

ORIGINAL PAPERS

Efficacy and safety of adalimumab in the treatment of Crohn's disease in children

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ABSTRACT

Objectives: to describe the efficacy and safety of adalimumab (ADA) in inducing clinical remission and reducing inflammation of intestinal mucosa in children with Crohn's disease (CD).

Methods: we carried out a descriptive, observational study with all patients diagnosed with CD and treated with ADA between January 2007 and March 2013. Disease activity was determined using the Pediatric Crohn's Disease Activity Index (PCDAI), and the degree of mucosa inflammation by fecal calprotectin (FC).

Results: sixteen patients were included. Mean age at diagnosis was 10.6 ± 2.5 years, with a mean age at start of ADA treatment of 12.4 ± 1.8 years, and a median of 1.4 years (IQR 0.5-3) duration from CD diagnosis to start of treatment. Twelve patients were naïve to anti-TNF- α . The PCDAI score at start of ADA treatment was significantly reduced at 12 weeks of follow-up (31.25 IQR 26.8-37.5 vs. 1.2 IQR 0.0-5.0; $p = 0.001$). Similarly, the FC level decreased at 12 weeks (749 $\mu\text{g/g}$ IQR 514-898 vs. 126 $\mu\text{g/g}$ IQR 67.7-239.2; $p = 0.02$). Surgery was performed in 4 patients. Adverse events were reported in 4 patients. One patient developed lymphoma at 4 years of ADA treatment in monotherapy.

Conclusions: ADA has been shown to be effective in children with moderate-to-severe CD. Treatment benefits should be weighed against side effects. Multicenter longitudinal studies with longer follow-up periods are required to determine the true efficacy and safety of long-term ADA treatment.

Key words: Adalimumab. Crohn's disease. Inflammatory bowel disease. Children.

INTRODUCTION

The incidence of inflammatory bowel disease in children has increased both in Spain (1) and in other countries (2-5). Exclusive enteral nutrition (6,7), steroids (8), and immunomodulators (9) have shown to be effective for induction and maintenance of remission in children with Crohn's disease (CD) (10). In addition, the development of biologic agents has substantially changed the treatment of inflammatory bowel disease.

Infliximab (IFX, REMICADE[®], MSD, Madrid, Spain) is a human-murine anti-tumor necrosis factor- α (TNF) chimeric monoclonal antibody that is useful for both induction and maintenance of remission in children with CD (11,12).

Adalimumab (ADA, HUMIRA[®], Abbvie, Madrid, Spain) is the first completely human anti-TNF- α monoclonal antibody with a structure and half-life that are indistinguishable from human IgG1. It binds specifically to both soluble and transmembrane TNF- α and blocks its functionality (13). In pediatric clinical practice ADA is usually prescribed for patients who have lost response or developed intolerance to IFX (14). Data published thus far on the efficacy of treatment with ADA in children with CD comes from case series, retrospective studies (15-19) and a clinical trial (20). In the case series report-

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ed, more than 70 % of patients had initially been treated with IFX.

The purpose of our study was to describe the efficacy and safety of ADA in inducing clinical remission and reducing inflammation of intestinal mucosa in children with CD.

MATERIALS AND METHODS

We carried out a descriptive, observational study that included all patients diagnosed with CD and treated with ADA between January 2007 and March 2013. Diagnosis was performed following the Porto criteria (21-23). Exclusion criteria were the presence of active infection; heart, renal or liver failure; and neurological or immunodeficiency disorders. Infection with tuberculosis was excluded using the Mantoux and QuantiFERON-TB-Gold-Test in tube[®] (Cellestis Ltd; Carnegie, VIC, Australia) tests prior to starting treatment. Disease phenotype was determined according to the Paris classification (24), disease activity using the Pediatric Crohn's Disease Activity Index (PCDAI) (25,26) and the degree of mucosa inflammation by fecal calprotectin (FC, Calprest[®], Eurospital, Trieste, Italy). The PCDAI index and FC were determined at week 12 and thereafter repeated at each subsequent visit. Informed consent was obtained from all patients.

