A British Society of Paediatric Gastroenterology, Hepatology and Nutrition survey of the effectiveness and safety of adalimumab in children with inflammatory bowel disease

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Keywords: Crohn's disease, adalimumab, Children.

Background: Adalimumab is efficacious therapy for adults with Crohn's disease (CD).

Aim: To summarise the United Kingdom and Republic of Ireland paediatric adalimumab experience.

Methods: British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) members with Inflammatory Bowel Disease (IBD) patients <18 years old commencing adalimumab with at least 4 weeks follow up. Patient demographics and details of treatment were then collected. Response and remission was assessed using the Paediatric Crohn's Disease Activity Index (PCDAI) /Physicians Global Assessment (PGA).

Results: 72 patients (70 CD, 1 Ulcerative Colitis (UC), 1 IBD Unclassified (IBDU)) from 19 paediatric-centres received adalimumab at a median age of 14.8 (IQR 3.1, range 6.1-17.8) years; 66/70 CD (94%) had previously received infliximab. A dose of 80mg then 40mg was used for induction in 41(59%) and 40mg fortnightly for maintenance in 61 (90%). Remission rates were 24%, 58% and 41% at 1, 6 and 12 months respectively. Overall 43 (61%) went into remission at some point, with 24 (35%) requiring escalation of therapy. Remission rates were higher in those on concomitant immunosuppression cf. those not on immunosuppression [34/46 (74%) vs. 9/24 (37%) respectively ($X^2$8.8, p=0.003)]. There were 15 adverse events (21%) including 4 (6%) serious adverse events with 2 sepsis related deaths in patients who were also on immunosuppression and home parenteral nutrition (3% mortality rate).

Conclusions: Adalimumab is useful in treatment refractory paediatric patients with a remission rate of 61%. This treatment benefit should be balanced against side effects, including in this study a 3% mortality rate.

Introduction

The incidence of Crohn's disease (CD) in children continues to rise in the UK and throughout the world.[1-3] Despite early-onset CD being more extensive at diagnosis than adult-onset CD, and with more dynamic progression in location in the first years after diagnosis,[4] the evidence for effective treatment strategies in these children remains limited.[5;6] Initial induction of disease remission in UK practice is most commonly attempted with a course of exclusive enteral nutrition with steroids reserved for non-responders.[7] Disease relapse after induction of remission occurs frequently, requiring maintenance therapy with an immunomodulator, usually thiopurines initially.[8] In a large Scottish cohort, 50% of children needed immunosuppression within 1 year of diagnosis while more than 80% had received immunosuppression within 5 years of diagnosis.[4] Thiopurines are most commonly used as initial maintenance of remission treatment with Methotrexate remaining a useful alternative for patients who are intolerant/resistant to thiopurines.[9]

Infliximab (IFX) is a chimeric anti-tumour necrosis factor (TNF) monoclonal antibody treatment that is useful for both induction and maintenance of remission in children.[10] In line with adult studies, IFX use in UK children is predominantly as an adjuvant to other forms of immunosuppression.[11] It is also used in a small number of patients as a long term maintenance treatment in patients who are refractory or intolerant to other treatments and in whom more extensive surgery is not a viable option. IFX treatment allows catch up growth and reduces steroid use in paediatric patients with CD.[12-14]

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.[15;16] Adalimumab is used primarily in clinical practice for patients who are are primary anti-TNF responders, but become intolerant or non responsive to IFX.[17-19] Adalimumab is not currently licensed for use in paediatric IBD patients. The published experience to date of adalimumab in children with the exception of one large retrospective study[20] is limited mostly to case reports[21-24] and small clinical case series[25-28]. However it is increasingly clear that adalimumab is used widely in paediatric clinical practice.

In addition to limited information regarding paediatric efficacy there are continuing safety concerns around anti-TNF use, including that of adalimumab. Clinical experience outside the trial setting in adults has been mixed with reports of severe infective complications, malignancy and even death.[18;29] Specific concerns remain about the development of fatal Hepatosplenic T-cell lymphomas in young males with CD treated with thiopurines, infliximab or adalimumab.[30-32]

Evidence is awaited from prospective international clinical trials on the efficacy and safety of adalimumab in children with CD (in progress trials listed at clinical trials.gov). Here, we report our national experience on the indications and use of adalimumab in a survey of paediatric gastroenterology units across the United Kingdom and Republic of Ireland.

