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Observational study on the efficacy of adalimumab for the treatment of ulcerative colitis and predictors of outcome

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Abstract

Background: Information on efficacy and predictors of response to adalimumab in ulcerative colitis (UC) clinical practice is limited.
Aim: Assessment of response to adalimumab and its predictors in an observational cohort study.
Methods: Retrospective cohort study based on data obtained from ENEIDA registry. All patients diagnosed with UC treated with adalimumab were included. Response to adalimumab was

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evaluated at weeks 12, 28, and 54 according to the partial Mayo score, and requirement of colectomy until end of follow-up.
Results: 48 patients with UC treated with adalimumab were included; 39 (81.3%) had previously received infliximab. Response rates at weeks 12, 28 and 54 were 70.8%, 43.2% and 35% respectively. Response to prior treatment with infliximab was the only predictive factor of response to adalimumab at week 12, which was obtained in 90% of infliximab remitters, 53.8% of responders and 33.3% of primary non-responders ($p=0.01$).
Colectomy was required in 11 patients (22.9%), after a mean time of 205 days. The only clinical independent predictor of colectomy was non-response to adalimumab at week 12: colectomy rates were 5/34 (14.7%) in responders and 6/14 (42.9%) in non-responders ($p=0.035$), time free of colectomy was significantly reduced in non-responders ($p=0.01$). Adalimumab withdrawal due to adverse events occurred in 4.2% of patients.
Conclusion: This study shows that adalimumab is an effective treatment in patients with UC. If used as a second anti-TNF, previous achievement of remission with the first anti-TNF predicts response, and failure to achieve response at week 12 predicts colectomy.

1. Introduction

Ulcerative colitis (UC) can be adequately treated with 5-aminosalycilic acid preparations in about half of the patients. However, those requiring corticosteroids at any point face a severe disease course over time, with high requirements of immunosuppressant treatment and colectomy[1] and high cost for the healthcare system.[2] Treatment with the anti-TNF antibody infliximab has proven effective for induction and maintenance of remission in moderate to severe UC[3] as well as in steroid refractory severe UC,[4] resulting in a reduction on the requirement for colectomies.[3] More recently the efficacy of a second anti-TNF antibody, adalimumab, a fully human IgG1, for induction and maintenance of remission in UC has been demonstrated in two phase III trials.[5,6] Addition of this drug to the limited therapeutic armamentarium available for UC expands treatment choices of anti-TNF therapy to a subcutaneous drug, which may be particularly advantageous for patients with difficult venous access, and offers an alternative for patients loosing response to infliximab.

Since the publication of the results of the first adalimumab randomized controlled trials in UC,[5] some concerns raised on the efficacy of the drug that might be related in part to dosing and in part to inclusion of a proportion of cases with previous failure to infliximab. In this regard, observational data on the use of adalimumab for treatment of UC derived from clinical practice may be relevant for positioning the drug in the therapeutic algorithm of UC. Prior observational studies suggest that adalimumab is efficacious for treatment of UC,[7–10] even in the difficult to treat population with previous failure to infliximab.

In the current observational study we analyzed the data of the Spanish inflammatory bowel disease (IBD) database on the use of adalimumab in UC previous to marketing approval. The primary objectives of the present study were to determine the efficacy of adalimumab for the induction and long term maintenance of remission in UC and to determine the need for colectomy after adalimumab treatment. Secondary objectives included the identification of predictors of clinical response to adalimumab and predictors of colectomy, based on demographic data, disease characteristics, concomitant medication and previous response to infliximab; to assess the need for dose escalation and its efficacy, and to assess adalimumab safety profile in clinical practice.

2. Patients and methods

This is a multicenter retrospective cohort study. Demographic, clinical and therapeutic data were obtained from the multicenter Spanish database of patients with IBD ENEIDA (Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales). This project is a large prospectively maintained database that captures clinical response to IBD therapies, adverse events, and surgeries. The use of the database was approved by the ethics committee of each participating center, and the study was approved by the committee of the Spanish IBD organization (GETECCU: Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa) in 2009. All patients included in ENEIDA signed an informed consent authorizing the use of their clinical data for research purposes. For the sake of data completeness and accuracy, data on the patients included was double-checked and updated by each participating center.

