

ORIGINAL PAPERS

Adalimumab induction and maintenance therapy for Crohn's disease. An open-label study

N. López Palacios, J. L. Mendoza, C. Taxonera, R. Lana¹, M. Fuentes Ferrer² and M. Díaz-Rubio

Unit of Inflammatory Bowel Disease. Departments of the Digestive Tract, ¹Internal Medicine and ²Statistics. Hospital Clínico San Carlos. Madrid, Spain

ABSTRACT

Background: adalimumab has been shown in placebo-controlled clinical trials and uncontrolled studies to be effective in luminal and perianal fistulizing CD.

Objective: to evaluate the efficacy and safety of adalimumab for induction and maintenance therapy in CD.

Methods: twenty-two patients with CD treated with adalimumab (16 for luminal disease and 6 for active perianal fistulizing disease) were included. Twenty-one patients had previously received IFX. All patients received induction therapy with 160 mg s.c. at week 0, and 80 mg s.c. at week 2. Responders received maintenance therapy with 40 mg s.c. every 14 days. Response was assessed at 4 weeks after the initial dose, and classified as remission, partial response, or non-response.

Results: after induction, 25% of patients with luminal disease had a complete remission, and 56.3% had a partial response. Clinical response was maintained in 71.6% of patients at 1 year, in 53.7% at 18 months, and in 35.8% at 48 months. No differences in response were observed between patients with hypersensitivity reactions or loss of response to IFX.

All patients with perianal fistulizing disease (n = 6) had been previously treated with IFX. After induction 16.7% entered remission, and 66.7% had a partial response. All patients maintained remission or response over time, with a median follow-up of 15 months.

Conclusions: adalimumab is an effective and safe treatment for the induction and maintenance of response in luminal and perianal fistulizing CD. These results confirm that the findings obtained in controlled clinical trials are reproducible in clinical practice.

Key words: Adalimumab. Maintenance therapy. Crohn's disease. Luminal. Perianal fistulizing disease.

RESUMEN

Introducción: el adalimumab ha demostrado, en ensayos clínicos controlados con placebo y en estudios no controlados, ser efectivo en la EC luminal y fistulosa perianal.

Objetivo: evaluar la eficacia y seguridad del adalimumab como tratamiento de inducción y mantenimiento en la EC.

Metodología: se incluyeron 22 pacientes con EC tratados con adalimumab (16 por enfermedad luminal y 6 por enfermedad fistulosa perianal activa). Veintiún pacientes habían recibido previamente IFX. Se realizó tratamiento de inducción con 160 mg s.c. en la semana 0 y 80 mg s.c. a las 2 semanas. Los respondedores recibieron 40 mg s.c. cada 14 días como tratamiento de mantenimiento. Se valoró la respuesta a las 4 semanas de la dosis inicial, y se clasificó la respuesta como remisión, respuesta parcial o ausencia de respuesta.

Resultados: tras la inducción, el 25% de los pacientes con enfermedad luminal tuvieron remisión completa y el 56,3% respuesta parcial. La respuesta clínica se mantuvo al año en el 71,6% de los pacientes, a los 18 meses en el 53,7% y a los 48 meses en el 35,8%. No se objetivaron diferencias en la respuesta entre pacientes que presentaron reacciones de hipersensibilidad o pérdida de respuesta a IFX.

Todos los pacientes con enfermedad fistulosa perianal (n = 6) habían recibido previamente tratamiento con IFX. Tras la inducción un 16,7% entran en remisión y un 66,7% presentan respuesta parcial. Todos los pacientes mantienen remisión o respuesta en el tiempo con una mediana de seguimiento de 15 meses.

Conclusiones: el adalimumab es un tratamiento eficaz y seguro en la inducción y mantenimiento de la respuesta en la EC luminal y fistulosa perianal. Estos resultados confirman que los hallazgos obtenidos en los ensayos clínicos controlados son reproducibles en la práctica clínica diaria.