Materials 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 during the summer of 2008 with a further follow up call for additional cases in early 2009. Members were asked to identify any Inflammatory Bowel Disease (IBD) patients aged <18 years of age at the time of commencing adalimumab in a paediatric centre with at least 4 weeks of follow up. Members who agreed to take part were sent a proforma to collect a standard dataset from case notes retrospectively (full proforma available on request). Data collected included; patient demographics, drug treatments (including previous IFX use) and details of any prior surgery. As an audit of routinely held clinical data, the Lothian Research Ethics Committee confirmed that informed consent from patients/families was not needed.

Specific details on adalimumab use collected included; dosing schedule, need for dose escalation and documented adverse effects. 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.[33] Standard definitions were used for PCDAI disease status and response (remission, PCDAI ≤10) and significant response in PCDAI was a decrease ≥12.5.[33] PGA of clinical status in terms of response to induction doses of adalimumab was defined as "remission", "steroid-free remission", "response without remission" or "no response". Response to adalimumab was recorded at 1, 6 and 12 months and at study end. The study end point was defined as the last paediatric follow up visit (i.e. when seen in clinic last at data

accrual or before transition to adult services, before transfer out of region, or prior to death). CD was diagnosed using standard criteria.[34;35] Disease location and behaviour at the time of commencing adalimumab treatment were defined using the Montreal classification.[36] Some data relating to 11 patients has been published previously as part of a Scottish adalimumab audit involving both children and adults.[37]

Two authors (RKR and DCW) reviewed the proformas from all centres for completeness and sense checking, and clarified missing or possibly incorrect data in all cases. One author (MLW) entered all data using double data entry to a dedicated database. Two authors (MLW, DCW) performed all statistical analyses.

Statistics

Continuous parametric data are presented as mean (standard deviation) and non-parametric data as a median followed by (range, interquartile range). Categorical data are presented as number of cases with percentage of total cases (%). Chi-squared analysis was used to compare frequencies and $p<0.05$ was considered significant.

Results

A total of 19 centres returned at least one case or more (14 Manchester, 10 Edinburgh, 8 Dublin, 7 GOSH, 6 Bart's and the London, 5 Glasgow, 4 Dundee and Royal Free, 3 Oxford, 2 Cardiff), totalling 72 patients. Of these 70 had CD (47(67%) males), 1 Ulcerative Colitis (UC) and one Inflammatory Bowel Disease Unclassified (IBDU). Results are given below for patients with CD, while patients with IBDU and UC are described individually at the end of the results section. The median age at CD diagnosis was 10.5 years (3.6, 2.8-15.7), with a median age at start of adalimumab of 14.8 years (3.1, 6.1-17.8) with a median of 4.3 years (3.7, 0.1-10.5) duration from CD diagnosis to starting treatment. At start of adalimumab treatment the commonest disease location was L3 + L4 in 24 (34.3%) and behaviour type B1 37 (52.9%) with 29 (41%) having perianal disease.

Surgery

A total of 26 patients (37%) had 47 surgical procedures before or during the study period. Prior to adalimumab, 18 had surgery at a median (IQR, range) of 2.4 (1.7, 0.7-6.4) years post diagnosis. Eight patients required surgery at a median of 0.6 (0.4, 0.3-1.9) years after adalimumab commencement, with 5 requiring more than 1 procedure.

Previous treatments

In terms of previous treatment 86% had at least one previous course of exclusive enteral nutrition, 90% at least one course of steroids (60% steroid dependent with inability to wean despite 3 months continuous treatment, 25% steroid-resistant and 27% having unacceptable steroid side effects) , 91% had prior thiopurines (azathioprine and/or 6-mercaptopurine; with 31% being resistant, 11% intolerant and

63% developing loss of response) and 49% had prior methotrexate usage (with 15% being resistant, 12% intolerant and 50% developing loss of response. Sixty-six (94%) had prior infliximab usage, with 12 primary non-responders, 33 with loss of response, 3 a long drug holiday and 26 an allergic reaction necessitating discontinuation. The median (range) number of infliximab doses was 5 (1-27) with 17 (26%) had required a change in their dosing schedule. Two patients with juvenile arthritis developed CD whilst their arthritis was in remission on etanercept and were then changed to adalimumab therapy. Significant other therapies at adalimumab start included filgrastim (recombinant human G-CSF), parenteral nutrition, mycophenolate mofetil, sirolimus, thalidomide and basalixumab in 1 patient each.

