Early anti-TNF treatment in pediatric Crohn's disease. Predictors of clinical outcome in a population based cohort of newly diagnosed patients.

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Short title: Early infliximab treatment in pediatric Crohn's disease.

Abbreviations: CD (Crohn's Disease), TNF (tumor necrosis factor), MRI (Magnetic Resonance Imaging), CRP (C- reactive Protein), ESR (elevated sedimentation rate), IBD (inflammatory bowel disease), PCDAI (Pediatric Crohn's Disease Activity Index), EEN (exclusive enteral nutrition), 5- ASA (5-aminosalicylic acid)

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Abstract

Objective: Pediatric Crohn's disease (CD) is often debilitating, with upper gastrointestinal involvement and complications over time. Treatment with TNF blockers can induce and maintain remission. We wanted to evaluate the outcome of patients medically treated for CD to investigate whether clinical, endoscopic and biochemical factors at diagnosis are associated with the early initiation of treatment with the TNF blocker infliximab.

Materials and Methods: Patients aged <18 years, diagnosed with CD were characterized according to the Porto criteria, with endoscopy, MRI and biochemical tests before individual treatment. They were followed prospectively until a prescheduled examination within two years.

Results: Thirty-six pediatric patients were included, 18 (50%) received infliximab. Infliximab treated patients had shorter disease duration, more upper gastrointestinal involvement ($p=0.03$) and higher median CRP (28 versus 7.5 mg/l, $p=0.02$), ESR (32 versus 18 mm/h, $p=0.01$) and fecal calprotectin (1506 versus 501 mg/kg, $p=0.01$) levels.

Infliximab treatment was well tolerated, and 15 /18 of patients achieved clinical remission. At follow up 11/17 in the infliximab group and 8/13 in the non-infliximab group achieved ileocolonic mucosal healing. A majority in the infliximab group had a marked reduction of CD specific upper gastrointestinal lesions but persistence of unspecific upper GI inflammation at follow-up.

Conclusion: High levels of inflammatory markers and upper gastrointestinal lesions were associated with initiation of infliximab treatment. A substantial proportion of patients still had unspecific lesions in the upper GI regardless of treatment. Future studies must clarify the prognostic role of persistent upper gastrointestinal-involvement despite mucosal healing in the ileocolon.

Keywords: Pediatric IBD, Crohn's disease, infliximab, upper gastrointestinal lesions, mucosal healing

Introduction

Crohn's disease (CD) is a chronic inflammatory disease that can affect all parts of the gastrointestinal (GI) tract. Pediatric CD is often debilitating, characterized by extensive inflammation, upper gastrointestinal involvement and a tendency for complications over time. The introduction of tumor necrosis factor (TNF) blockers in the treatment of adults with CD represented a great improvement in treatment efficacy (1, 2), inducing rapid disease remission in up to two thirds of patients. TNF blockers have shown to maintain remission (3).

Concerns related to adverse events of TNF blockers delayed the introduction among children and adolescents. After the initial reports on efficacy in pediatric cases, an emerging experience from hospital series has been reported (4-6), with a higher response rate to TNF blockers in pediatric patients compared to adults, and with a high tolerability (7). A young age at diagnosis, ileal and upper GI involvement as well as fistulizing disease, are indicators of a serious disease course (8, 9). TNF blockers may restore puberty and accelerate growth (10) and it has been proposed that by inducing mucosal healing the disease course may become more favorable and complications can be prevented (11-13). There are few publications on the effect of early TNF blocker treatment in pediatric patients, and more knowledge is warranted.

The aim of this prospective population based study was to evaluate if early intervention with biologic treatment in children and adolescents with CD, would be safe and highly efficient in inducing and maintaining remission within the first one to two years after diagnosis.

We also wanted to study whether clinical, endoscopic and biochemical markers at diagnosis can predict the need for early initiation of treatment with TNF blockers in pediatric CD patients.

Materials and Methods

Patients and controls:

All patients aged <18 years, with newly diagnosed inflammatory bowel disease (IBD) from the catchment areas of two university hospitals in Norway, Akershus University Hospital and Oslo University Hospital, were invited to participate in the study (14). This was a part of a large-scale prospective study of inflammatory bowel disease in South-Eastern Norway (The IBSEN II- study). The inclusion period was from May 1st 2005 to December 31st 2007. All treatments were initiated after the inclusion in the study. A follow-up examination was offered within two years after the diagnosis.