Patients diagnosed with UC who had received at least one dose of adalimumab between June 2009 and May 2011, and with a minimum follow-up of 12 weeks were included. Demographic data, disease characteristics, prior and concomitant therapies, and clinical data at the time of adalimumab initiation and response, as well as adverse events were registered. Disease extent was defined according to the Montreal classification. Clinical activity was evaluated according to the Mayo score (remission defined as Mayo score ≤ 2 with no individual subscore >1; response defined as decrease in Mayo score ≥ 3 points and $\geq 30\%$ from baseline and a decrease in the rectal bleeding subscore ≥ 1 or an absolute rectal bleeding subscore of 0 or 1).[3] The partial Mayo score was used when endoscopy was not available; the criterion for remission was a score ≤ 1, and the criterion for response was the same as for the full Mayo score. The therapeutic efficacy was evaluated at weeks 12, 28, and 54. Need for colectomy at any time since the administration of the first dose was recorded.

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All data were analyzed using statistical package SPSS version 15.0 (SPSS, Inc., 1989–2006, Chicago, IL). Univariant and subsequently binary logistic regression analysis were applied for those variables with statistical significance in order to determine independent predictors of response and colectomy. Kaplan–Meyer curves for survival time free of colectomy were calculated and compared using the log-rank test; independent predictors of survival time free of colectomy were analyzed using the Cox regression model. Data are expressed as median and inter-quartile range (IQR) for quantitative variables where possible; mean values are provided when calculation of the median was not possible in survival time analyses. Percentage is used for qualitative variables. Odds-ratio and 95% confidence interval were calculated where appropriate. Statistical significance was set at $p<0.05$.

3. Results

3.1. Clinical characteristics of patients

From 4735 patients diagnosed with UC and registered in the ENEIDA project a total of 48 patients from 13 different centers had received at least one dose of adalimumab. The demographic and clinical characteristics of patients included are shown in Table 1. A majority of patients were young men with extensive colitis. Median disease duration was 4.9 years (IQR 2.3–9.5). The majority of patients (95.8%) had been previously treated with immunomodulators and 81.3% with infliximab (Table 2). Assessment of previous response to infliximab was categorized as remission in 51.3%, response in 33.3% and primary non-response in 15.4%. All initial responders to infliximab received adalimumab after a documented loss of response to the drug. When adalimumab therapy was started 22.9% of patients received steroids and 72.9% received thiopurines as concomitant therapy (Table 3). The induction dose used was 160/80 mg in 93.7% of cases, and the initial maintenance dose was 40 mg eow. The median follow-up time since starting adalimumab was 44.7 weeks (IQR 17.9–79.4).

Table 1 Demographic characteristics of patients included (n=48).

Male (%)	29 (60.4%)
Family history of IBD	8 (16.7%)
Smoking	
Never	34 (70.8%)
Active	5 (10.4%)
Ex-smoker	9 (18.8%)
Age at diagnosis, mean (IQR)	32.5 (23.3–42.7)
Disease duration, mean (IQR)	4.9 (2.3–9.5)
Disease extension (%)	
Distal	8 (16.7)
Left-sided	7 (14.6)
Extensive	33 (68.8)
Extraintestinal manifestations (%)	
Peripheral arthropathy	10 (20.8)
Axial arthropathy	2 (4.2)
Skin	7 (14.6)
Ocular	2 (4.2)
Thrombosis	1 (2.1)
CRP mg/L, mean (SD)	26.5 (15.4)

Table 2 Previous treatments before starting adalimumab.

Steroids (%)	42 (87.5)
Response to steroids (%)	
Steroid dependence	25 (52.1)
Steroid refractory	20 (41.7)
Azathioprine/mercaptopurine (%)	46 (95.8)
Cyclosporine (%)	12 (25)
Infliximab (%)	39 (81.3)
Response to infliximab (%)	
Remission	20 (51.3)
Response	13 (33.3)
Primary non response	6 (15.4)

3.2. Therapeutic efficacy

3.2.1. Clinical response

Using a last observation carried forward analysis for treatment failures the patients responding to adalimumab therapy at weeks 12, 28 and 54, were 70.8% (34/48), 43.2% (19/44) and 35% (14/40) (Fig. 1); The proportion of patients achieving remission at these time points were 50% (24/48), 34.1% (15/44), and 30% (12/40). The decreasing denominators relate to censoring of responders, as loss of response that is not regained after drug intensification is considered as a treatment failure in all subsequent time points. In order to determine predictive factors of response to adalimumab at week 12, the variables analyzed included: age, sex, disease duration, previous and concomitant treatment with thiopurines, previous treatment with cyclosporine, concomitant steroid therapy, previous infliximab treatment and response, and baseline CRP. Both in the univariate and binary logistic regression analysis, the response to prior treatment with infliximab was the only predictive factor of response to adalimumab at week 12, which was obtained in 90% of remitters, 53.8% of responders and 33.3% of primary non-responders to infliximab ($p=0.01$) (Fig. 2). Patients who obtained remission under treatment with infliximab had an OR of 9.5 (CI 95%: 1.64–55.1) ($p=0.037$) for response to adalimumab at week 12 compared to those who had obtained response without remission or were primary non-responders.