Adalimumab

Baseline data

The induction dose of adalimumab used was 160mg then 80mg in 3 patients (4%), 80/40 in 41 patients (59%), 24mg/m^2 in 16 patients (23%) and 10 received other dosing regimens (14%). At baseline 1 patient was in remission. There were 26 (37%) patients on steroids when adalimumab was started and 46 (66%) on immunosuppression of whom 27 were on a thiopurine and 19 on methotrexate.

Remission (Table 1)

The number of patients in remission at 4 weeks, 6 and 12 months after starting therapy out of the total number assessed at each time point is listed in table 1. Forty-three of 70 (61%) achieved remission on adalimumab at any point in the study period after a median of 0.2 (0.3, 0.04- 0.76) years and after a median of 6 (6.5, 2-23) doses of adalimumab. Of the 50 patients (71%) who either entered remission (n=43, 61%) or had a significant clinical response (n=7) 15 had a subsequent loss of response

on maintenance adalimumab therapy after a median (IQR, range) of 17 (12, 7-40) adalimumab doses and at a median duration of 0.4 (0.4, 0.1-1.2) years.

Of the 46 patients taking concomitant immunosuppression at the start of the study a significantly higher number achieved remission compared to those with no concomitant therapy [34/46 (74%) vs. 9/24 (37%) respectively ($X^2$8.8, p=0.003)]. Thirteen received adalimumab within 2 years of CD diagnosis but were no more likely to achieve remission than those commencing adalimumab later in their course (p=0.53).

PCDAI

A PCDAI score was available for 48 patients at baseline with remission in 1, mild CD in 16 and moderate-severe CD in 31. The median PCDAI was 37.5 (20, 7.5-65) at baseline. Forty-two of the 48 who had a PCDAI at baseline also had one calculated at 4 weeks, with a median score of 15 (12.5, 0-45) and with 10 (24%) being in remission, 24 (57%) mild CD activity and 8 (19%) moderate-severe CD activity; 25 of 42 (60%) had a significant (≥12.5) change in PCDAI score.

Maintenance therapy and dosing changes during adalimumab treatment

Sixty-eight (97%) CD patients went on to maintenance adalimumab therapy, of which 66 started on fortnightly therapy and 2 on weekly therapy, with an initial dose of 80mg in 1 patient (1%), 40mg in 61 patients (90%), 24 mg/m^2 in 3 patients (4%) and other dosing regimens in 3 patients (4%). Twenty-four (35%) required dose escalation of which 4 required an increased dose only, 17 the dosing interval shortened from fortnightly to weekly only, and 3 had both changes made. There was no influence of concomitant immunosuppressive usage on need for dose escalation (p=0.9). Nineteen of these 24 had dose escalation within 12 months of starting adalimumab. Five of

these 24 patients then had reversal of escalation at a later stage, with 4 returning to fortnightly dosing and 1 also having a reduction of adalimumab dose. 8 patients with incomplete response had had maintenance therapy with dose escalation; of these 4 achieved remission and 4 did not. 5 patients with no response at all had maintenance therapy with dose escalation; 2 of these achieved remission and 3 did not.

Study outcomes

The median number of adalimumab doses given was 19 (22, 3-103). A total of 1662 doses were given in the 70 CD patients. These 70 CD patients were followed up for a median duration of 0.8 (0.8, 0.1-2.8) years with a total of 72.5 years of patient follow up. At study end, 22 had discontinued Adalimumab (primary non-response in 12, loss of effect in 6, a long drug holiday in 2 and allergic reaction in 2), 2 had died whilst receiving adalimumab and 46 were alive and receiving ongoing maintenance adalimumab therapy.

UC and IBDU

There were 2 patients both from one centre who responded to adalimumab for UC and IBDU having both lost response to infliximab and having failed/been intolerant to thiopurines previously.