Patients referred to the hospital due to GI symptoms during the inclusion period, but who displayed no evidence of inflammation during work up, were included as symptomatic non-IBD controls (14). These controls were offered a follow-up examination within two years after the first work-up of their symptoms, which confirmed no IBD. The Vienna classification was used to characterize the disease distribution and behavior (15).

Examinations

Data on age, gender, and date of first symptoms, disease history and family history of IBD were collected (14). Symptoms were scored according to the Pediatric Crohn's Disease Activity Index (PCDAI) (16), and weight, height, and pubertal development including Tanner stadium (17) were recorded both at inclusion and repeated at the follow-up examination. A PCDAI score below 10 was considered clinical remission.

Biochemistry and fecal testing

Blood specimens were collected for analyses including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hematocrit and albumin level. Fecal samples were collected before

bowel cleansing procedures and investigated for calprotectin (18) (FeCal-test, Bühlmann, Basel, Switzerland), and microbiology.

Endoscopy and histology

All patients were examined with upper and lower endoscopies according to the Porto criteria, both at baseline and at follow-up, by experienced endoscopists (19). Biopsies were taken from the duodenum, ventricle, esophagus, the ileum, the rectum and all segments of the colon. Macroscopic erosions, aphthous lesions and ulcerations were regarded as CD specific lesions of the upper and lower GI. Microscopic chronic focal active inflammation and villous atrophy were accounted for, and helicobacter pylori infection and celiac disease were ruled out. The mucosal appearance was scored in accordance with the SES-CD. Mucosal healing was defined as disappearance of ulcerations, multiple erosions, bleeding, and friability. Both complete normalization (grade 0) and light hyperemia and granularity (grade 1) were considered as endoscopic healing (20). Disappearance of ulcerations and erosions, active inflammation and cellular infiltrates were considered as histologic healing as well as light structural changes (21).

Treatment

Initial treatment options were 1) exclusive enteral nutrition (EEN), or 2) medical treatment with corticosteroids/ azathioprine and/or 5-aminosalicylic acids (5-ASAs). Treatment was decided individually at the courtesy of the treating physician.

The indication for treatment with infliximab was failure to enter clinical remission with induction treatment, or early relapse. EEN consisted of Modulen IBD® (Nestlé, Vevey, Switzerland), a polymeric formula, Elemental 028 extra® (Nutricia, Liverpool, UK) or an amino acid based hypoallergenic formula. Patients receiving EEN avoided all other types of

food and liquids except the chosen formula and water for 6-8 weeks. Corticosteroids were given as prednisolone 1-2 mg/kg or budesonide capsules (9 or 6 mg initial dosage depending on weight) and tapered slowly.

As maintenance therapy azathioprine was in general started simultaneously in a dose resulting in a 6-thioguanine level of 3-5 micromol/l.

Infliximab was given in dosages of 5 mg/kg, starting with a standard induction regimen, at week 0, 2 and 6 and thereafter every 8 weeks if the patient responded. Adverse events were systematically recorded.

Statistics

Data were described with median and observed range (continuous variables) and with frequencies and percentages (categorical variables). Due to a limited sample size, non-parametric methods were used. The Mann-Whitney Wilcoxon test for unpaired samples was used for comparisons between groups with regards to continuous variables. Crude associations between pairs of categorical variables were assessed with Chi-square test. All tests were two-sided. P-values <0.05 were considered statistically significant. We regarded our study as an exploratory analysis; therefore we did not adjust for multiple testing. All analyses were performed using SPSS, statistical software SPSS (SPSS Inc., Chicago, IL, USA).

Ethics

The study was performed in accordance with the Helsinki declaration and with approval of the Regional Ethics Committee. Written informed consent was collected from all parents and patients.

Results

Patients, clinical characteristics and histology at diagnosis

Thirty-six children, 20 boys and 16 girls, were diagnosed with CD. Median age at inclusion was 13 years (range 2-17). Thirty-eight patients with no evidence of pathology in the GI-tract with gastrointestinal symptoms served as non- IBD controls, with median age 12 years (range 2-17) (14).

