) therapy reducing inflammation, improving mucosal healing and reducing disease relapse/corticosteroid usage, however finding a therapy which can improve long term linear growth has proven more elusive<sup>1-3</sup>. The presence of poor growth and short stature in PIBD, and more specifically, Crohn's Disease (CD) has been described for some time; this can lead to a significant impact on final adult height with varying reports of 20-30% of children with CD having a reduced adult height<sup>4</sup>. The potential reasons for this negative effect on growth are likely to be multifactorial and include: malabsorption, decreased oral intake, uncontrolled inflammation, increased requirements and losses of energy and nutrients; this can often be exacerbated by impaired growth which can precede clinical symptoms in 42% of children<sup>5</sup>. Further research into the mechanisms surrounding growth failure have shown a modulatory role of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF $\alpha$ ) and interleukins (IL) as well as a degree of growth hormone resistance<sup>6,7</sup>.

As anti-TNF therapy usage has increased, the evidence on the long-term efficacy has improved<sup>8</sup>. Despite further evidence and better understanding, many issues have yet to be resolved including identifying patients likely to have a prolonged treatment response and then balancing the risk/benefit of combination therapy with anti-TNF and immunomodulator vs monotherapy with anti-TNF therapy alone. The two most commonly used anti-TNF agents in PIBD are Infliximab (IFX) and Adalimumab (ADA). Both have both been shown to be effective in the induction and maintenance of remission for pediatric CD and similarly for infliximab in Ulcerative Colitis (UC)<sup>1,9-11</sup>. The evidence on the efficacy of Infliximab (IFX) on short term growth is generally supportive with several studies showing clear benefit<sup>12-16</sup> however other published studies have shown no beneficial effect<sup>17-20</sup>. A recent systematic

review on pediatric anti-TNF therapy concluded that IFX did have a positive effect on growth in CD, particularly in pre or early puberty but did not mention growth outcomes of those treated with ADA<sup>21</sup>. Fewer growth data exist on ADA but ADA does also demonstrate an improvement in short term<sup>22</sup> and long term growth<sup>10</sup> more pronounced in those who enter remission<sup>23</sup>.

The aim of this study was to characterise growth in a population-based cohort of children with all types of IBD, treated with ADA and/or IFX between 2000-2012 in Scotland, using data from the Scottish PIBD biologicals register.

## **Methods**

Data were gathered from the 3 regional Pediatric Gastroenterology, Hepatology and Nutrition (PGHAN) shared care networks (West, South-East and North of Scotland,) involving all 3 tertiary PGHAN centres (Glasgow, Edinburgh and Aberdeen) and all pediatric units in district general hospitals, which form a Scottish PGHAN managed service network, covering all PIBD patients in pediatric services.

### **Case identification**

All PIBD patients within pediatric services were included in the Scottish Pediatric Biologicals Registry if aged <18 years at biological therapy start from 01/01/2000 to 31/12/2012 with 10 weeks minimum follow up, as previously described<sup>24</sup>. Patients were included who had growth data available for a minimum of 24 months; 12 months prior to commencing anti-TNF therapy and for 12 months after treatment commenced, if further growth data was available this was also captured. Data on some of the patients within the current study have been included in previous related publications<sup>2,11,23</sup>. Patients were given

IFX for fistulating CD outside of the licenced indications. One patient was excluded as was receiving recombinant human growth hormone as growth promoting treatment. Drug administration and dose adjustment was given as previously described<sup>24</sup>.

### **Data collection**

Data were collected as previously described on demographics including disease phenotype as per the Montreal criteria<sup>25</sup>; biological schedule and regimen (induction only; induction then maintenance); medications (including corticosteroids, thiopurines and methotrexate) and surgery before, at and after biological start<sup>24</sup>. Disease activity was assessed by physician global assessment (PGA) through history, clinical examination, anthropometry and laboratory values by the clinician and divided into quiescent (remission), mild, and moderate/severe. A treatment course was defined as the duration of each anti-TNF agent the patient received.

Data were collected until study end on 31/03/2013 unless prior transition to adult services or emigration from Scotland. Height and weight data were collected for IFX over 48 months for all PIBD subtypes (CD, UC, IBDU) at the following time points: 12 months prior to commencing IFX (T-12), at start of IFX (T0), 12 (T+12), 24 (T+24) and 36 (T+36) months post IFX start). Due to transition and variable length of follow up for each patient, a smaller cohort had growth data available for 24 and 36 months post start of IFX (**Figure 1**). For ADA, height and weight data were collected over 24 months (at 12 (T-12) and 6 months prior to commencing ADA(T-6) at start of ADA (T0), 6 (T+6) and 12 months (T+12) post ADA). Satisfactory growth data reflects 12 months prior to commencing anti-TNF therapy to 12 months after start date whilst extended growth data covers data collected up to 36 months after starting anti-TNF therapy.

Height was measured using wall mounted stadiometers according to Frankfurt plane position and weight measured wearing minimal clothing using calibrated seat scales to the nearest 100g. These data were converted to standard deviation scores for height (Ht SDS), weight (Wt SDS) and BMI (BMI SDS) using 1990 British childhood standards<sup>26,27</sup>, then  $\Delta$  height SDS ( $\Delta$  ht SDS) and height velocity(HV) were calculated for T0 and T+12. Delta ht SDS at T0 was calculated by subtracting the ht SDS at T0 from ht SDS at T-12, for delta ht SDS at T+12 then ht SDS at T12 was subtracted from ht SDS at T0. Pubertal staging was assessed using either a validated self-assessment form or by clinical examination<sup>28,29</sup> and was documented at baseline, 12, 24 and 36 months where available.

Ethical approval is not required in NHS Scotland for retrospective case record reviews with examination of departmental databases of service design/delivery, such as in PISA (the Paediatric-onset IBD Scottish Audit), comprising epidemiology<sup>30</sup> and the Scottish PIBD biologicals register<sup>24</sup>.

## **Statistics**

Descriptive statistics are presented as median with 90<sup>th</sup> percentiles. Wilcoxon was used to examine differences in height, weight and BMI SDS scores. A standard significance level of 0.012 was adopted due to multiple comparison testing and was calculated using a Bonferroni correction. Analyses were carried out using SPSS (IBM 19, Chicago Ill) IBM. Multiple logistic regression was performed using R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and all patients with satisfactory growth data were combined. Confounders including type of IBD, small bowel involvement, azathioprine use, methotrexate use, duration of disease, Tanner pubertal staging, remission, corticosteroid use at baseline,

PGA at baseline, height SDS at baseline and whether patients received maintenance therapy with anti-TNF were entered into the model. There was a degree of duplication in the data as certain patients received both IFX and ADA so for those patients, one of the treatment periods was randomly excluded to ensure a robust model with no autocorrelation. A general linear model was used; a correction was performed to minimise the effect of missing Tanner staging data using the adjusted general linear model.

## **Results**

### **General characteristics**

One hundred and ninety-five patients were included in the initial cohort who were treated with 240 courses of therapy with a biologic, 164 (85%) had CD, 28 (14%) had UC and 3 (1%) Inflammatory Bowel Disease Unclassified (IBDU). Most, 115 (60%) were boys with a median age of 11.2 years (range 2.7-17.2) at diagnosis. 191 received IFX and 49 received ADA (4 received ADA alone).

