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**Adalimumab induction and maintenance therapy for
ulcerative colitis patients previously treated with
Infliximab.**

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6 Adalimumab induction and maintenance therapy for ulcerative colitis
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9 patients previously treated with Infliximab.

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54 Some aspects of the study were presented at UEGW/WCOG 2009, London and DDW
55 2010, New Orleans.
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3 ABSTRACT
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5 **Background:** The long term efficacy of adalimumab in ulcerative colitis (UC) patients
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7 is not well known.
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10 **Aim:** To evaluate the short- and long-term outcomes of adalimumab in UC patients
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12 previously treated with infliximab.
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15 **Methods:** Patients with active UC were treated with adalimumab after failure of other
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17 therapies including infliximab. Short-term clinical response and remission were
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19 assessed at weeks 4 and 12. The proportion of patients who continued on adalimumab
20
21 and the proportion of patients who remained colectomy-free were assessed over the long
22
23 term.
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26
27 **Results:** Clinical response at weeks 4 and 12 was achieved in 16 (53.3%) and 18 (60%)
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29 patients, respectively, and clinical remission was obtained in 3 (10%) and 8 (26.7%)
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31 patients, respectively. After a mean 48 weeks follow-up, 15 patients (50%) continued on
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33 adalimumab. Six patients (20%) required colectomy. All patients who achieved clinical
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35 response at week 12 were colectomy-free at long term.
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39 **Conclusions:** Adalimumab was well tolerated and induced durable clinical response in
40
41 many patients with otherwise medically refractory UC. Patients achieving clinical
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43 response at week 12 avoided colectomy over the long term.
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47
48 Running title: Adalimumab for ulcerative colitis.
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51 Key Words: Ulcerative colitis, adalimumab, infliximab, Tumor necrosis factor- α ,
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53 colectomy
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INTRODUCTION

Tumor necrosis factor- α (TNF) is an important cytokine involved in the pathogenesis of inflammatory bowel disease. While the role of TNF in ulcerative colitis has been subject of debate, several studies have shown that TNF does it plays a key role in the pathogenesis of the disease, and that targeting this cytokine is an effective therapy not only in Crohn's disease (1-4) but also in ulcerative colitis (5). Infliximab is effective in inducing and maintaining response in patients with moderate to severe ulcerative colitis (5), though it is immunogenic and repeated infusions can result in the development of antibodies. Patients positive for antibodies to infliximab are more likely to lose response or become intolerant as a result of acute infusion reactions or delayed hypersensitivity reactions to the drug (6).

Adalimumab, a fully human anti-TNF monoclonal antibody which do not share immunogenicity with infliximab, is effective and safe for inducing and maintaining remission in patients with Crohn's disease naïve to anti-TNF or who have responded to infliximab and then lost response or became intolerant (3,4). No controlled studies assessing the efficacy of adalimumab in ulcerative colitis have been published to date. Preliminary evidence suggests that adalimumab may have limited efficacy in patients with ulcerative colitis who previously responded to infliximab and then lost response or became intolerant (8,9), as well as in infliximab-naïve patients (10).

The present study describes our short and long-term clinical experience regarding the efficacy and safety of adalimumab when administered in the context of a multi-center compassionate use program in patients with ulcerative colitis who had previously received infliximab.

MATERIALS AND METHODS

Selection of patients

All consecutive patients with ulcerative colitis treated with adalimumab in the context of a compassionate use program after failure of other therapies including infliximab were enrolled in the study. Eligible patients included men and women who were at least 18 years of age and had a diagnosis of ulcerative colitis with disease duration of at least 6 months. All patients were previously treated with infliximab, since regulatory approval of adalimumab therapy in ulcerative colitis requires previous use of the anti-TNF agent already accepted in the Summary of Product Characteristics for that treatment indication. Reasons for infliximab discontinuation were considered by the investigators and could include loss of response, the development of intolerance (due to acute or delayed hypersensitivity reactions), or primary non-response to the drug. To be enrolled in the compassionate use program, patients were required to have active ulcerative colitis.

Based on the safety recommendations, patients were not eligible for inclusion in the program if they had active infection, previously untreated tuberculosis or concurrent tuberculosis, previous demyelinating disorders or malignancies, severe heart failure, previous colectomy, toxic megacolon, or any poorly controlled medical condition. Pregnant or breastfeeding female patients were not eligible.

Study design

The study consisted of an uncontrolled, open-label retrospective case series with adalimumab administered in a compassionate use program in 12 centers in Spain. Inclusion in this program was carried out in accordance with the regulations of the Spanish Ministry of Health. Written informed consent was obtained from all patients.