In patients with a bodyweight below 40 kg, ADA was administered subcutaneously at an initial dose of 80 mg followed by 40 mg in week 2. Thereafter, ADA was administered at doses of 40 mg every 2 weeks. Patients with a bodyweight of 40 kg or more were given an initial dose of 160 mg, followed by 80 mg in week 2 and thereafter a maintenance regimen of 40 mg every 2 weeks. The first two doses of ADA were injected at the hospital under medical supervision. Subsequent doses were administered at the patient's home by parents or at their health care center. Patients continued with any medication they were already receiving at the time of the initial ADA dose until response was verified. In only one case ADA was administered as part of a Top-Down strategy (27).

Statistical analysis

Continuous parametric variables were expressed as the mean plus standard deviation, while non-parametric variables were expressed as the median and interquartile range (IQR). The Wilcoxon test for paired samples was used to analyze changes in patient FC and PCDAI. Statistical significance was considered to be $p < 0.05$.

Ethical considerations

Informed consent was obtained from all patients or their parents. The study was approved by the Ethic's Committee.

RESULTS

Patient characteristics

We included 16 patients (8 males) with a mean age at diagnosis of 10.6 ± 2.5 years (Table I), a mean age at start of ADA of 12.4 ± 1.8 years, and a median of 1.4 years (IQR 0.5-3) duration from CD diagnosis to start of treatment. The time from the onset of symptoms until diagnosis of the disease was 6 months (IQR 2.25-12). Of the 16 patients, 12 (75 %) were naïve to anti-TNF- α . Reasons for switching to treatment with ADA were loss of response to IFX (2 patients), adverse cutaneous reaction (1 patient), and patient refusal of the previous treatment (1 patient). Patients had received a mean of 7.8 ± 2.5 infusions of IFX. Administration of ADA was performed in combination with thiopurines in 14 patients, of who 13 received azathioprine, and 1 mercaptopurine due to azathioprine-intolerance. Perianal disease was mild in 5 patients (fissures and skin TAGs) and moderate to severe in 2 (simple perianal fistula and abscess).

Response to treatment

At start of ADA treatment, 14 of 16 patients were experiencing a relapse (not including one patient who presented with a cutaneous reaction and another who refused further infusions with infliximab) with a PCDAI score of 31.25 (IQR 26.8-37.5), diminishing to 1.2 (IQR 0.0-5.0; $p = 0.001$) at 12 weeks of follow-up. At 12 weeks, all 16 were in clinical remission (PCDAI < 10). A significant decrease was also seen in FC levels, from 749 $\mu\text{g/g}$ (IQR 514-898) at start of ADA treatment to 126 $\mu\text{g/g}$ (IQR 67.7-239.2) at 12 weeks. There was a significant increase in weight, albumin, hemoglobin, and hematocrit levels together with a significant decrease in FC, CRP, ESR, WBC and platelets at week 12. The lowest level of FC found was 74.5 $\mu\text{g/g}$ (IQR 35.0-160.0), achieved at 4.5 months (IQR 2.3-8.5) of follow-up. Although all patients were in clinical remission, FC levels rose to 184 $\mu\text{g/g}$ (IQR 44-460) in the 6.9 months (IQR 4.7-13.2) after discontinuation of combined therapy (Fig. 1).

Clinical progress

Of the 16 patients administered ADA, 2 have experienced loss of response (the same with previous loss of response to infliximab) and 14 patients continued to be in clinical remission at 2.75 years (IQR 1.0-3.4) after the start of ADA treatment. Four patients have required intensification of the regimen, and 1 has required administration of steroid therapy (previous loss of response to infliximab and relapse unresponsive to adalimumab intensification regimen). In one case, treatment was stopped because the patient developed lymphoma.

The median number of ADA doses administered was 33 (IQR 12-60). A total of 609 doses were administered in all in the 16 patients. The median duration of combined therapy of 9.5 months (IQR 3.7-11.2). Outcome of perianal