### **Infliximab cohort**

Satisfactory 24-month growth data were available for 93/191 (49%) (see **Figure 1**); 57 (61%) were boys and 86 (92%) had CD with 7 (8%) having UC. Median age at diagnosis was 10.4 years (range 2.7-15.2) and median age at start of IFX was 13.8 years (range 5.9-17.6). In the 93 where satisfactory growth data were available for 24 months, the most common disease location in CD was panenteric in 28 (33%) children with inflammatory the most common behaviour in 76 (88%) whilst 86% had extensive UC. The commonest indication for starting IFX was active luminal disease followed by immunomodulator failure in CD whilst for UC it was chronic active colitis followed again by immunomodulator failure (see **Table 1**). At treatment start 18% had Ht SDS <-2, improving only to 15% then 7% at 1 year and 2 years respectively after treatment with IFX ( $p>0.05$ ). Forty-one patients underwent

surgery (18 pre IFX); all of whom had CD. Most patients had disease for greater than 2 years (n=62) having a median duration of 3.5yrs prior to starting IFX whilst those <2yrs (n=31) had their disease for 1.3yrs. Pubertal data were available in 65/93.

Sixty-six patients received further IFX post induction, including 6 patients who received episodic dosing prior to 2007, with 42 subsequently discontinuing maintenance IFX after a median of 1.0 years (range 0.2-3.2) receiving a median of 8 doses (range 1-25) (see **Figure 1**). The most common reasons for discontinuation of those on maintenance IFX were loss of response in 15, planned drug withdrawal in 13, primary non-response in 8, 5 had an allergic reaction and 1 had an adverse event. Thirty (45%), all with CD, required dose escalation, most commonly increased frequency in 23 (77%) whilst 22 (73%) had an increased dose.

In the 93 children with satisfactory 24 month growth data, median Ht SDS at T-12 was -0.7 (-2.2,-0.7), worsened to median Ht SDS -0.8 (-2.5,-0.5) at T0 and remained similar with a median Ht SDS -0.8 (-2.3,0.7) at T+12 ( $p<0.001$ ). Median  $\Delta$  Ht SDS was -0.2 (-0.6,0.3) at T0 and increased to a median  $\Delta$  Ht SDS at T+12 of 0.1 (-0.4,0.6) ( $p<0.001$ ). Median HV at T0 was 3.5 (1.0, 7.2) cm/yr and which increased to 4.4 (1.2,9.1) at T12 ( $p=0.003$ ). No further sustained improvement in linear growth was seen beyond 12 months post-anti-TNF start in those who were followed up for 36 months, the extended growth cohort (see **Table 2**).

### **Factors affecting growth**

Achieving remission was associated with a significant improvement in median Ht SDS,  $\Delta$  Ht SDS and HV (see **Figure 2**). Early stages of puberty,

Tanner stages 1-3, were associated with an increase in  $\Delta$  Ht SDS and HV (see **Figure 3**).

22/94 were Tanner stage 4-5 and showed no significant change in Ht SDS and  $\Delta$  Ht SDS and a decrease in HV; Ht SDS at T0 -0.2 (-1.8,1.1) to -0.3 (-2.0, 1.1) at T+12 ( $p=0.78$ ),  $\Delta$  Ht SDS at T+0 -0.14 (-0.5, 0.9) then  $\Delta$  Ht SDS at T+12 -0.01 (-0.5, 0.9) ( $p=0.78$ ) and HV at T0 3.5(1.0,9.8) decreased to 2.1 (0.2, 4.4) at T+12 ( $p=0.001$ ). 60 (65%) of those treated with IFX had a disease duration greater than 2 years at the start of their treatment with IFX and had increased Ht SDS,  $\Delta$  Ht SDS and HV at T+12 compared to those with disease duration less than 2 years (see **Table 3**).

Boys growth improved compared to girls, with boys  $\Delta$  Ht SDS and HV increasing significantly whilst girls only increased  $\Delta$  Ht SDS (see **Table 3**). In those with moderate disease, improvement was noted in  $\Delta$  Ht SDS and HV (see **Table 3**). 82 (88%) were on immunomodulators (IM) at baseline and increase in Ht SDS,  $\Delta$  Ht SDS and HV at T+12 was noted in this cohort compared to no improvement in those not on IM. Further analysis was performed on type of immunomodulator, given that 42 patients were on azathioprine (AZA) and 40 on methotrexate (MTX); there was no significant difference between the AZA and MTX groups in  $\Delta$  Ht SDS at T+12 ( $p=0.64$ , 95%CI -0.2, 0.1). Azathioprine usage was associated with increased Ht SDS,  $\Delta$  Ht SDS and HV compared to only improvement in  $\Delta$  Ht SDS and HV in those on MTX (see **Table 3**).

Patients who received induction and maintenance ( $n=66$  (I&M)) showed improvement in Ht SDS,  $\Delta$  Ht SDS and HV compared to those who received induction only where only  $\Delta$  Ht SDS increased ( $n=37$  (I only)). Patients who were established on maintenance IFX for greater than 12 months from first induction dose had significantly increased  $\Delta$  Ht SDS and HV (see **Table 3**). Corticosteroid use at baseline was associated with significant

improvement in Ht SDS and  $\Delta$  Ht SDS (see **Table 3**). Increase was noted in Ht SDS,  $\Delta$  Ht SDS, and HV in those who did not have surgery (n=68) whilst no significant improvement was observed in those who underwent surgery post-IFX (n=25) (see **Table 3**). No improvement in Ht was observed in those with Ulcerative Colitis (data available on request).

### **General characteristics for Adalimumab**

Growth data for 12 months were available for 28 patients treated with ADA; 12 were girls, 27 with CD (see **Table 1**) and 18 of whom had IFX growth data analysed previously. All patients treated with ADA increased  $\Delta$  Ht SDS at 12 months only (see **Supplemental Digital Content, Table 1**, <http://links.lww.com/MPG/A764>). Early stages of puberty (Tanner stage 2 and 3) were associated with increased  $\Delta$  Ht SDS and HV and improvement was seen in  $\Delta$  Ht SDS in males only (see **Supplemental Digital Content, Table 2**, <http://links.lww.com/MPG/A764>). No improvement was seen in those who were not on corticosteroids at baseline (n=16) or those who achieved remission at week 4 (n= 5) (data available on request).

### **Multiple regression**

Multiple regression models were used to determine associations of therapy and disease on  $\Delta$  Ht SDS at T+12 for both IFX and ADA combined. The following variables were inserted into both models:  $\Delta$  Ht SDS T0, remission, Tanner staging of puberty, azathioprine use, methotrexate use, corticosteroid usage at baseline, type of IBD, PGA at baseline, small bowel involvement, maintenance therapy given and duration of disease until anti-TNF commenced. In the final model only corticosteroid use at baseline was associated with an improvement in  $\Delta$  Ht SDS at 12 months (p=0.02) (95%CI 0.03,0.39).

## Discussion

In our Scottish population-based cohort of children with all subtypes of PIBD treated with either IFX or ADA, anti-TNF therapy was associated with improved linear growth as has been demonstrated in other population based cohorts for IFX<sup>31,32</sup>; however, to our knowledge this is the first population-based ADA study. At induction of IFX, 18% of children had a Ht SDS <-2, improving to 15% then 7% at 1 year and 2 years respectively after treatment. We have also demonstrated that IFX therapy improved linear growth in those who achieved remission, had disease duration for over 2 years at anti-TNF start and were in the early stages puberty (Tanner stage 1-3). In addition, we have also shown that improved  $\Delta$  ht SDS at 12 months' post-start of anti-TNF therapy is associated with corticosteroid use at baseline.

The rates of growth failure seen in our cohort are similar to other population based cohorts of a similar size. In the largest population-based multicentre inception cohort from Northern France, around 10% of all newly diagnosed children with CD had severe growth failure (height SDS <-2 SDS), improving only slightly to 8% at 1 year and 6.5% at 2 years<sup>31</sup>; however, no pubertal data were provided. At diagnosis, children had a mean ht SDS of -0.57 $\pm$ 1.2 compared to -0.83 $\pm$ 1.1 in our cohort. Rates of immunomodulation were similar in both cohorts but the median age at first IFX dose in the French group was 18 years contrasting with 13.2 years in our cohort (given data on PIBD cases in EPIMAD are collected both before and after transition to adult IBD services; time of transition is study end in the Scottish PIBD biologicals register); the younger age in our cohort may explain the increase in poor growth as the disease may have presented earlier so having an adverse effect at crucial point in the child's growth. The two other nationwide population-based study examining use of IFX showed differing results; firstly De Ridder observed that in 6 CD patients with ht SDS

<1 at initiation of IFX, 3 subsequently resumed normal growth velocity who remained on IFX post induction<sup>32</sup>. However, Wewer showed that in 10 CD patients who had IFX in part due to growth failure had no improvement was noted in height velocity when compared before and after treatment (no pubertal data or ht SDS were provided for this cohort)<sup>18</sup>.