Ileocolonoscopy with biopsies was performed in all 36 patients, and in 91% the ileum was intubated for biopsies. Upper endoscopy was completed in 34/36 (94 %), and MRI in 31/36 (86%) patients. All non-IBD controls had normal macroscopic and microscopic appearance at upper and lower endoscopies and normal median values of CRP, ESR and calprotectin (14).

The disease distribution of the CD patients at diagnosis was ileocolonic in 26 (72%), isolated colitis in 8 (22%), and isolated ileitis in 5 (14%) (Table1). Macroscopic changes were seen at upper endoscopy in 26 (76%) patients, most commonly in the stomach and duodenum.

Fifteen infliximab treated patients had upper GI lesions, 73% displaying CD specific lesions, versus seven in the non-infliximab treated group. The differences between the two treatment groups are shown in Table 1. None of the patients had isolated upper GI inflammation. Fifteen of the 36 patients had granulomas at diagnosis, with the distribution most commonly being in the colon followed by the ileum. Two patients had only upper GI granulomas.

Five patients had stricturing disease and two had intestinal penetrating disease. Four patients had orofacial granulomatosis (OFG) and in four patients perianal CD was present, two with concomitant OFG. Erythema nodosum and arthritis was present in one patient each.

Symptoms at diagnosis were most commonly abdominal pain in 29/36, altered bowel habits in 23/36 and limitation of daily activities in 22/36 of patients. As compared to the non- IBD patients, the CD patients had a lower height and bodyweight than normal for age and a slight delay in pubertal development. Altogether four patients had, in spite of a PCDAI score less

than 10, with the lowest score being 2, extensive inflammation detected on endoscopy.

Further details describing the patients and non-IBD controls at diagnosis have been published (14). The median follow-up time for the study group was 18 months (range 12-24).

Treatment given

During the first year after the diagnosis, half of the patients, 10 boys and eight girls, received infliximab due to failure to achieve remission, or to early relapse with conventional treatment. All had received azathioprine and 14 (78%) were initially treated with EEN. Patients who were given infliximab had significantly higher levels of fecal calprotectin, CRP and ESR at diagnosis (Table 2). They also had a more extensive disease distribution than the group who received other treatment modalities with significantly more upper GI involvement (15 versus eight patients ($p=0.01$)) (Table 1).

Median time from diagnosis to initiation of infliximab therapy was two months (range 0.5- 6 months). Infliximab treated patients had significantly shorter symptom-duration, with a median of five months compared to 16 months in the non-infliximab treated patients ($p=0.03$). Of those receiving infliximab, 15 (83%) achieved clinical remission, all within six weeks. The response was sustained during the study period of two years for all responders. Two of those not responding, required surgery, and the third needed additional steroids. One patient experienced a hypersensitivity reaction after the second dose of infliximab; apart from this no adverse events were observed.

In the group of patients who did not receive infliximab, 15 (83%) gained clinical remission. Nine patients received corticosteroids, nine azathioprine, six EEN and six 5-ASAs.

Patient and clinical characteristics including mucosal healing at follow-up

Thirty-four (94 %) of the 36 CD patients attended follow-up examinations. Median time from diagnosis to follow-up was 20 months (range 12-24). Upper and lower endoscopy was

conducted and biopsies taken in 17/18 of infliximab treated patients and in 13/18 of non-infliximab treated patients.

After treatment, the PCDAI scores, levels of CRP, ESR, and calprotectin dropped in both treatment groups (Table 2). The non-IBD controls had a normal PCDAI score at follow-up, as well as normal inflammatory markers and normal macro and microscopic findings in the upper and lower GI tract. At follow-up, the proportions of patients who had ileomucosal healing was similar in both groups, 11/17 of the infliximab treated group and 8/13 in the non-infliximab treated group. The most common inflammation in the upper GI after treatment was gastritis, found in nine patients in the infliximab group and three in the non-infliximab treated group. Overall 13 patients had an altered disease distribution; four patients with normal endoscopy at baseline had inflammation detected at follow-up.