Side effects/safety

There were 4 serious adverse events (SAE rate of 6%) including 2 deaths (mortality rate of 3%) in this cohort of 72 patients. The 2 deaths in the cohort were both from central venous catheter (CVC) sepsis leading to septic shock in patients requiring home parenteral nutrition and receiving multiple immunosuppressive therapies.

The first was a boy who developed panenteric CD at 8.4 years of age who had thiopurine intolerance, methotrexate resistance and loss of response of infliximab despite dose alteration. He was receiving overnight supplementary enteral nutrition via gastrostomy tube and methotrexate therapy when also given 24mg/m^2 adalimumab at 15.5 years of age. Five days after starting adalimumab he had a CVC inserted and parenteral nutrition started. He achieved clinical remission after 7 doses (40mg fortnightly maintenance) in total but died seven months later after 20 doses of adalimumab plus ongoing methotrexate, due to coagulase-negative staphylococcal CVC sepsis. This escalated to invasive pulmonary aspergillosis, which in turn led to septic shock and multi-system organ failure. Death was not considered as a likely outcome by his clinical team prior to the development of septic shock.

The second death was of a boy who developed ileo-colonic and perianal CD at 5.2 years of age complicated by stricturing disease. This was despite high dose steroids, azathioprine (with loss of effect), and sigmoid colostomy with mucous fistula formation at 6.4 years of age. He developed severe pelvic and perianal CD and proceeded to trials of filgrastim and infliximab (loss of response). He received 40mg/40mg induction dosing at 12.8 years of age when he was receiving azathioprine and filgrastim for severe CD with extensive perianal disease, growth and pubertal delay, and peristomal Pyoderma gangrenosum. Extensive investigations had shown no evidence of underlying immunodeficiency. He was commenced on home parenteral nutrition via CVC. He had a clinical response to adalimumab and proceeded to maintenance at 40mg fortnightly. He never achieved remission and died at age 13.5 years after 19 doses of adalimumab due to combined E. coli and Candida CVC sepsis. He developed septic shock and multi-system organ failure whilst

receiving adalimumab, azathioprine, filgrastim and hyperbaric oxygen. In contrast with the first case, death was considered as a possible outcome by his clinical team due to the severe and refractory disease with extensive skin and tissue loss.

There was also one severe case of *Clostridium Difficile* needing hospitalisation, and one development of a stomal abscess with subsequent fistulisation and requiring prolonged hospitalisation. Other adverse events included 30 (43%) experiencing pain at the injection site, none of whom stopped treatment. A further 11 (16%) patients suffered minor adverse events that were not related to injection site pain – worsening colitis in 2, neutropaenia and lymphopaenia in 2, and 1 each of multisystem upset (dyspnoea, fatigue, arthritis), transient visual loss, nausea with pain, respiratory viral illness, stomal bleeding, rash and paronychia.

Adalimumab was discontinued because of side effects in 8 (11%) of patients because of pyrexia in 2, sepsis in 4, rash in 1 and worsening diarrhoea in 1; 4 out of 8 (50%) required permanent discontinuation.

Discussion

This study has demonstrated that adalimumab is effective in treating children with otherwise treatment-resistant CD. In total 61% of patients achieved remission, but the time taken to reach remission was longer than that seen in prospective adult studies, particularly clinical trials.[15] Serious adverse events occurred in 6% of cases, with a mortality rate of 3%, the latter reflecting the severe disease spectrum of some children in this cohort.

Although there is a recognised morbidity and mortality rate in adult clinical studies, the combined mortality rate in clinical trials of adalimumab has not been reported to be higher than that expected of patients with CD overall.[38] However, deaths in young adults have been reported outside of clinical trials.[37] With the exception of this study, there have been no reported deaths in short term follow up of paediatric adalimumab studies (all studies summarised in table 2). The other published paediatric studies have reported no increased safety concerns with adalimumab, but of note all except one have been smaller than the present study and the length of follow up to describe these potential complications has been relatively short. Both fatalities in this study occurred as a result of overwhelming sepsis, also reported in adult studies to be the most significant and serious side effect of patients treated with adalimumab.[37;38] The specific complication of Aspergillosis and death on adalimumab has also been reported by other groups.[39] A French group have recently reported 2 deaths in long-term follow up of paediatric patients, one as a result of colonic adenocarcinoma and the second due to multi-organ failure secondary to dehydration in a patient with a stoma. In contrast to the present study, these were both recorded many years (both >6