The effect of pubertal stage on linear growth change in children treated with IFX remains controversial. Initially growth was shown to be dependent on progression through puberty with no improvement seen in those Tanner 4 and 5 compared to Tanner 1-3, although it was noted that those in Tanner 1-3 grew at a suboptimal rate<sup>12</sup>. This was again demonstrated in a larger cohort of newly diagnosed patients in North America who were treated with IFX where greater improvement was seen in those in early puberty; the improvement in growth was hypothesised to be related to pubertal progress after initiation of IFX<sup>17</sup>. This contrasts with the findings of Malik and colleagues who demonstrated improved HV SDS 6 months after IFX after analysis was adjusted for pubertal staging<sup>2</sup>. In our study, we observed similar results to Malik with improvement seen in Tanner 1 and in Tanner 2/3 in  $\Delta$  height SDS and height velocity but we did not observe an improvement in height SDS in either group; this supports the theory that the improvement in growth is not only due to pubertal progression, with similar improvements seen in pre-pubertal children as those in puberty. A further theory is that IFX merely prevents further deterioration in height without improving overall height<sup>33</sup>. However, only half on those who were Tanner stage 1 at start of IFX remained Tanner 1 at 12 months which may have influenced their growth.

Growth improves with greater disease control as can be seen in our results, where no improvement in growth was observed in those who did not achieve remission after induction. In those that achieved remission post-induction, improvement was seen in all measures of growth suggesting that these patients may demonstrate catch up growth now that the inflammatory process has been 'switched off' rather than the anti-TNF therapy agents

themselves. This has previously been demonstrated in the extension to the REACH study which followed patients up to 12 months and observed a trend towards continued improvement in height SDS score in those with sustained remission<sup>34</sup>. However, other therapies which have been proven to be highly successful at inducing remission, such as exclusive enteral nutrition, have not shown similar improvements in linear growth potentially due to the relatively short term effect of this treatment.

An interesting finding of this study was the associated improvement in linear growth in those receiving corticosteroids at induction, most evidence would suggest that corticosteroid usage is associated with poor growth<sup>35</sup> yet not in this cohort. There are several possibilities for this, one is that these children had received steroids prior to anti-TNF therapy and with the introduction of these agents corticosteroids were able to be weaned leading to improved growth<sup>17</sup>, another is that corticosteroid usage combined with anti-TNF therapy resulted in these children entering remission earlier consequently resulting in improved growth. The definition of remission used in studies varies; some would define remission only as clinical resolution of symptoms, some combine this with specified disease activity indices (eg PCDAI <10), others include normality of laboratory tests including faecal calprotectin, whilst the current definition of true remission for many now includes mucosal healing in addition to clinical and biochemical improvement<sup>36</sup>. Mucosal healing has been associated with prolonged remission after induction treatment with IFX<sup>37</sup> and could potentially be associated with sustained improvement in linear growth too. Potentially those who improved growth parameters only slightly despite being in clinical remission had not in fact achieved mucosal healing, which may then have continued to adversely affect their height. Further evidence for improved growth after the inflammatory process has been stopped is the improved growth seen in those who continued on IFX for 12 months - these were patients who were more likely to have had a response and it is possible that the IFX in addition to

stopping the inflammatory process had an independent role in improving growth. A study which directly correlates the degree of mucosal healing and growth response to biologics would help address whether optimal growth outcomes need so-called ‘deep remission’.

In our study, those who had disease for  $\geq 2$  years had improved height SDS after 12 months of treatment,  $\Delta$  height SDS and height velocity compared to those with a shorter disease duration of less than 2 years. This contrasts with most current evidence which suggests that those with shorter disease duration have a better outcome when treated with anti-TNF; exemplars are the REACH study and ACCENT 1 trial. In the REACH study children had a median duration of disease of 1.6 years prior to IFX and had an 88% response and 59% remission rate post-induction contrasting with a 66.7% response and 39.1% remission rate in adults in ACCENT 1 trial where the median duration of disease was 7 years prior to initiation of IFX<sup>1,38</sup>. Further evidence is provided by another prospective multicentre North American study that observed improved growth and clinical outcome at 12 months of those treated with early IFX (within 3 months of diagnosis) compared with early immunomodulator therapy or no therapy<sup>39</sup>. The reason for improved growth in those with a longer disease course in our cohort could be that the growth and/or pubertal development has been impaired for a prolonged period due to the cytokine-driven inflammatory process but when the inflammation is ‘switched off’ with anti-TNF therapy, improved growth is then seen.

In our study, including all subtypes of IBD, we found a significant improvement in linear growth in those treated with combination therapy of AZA and IFX which contrasts with other studies examining the effect of AZA on growth. The only paediatric RCT on the use of AZA from 2000 observed no significant difference in linear growth between those treated with AZA and placebo at 18 months<sup>40</sup>. This was confirmed by Pfefferkorn who found no improvement in height at 12 or 24 months for AZA<sup>17</sup>. However, a UK study did show

improved height with treatment with AZA but this was not statistically significant. Caution must be observed interpreting the results of this UK study as it was retrospective, before IFX was commonly used and with growth data only available for 44 patients with confounders including concurrent corticosteroid use, disease severity and pubertal staging data unavailable<sup>41</sup>. Other studies have shown improvement in growth with both MTX monotherapy and used in combination with IFX; in a cohort of 12 patients MTX and IFX combination therapy was effective in improving linear growth<sup>2</sup> whilst MTX monotherapy consistently demonstrates improvement in height velocity<sup>42</sup>. As yet, there is no mechanism proposed at to potential pathways which may explain this improvement in growth for either AZA or MTX.

Children who received at least 12 months of therapy with IFX demonstrated improved linear growth compared to those who received induction only or stopped IFX before 12 months. Potential explanations could be that those who continued treatment until 12 months were more likely to achieve remission (only 15% did not achieve remission) thereby having a reduction in inflammation resulting in improvement in linear growth. This theory is supported by evidence from the REACH extension study which demonstrated an improved trend in those who continued with no disease (n=11) vs those with mild/moderate disease (n=39).

Limited data exists on the effects of ADA on growth and is divided with only one RCT, the Imagine trial, which found improvement in height velocity z scores at 6 and 12 months in both the higher and lower doses of ADA, however, no pubertal data was provided<sup>10</sup>. A multicentre UK and Irish audit demonstrated improved short term growth and our results are similar to that study demonstrating an improvement in  $\Delta$  height SDS at 6 months after initiating ADA which continued in our cohort to 12months; we did not observe the increase in height velocity previously observed<sup>23</sup>. This UK and Irish study provided crucial pubertal data and showed improved growth in those in Tanner stage 1-3, however, we

found no such improvement in those who were prepubertal (Tanner stage 1) but significant improvement in those in Tanner stage 2 and 3 for  $\Delta$  height SDS and height velocity suggesting that development through puberty may at least partially explain the improvement in height. No improvement was seen in those in Tanner 4 and 5 as would be expected and been previously shown<sup>23</sup>. Data on lack of effect comes from a single centre study from Israel which found no improvement in height at last follow up (median of 17.3 months) again no pubertal data was provided<sup>43</sup>.