At follow-up there was resolution of fistulas in one of the two patients and none had stricturing disease.

Growth and puberty

At follow-up all patients except one non-responder in the infliximab group had normalized and improved pubertal development and growth, demonstrating higher Tanner scores, regardless of therapy received. Those who were stunted at inclusion had experienced accelerated growth.

Discussion

In this prospectively followed, well-defined, pediatric cohort with newly diagnosed CD in southeastern Norway, half of the patients received infliximab within the first year from diagnosis, due to failure to achieve remission or the occurrence of early relapse with conventional treatment. Variables associated with the need of infliximab treatment were short

disease duration, widespread disease distribution with upper gastrointestinal involvement and high levels of the inflammatory markers CRP, ESR and fecal calprotectin at diagnosis. These findings indicating aggressive disease behavior are in accordance with other studies (22).

However, some of the patients in the infliximab-treated group had relatively low levels of fecal calprotectin. This correlates with the clinical experience that pediatric patients with CD may have a normal or next to normal calprotectin level even though they have inflammation, especially if this inflammation is localized in the small intestine and/or upper GI or if the inflammation in the colon is of low grade.

The infliximab treatment was initiated early after diagnosis, usually within the first two months, and we speculate that this may have contributed to the good outcome. Studies have reported a better response to infliximab when it is given early in the disease course (23, 24). The response was sustained as most of our patients had received infliximab treatment for over a year at the time of follow-up, confirming the ability of TNF blockers to both induce and maintain remission (25). All patients treated with infliximab were also given azathioprine, which may have contributed to the sustained treatment effect (26) whereas the limited treatment period on azathioprine before infliximab initiation was unlikely to have contributed to remission. Treatment with infliximab was well tolerated and no serious adverse events were recorded.

The overall outcome was good as both infliximab and non- infliximab treated patients achieved a clinical remission rate of above 80 % with normalized PCDAI scores. The rate of ileocolonic mucosal healing was high and comparable for both treatment groups, confirming the ability of conventional treatment to achieve endoscopic remission (27). Moreover, it has highlighted the importance of individualizing treatment, and that anti TNF treatment is not necessary for all patients (28).

The prevalence of upper GI-manifestations was high in our pediatric cohort. This is in accordance with previous studies reporting that upper GI manifestations are more common in children and adolescents than in adults with CD (22, 30). A prospective study comparing pediatric CD patients with and without upper GI involvement, reported that patients with upper GI manifestations had more active disease, more extraintestinal manifestations, more widespread lower GI disease distribution and more often needed immunomodulating therapy and TNF blockers in order to induce and maintain remission (9). This is in agreement with the present results, with a significantly higher prevalence of upper GI lesions in the infliximab treated group. The most common site of upper GI manifestation was the stomach and duodenum at diagnosis, with a high frequency of CD specific lesions. In our cohort it seemed that infliximab healed ulcerations, aphtous lesions and erosions in the gastric mucosa and duodenum, but that in several patients unspecific inflammation remained or developed despite treatment. Some case reports have documented the efficacy of infliximab in treating upper GI CD (31, 32) but due to lack of large materials and also universally accepted definitions for upper CD characterization, no definitive comparisons can be made.

There is evidence for microscopic gastric inflammation to be more common in children and adolescents with IBD compared to controls, (29, 33). This is confirmed by our study with none of the symptomatic non-IBD controls displaying macroscopic or microscopic evidence of upper GI inflammation. Some of our patients had new upper GI lesions detected at follow up in spite of being asymptomatic and having normalization of CRP, ESR and fecal calprotectin levels. Lesions in the upper GI, like duodenitis, gastritis and esophagitis might be unspecific findings and could for some of our patients have other etiologies than CD. As none of the patients in the non- IBD control group had gastritis or other upper GI lesions detected, we speculate that the inflammatory findings in the upper GI were associated with CD. The

higher frequency of upper GI lesions in the infliximab group may support this assumption. It has been shown that a large proportion of CD patients have upper GI inflammation when looked for, and that many of these patients are asymptomatic- (34, 35). The prognostic significance of these upper GI findings is uncertain, and should be evaluated in future studies.