Table I. Characteristics of patients treated with adalimumab

Males	8/16 (50 %)	
Age at diagnosis (years)	10.6 ± 2.5	
Age at adalimumab started (years)	12.4 ± 1.8	
Disease duration (years)	1.4 (IQR 0.5-3)	
Weight (kg)	37 ± 10.71	
Adalimumab induction dose	160/80	80/40
< 40 kg	0	10
> 40 kg	3	3
<i>Location (Paris)</i>		
L3	8 (50 %)	
L3 + L4 (extensive)	8 (50 %)	
B1	12 (75 %)	
B2	2 (12.5 %)	
Perianal disease (p)	7 (43 %)	
Baseline PCDAI	31.25 (IQR 26.8-37.5)	
	PCDAI ^a	PCDAI ^b
Remission	2 (12.5 %)	2 (12.5 %)
Mild	7 (43.7 %)	5 (31.3 %)
Moderate	*	6 (37.5 %)
Severe	7 (43.7 %)	3 (18.7 %)
<i>Previous treatment</i>		
Exclusive enteral nutrition	13 (81 %)	
Corticosteroids	3 (19 %)	
Aminosalicilates	8 (50 %)	
Azathioprine	13 (81 %)	
Mercaptopurine	1 (6 %)	
Budesonide	1 (6 %)	
Infliximab	4 (25 %)	
<i>Treatment when adalimumab was started</i>		
Exclusive enteral nutrition	2/16 (12.5 %)	
Corticosteroids	1/16 (6 %)	
Azathioprine/mercaptopurine	14/16 (87.5 %)	
Baseline fecal calprotectin (mcg/g)	749 (IQR 514-898)	
Baseline CRP (mg/L)	14.5 (IQR 3.9-25.5)	
Baseline ERS (mm/h)	23 (IQR 13.7-37.8)	
Baseline albumin (g/dl)	3.8 (IQR 3.6-4)	
Baseline Hb (g/dl)	12.7 (IQR 11.7-13.2)	
Baseline Hto (%)	37.7 (IQR 34.6-39.7)	
Baseline platelets (x10 ³ /µL)	381 ± 122	
Baseline WBC (x10 ³ /µL)	8150 ± 3667	
Surgery	4 (25 %)	

^aRemission ≤ 10; Mild 11-30; Moderate to Severe* > 30 points. Adapted from ref. 25. ^bRemission < 10; Mild 10-27.5; Moderate 30-37.5; Severe > 37.5 points. Adapted from ref. 26. PCDAI: Pediatric Crohn's Disease Activity Index; CRP: C-reactive protein; Hb: Hemoglobin; Hto: Hematocrit; ESR: Erythrocyte sedimentation rate; WBC: White blood cells; IQR: Interquartile range.

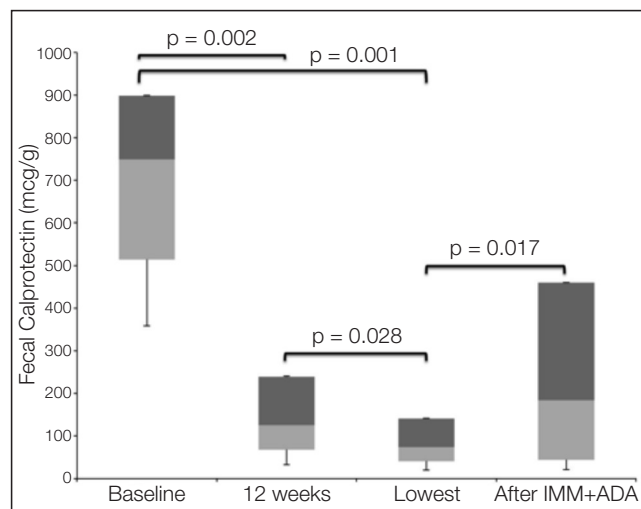


Fig. 1. Changes in fecal calprotectin (FC) levels. Baseline: Before ADA treatment; Lowest: Lowest FC level during combined therapy; After IMM+ADA: FC levels when combined therapy was discontinued; w: Weeks; IMM: Immunomodulators.

disease was satisfactory in all cases, the abscesses were drained and the simple perianal fistula closed after ADA treatment.

Surgery

A total of 4 patients (25 %) had 6 surgical procedures before or during the study period. Prior to adalimumab, 3 had surgery (1 bowel resection and 2 abscess drainages), and after ADA was started 2 underwent surgery. The two patients requiring surgery were 13.4 and 13.6 years of age, were undergoing maintenance treatment with azathioprine, and were experiencing moderate-to-severe exacerbation. Radiological studies (ultrasound and magnetic resonance enterography) and endoscopy showed severely inflamed stenotic segments of 20 and 25 cm, respectively, of the terminal ileum. Based on these findings it was decided to initiate ADA treatment prior to surgery. At 12 weeks, both patients were in remission, FC levels had normalized, and the colonic inflammation, but not all the luminal ileal stenosis, had disappeared. At this point, surgery was performed without incident. No postsurgical recurrence has been observed in the follow-up period.