Palabras clave: Adalimumab. Tratamiento de mantenimiento. Enfermedad de Crohn. Luminal. Enfermedad fistulosa perianal.

López Palacios N, Mendoza JL, Taxonera C, Lana R, Fuentes Ferrer M, Díaz-Rubio M. Adalimumab induction and maintenance therapy for Crohn's disease. An open-label study. *Rev Esp Enferm Dig* 2008; 100: 676-681.

Received: 26-02-08.

Accepted: 15-07-08.

Correspondence: Natalia López Palacios. C/ Carboneras, 15, 1º C. 28047 Madrid, Spain. email: natalia.lopa@gmail.com

INTRODUCTION

Adalimumab is a fully human recombinant IgG1 monoclonal antibody that binds with high affinity and specificity to both soluble and membrane-bound tumor necrosis factor alpha (TNF α) forms (1,2). Recently, adalimumab has been shown to be effective as induction therapy in moderate to severe Crohn's disease (CD) (3,4), and as therapy for maintenance of remission (3,5). It has also been shown to be effective in anti-TNF α -naïve patients (3) and in patients with loss of response or intolerance to infliximab (IFX) (6).

TNF α is proinflammatory cytokine implicated in the pathogenesis of inflammatory bowel disease (IBD). The first anti-TNF α agent that showed efficacy in luminal or fistulizing CD was IFX (7,8), a chimeric anti-TNF α monoclonal antibody. IFX has a 25% murine fraction, however, which has been associated with the development of immunogenic reactions in 30% of patients (9). The presence of anti-infliximab antibodies (ATIs) has been associated with loss of response to this drug and the occurrence of acute and delayed hypersensitivity reactions that have sometimes required therapy discontinuation (7). ATIs appear more frequently when IFX is used episodically or without concomitant immunosuppression (10). Loss of response to IFX is a complex problem, which leaves room for the development of new anti-TNF α drugs that lack cross-immunogenicity with IFX, including adalimumab among others. This fully human anti-TNF α antibody is immunogenic (4,5), but the role that anti-adalimumab antibodies have in loss of response and potential hypersensitivity reactions is unknown.

OBJECTIVE

The aim of this study was to assess the efficacy and safety of adalimumab therapy in a series of consecutive CD patients from a single center.

MATERIAL AND METHODS

A descriptive, longitudinal, open-label, retrospective, follow-up efficacy and safety study in CD patients treated with adalimumab.

Twenty-two patients with CD diagnosed by clinical, endoscopic, and histological criteria and who were treated with adalimumab at *Hospital Clínico San Carlos*, Madrid, between March 2004 and December 2007 were consecutively included.

Of the 22 patients, 8 were men and 14 were women, with a median age at diagnosis of 23.7 years (IQR: 15.2-30.5), and a median follow-up since diagnosis of 13.1 years (IQR: 6.5-18.7). Twenty-one patients had previously received IFX (Table I). Sixteen patients re-