Our results should be interpreted with a degree of caution; this population based study includes only those treated with anti-TNF therapy which undoubtedly represents the more severe end of the disease spectrum and where a relatively higher rate of growth failure would be expected. Furthermore, satisfactory growth data was available for only 49% of our cohort of anti-TNF treated patients and full pubertal status data in 71% of these. As a 'real life' clinical experience from a nationwide group managed from 3 different centres over a 13 year period there is significant heterogeneity in the data due to changing treatment practices as new evidence emerged and differing rates of uptake of change within these centres; example of these include episodic dosing with IFX in 2000-2007<sup>24</sup> and induction only moving to induction plus maintenance given improved outcomes in those that continued<sup>44</sup>. Now treatment algorithms have changed considerably, IFX is given earlier on in treatment course in those patients with a severe phenotype such as those with widespread colonic deep mucosal ulceration, growth failure or severe perianal disease with episodic treatment abandoned and long term maintenance being the norm. Other studies have shown the benefit to early aggressive treatment in altering the disease progression<sup>38</sup>, so it is possible that if IFX is given earlier the somewhat modest improvement in growth seen in this study will become more pronounced.

The results of our large retrospective population-based cohort study shows growth failure is relatively common in the Scottish population who were treated with anti-TNF therapy, with 18% of pediatric patients who subsequently received anti-TNF therapy demonstrating severe growth failure at start of therapy. We have demonstrated that Infliximab and possibly Adalimumab are associated with improved linear growth at 12 months after treatment start. In those treated with Infliximab most improvement is seen in those who achieved remission, had disease for longer than 2 years, received combination therapy with azathioprine, received maintenance therapy and were Tanner stages 1-3. For Adalimumab we have shown probable improvement in growth again in those who were Tanner stages 2 and 3. The exact role that anti-TNF therapy plays in improving growth requires further study, including elucidation of more effective treatment strategies to reduce the inflammatory process and promote catch-up growth, so ensuring that young people with IBD can achieve their full growth potential.

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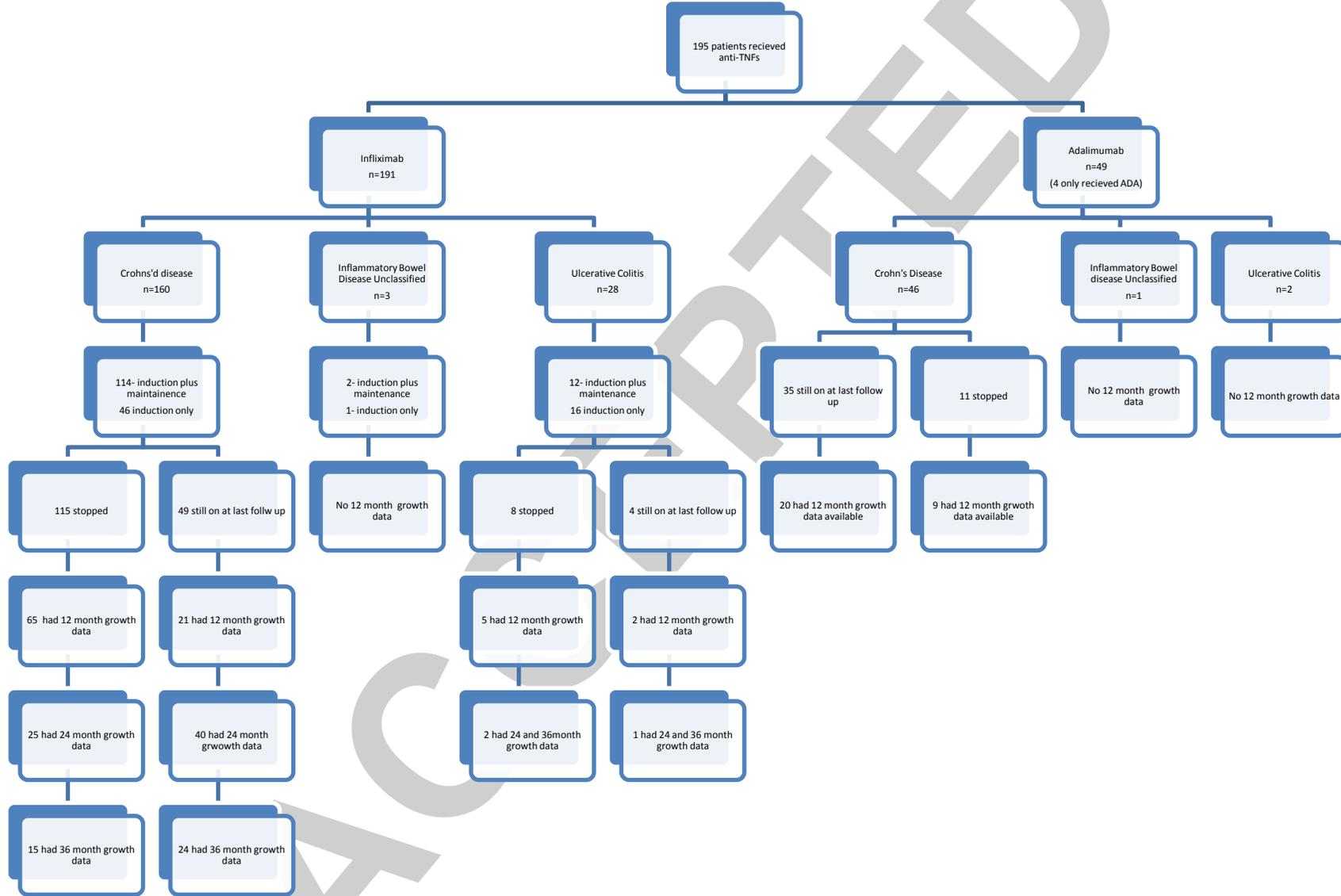
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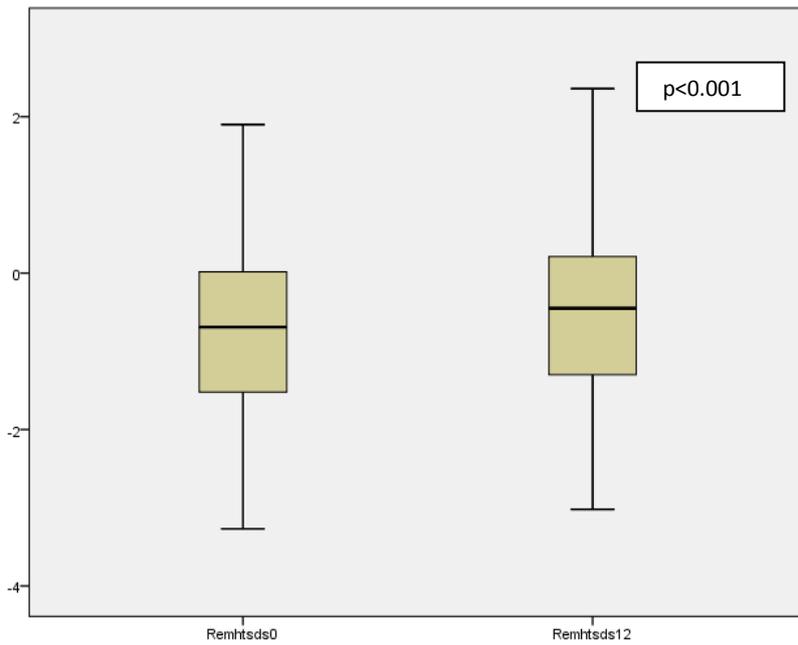
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Figure 1- Status of patients in Scottish National biologicals registry over study period