Adverse reactions

During the study, various adverse events were reported in 4 patients treated with ADA in monotherapy: Eczema of the retroauricular scalp and the perianal region, recurrent episodes of amaurosis fugax, tremor, depressive syndrome requiring pharmacological treatment and 1 episode of self-limiting alopecia areata. A 17-year-old patient with

severe atopic dermatitis, perianal CD, previously treated with azathioprine during 4 years, and loss of response to infliximab who was on ADA treatment (which had to be suspended on several occasions due to cutaneous abscesses requiring surgical drainage) developed a non-Hodgkin's lymphoma (non hepatosplenic T-cell lymphoma) after 4 years of ADA monotherapy. She has already finished the chemotherapy treatment and is doing well. A second patient presented with infection of a thyroglossal cyst during treatment with ADA. A third patient developed psoriasis of the trunk and scalp that did not require discontinuation of treatment. Mild adverse reactions were also observed locally at the injection site.

DISCUSSION

In our study, steroid-free clinical response was achieved in all 16 patients at week 12 and week 26 of treatment. This response rate is better than those reported by other authors (Table II). One explanation for the difference in results could be related to the duration of disease, which in our study was 1.4 years (IQR 0.5-3), well below that reported in other studies. Another possible explanatory factor is the percentage of patients in our study who were naïve to anti-TNF- α (75 %), which was much higher than those in other published studies. Other factors influencing the high response rate in our study may be the maintenance dose of 40 mg every 2 weeks used in all patients, regardless of bodyweight, a regimen very similar to that used in other studies (13,14,17).

In 2 patients, ADA was administered in spite of the presence of luminal stenosis. All stenotic lesions present an inflammatory component that could be controlled with an anti-TNF- α agent (28). This therapeutic approach, which may be considered controversial, can lead to improved postsurgical progression as it also improves the surgical area and reduces inflammatory activity in the remainder of the affected intestine.

FC is an excellent inflammatory marker and its levels have been found to correlate with the extent and severity of colon involvement in patients with CD (29), although the cut-off levels are not well standardized in IBD. In our study, a significant reduction in FC levels was seen at 12 weeks of treatment, with normalization of levels at

4.9 months of combined therapy. This reduction and normalization in some cases suggests mucosal healing, a fundamental objective of treatment in CD (30-32). Following suspension of the combined therapy, although the patients were in clinical remission, FC levels rose significantly, suggesting a possible synergistic effect of the combined therapy for mucosal healing.

In our series, 3 patients with a bodyweight over 40 kg received an induction regimen of 80 mg and then 40 mg. These patients in our study were the first at our hospital to be treated with ADA, at a time (2007-2008) in which experience with this agent in children was very limited and the CLASSIC I (33) clinical trial had only recently been published. Subsequently, the publication of new studies in adults –CLASSIC II (34), CHARM (35) and ADHERE (36)– and in children (Table II), together with the recent publication of IMAGINE 1 (20) provide clinical evidence for starting with an induction regimen of 80 mg then 40 mg in patients with a bodyweight under 40 kg and of 160 mg then 80 mg in patients with a bodyweight of 40 kg or more.

Although the sample size in our case series is small compared to other published studies (14,17,20) the follow-up period we present for patients receiving ADA treatment is the longest of any published study. The appearance of a side effect as severe as a case of non-Hodgkin's lymphoma at 4 years of treatment with ADA should be kept firmly in mind, and monitoring of these patients should be thorough and continuous. Although controversial, inflammatory bowel disease in itself is not considered to increase the risk of lymphoma compared with the general population, previously published data suggest that thiopurine and anti-TNF- α may increase the relative risk of lymphoma several-fold (37,38).

This study's main limitation is the small sample size, essentially due to the fact that all patients were recruited from a single hospital. Nevertheless, our series consists of the longest follow-up of patients treated with adalimumab.

In summary, we have demonstrated that ADA can be an effective treatment for pediatric CD patients who develop loss of response to IFX or are naïve to biological treatment, as well as in patients with extensive CD and perianal disease. Treatment benefit should be weighed against side effects. Multicenter longitudinal studies with longer follow-up periods are required to determine the true efficacy and safety of long-term ADA treatment.