Table I. Baseline characteristics of patients with CD who received adalimumab

Variables	Results
Sex	
Male/female	8:14
Age at diagnosis (years)	23.71 (IQR: 15.24-30.53)
Time from diagnosis to start of adalimumab therapy (years)	13.08 (IQR 6.53-18.69)
<i>Montreal Classification</i>	
<i>Age at diagnosis</i>	
0-15 years	6 (27.3%)
16-40 years	15 (68.2%)
≥ 40 years	1 (4.5%)
<i>Location</i>	
Ileum	6 (27.3%)
Colon	4 (18.2%)
Ileocolon	10 (45.5%)
Upper gastrointestinal	2 (9.1%)
<i>Behavior</i>	
Inflammatory	6 (27.3%)
Strictureing	2 (9.1%)
Penetrating	5 (22.7%)
Inflammatory + perianal	4 (18.2%)
Strictureing + perianal	1 (4.5%)
Penetrating + perianal	4 (18.2%)
<i>Harvey-Bradshaw Index median</i>	
median [range] luminal group (n = 17)	10 (IQR 7-12.5)
<i>Associated perianal involvement</i>	
n (%)	9 (41%)
<i>Prior surgery</i>	
n (%)	15 (68.2)
<i>Resection</i>	
Perianal surgery	8 (36.4%)
<i>Concomitant medication: Immunosuppressants</i>	
n (%)	18 (81.8%)
<i>Anti-TNF treatment n (%)</i>	
Anti-TNF naïve	1 (4.5%)
Infliximab treatment	21 (95.5%)
Episodic administration	4 (18.19%)
Reason for medication discontinuation	
Loss of response	8 (36.38%)
Hypersensitivity reaction	8 (36.38%)
Loss of response + hypersensitivity	1 (4.55%)

ceived adalimumab for luminal disease and 6 for active perianal fistulizing disease (Table II).

All patients received induction therapy with 160 mg adalimumab s.c. at week 0 followed by 80 mg s.c. at week 2. Responders received maintenance therapy with 40 mg s.c. every 14 days. In the event of loss of respon-

Table II. Baseline characteristics of patients with CD who received adalimumab by indication

Variables	Luminal CD	Perianal fistulizing CD
Number of patients	16	6
Median age at diagnosis (IQR)	21.27 (15.23-27.34)	35.32 (21.46-40.23)
Time from diagnosis to treatment	11.21 (6.18-15.52)	19.35 (9.11-32.23)
Sex: male/female	5:11	3:3
Montreal Classification n (%)		
Age		
0-15 years	5 (31.3%)	1 (16.7%)
16-40 years	11 (68.8%)	4 (66.7%)
> 40 años	-	1 (16.7%)
Location		
Ileum	3 (18.8%)	3 (50%)
Colon	3 (18.8%)	1 (16.7%)
Ileocolon	8 (50%)	2 (33.3%)
Upper gastrointestinal	2 (12.5%)	-
Behavior		
Inflammatory	6 (37.5%)	-
Stricturing	2 (12.5%)	-
Penetrating	5 (31.3%)	-
Inflammatory + perianal	1 (6.3%)	3 (50%)
Stricturing + perianal	1 (6.3%)	-
Penetrating + perianal	1 (6.3%)	3 (50%)
Median HBI (IQR)	9.50 (7-12.75)	-
Surgery n (%)	9 (56.3%)	6 (100%)
Surgical resection n (%)	7 (43.8%)	5 (83.3%)
Concomitant medication: immunosuppressant	13 (81.3%)	5 (83.3%)
Infliximab	15 (93.8%)	6 (100%)
Loss of response	4 (25.01%)	4 (66.7%)
Hypersensitivity reaction	6 (37.52%)	2 (33.3%)
Loss of response + hypersensitivity reaction	1 (6.25%)	-
Episodic administration	4 (25.01%)	-

se the dosing interval was decreased to 40 mg s.c. every week. Adverse reactions to treatment during the follow-up period were collected and recorded in the medical history.

Loss of response to IFX was defined as a lack of response after decreasing the interval between infusions to less than 6 weeks, or after increasing the dose to 10 mg/kg body weight. An acute hypersensitivity reaction to IFX was defined as the presence of any of the following signs or symptoms during or within 2 hours of IFX infusion: hypotension, urticaria, skin rash, edema (face, hand, lip or mouth), headache, or dyspnea. A delayed hypersensitivity reaction was defined as the presence of at least 2 of the following signs

or symptoms occurring within the first days after infusion: rash, fever, myalgia, or polyarthralgia.

Episodic IFX administration was defined as the administration of this drug on demand according to when the patient had a relapse of symptoms.

A medical history was obtained for all patients, including a history of contact with tuberculosis, tuberculin Mantoux skin test, chest radiograph, antinuclear antibodies, anti-double-stranded DNA, and VHB and VHC serology, with negative results on all tests.