At present, high costs and risk of serious adverse events prevent the use of TNF blockers as standard first line treatment in CD. Large randomized studies are needed to show if the long-term outcomes can be improved by early intervention with TNF blockers (36). The challenge then will be to identify patients for first line treatment with TNF blockers.

Even if the efficacy of conventional, non-infliximab treatment in our patients seems to be good, a prolonged follow up is needed to compare the effect on the long-term course of disease between the treatment groups. Nevertheless, the present study demonstrates a high efficacy and safety of early intervention with TNF blockers in children initially not responding to conventional treatment. The clinical and biochemical characterization at baseline of the patients later selected for TNF blockers, give support to the use of clinical and laboratory markers for the selection of patients to early intervention with this treatment.

As CD in 30- 40% of pediatric patients becomes more aggressive with stricturing and fistulizing features over time (37), our follow-up of 1-2 years is too short to compare the effect of the different treatment modalities on the occurrence of intestinal and extraintestinal complications.

Ideally, the use of univariate and multiple logistic regression analysis and the construction of Rock curves would have been preferable to describe the value of clinical and biochemical factors in predicting the initiation of infliximab treatment. However, a much larger data set would have been needed, most likely based on a registry study. Patients entered into such a large scale study would probably not have had the same meticulous work-up and follow-up as our cohort. The strength of this study was the use of a detailed, standardized, extensive

protocol for diagnosis; clinical characterization with endoscopy and biopsies, applied at baseline and at prescheduled follow up within 2 years. A weakness of the study was the limited number of cases. Moreover no randomization was performed prior to infliximab treatment with infliximab, which was decided on the basis of individual disease course. On the other hand the present study reflects everyday practice.

The fact that 50 % needed infliximab within the first year illustrates and confirms that CD in children and adolescents is an aggressive disease and that potent treatment often is necessary to induce remission (38).

Conclusion

In this pediatric cohort with newly diagnosed CD, clinical remission was achieved in 83% of patients, with half of the patients needing infliximab, all within the first year after diagnosis. Short disease duration, high levels of the inflammatory markers CRP, ESR and fecal calprotectin, as well as widespread disease distribution with upper GI lesions were associated with the need of infliximab to gain remission. In spite of clinical remission and a high rate of ileocolonic mucosal healing, a substantial proportion of the patients had persistent or new upper GI involvement at follow-up regardless of treatment received. The significance of these findings needs further elucidation. The study confirms the safety and high degree of efficacy of early intervention with biologic treatment in children with CD, for the first time demonstrated within the first year after diagnosis.

Acknowledgements

CO carried out the studies and data analyses and drafted the manuscript. BN helped with analysis of data, provided significant advice and helped to draft the manuscript. MC participated in the design of the study and performed the statistical analysis. ETE helped with

analysis of data, provided significant advice and helped to draft the manuscript. MHV conceived the study, participated in its design and coordination and helped to draft the manuscript. GP conceived the study, helped in collecting the data, participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

References

1. Hanauer S, Feagan B, Lichtenstein G, Mayer LF, MD, Schreiber S, Colombel JF et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002; 359: 1541-9.
2. Sands, FH. Anderson, CN. Bernstein Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*, 2004; 350: 876–885.
3. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004 Feb; 126(2): 402-13.
4. Hyams JS, Markowitz J, Wyllie R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. *Pediatr* 2000; 137:192–196.
5. Veres G, Baldassano RN, Mamula P. Infliximab therapy in children and adolescents with inflammatory bowel disease. *Drugs*. 2007; 67(12): 1703–1723.
6. de Ridder L, Benninga MA, Taminiau JA, Hommes DW, van Deventer S et al. Infliximab use in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2007; 45 (1): 3–14.
7. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johannis J et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007; 132: 863-73.
8. Zallot C, Peyrin-Biroulet L. Clinical risk factors for complicated disease: how reliable are they? *Dig Dis*. 2012; 30. Suppl 3: 67-72.
9. Crocco S, Martelossi S, Giurici N, Villanacci, Ventura A. Upper gastrointestinal involvement in paediatric onset Crohn's disease: Prevalence and clinical implications. *Journ Crohn and Colitis* (2012) 6, 51-55.
10. Walters TD, Gilman AR, and Griffiths AM. "Linear growth improves during infliximab

therapy in children with chronically active severe Crohn's disease," *Inflamm Bowel Dis* 2007; 13: 424-430.