years) after the last dose of anti-TNF therapy.[40] Children on a combination of adalimumab, multiple immunosuppressants and parenteral nutrition via a central line clearly have the most severe forms of CD. As such patients on a combination of adalimumab, other immunosuppressants and parenteral nutrition given via a central line represent an extremely high risk group. Whilst this combination of treatment should be avoided if at all possible, we recommend early and aggressive treatment of sepsis and also that appropriate prophylaxis in this group of patients should be mandatory.

Another significant concern is the risk of malignancy especially lymphoma in paediatric patients treated with Adalimumab and other anti-TNF agents.[31;32] No such events were recorded in this study but the relatively small study population (n=72), the short length of total follow up (total 74.8 years in all 72 cases) and the rarity of this complication limit our ability to detect such complications in this study cohort. The role of concurrent immunosuppression with thiopurines or methotrexate in most cases makes the association with anti-TNF therapy unclear; this remains an area of intense scrutiny, particularly following further reports of malignancies in paediatric rheumatology studies using anti-TNF agents.[41]

Adalimumab studies in adults are now demonstrating longer term clinical benefits over years,[42] but as shown in previous studies, a significant number of patients lose response to adalimumab over time, requiring either dose increase or reduction in dosing interval[20;43] Adalimumab studies in adult patients with CD suggested a longer delay to requiring treatment escalation in patients who received concomitant immunosuppression.[44] The need for treatment escalation in this study was not affected

by co-immunosuppression. However, concomitant use of immunosuppressants did significantly improve the chances of attaining initial remission on adalimumab therapy. By contrast, the other large paediatric study noted that clinical response rate was significantly *lower* with co-immunosuppression at 6 months into therapy.[20] Adalimumab studies in adults with CD have not demonstrated a difference in initial response with co-immunosuppression but have in some suggested a longer time to treatment escalation in patients who are co-immunosuppressed.[44] Recent adult infliximab studies have supported the use of concurrent immunosuppression in the context of maintenance therapy with IFX.[11;45] Interestingly, the paediatric rheumatology trial of adalimumab (with or without methotrexate), resulted in significantly higher levels of adalimumab antibodies (26% vs. 6%) in the group not given methotrexate, although this was not associated with different clinical outcomes in the short term.[46] This issue can only appropriately be addressed by prospective studies randomising children to either monotherapy or therapy with co-immunosuppression.

At present there are no published paediatric studies that adequately demonstrate the optimal dosing of adalimumab for paediatric patients with CD, either for the induction or maintenance of remission. Doses used in paediatric practice are therefore extrapolated from relevant adult studies,[15;47], from paediatric rheumatology studies[46] or from retrospective paediatric cases series (listed in table 2). Doses used in this retrospective study were heterogeneous, and hence it is difficult to draw any firm conclusions about optimal dosing. However, it may in part explain our longer time to treatment response, as a number of patients did not receive larger induction dosing before moving onto maintenance therapy. Although we found that time from

diagnosis did not influence response to adalimumab the number of patients in our study treated within 2 years of diagnosis was small (n=13). Time from diagnosis was demonstrated to be important in the pivotal paediatric infliximab trial compared to the corresponding adult study,[10;48] but not the North American retrospective paediatric adalimumab study nor in our study.[20]

In summary, we have demonstrated that adalimumab can be an effective treatment for paediatric CD patients unresponsive, intolerant to or with loss of effect to other therapies, including infliximab. This case series shows the high risk that patients are exposed to on immunosuppression, particularly on some combinations of therapies. The study has also highlighted the need for prospective monitoring of these patients on a national and international basis via biological registries to most accurately contextualise the risk-benefit balance of adalimumab in children and young people with IBD, and allow seamless long term followup as transition to adult services occurs.