Clinical follow-up was performed by periodic visits to the IBD unit, every 15 days for the first 2 months, once a month for the next 3 months, and then every 2 months until the end of follow-up. Response to induction was assessed at 4 weeks from the initial dose of adalimumab.

Response was classified as remission, partial response, or nonresponse. Response in luminal CD was assessed by the Harvey-Bradshaw index (HBI) (11). Remission was defined as the cessation of abdominal pain and diarrhea, and improvement of general condition with an HBI of 4 points or less, and partial response as a reduction in HBI of 4 or more points from baseline. All other situations were considered nonresponse to treatment.

Response in perianal fistulizing disease was assessed by number of fistulas, fistular drainage, and presence or absence of pain in the perianal area. Remission was defined as the total closure of all fistulas with cessation of fistular drainage, and partial response as a decrease in the number, form, drainage, or discomfort associated with fistulas.

All patients signed an informed consent to receive treatment with adalimumab under compassionate use.

Statistical analysis

Qualitative variables are presented with their distribution of frequencies. Quantitative variables are summarized by their mean and standard deviation (SD), or their median and interquartile range (IQR) for variables without a normal distribution.

The association between qualitative variables was assessed with the χ^2 test or Fisher's exact test when more than 25% of the expected values were smaller than 5. Survival functions were estimated by the Kaplan-Meier method to evaluate the reason (perianal or inflammatory) for the study of the event "response to treatment". Plots are presented of the estimated curves, with the median values of the distribution with their confidence interval. A comparison of the survival functions of the different subgroups was done using Breslow's exact test.

In all hypothesis comparisons, the null hypothesis was rejected with a type 1 or α error of less than 0.05. Statisti-

cal analyses were performed using SPSS version 15.0 for Windows.

RESULTS

Efficacy of adalimumab therapy

Induction therapy in luminal disease

At week 4, of all 16 patients with luminal disease who received induction therapy with adalimumab 4 patients (25%) achieved remission and 9 patients (56.3%) had a partial response. Early discontinuation of induction therapy was necessary in one patient who required surgery for bowel obstruction.

Of all 15 patients previously treated with IFX, 3 patients (20%) experienced remission and 9 patients (66.7%) had a partial response. Six of these patients had previously had hypersensitivity reactions to IFX, 4 had experienced loss of response, 1 had shown loss of response and hypersensitivity, and 4 had received episodic IFX treatment.

Induction therapy in perianal fistulizing disease

At week 4, of all 6 patients with active perianal fistulizing disease, 1 patient (16.7%) entered remission and 4 patients (66.7%) had a partial response. All patients had previously received IFX (4 patients belonged to the loss of response group and 2 to the hypersensitivity reaction group).

Maintenance therapy in luminal disease

Thirteen patients (twelve of them previously treated with IFX) continued with maintenance therapy, with a median follow-up of 12.6 months (IQR 4.6-16.8). The percentage of patients who maintained response at 6 months was 81.8% (95% CI 45-95). Response was maintained at 12 months in 71.6% (95% CI 35-90), at 18 months in 53.7% (95% CI 15-81%), and at 24 months in 35.8% (95% CI 5-69%) (Table III and Fig. 1).

Table III. Percentage of patients with luminal CD who maintained response or remission over time

Time	Percentage of response/remission	
	%	95% CI
6 months	81.8	45-95
12 months	71.6	35-90
18 months	53.7	15-81
24 months	35.8	5-69