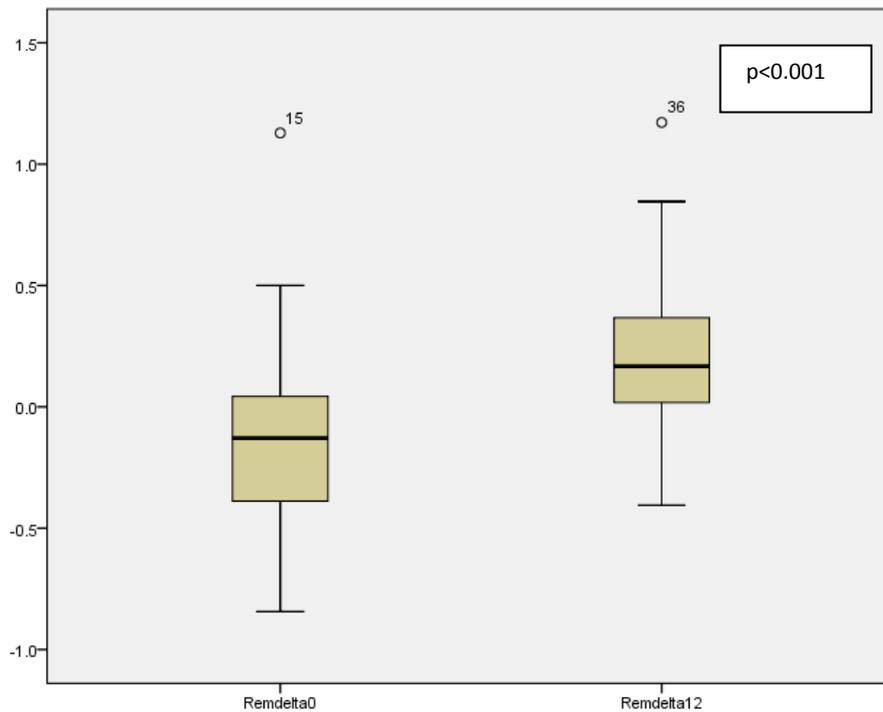


**Figure 2- Improvements in linear growth are seen at 12 months in those treated with Infliximab who achieve remission post induction (n=56)**

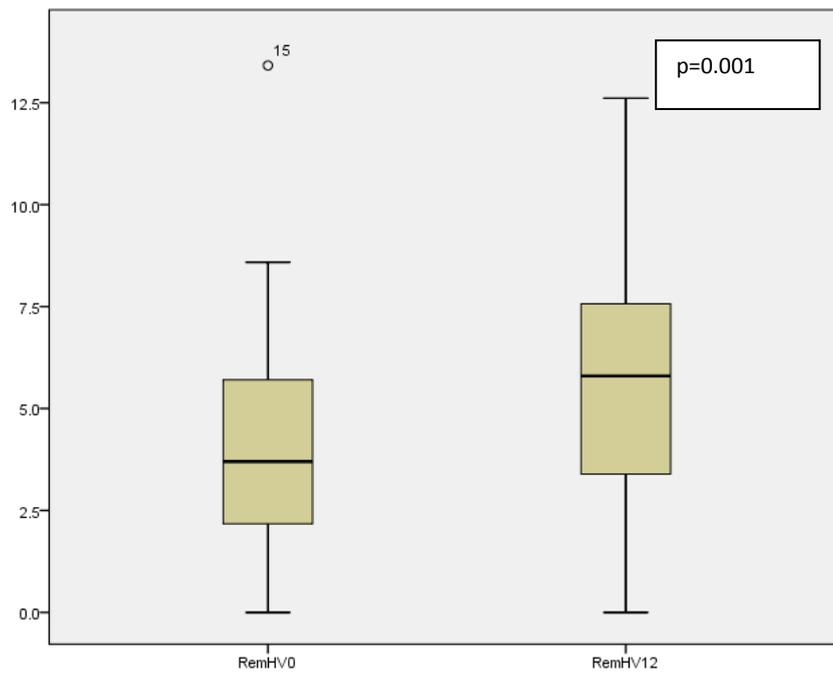
A. Improvement seen in median ht SDS at T+12 compared to T0



B. Improvement seen in Delta ht SDS at T+12



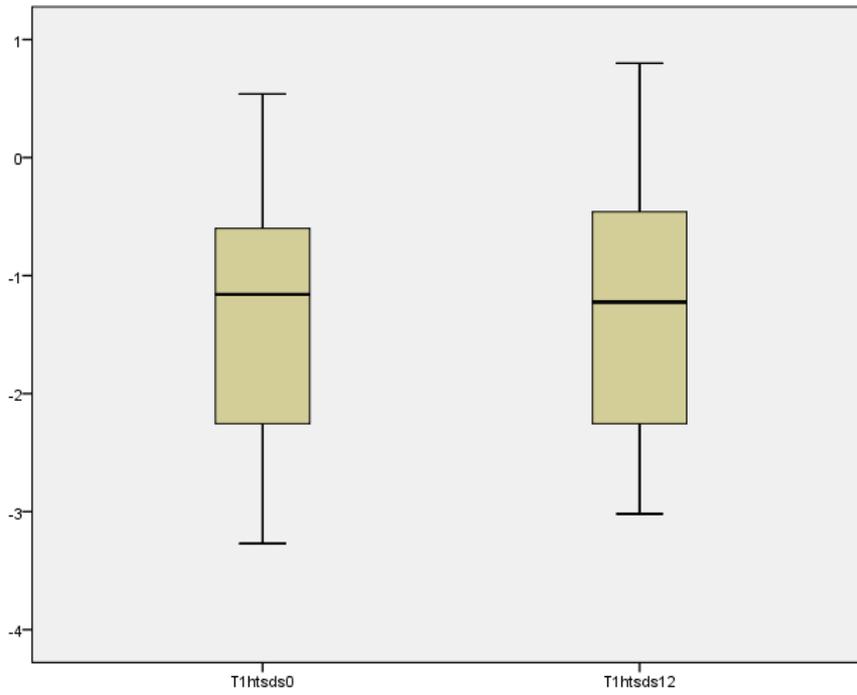
C. Improvement seen in height velocity



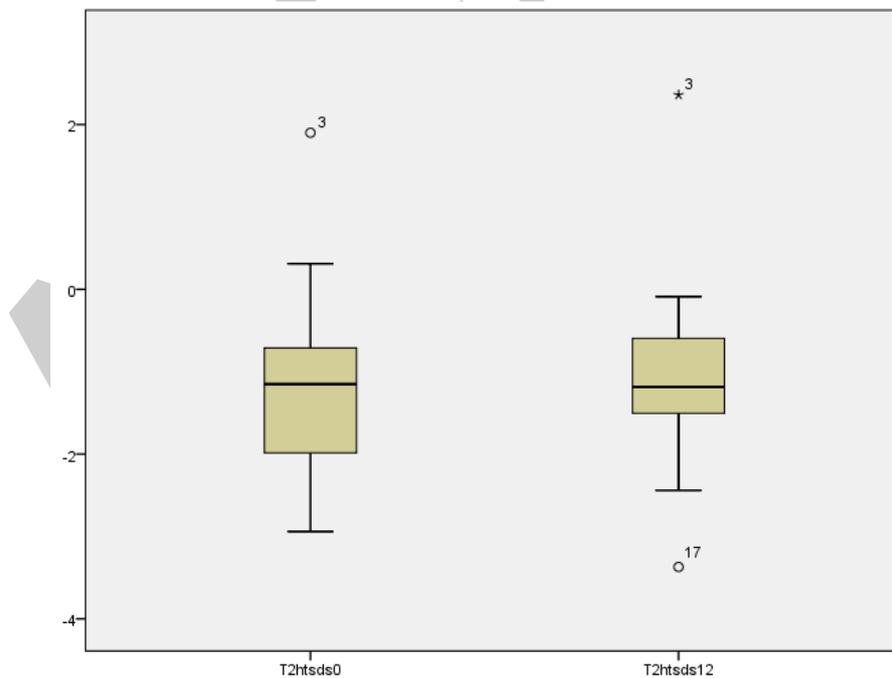
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**Figure 3. Tanner stage 1-3 shows improvement in height velocity and delta height SDS at T0 to T+12 without improvement in height SDS (n=24)**