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. PM has received speaker's fees from Nestle Nutrition. 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. GH has received support to attend academic meetings from Abbott, Schering-Plough, Shire and Proctor and Gamble, honoraria from Abbott, Shire, Otsuka Pharmaceuticals and Astra Zeneca for presentations at academic meetings and an educational grant from Shire. AR has received course fees and travel bursaries from Mead Johnson Nutritionals. MSM currently holds IBD research funding from Centocor and SHS International Ltd. ID has received course fees and travel sponsorship from Nutricia and Pfizer & speaker's fees from Astra Zeneca.

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Table 1 – Efficacy of Adalimumab at various time points

	Baseline (n=70)	4 weeks (n=70)	6 months (n=55)	12 months (n=29)
Remission*	1	17 (24%)	32 (58%)	12 (41%)
Steroid free# remission	0	4	15	6
No remission	69	18 (26%)	12 (22%)	5 (18%)
Response but not remission	n/a	35 (50%)	11 (20%)	12 (41%)

*defined using Physicians global assessment

lists the number of patients who were in remission off steroids

Overall 43/70 (61%) of patients went into remission at some point during study follow up which occurred for most patients between 4 weeks and 6 months.

Table 2: Published Paediatric Adalimumab studies to date

Population	No of IBD patients	No of CD patients	Prior Infliximab	Initial Dosing used (mg)	Clinical response	Comments
UK & ROI (current study)	72	70	94%	160 / 80 (3) , 80 /40 (41) 24mg/m^2 (16) other (10)	71%	2 deaths
USA[28]	10	7	100%	80/40 (4), 40 (5), 80 (1)	80%	Mean PCDAI 12 at start
USA[26]	15	15	100%	80/40 (11), 40(1), 80 (1), 40/20(1), 160/80 (1)	64%	Included >18 years
USA[20] (RESEAT)	115	115	95%	160 / 80 (22) , 80 /40 (51) 40/40 (17) other/unknown (9)	65%	Short follow up period
Israel[27]	14	14	71%	Dosing schedule not available	85%	Included >18 years
Italy[25]	23	23	61%	160 / 80 (13), 120/80 (2),	91%	Prospective;80mg maintenance in most

In addition to the case series listed there have been at least 4 published paediatric case reports.[21-24]

Reference List

(1) Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van LJ, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: A systematic review of international trends. *Inflammatory Bowel Diseases* 2011; 17(1):423-439.

(2) Armitage E, Drummond H, Ghosh S, Ferguson A. Incidence of juvenile-onset Crohn's disease in Scotland. *Lancet* 1999; 353(9163):1496-1497.

(3) Sawczenko A, Sandhu BK, Logan RF, Jenkins H, Taylor CJ, Mian S et al. Prospective survey of childhood inflammatory bowel disease in the British Isles. *Lancet* 2001; 357(9262):1093-1094.

(4) Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008; 135(4):1114-1122.

(5) Akobeng A. Crohn's disease: current treatment options. *Arch Dis Child* 2008; 93(9):787-792.

(6) Wilson D, Thomas A, Croft N, Newby E, Akobeng A, Sawczenko A et al. Systematic Review of the Evidence Base for the Medical Treatment of Paediatric Inflammatory Bowel Disease. *Journal of Pediatric Gastroenterology & Nutrition* 2010; 50(Suppl 1):S14-S34.

(7) Sandhu BK, Fell JM, Beattie RM, Mitton SG, Wilson DC, Jenkins H. Guidelines for the Management of Inflammatory Bowel Disease in Children in the United Kingdom. *Journal of Pediatric Gastroenterology & Nutrition* 2010; 50(Suppl 1):S1-S13.

(8) Mossop H, Davies P, Murphy MS. Predicting the need for azathioprine at first presentation in children with inflammatory bowel disease. *Journal of Pediatric Gastroenterology & Nutrition* 2008; 47(2):123-129.

(9) Turner D, Grossman AB, Rosh J, Kugathasan S, Gilman AR, Baldassano R et al. Methotrexate Following Unsuccessful Thiopurine Therapy in Pediatric Crohn's Disease. *The American Journal of Gastroenterology* 2007; 102(12):2804-2812.

(10) Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007; 132(3):863-873.

(11) Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. *N Engl J Med* 2010; 362(15):1383-1395.