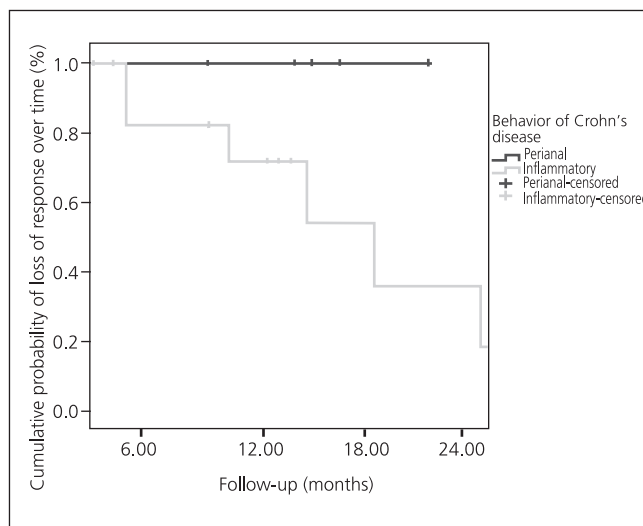


Fig. 1. Cumulative probability of loss of response over time.

Six patients (27.3%) required a decrease in their dosing interval after a median follow-up of 9.2 months (IQR 3.1-13.4). Four patients maintained response with 40 mg adalimumab weekly, whereas the other two patients finally lost response at 2 months after decreasing the dosing interval.

Maintenance therapy in perianal fistulizing disease

Five patients (3 with loss of response to IFX and 2 with hypersensitivity reactions) continued with maintenance therapy, with a median follow-up of 15.2 months (IQR 11.7-19.4). All patients maintained remission or response over time.

Tolerance and adverse effects of adalimumab therapy

Seven patients (31.8%) developed side effects. Four of them had local reactions in the injection site that did not require drug discontinuation. Early discontinuation of treatment was necessary in one patient due to a CD complication: a bowel obstruction that required surgery. Another patient developed acute nasopharyngitis that resolved with conventional antibiotic treatment.

DISCUSSION

Adalimumab has been shown in placebo-controlled clinical trials (3-6) and uncontrolled studies (12-16) to be effective as induction and maintenance therapy for

luminal and perianal fistulizing CD. Our study shows that adalimumab can be effective in clinical practice for patients with CD who have lost response or become intolerant to IFX.

The first data published on the efficacy of adalimumab for luminal CD in patients who had previously received IFX are from open-label uncontrolled studies (12-16). In the study of Sandborn et al. (16) with induction doses of 80/40 mg, remission was obtained in 12% of patients and partial response in 41%. In the study by Hinojosa et al. (13) with induction doses of 160/80 mg, the remission and response rates obtained were 42% and 33%. The data obtained in open-label studies were confirmed in the GAIN clinical trial (6), a double-blind, multicenter, placebo-controlled trial of 325 CD patients with prior loss of response or intolerance to IFX. Induction therapy was performed with 160/80 mg and response was assessed at 4 weeks: 21% of patients entered in remission and 38% had a partial response. In the abovementioned studies no differences were found in efficacy with regard to the reason leading to IFX discontinuation. In our series, the remission and partial response rates obtained were 20 and 66.7%, respectively, data with only relative value due to the obvious limitations of our study (small sample size and lack of control group).

Adalimumab has also shown its efficacy in maintaining clinical response when compared to placebo in controlled studies such as the CLASSIC II trial (3, 5), and in open-label studies (12). The CHARM trial (3) was a controlled clinical trial with an open-label phase for both anti-TNF α naïve and experienced patients. All patients (n = 499) received induction therapy with 80/40 mg, and were subsequently randomized to receive adalimumab 40 mg every other week, 40 mg weekly, or placebo. At week 56, the remission rates for patients in the adalimumab weekly and every other week groups were 47% and 41%, respectively, with no differences between both regimens. The CHARM trial did not find differences in remission and response rates depending on whether patients had previously received IFX or otherwise. In our study, 72% of patients with luminal disease maintained response at 48 weeks and 54% at 72 weeks, which confirms the efficacy of adalimumab as maintenance therapy in this indication. In 27% of patients, a decreased dosing interval was required to maintain response.