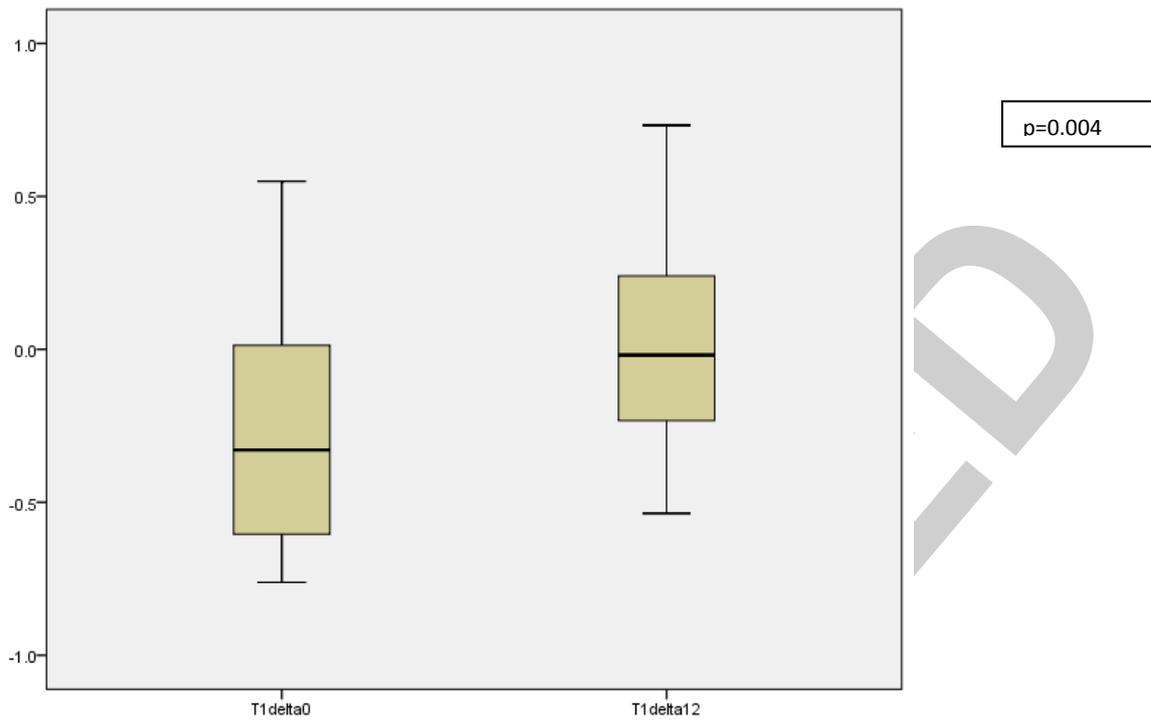
A. Tanner stage 1 ht SDS shows no improvement in ht SDS at T+12



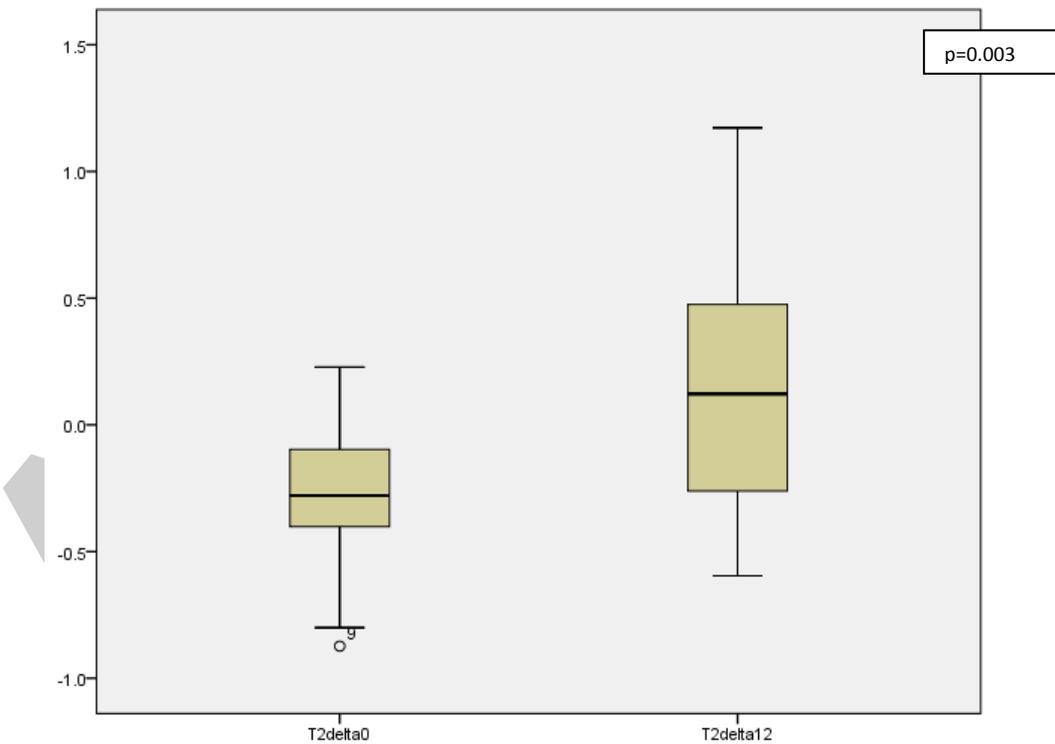
B. Tanner stage 2&3 shows no improvement in ht SDS at T+12 (n=20)



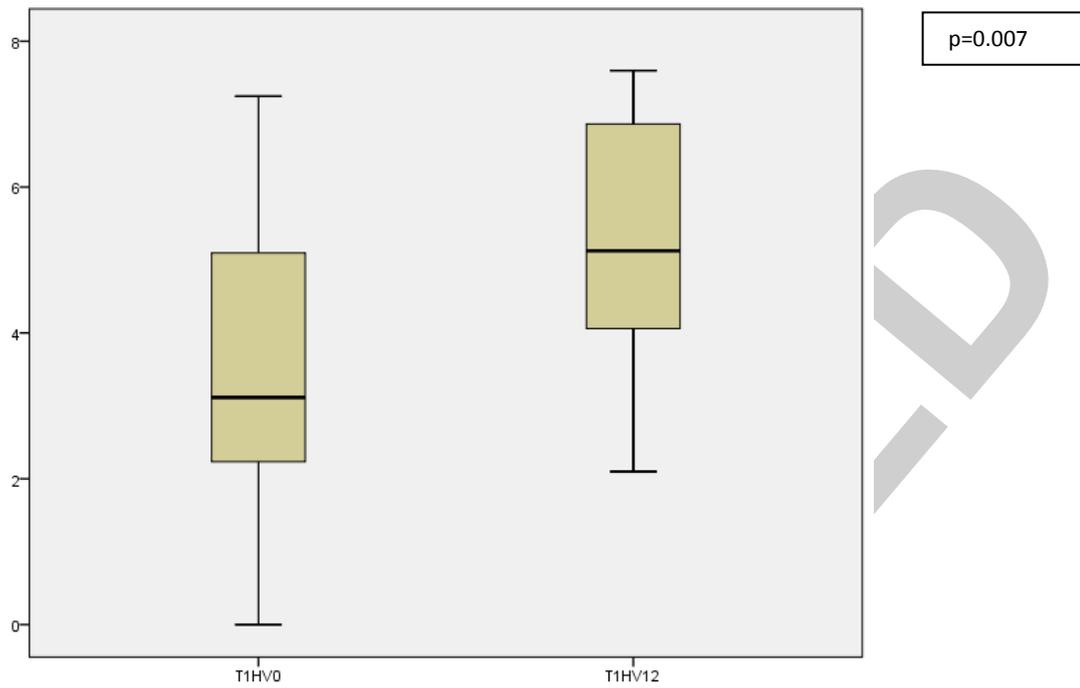
C. Tanner stage 1 shows improved delta ht SDS at T+12