11. D'Haens G. "Mucosal healing in pediatric Crohn's disease: the goal of medical treatment," *Inflamm Bowel Dis*. 2004; 10:479–80.

12. Vatn MH. Mucosal healing: impact on the natural course or therapeutic strategies. *Dig Dis* 2009; 27:470–475.

13. Borrelli O, Bascietto C, Viola F. Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. *Dig Liver Dis* 2004, 36(5): 342-347.

14. Perminow G, Brackmann S, Lyckander LG , Franke A, Borthne A, Rydning A, Geir Aamodt et al. A characterization in childhood inflammatory bowel disease, a new population-based inception cohort from South-Eastern Norway, 2005-07, showing increased incidence in Crohn's disease. *Scand J Gastroenterol*. 2009; 44 (4): 446-56.

15. Gasche C, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine JE et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000; 6:8-15.

16. Hyams JS, Ferry GD, Mandel FS , Gryboski JD, Kibor PM, Kirschner B et al. Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr* 1991; 12: 439-47.

17. Tanner JM, Whitehouse RH, Takasashi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. *Arch Dis Child* 1966; 41: 454-71.

18. Fagerberg UL, Loof L, Lindholm J, Hansson L-O, Finkel Y. Fecal calprotectin: a quantitative marker of colonic inflammation in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2007; 45: 414–420.

19. Escher JC, Amil Dias J, Bochenek K S, Buderus M, Bueno de Mesquita Y, Bujanover and the IBD working group of ESPGHAN. Inflammatory bowel disease in children and adolescents: Recommendations for diagnosis-the Porto criteria. *J Pediatr Gastroenterol Nutr.* 2005 Jul;41(1):1-7.
20. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*, 60 (2004), pp. 505–512.
21. Froesli KF, Jahnsen J, Moum BA, Vatn MH and the IBSEN group. Mucosal healing in inflammatory bowel disease. *Gastroenterology* 2007; 133:412–422.
22. Yarur AJ, Strobel SG, Deshpande AR, Abreu MT. Predictors of aggressive inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2011 Oct; 7 (10): 652-9.
23. Lionetti P, Bronzini F, Salvestrini C, Bascietto C, Canani RB, Dé Angelis GL et al. Response to infliximab is related to disease duration in pediatric Crohn's disease. *Aliment Pharmacol Ther* 2003; 18: 425-31.
24. Kugathasan S, Werlin SL, Martinez A, Rivera MT, Heikenen JB, Binion DG. Prolonged duration of response to infliximab in early but not late pediatric Crohn's disease. *Am J Gastroenterol*. 2000; 95(11): 3189–3194.
25. Hyams JC, Lerer T, Griffith A, Pfefferkorn M, Kugathasan S, Evans J et al. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflamm Bowel Dis*. 2009; 15: 816-822.
26. Colombel J-F, 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: 1383–95

27. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; 119: 895-902.

28. Latella G, Papi C. Crucial steps in the natural history of inflammatory bowel disease. *World J Gastroenterol.* 2012 Aug 7; 18(29): 3790-3799.

29. Hummel TZ, ten Kate FJ, Reitsma JB, Benninga MA, Kindermann A. Additional value of upper GI tract endoscopy in the diagnostic assessment of childhood IBD. *J Pediatr Gastroenterol Nutr.* 2012; 54:753–57.

30. Ushiku T, Moran CJ, Lauwers G. Focally enhanced gastritis in newly diagnosed Pediatric Inflammatory Bowel Disease. *Am J Surg Pathol.* 2013 Dec; 37(12): 1882-8.

31. Annunziata ML, Caviglia R, Papparella LG, Cicala M. Upper Gastrointestinal involvement of Crohn's Disease: A prospective Study on the Role of upper Endoscopy in the Diagnostic Work-Up. *Dig Dis Sci* (2012) 57: 1618-1623.

32. Turner D, Griffith AM. Esophageal, Gastric, and Duodenal Manifestations of IBD and the Role of Upper Endoscopy in IBD diagnosis. *Curr Gastroenterol Reports* 2007, 9:475-478.