With regard to data available on perianal disease in the CLASSIC I trial (4) (perianal and enterocutaneous fistulizing disease), no differences in efficacy were observed between adalimumab and placebo. In the previously mentioned CHARM trial (3), a subanalysis was performed for 130 patients (15.2%) who had perianal or enterocutaneous fistulas. At 56 weeks, a total closure of perianal fistulas occurred in 30% of patients in the adalimumab group versus 13% in the placebo group (p = 0.043). In the uncontrolled study by Hinojosa et al. (13), 64% of 22 patients with perianal fistulizing disease had remission (23%) or partial response (41%) at week 4. At week 20, half of patients

maintained remission (12.5%) or partial response (37.5%). In our study, 5 of 6 patients treated for perianal fistulizing disease experienced remission or response with induction therapy and all maintained the response over time, with a median follow-up of 15 months.

A recent single-center study with a similar number of patients as compared to ours confirmed the efficacy and safety of adalimumab in CD refractory to conventional treatment and with prior IFX administration (17).

The safety of adalimumab in CD (3-6) is similar to that observed with other anti-TNF α agents (7,8) and in studies conducted in rheumatoid arthritis (18). In our series, side effects were mild and well tolerated, and the only serious effects requiring treatment discontinuation were related to poor disease control (bowel obstruction). No patient in our group had severe infection or hypersensitivity reactions to the drug.

With the obvious limitations of the study (lack of control group, limited number of patients), we can state that the results obtained in our series confirm that adalimumab is effective and safe for the treatment of CD in the context of clinical practice.

REFERENCES

- Papadakis KA. Adalimumab for the treatment of Crohn's disease. *Expert Rev Clin Immunol* 2006; 2(1): 11-5.
- Martinez-Montiel MP, MT Munoz-Yague. Biologic therapies for chronic inflammatory bowel disease. *Rev Esp Enferm Dig* 2006; 98(4): 265-91.
- Colombel JF, Sandborn WJ, Rutgeerts P, 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.
- Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; 130(2): 323-33.
- Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II Trial. *Gut* 2007; 56: 1232-9.
- Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab Induction Therapy for Crohn's disease previously treated with infliximab. A randomized trial. *Ann Intern Med* 2007; 146(12): 829-38.
- Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I trial. *Lancet* 2002; 359(9317): 1541-9.
- Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease: the ACCENT II trial. *N Engl J Med* 2004; 350(9): 876-85.
- Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; 348(7): 601-8.
- Vermeire S, Noman M, van Assche G, et al. The effectiveness of concomitant immunosuppressive therapy to suppress formation of antibodies to infliximab in crohn's disease. *Gut* 2007; 56(9): 1226-31.
- Best WR. Predictig the Crohn's disease activity index from the Harvey-Bradshaw Index. *Inflamm Bowel Dis* 2006; 12(4): 304-10.
- 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. *Aliment Pharmacol Ther* 2007; 25(6): 675-80.

13. Hinojosa J, Gomollon F, García S, 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. *Aliment Pharmacol Ther* 2007; 25(4): 409-18.
14. Papadakis KA, Shaye OA, Vasiliauskas EA, et al. Safety and efficacy of adalimumab (D2E7) in Crohn's disease patients with an attenuated response to infliximab. *Am J Gastroenterol* 2005; 100(1): 75-9.
15. Youdim A, Vasiliauskas EA, Targan SR, et al. A pilot study of adalimumab in infliximab-allergic patients. *Inflamm Bowel Dis* 2004; 10(4): 333-8.
16. Sandborn WJ, Hanauer S, Loftus EV Jr, et al. An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. *Am J Gastroenterol* 2004; 99(10): 1984-9.
17. Ho GT, Smith L, Aitken S, Lee HM, Ting T, Fennell J. The use of adalimumab in the management of refractory Crohn's disease. *Aliment Pharmacol Ther* 2008; 27(4): 308-15.
18. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; 65(7): 889-94.