All patients were intended to be treated with induction followed by maintenance with adalimumab. At the time of maximal follow-up (206 weeks) the proportion of patients persisting under adalimumab maintenance was 43.8%. The median time of treatment was 107 weeks (95% CI 9–205 weeks); Fig. 3 illustrates survival under adalimumab treatment. Escalation of adalimumab to weekly dosing was required in 37.5% of patients after a median time of 14.8 weeks (IQR: 10.6–32.3). After dose escalation 44% of patients achieved remission, 41.6% response, and 14.3% did not respond.

3.2.2. Colectomy

Colectomy was required in 11 patients (22.9%), after a mean time of 205 days. The only clinical independent predictor of colectomy was response to adalimumab at week 12 (Table 4):

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Table 3 Characteristics of patients responding and non-responding to adalimumab at week 12.

	Responders (n=34)	Non responders (n=14)	p
Age (years) (median) (IQR)	39.1 (IQR 33.5–51.8)	39.6 (33.6–45.1)	n.s.
Sex (male) (%)	58.8	64.3	n.s.
Smoking status (%)			n.s.
Never	25 (73.5)	9 (64.3)	
Active	3 (8.8)	2 (14.3)	
Ex-smoker	6 (17.7)	3 (21.4)	
Disease duration (years) (median) (IQR)	5.3 (2.4–9.9)	3.6 (1.3–9.5)	n.s.
Previous immunomodulators (%)	33 (97.0)	13 (93.9)	n.s.
Concomitant immunomodulators (%)	26 (76.5)	9 (64.3)	n.s.
Previous treatment with cyclosporine (%)	7 (20.6)	5 (35.7)	n.s.
Concomitant steroid therapy (%)	9 (26.4)	2 (14.3)	n.s.
Previous infliximab (%)	27 (79.4)	12 (85.7)	n.s.
Response to infliximab (%)			p=0.01
Remission	18 (66.7)	2 (16.7)	
Response	7 (25.9)	6 (50)	
Non-response	2 (7.4)	4 (33.3)	
CRP ml/L, mean (SD)	21.3 (21.7)	29.8 (20.3)	n.s.

colectomy rates were 5/34 (14.7%) in responders and 6/14(42.9%) in non-responders (p=0.035), with a significantly reduced time free of colectomy in non-responders (148 days, 95% CI 82.1–214.2) compared to responders (226 days, 95% CI 197.4–255.8) (p<0.01) (Fig. 4). Cox regression model confirmed response to adalimumab as the only independent predictive factor for survival time free of colectomy (p<0.01). Other variables including age, sex, smoking status, disease extension, concomitant use of immunomodulators, or use of steroids at initiation of adalimumab therapy, or response to previous infliximab, did not have a significant effect on the requirement of colectomy.

3.2.3. Adverse events

Significant adverse events were recorded in 6.3% of the patients (3/48), and included hair loss, psoriasis and herpes zoster; in the cases with psoriasis and herpes zoster the adverse event led to treatment discontinuation. The patient that developed psoriasis had previously suffered the same adverse event with infliximab. Adverse events considered non-significant by the clinician are not captured in the database.

4. Discussion

This observational study shows that adalimumab induces and maintains response and remission in active UC, in a population of patients in which the majority had previous loss of response to infliximab, and identifies that achieving remission with infliximab is an independent predictor of response to adalimumab. In addition, response to induction treatment significantly reduces the requirement of colectomy.