33. Sharif F, McDermott M, Path MRC, Drumm B, Rowland M, Imrie C et al. Focally enhanced gastritis in children with Crohn's disease and ulcerative colitis. *Am J Gastroenterol* 2002;97:1415 – 20.

34. Castellaneta SP, Afzal NA, Greenberg M, Deere H, Davies S, Murch SH, et al. Diagnostic Role of Upper Gastrointestinal Endoscopy in Pediatric Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr* 2004;39:257–61.

35. Kovacs M, Muller KE, Arato A, Lakatos PL, Kovacs JB, Varkonyi A et al. Diagnostic

yield of upper endoscopy in paediatric patients with Crohn's disease and ulcerative colitis.

JCC 2012; 6, 86-94

36. Vermeire, S, van Assche G, Rutgeerts P. (2007) Review article: Altering the natural history of Crohn's disease. Evidence for and against current therapies. *Aliment Pharmacol Ther* 2007 Jan 1; 25 (1): 3-12.

37. Van Limbergen J, Russel RK, Drummond HE Aldhous MC, Round NK, Nimmo ER et al. Definition of Phenotypic Characteristics of Childhood-Onset Inflammatory Bowel Disease. *Gastroenterology* 2008; 135: 1114-1122.

38. Vernier-Massouille G, Balde M Salleron J, Turck D, Dupas JL, Mousterde O et al. Natural History of Pediatric Crohn's Disease: A Population-Based Cohort Study. *Gastroenterol* 2008; 135:1106-1111.

Table 1. Disease distribution and behavior at diagnosis and at follow-up in infliximab and non- infliximab treated pediatric Crohn´s Disease.

Disease distributio n	At diagnosis, n (%)	At follow-up, n (%)	P values			
Total number of patients	Inflixima b 18 (100)	Non-infliximab 18 (100)	Infliximab 17 (100)	Non-inflixi mab 13 (100)	At diagnosis ¹	At fo#llow- up ²
Upper GI lesions, total	15 (83)	7 (39)	13 (76)	5 (38)	0.01	0.03
Upper GI CD specific lesions	11 (61)	5 (28)	2 (12)	2 (15)		
Ileum	0	1 (6)	3 (18)	0	0.8	0.4
Colon	2 (11)	6 (33)	1 (6)	3 (23)	0.7	0.5
Ileocolon	16 (89)	10 (56)	2 (12)	2 (15)	0.3	0.5
Strictures	5 (28)	0	0	0	0.2	0.6
Fistulas	2 (11)	0	1 (6)	0	0.8	0.3
Perianal	2 (11)	2 (11)	2 (12)	2 (15)		
Granulom as	9 (50)	6 (33)	5 (29)	2 (15)		
OFG	2 (11)	2 (11)	2 (11)	2 (11)		

• ¹Infliximab treated group versus non- infliximab treated group at diagnosis

• ² Infliximab treated group versus non- infliximab treated group at follow up

Table 2. Clinical markers at diagnosis and at follow-up in infliximab and non- infliximab treated pediatric Crohn´s Disease.

	At diagnosis, n (%)	At follow-up, n (%)	P values			
Treatment	Infliximab 18 (100)	Non-infliximab 18 (100)	Infliximab 17(100)	Non-infliximab 13 (100)	At diagnosis ¹	At follow-up ²
Biochemical markers	Median (range)	Median (range)				
ESR, mm/h	32 (3-90)	18 (3-92)	7 (2-28)	4.5 (2-18)	0.01	0.1
CRP, mg/l	28 (1-165)	7.5 (1-125)	5 (1-19)	5 (1-7)	0.02	0.5
Fecal calprotectin, mg/kg	1506 (193-8625)	501 (31-2000)	109 (15-1938)	70 (15-927)	0.01	0.9
PCDAI*	25 (2-50)	23 (0-63)	5 (0-25)	8.75 (0-20)	0.08	0.4

*PCDAI: Pediatric Crohn´s disease Activity Index

¹Infliximab treated group versus non- infliximab treated group at diagnosis

² Infliximab treated group versus non- infliximab treated group at follow up