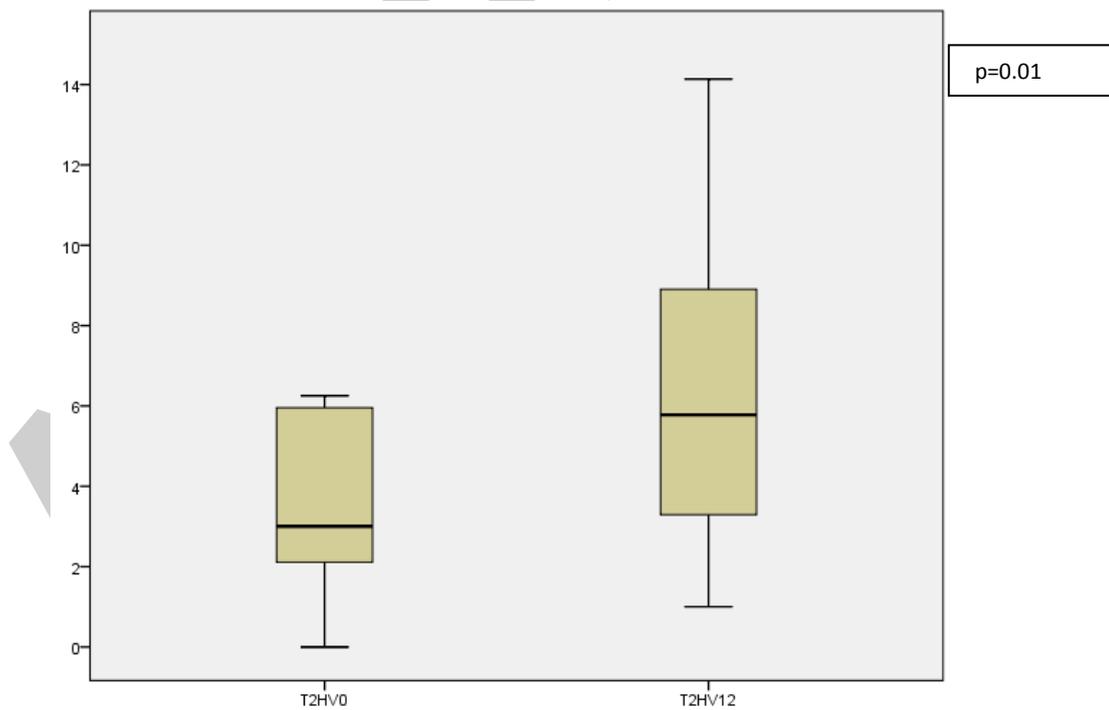
D. Tanner stage 2&3 shows improvement in delta ht SDS at T+12



E. Tanner stage 1 shows improvement in Height Velocity at T+12



F. Tanner stage 2 and 3 shows improvement in Height Velocity at T+12



## Tables

1. Improved growth parameters seen at Baseline characteristics of 93 patients requiring Infliximab and 28 patients receiving ADA with satisfactory growth data for 24 months; results are expressed as median (range) and number (%)
2. Long term follow up to 36 months shows no further improvement in height velocity and delta height SDS beyond 12 months with improvement seen in weight and BMI SDS at 12 months post-IFX treatment.
3. 12 months in those treated with IFX (n=93)

**Table 1 Baseline characteristics of 93 patients requiring Infliximab and 28 patients receiving ADA with full growth data for 24 months; results are expressed as median (range) and number (%)**

	IFX- Crohn's disease (CD)	Ulcerative colitis (UC)	ADA- Crohn's disease (CD)	Ulcerative colitis (UC)
Number of patients	86 (92%)	7 (7%)	28(97%)	1 (3%)
-Female	38 (44%)	1 (14%)	12 (43%)	1 (3%)
Median age at diagnosis (range yrs.)	10.5 (2.72-15.1)	10.2 (8.48-14.7)	10.3 (4.89-14.9)	12.1
Median Age at start of IFX (range yrs.)	13.8 (5.9-16.9)	13.7 (9.2-17.6)	13.4 (6.8-17.2)	13.7
Median Duration from diagnosis to start IFX (range yrs.)	2.86 (0.15-9.45)	2.66 (0.78-5.6)	3.4 (0.04-8.4)	1.5
Montreal classification	L1 and L4 2 (2%)    B1 75 (87%) L2 15 (17%)        B2 9 (10%) L2 and L4 12 (14%)    B3 2 (2%) L3 20 (23%) L3 and L4 36 (42%) L5 1 (1%)	E1 0 E2 1 (14%) E3 6 (86%)	L2 9 (32%)        B1 20 (71%) L2 and L4 3 (11%)    B2 5 (18%) L3 6 (21%)        B3 3 (11%) L3 and L4 10 (36%)	E1 0 E2 0 E3 1 (100%)
Concomitant medications at IFX start				
- Corticosteroids	40 (47%)	4 (57%)	12 (43%)	1 (100%)
- Methotrexate	40 (47%)	0 (0%)	16 (57%)	0 (0%)
- Azathioprine/6-MP	38 (44%)	4 (57%)	3 (11%)	0 (0%)
Indications to start IFX/ADA (more than 1 indication is possible)	Active Luminal disease 72 (84%) Immunomodulator failure 65 (76%) Bridge to immunosuppression 12 (14%) Perianal disease 16 (19%) Growth+/- pubertal delay 4 (5%)	Chronic active UC 5(71%) Acute severe colitis 2 (29%) Steroid dependency 3 (43%) Immunomodulator failure 4 (57%)	IFX primary non responder 12 (41%) Loss of response to IFX 10 (36%) Allergic reaction 1 (3%) Family choice 2 (7%) Previous JIA 2 (7%) Possible JIA at CD diagnosis 1 (3%)	IFX primary non responder 1 (100%)
Disease severity at induction				
- Remission	2 (2%)	0	0	0
- Mild	20 (24%)	0	8 (39%)	0
- Moderate/severe	64 (74%)	7 (100%)	20 (71%)	1 (100%)
Response post induction	-Steroid free remission 35 (33%) -Remission 20 (24%)	-Steroid free remission 3(43%)	-Steroid free remission 1 (4%) -Remission 4 (14%)	-Steroid free remission 0 -Remission 0

	Response not remission 27 (31%) No response 9 (10%)	Remission 1 (14%) Response but not yet remission 2 (29%) No response 1 (14%)	Response but not yet remission 17 (61%) No response 6 (21%)	Response but not yet remission 0 No response 1 (100%)
Prior medication usage				
- <u>Corticosteroids</u>	72 (84%)	7 (100%)	25 (89%)	1 (100%)
- <u>Methotrexate</u>	42 (49%)	0	20 (71%)	1 (100%)
- <u>Azathioprine/6-MP</u>	77 (90%)	14 (88%)	25 (89%)	1 (100%)
- Exclusive enteral nutrition	75 (86%)	0	22 (79%)	0
- <u>Adalimumab</u>	66 (77%) 1 (1%)	0	1 (1%) 0	1 (100%) 0
Surgery				
Pre IFX	Small bowel resection 4 Right hemicolectomy 2 Left colonic resection 3 Defunctioning stoma 1 Perianal surgery 12 Colectomy and end ileostomy 0		Small bowel resection 0 Right hemicolectomy 0 Defunctioning stoma 0 Perianal surgery 7 Colectomy and end ileostomy 0	
Post IFX	Small bowel resection 0 Right hemicolectomy 4 Left colonic resection 2 Defunctioning stoma 5 Perianal surgery 7 Colectomy and end ileostomy 10	Defunctioning stoma 1 Colectomy and end ileostomy 3	Small bowel resection 1 Right hemicolectomy 1 Defunctioning stoma 1 Perianal surgery 1 Colectomy and end ileostomy 3	Colectomy and end ileostomy 1