Response and remission rates observed in the current study are higher than those reported in previous observational studies. In a study including 10 patients with UC having lost response to infliximab, only 1 patient achieved remission and 3 responded at week 4.[8] Another study evaluated 20 patients, 35% of them naïve to biological therapy; at week 8 25% of patients had clinical response and 30% showed mucosal healing.[7] Finally a study including 30 patients that lost response to infliximab observed that at week 12, 60% of patients achieved clinical response and 26.7% achieved clinical remission.[9] Data from these observational studies, and also from the randomized double blind trials of adalimumab for treatment of UC,[5,6] show an increasing number of responders over the initial 12 week period of treatment, and

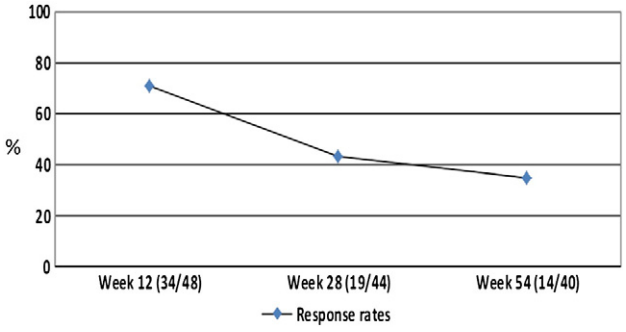

Figure 1 Response rates of ulcerative colitis patients to induction and maintenance treatment with adalimumab.

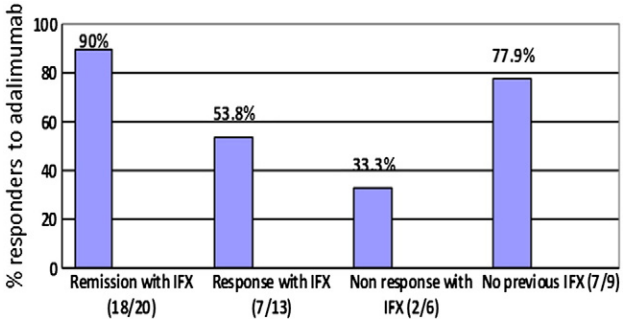

Figure 2 Response to adalimumab at week 12 according to previous response to infliximab.

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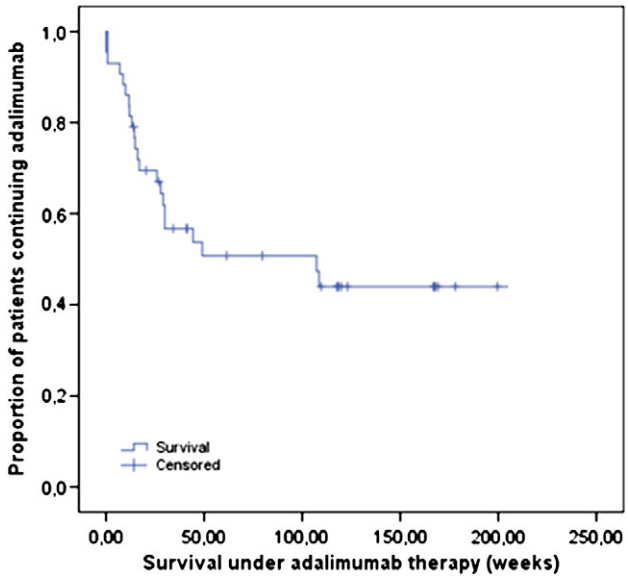

Figure 3 Proportion of patients persisting under adalimumab treatment.

the response and remission rates observed in the current study are in keeping with the data of the previous observational study evaluating patients at week 12.[9]

Higher rates of remission and response observed in the current study relative to the randomized controlled trials may have various explanations. The most relevant is probably that in the current study response was evaluated in the majority of patients without the use of endoscopy, the best objective measure of efficacy, using the partial Mayo score. Another important factor may be that after induction therapy, patients loosing response to adalimumab were dose-escalated to 40 mg weekly, and considered as responders if treatment intensification was effective to meet the criteria for response or remission. In addition, patients were not treated in the context of a controlled trial, thus possibly increasing the placebo effect in subjective variables. Finally, concomitant medications, including steroids, are adapted in clinical practice to obtain a maximum clinical benefit.

Our study provides relevant clinical information in choosing candidates for adalimumab therapy in the group of patients previously treated with infliximab. Patients that achieved remission, as opposed to response without remission or non-response to infliximab have a significantly higher probability of responding to adalimumab if used as the second anti-TNF drug. A negative result of the current study, but also relevant for clinical practice, is that other factors that have been linked to therapeutic responses to various agents in UC such as disease extension or elevation of serum biomarkers were not related with the response to adalimumab.

Adalimumab intensification was frequently needed (37.5%) in our patients, nevertheless, most of them responded (91.6%) and avoided colectomy (83.3%). These data are similar to those of another recent observational study with long-term follow-up,[9] in which intensification was required in 36.7% after 10 weeks and colectomy was avoided in 72.7%.