(12) Malik S, Wong SC, Bishop J, Hassan K, McGrogan P, Ahmed SF et al. Improvement In Growth Of Children With Crohn's Disease Following Anti-

TNF-α Therapy Can Be Independent Of Pubertal Progress And Glucocorticoid Reduction. *Journal of Pediatric Gastroenterology & Nutrition* 2011; 52(1):31-37.

(13) Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. *Inflammatory Bowel Diseases* 2007; 13(4):424-430.

(14) Bultman E, Kuipers EJ, Van Der Woude CJ. Systematic review: steroid withdrawal in anti-TNF-treated patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics* 2010; 32(3):313-323.

(15) Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; 132(1):52-65.

(16) Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R et al. Adalimumab Induction Therapy for Crohn Disease Previously Treated with Infliximab: A Randomized Trial. *Ann Intern Med* 2007; 146(12):829-838.

(17) Peyrin-Biroulet L, Laclotte C, Bigard MA. Adalimumab maintenance therapy for Crohn's disease with intolerance or lost response to infliximab: an open-label study. *Alimentary Pharmacology & Therapeutics* 2007; 25(6):675-680.

(18) Ho GT, Smith L, AITKEN S, LEE HM, TING T, Fennel J et al. The use of adalimumab in the management of refractory Crohn's disease. *Alimentary Pharmacology & Therapeutics* 2008; 27(4):308-315.

(19) HINOJOSA J, GOMOLLON F, GARCIA S, BASTIDA G, CABRIADA JL, SARO C et al. Efficacy and safety of short-term adalimumab treatment in patients with active Crohn's disease who lost response or showed intolerance to infliximab: a prospective, open-label, multicentre trial. *Alimentary Pharmacology & Therapeutics* 2007; 25(4):409-418.

(20) Rosh JR, Lerer T, Markowitz J, Goli SR, Mamula P, Noe JD et al. Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in Pediatric Crohn's Disease. *American Journal of Gastroenterology* 2009; 104(12):3042-3049.

(21) Veres G, Putz R, Szabo D, Molnar K, Bodanszky H, Dezsofi A et al. [Adalimumab treatment in infliximab-resistant pediatric patient with Crohn's disease]. *Orvosi Hetilap* 2009; 150(40):1858-1860.

(22) Nguyen KDK, Alexis R, Schwarz SM. Oropharyngeal and Proximal Esophageal Involvement During Adalimumab Treatment of Crohn Disease. *Journal of Pediatric Gastroenterology and Nutrition* 2010; 50(2):225-226.

(23) Mian S, Baron H. Adalimumab, a Novel Anti-Tumor Necrosis Factor-[alpha] Antibody in a Child with Refractory Crohn's Disease. *Journal of Pediatric Gastroenterology & Nutrition* 2005; 41(3):357-359.

(24) Hadziselimovic F. Adalimumab Induces and Maintains Remission in Severe, Resistant Paediatric Crohn Disease. *Journal of Pediatric Gastroenterology & Nutrition* 2008; 46(2):208-211.

(25) Viola F, Civitelli F, Di NG, Barbato MB, Borrelli O, Oliva S et al. Efficacy of adalimumab in moderate-to-severe pediatric Crohn's disease. *American Journal of Gastroenterology* 2009; 104(10):2566-2571.

(26) Wyneski MJ, Green A, Kay M, Wyllie R, Mahajan L. Safety and efficacy of adalimumab in pediatric patients with Crohn disease. *Journal of Pediatric Gastroenterology & Nutrition* 2008; 47(1):19-25.

(27) Rosenbach Y, Hartman C, Shapiro R, Hirsch A, Avitzur Y, Shamir R. Adalimumab Treatment in Children with Refractory Crohns Disease. *Digestive Diseases and Sciences* 2010; 55(3):747-753.

(28) Noe JD, Pfefferkorn M. Short-term response to adalimumab in childhood inflammatory bowel disease. *Inflammatory Bowel Diseases* 2008; 14(12):1683-1687.

(29) LEES CW, Ironside J, Wallace WA, Satsangi J. Resolution of non-small-cell lung cancer after withdrawal of anti-TNF therapy. *New England Journal of Medicine* 2008; 359(3):320-321.