**Table 2 Long term follow up to 36 months shows no further improvement in height velocity and delta height SDS beyond 12 months with improvement seen in weight and BMI SDS at 12 months post-IFX treatment.**

	T-12 (n=42)	T0 (n=42)	P value for T-12 vs T0	T+12 (n=42)	P value for T0 vs T+12	T+24 (n=42)	P value T+12 vs T+24	T+36 (n=42)	P value For T+24 vs T+36
Ht SDS	-0.9 (-2.4,0.4)	-1.0 (-2.9,0.04)	P<0.0001	-1.1 (-2.6,-0.03)	p=0.39	-0.9 (-2.5,-0.08)	p=0.33	-0.8 (-2.6,0.06)	p=0.29
Δ ht SDS	n/a	-0.25 (-0.7,0.2)	n/a	0.07 (-0.5,0.4)	p=0.009	0.08 (-0.4, 0.6)	p=0.01	0.06 (0.3,0.6)	p=0.90
HV	n/a	3.8 (1.2,7.1)	n/a	4.8 (1.5,9.1)	p=0.04	5.5 (0.9,8.8)	p=0.79	4.8 (0.0,7.8)	p=0.10
Weight SDS*	-0.5 (-1.9,1.1)	-0.6 (-1.9,1.1)	p=0.001	-0.4 (-2.0,1.2)	p=0.002				
BMI SDS*	0.1 (-1.6,1.5)	-0.3 (-1.9,1.7)	p=0.05	0.1 (-1.5,1.9)	p=0.003				

HV= height velocity \*n=94

**Table 3 Improved growth parameters seen at 12 months in those treated with IFX (n=93)**

	Ht SDS T-12 Median (IQR)	Ht SDS T0 Median (IQR)	P value for T-12 vs T0	Ht SDS T+12 Median (IQR)	P value For T0 vs T+12	Delta Ht SDS T0 Median (IQR)	Delta Ht SDS T+12 Median (IQR)	P value for DeltaT0 vs Delta T+12	Height Velocity T0 Median (IQR)	Height Velocity T+12 Median (IQR)	P value for Height Velocity 0 vs Height Velocity 12
Disease duration <2yrs	-0.7 (-2.2, 0.7)	-0.8 (-2.4,0.4)	P=0.002	-0.9 (-2.2,0.4)	P=0.85	-0.3 (-0.8, 0.3)	0.03 (-0.5, 0.6)	P=0.01	3.3 (0.8, 6.9)	4.1 (0.9, 9.4)	P=0.06
Disease duration >2yrs	-0.8 (-2.4,0.7)	-0.8 (-2.5, 0.8)	P=0.007	-0.7 (-2.4, 0.8)	P=0.005	-0.1 (-0.6,0.3)	0.08 (-0.3, 0.6)	P<0.001	3.6 (1.1,7.2)	4.9 (1.3, 9.2)	P=0.01
Gender											
-Males	-0.73 (-2.3,0.7)	-0.81 (-2.5,-0.5)	p<0.001	-0.9 (-2.4,0.6)	p=0.16	-0.2 (-0.7,0.2)	0.1 (-0.5,0.6)	p<0.001	3.8 (1.0,7.3)	5.2 (2.6,9.6)	p=0.001
-Females	-0.8 (-2.3,1.1)	-0.7 (-2.3,1.0)	p=0.07	-0.7 (-2.2,1.1)	p=0.10	-0.1 (-0.5,0.5)	0.10 (-0.3,0.6)	p=0.01	3.2 (0.7,6.7)	3.2 (0.8,8.0)	p=0.41
Moderate disease at baseline	0.7 (-2.2,0.8)	-0.7 (-2.5,0.5)	<0.001	-0.8 (-2.3,0.7)	p=0.23	-0.3 (-0.7,0.2)	0.04 (-0.5,0.6)	p<0.001	2.9 (1.0,7.1)	4.4 (1.1,9.5)	p=0.002
Immunomodulator use	-0.8 (-2.2,0.7)	-0.9 (-2.5,0.5)	p<0.001	-0.9 (-2.3,0.7)	p=0.005	-0.2 (-0.6,0.3)	0.1 (-0.3,0.6)	p<0.001	3.5 (1.1,7.2)	4.9 (1.6,9.3)	p=0.001
No Immunomodulators	0.2 (-2.6,1.2)	-0.1 (-2.5,0.8)	p=0.33	-0.4 (-2.2,0.7)	p=0.16	-0.1 (-0.8,0.3)	-0.2 (-0.7,0.5)	p=0.5	5.0 (0.0,7.1)	3.5 (0.0, 5.2)	p=0.53
Azathioprine at baseline	-0.4 (-2.4,0.9)	-0.7 (-2.8,0.7)	p=0.002	-0.7(-2.4,0.9)	p=0.03	-0.3 (-0.7,0.3)	0.1 (-0.3,0.6)	p<0.001	3.0 (1.0,7.3)	4.6 (1.3,9.3)	p=0.005
Methotrexate at baseline	-0.9 (-2.2,0.3)	-1.0 (-2.4,0.2)	p=0.02	-1.0 (-2.0, 0.3)	p=0.06	-0.1 (-0.5,0.4)	0.05 (-0.4,0.8)	p=0.002	4.1 (1.2, 7.1)	5.3 (1.8,9.4)	p=0.03

Induction only	-0.8 (-2.5,0.9)	-0.9 (-2.6,0.9)	p=0.009	-1.1 (-2.4,0.8)	p=0.93	-0.3 (-0.7,0.3)	0.04 (-0.4,0.6)	p=0.003	3.0 (0.6,6.4)	3.5 (1.1,9.6)	p=0.17
Induction plus maintenance	-0.7 (-1.9,0.6)	-0.8 (-2.3,0.5)	p=0.002	-0.8 (-2.3,0.6)	p=0.02	-0.1 (-0.6,0.3)	0.10 (-0.4,0.6)	p<0.001	3.8 (1.1,7.3)	5.0 (1.2,9.0)	p=0.004
IFX at 12 mths	-0.7 (1.8,0.5)	-0.8 (-2.4,0.5)	p=0.001	-0.8 (-2.0,0.4)	p=0.03	-0.2 (-0.6,0.3)	0.1 (-0.5,0.7)	p<0.001	3.8 (1.4,7.3)	5.8 (2.0,9.7)	p=0.001
Corticosteroid use baseline	-0.4 (-2.0,1.4)	-0.5 (-2.7,1.1)	p<0.001	-0.5 (-2.3,1.1)	p=0.29	-0.3 (-0.7,0.2)	0.05 (-0.5,0.6)	p<0.001	2.7 (0.9,6.1)	4.4 (1.4,9.4)	P=0.001
Corticosteroid free baseline	-0.9 (-2.4,0.4)	-1.0 (-2.4,0.5)	p=0.21	-0.9 (-2.3,0.3)	p=0.05	-0.08 (-0.4,0.5)	0.06 (-0.4,0.6)	p=0.01	4.3 (1.2,7.3)	4.9 (1.1,9.5)	p=0.30
Surgery	-0.74 (-2.4,0.6)	-0.8 (-2.3,0.5)	P=0.006	-1.0 (-2.6,0.3)	P=0.15	-0.20 (-0.7,0.3)	-0.1 (-0.5,0.4)	P=0.065	3.4 (0.9,7.1)	4.0(1.0,8.0)	P=0.17
No surgery	-0.7 (-2.2,0.8)	-0.8 (-2.5,0.8)	P=0.002	-0.8 (-2.2,0.8)	P=0.001	-0.17 (-0.6,0.3)	0.1 (-0.3,0.6)	P<0.001	3.5 (1.1,7.3)	4.9 (1.3,9.5)	P=0.005