Table II. Published pediatric adalimumab studies to date

Study	n	Prior IFX	Disease duration (y)	Age (y)	Initial dosing used in mg (number of patients)	Number of ADA doses or treatment duration	% patients needed dose escalation	Follow-up (m)	Comments regarding response, remission and adverse events
Hyams, 2012 (20) IMAGINE 1	192	43 %	NA	13.5 ± 2.47 13.7 ± 2.52	160/80 (≥ 40 kg) 80/40 (< 40 kg)	52 w ^a	111/188 (59 %)	52 w	Response (PCDAI): 82 % (4 w); 53.7 % (26 w); 35 % (52 w) Remission (PCDAI): 52 % (4 w); 33.5 % (26 w); 28.2 % (52 w) Higher remission and response rates in the high-dose group Patients previously treated with infliximab had a lower response to adalimumab therapy
Rusell, 2011 (14)	72	94 %	4.3 y (0.1-10.5)	14.8 (6.1-17.8)	160/80 (3), 80/40 (41), 24 mg/m ² (16), others (10)	19 doses (IQ, 3-103) 1,662 doses in 70 patients	24/68 (35 %)	0.8 (0.1-2.8)	61 % remission at any point in the study period (PCDAI) Remission: 24 % (4 w); 58 % (6 m); 41 % (12 m) Response: 50 % (4 w); 20 % (6 m); 41 % (12 m) 30 % loss of response after 0.4 y (0.1-1.2) 2 deaths: Parenteral nutrition via central line, ADA + IMM
Martin de Carpi, 2010 (13)	4	0 %	0.67 y (0.23-1.06)	13.95 ± 2.57	160/80 Maintenance dose: 40 mg eow	41 doses (24,2-42,7) 144 doses en 4 patients	0 %	19.5 (11-20)	Remission (PCDAI): 100 % after first dose 100 % at the end of the follow-up period No adverse events reported
Rosenbach, 2010 (15)	14	100 %	3.9 y (1.2-7.1)	13.4 (1.9-19.1)	1 st dose: 160 mg/1.73 m ² 1 st dose: 160 mg/1.73 m ² 2 nd dose: 80 mg/1.73 m ² Maintenance dose: 40 mg/1.73 m ²	10 m (IQ, 12-19)	8/14 (57 %)	1.2 (0.8-2)	Complete response (Harvey-Bradshaw score): 50 % Partial response: 50 %
Viola, 2009 (16)	23	61 %	4.3 ± 3.5 y	16.1 (9-20)	160/80 (> 40 kg) (13) 80/40 (< 40 kg) (8)	48 w	14/23 (61 %)	48 w	Remission (PCDAI): 36.3 % (2 w); 60.8 % (4w); 30.5 % (12 w); 50 % (6 m); 65.2 % (12 m) Response (PCDAI): 87 % (2 w); 88 % (4 w); 70 % (12 w); 86 % (6 m); 65.2 (12 m)
Rosh, 2009 (17) RESEAT	115	95 %	4.7 ± 2.8 y	15.8 ± 3.0	160/80 (22), 80/40 (51), 40/40 (17), others (25)	NA	29/115 (25 %)	0.9 ± 0.7	Remission (PCDAI): 32 % (3 m); 40 % (6 m); 83 % (12 m) Response (PCDAI): 84 % (3 m); 100 % (6 m); 92 % (12 m) Remission (PGA): 32 % (3 m); 43 % (6 m); 49 % (12 m) Response (PGA): 65 % (3 m); 71 % (6 m); 70 % (12 m)
Wyneski, 2008 (18)	14	100 %	3.6 y (0.6-15.8)	17.9 (10.3-21.8)	80/40 (11), 40 (1), 80 (1), 40/20 (1), 160/80 (1)	272 doses in 14 patients	2/14 (14 %)	0.5 (0.2-1.2)	Response basis on weaned from steroids: Complete: 50 %; partial: 14 %; no response: 36 %.
Noe, 2008 (19)	7	100 %	NA	16 (16-17)	80/40 (3), 40 (3), 80 (1)	NA	2/7 (28 %)	1.8 (0.8-3.5)	Response (PCDAI): 85 %. 5 patients were on clinical remission (PCDAI < 10) when adalimumab was started

m: Months; y: Years; NA: Not available; PCDAI: Pediatric Crohn Disease Activity Index; PGA: Physician Global Assessment; IMM: Immunomodulators; ADA: Adalimumab. ^a124 of the 192 patients previously included completed the study (65 % of the patients).

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