In the present study colectomy is globally avoided in 77.1% of patients, and non-unexpectedly, response to induction with adalimumab predicted a favorable outcome avoiding colectomy long term. This finding is also relevant for clinical practice. If the condition of the patient is acceptable, a period of 12 weeks should be allowed for adalimumab to provide therapeutic benefit, but in those not responding by week 12 serious consideration should be given to surgery before the condition of the patient deteriorates.

As for the safety aspects, the number of significant adverse events captured in the database is low (6.3%), although similar to the number of serious adverse events found in the published randomized controlled trial of adalimumab in UC,[5] occurring in 7.6%, 3.8% and 4% of patients in the placebo, adalimumab 80/40 and adalimumab 160/80 mg groups, respectively. Other

Table 4 Characteristics of patients requiring colectomy.

	Colectomy (n=11)	No colectomy (n=37)	p
Age (years) (median) (IQR)	40.2 (31.1–55.6)	39.6 (33.6–47.4)	n.s.
Sex (%) (male)	45.5	64.9	n.s.
Smoking status (%)			n.s.
Never	8 (72.7)	26 (70.3)	
Active	0	5 (13.5)	
Ex-smoker	3 (27.3)	6 (16.2)	
Disease duration (years) (median) (IQR)	5.9 (0.9–15.7)	4.9 (2.8–8.8)	n.s.
Previous immunomodulators (%)	10 (90.9)	36 (97.3)	n.s.
Concomitant immunomodulators (%)	6 (54.5)	29 (78.4)	n.s.
Previous treatment with cyclosporine (%)	4 (36.4)	8 (21.6)	n.s.
Concomitant steroid therapy (%)	4 (36.4)	7 (18.9)	n.s.
Previous infliximab (%)	10 (90.9)	29 (78.4)	n.s.
Response to infliximab (%)			n.s.
Remission	5 (50)	15 (51.7)	
Response	3 (30)	10 (34.5)	
No response	2 (20)	4 (13.8)	
Response to adalimumab week 12 (%)			0.035
Response	5 (45.5)	29 (78.4)	
No response	6 (54.5)	8 (21.6)	

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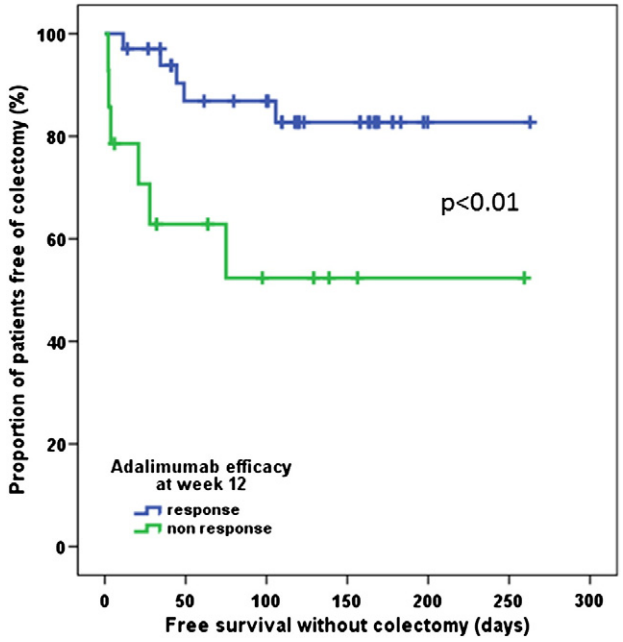

Figure 4 Survival time free of colectomy according to response to adalimumab on week 12.

observational studies including a reduced number of patients have reported higher rates of adverse events ranging from 30% (6/20)[7] to 38.5% (5/13).[8]

Some of the limitations of the study, including the assessment of therapeutic efficacy using the partial Mayo score, the heterogeneous use of concomitant medications, the significant placebo effect of knowing to be under active treatment, or the heterogeneity that may have governed surgery indications, have already been highlighted. As a consequence the recommendations of using the previous response to infliximab to choose candidates for adalimumab as a second anti-TNF, and considering the absence of response at week 12 as criteria for surgery should be taken with caution, and need confirmation in independent series of patients before these recommendations can be generalized.

Conflict of interest

JPG, PN, EG, XC and JP have received speaker and/or conultancy fees from Abbott and Merck Sharp & Dohme.

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