(30) Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M et al. A Systematic Review of Factors That Contribute to Hepatosplenic T-Cell Lymphoma in Patients With Inflammatory Bowel Disease. *Clinical Gastroenterology & Hepatology* 2011; 9(1):36-41.

(31) Mackey AC, Green L, Liang LC, Dinndorf P, Avigan M. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *Journal of Pediatric Gastroenterology & Nutrition* 2007; 44(2):265-267.

(32) Shale M, Kanfer E, Panaccione R, Ghosh S. Hepatosplenic T-Cell Lymphoma in Inflammatory Bowel Disease. *Gut* 2008; 57(12):1639-1641.

(33) Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS et al. Development and validation of a pediatric Crohn's disease activity index. *Journal of Pediatric Gastroenterology & Nutrition* 1991; 12(4):439-447.

(34) IBD Working Group of the European Society for Paediatric Gastroenterology HaN. Inflammatory Bowel Disease in Children and Adolescents: Recommendations for Diagnosis-The Porto Criteria. *Journal of Pediatric Gastroenterology & Nutrition* 2005; 41(1):1-7.

(35) Lennard-Jones JE. Classification of inflammatory bowel disease. *Scandinavian Journal of Gastroenterology* 1989; 170:2-6.

(36) Silverberg MS, Satsangi J, Ahmad T, Arnott I.D.R., Bernstein CN, Brant SR et al. Towards an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005

Montreal World Congress of Gastroenterology. *Canadian Journal of Gastroenterology* 2005; 19(Supplement A):5-36.

(37) Ho GT, Mowat A, Potts L, Cahill A, Mowat C, Lees CW et al. Efficacy and complications of adalimumab treatment for medically-refractory Crohn's disease: analysis of nationwide experience in Scotland (2004-2008). *Alimentary Pharmacology and Therapeutics* 2009; 29(5):527-534.

(38) Colombel JF, Sandborn WJ, Panaccione R, Robinson AM, Lau W, Li J et al. Adalimumab safety in global clinical trials of patients with Crohn's disease. *Inflammatory Bowel Diseases* 2009; 15(9):1308-1319.

(39) Manz M, Beglinger C, Vavricka SR. Fatal invasive pulmonary aspergillosis associated with adalimumab therapy. *Gut* 2009; 58(1):149.

(40) Crombé V, Salleron J, Savoye G, Dupas JL, Vernier-Massouille G, Lerebours E et al. Long- Term Outcome Of Treatment With Infliximab In Paediatric Crohn's Disease : A Population-based Study. *Journal of Crohn's and Colitis* 2010; 4(1):S6.

(41) Diak P, Siegel J, La GL, Choi L, Lemery S, McMahon A. Malignancy in children and tumor necrosis factor-alpha blockers: Forty-eight cases reported to the food and drug administration. *Arthritis & Rheumatism* 2010; e-pub.

(42) Panaccione R, Colombel JF, Sandborn WJ, Rutgeerts P, D'Haens GR, Robinson AM et al. Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. *Alimentary Pharmacology & Therapeutics* 2010; 31(12):1296-1309.

(43) Oussalah A, Danese S, Peyrin-Biroulet L. Efficacy of TNF antagonists beyond one year in adult and pediatric inflammatory bowel diseases: a systematic review. *Curr Drug Targets* 2010; 11(2):156-175.

(44) Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology* 2009; 137(5):1628-1640.

(45) Sokol H, Seksik P, Carrat F, Nion-Larmurier I, Vienne A, Beaugerie L et al. Usefulness of co-treatment with immunomodulators in patients with inflammatory bowel disease treated with scheduled infliximab maintenance therapy. *Gut* 2010; 59(10):1363-1368.

(46) Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K et al. Adalimumab with or without Methotrexate in Juvenile Rheumatoid Arthritis. *N Engl J Med* 2008; 359(8):810-820.

(47) Lichtiger S, Binion DG, Wolf DC, Present DH, Bensimon AG, Wu E et al. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. *Alimentary Pharmacology & Therapeutics* 2010; 32(10):1228-1239.

(48) Hanauer SB, Feagan BG, LICHTENSTEIN GR, Mayer LF, Schreiber S, Colombel JF et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; 359(9317):1541-1549.