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3 The investigators prepared reports justifying the request for the inclusion of each
4 individual patient in the adalimumab compassionate use program. The reports included
5 the reason for infliximab discontinuation. Before infliximab discontinuation due to
6 infusion reaction, premedication and slowing of infliximab infusion was attempted
7 according to the protocol in each center. Escalation of infliximab dose was mandatory
8 before considering a patient as having lost response to the drug. The indication was
9 initially evaluated by the Departments of Clinical Pharmacology of the different
10 hospital centers, and the requests were likewise submitted to the Spanish Medicines
11 Agency for evaluation and final approval. Following approval, the medication
12 (adalimumab 40 mg in 0.8 ml; Humira®, Abbott Laboratories) was administered to the
13 patients in the hospital pharmacy of each center. Administration of the drug, including
14 the initial induction dose, the need for intensification and the timing of treatment
15 discontinuation were not pre-established, but rather left to the investigators' discretion.
16
17 The decision to either continue or interrupt immunosuppressant and the corticosteroid
18 tapering schedule is determined at each center. The patients received a prescription of
19 the planned adalimumab dose to be dispensed at the pharmacy of each center at weeks
20 0, 2 and 4, and then every two weeks. The adalimumab induction doses at weeks 0 and
21 2 were administered in the centers by specialized personnel, who, in turn, instructed the
22 patients on self-administration via the subcutaneous route. The subsequent doses were
23 administered by the patients themselves, or by specialized personnel in each center,
24 depending on patient preference. The investigators based their decisions about long-
25 term continuation with adalimumab over the long term, depending on whether clinical
26 benefit could be expected and assuming the absence of relevant side effects.
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29 The study was approved by the Ethics Committee of the leading center (Hospital
30 Clínico, Madrid, Spain).
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Outcomes and measurements

Patients were assessed for short-term clinical response at weeks 4 and 12, and thereafter, at least every four weeks. Disease activity was assessed at weeks 0, 4 and 12 using the partial Mayo score (scores ranging from 0 to 9). The primary endpoint was the induction of clinical response at week 12. Clinical response was defined as a 3-point decrease in the partial Mayo score or a decrease of $\geq 50\%$ in the partial Mayo score and a final partial Mayo score of ≤ 2 , with a drop in the rectal bleeding subscore of at least one point or an absolute rectal bleeding score of 0 or 1. Clinical remission was defined as a partial Mayo score of 0 or 1. Patients who showed clinical response or who were in clinical remission at weeks 4 and 12 were considered to show sustained clinical response or to be in sustained clinical remission, respectively. Partial Mayo scores at weeks 4 and 12 were compared with the baseline score. Last observed data were carried forward for patients who had undergone colectomy prior to weeks 4 or 12. The proportion of patients with C-reactive protein ≥ 5 mg/L was determined at baseline and at weeks 4 and 12.

Ulcerative colitis was defined as extensive, left-sided or proctitis according to the Montreal classification (10). Previous use of any immunosuppressive agent was recorded. Concurrent therapies at baseline, including corticosteroids and immunosuppressive agents, were assessed. The interval between the last infliximab infusion and week 0 was recorded.

The primary outcome parameter over the long-term was the proportion of patients who continued on adalimumab therapy at each study visit, including the last follow-up visit. The probability of remaining on adalimumab was analyzed at weeks 4, 12, 20, 30 and 40. We assessed the proportion of patients whose corticosteroid treatment was

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3 discontinued before the last follow-up visit. The need for colectomy was also recorded
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5 during the entire duration of follow-up. For patients who discontinued adalimumab, the
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7 period between adalimumab withdrawal and the last follow-up visit was also considered
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9 in terms of the need for colectomy. The probability of avoiding colectomy was analyzed
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11 at weeks 4, 12, 20, 30, 40 and 60.
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15 We analyzed predictors of short-term response including age, gender, disease duration,
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17 extent of disease, corticosteroids or immunosuppressive use at baseline, reason for
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19 infliximab discontinuation, and interval between the last infliximab infusion and week
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21 0. At long-term we analyzed the predictive factors of adalimumab withdrawal and
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23 colectomy. The following variables were included: age, gender, disease duration,
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25 corticosteroids or immunosuppressive use at baseline, reason for infliximab
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27 discontinuation, clinical response at week 12, and the need for adalimumab escalation.
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31 The safety analysis included the ability to tolerate adalimumab and adverse events
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33 including those leading to adalimumab withdrawal. Injection site reactions were not
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35 recorded.
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38 39 40 41 *Statistical analysis*

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43 The intention-to-treat (ITT) population included all patients who received at least one dose
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45 of study treatment. All patients were included in the safety analysis. Statistical analysis of
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47 initial response and remission rates was limited to descriptive statistics. The follow-up
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49 quantitative variables were analyzed using the LOCF (last observation carried forward)
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51 technique in the patients who discontinued treatment or suffered events. Paired parametric
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53 and non-parametric tests were used to compare continuous variables, expressed as the
54
55 mean \pm standard deviation (SD) or median and interquartile range (IQR) (P25-P75),
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58 while categorical variables were compared using the chi-squared or Fisher tests.
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3 Logistic regression was performed for predictors of clinical response at 4 and 12 weeks.
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5 Variables shown by univariate analysis to exert a clinical influence were included in a
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7 multivariate logistic regression analysis. Adjusted odds ratios (adjORs) and their 95%
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9 confidence intervals (95%CI) were calculated.
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13 In the long-term, adalimumab withdrawal and colectomy-free survival rates were
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15 estimated using the Kaplan-Meier method. Time to event was analyzed from the date of
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17 the first adalimumab dose to the date of the event. The Breslow exact test was used to
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19 evaluate differences in the survival curves. Adjusted rates ratios (hazard ratios, HR)
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21 were calculated using Cox proportional hazard survival regression analysis. The null
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23 hypothesis was rejected in each statistical test when $p < 0.05$. Analysis was performed
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25 using the SPSS version 15.0 statistical package for Microsoft Windows.
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RESULTS

Characteristics of the patients

Thirty patients entered the compassionate use program and were enrolled in the study between September 2006 and March 2009 in a total of 12 centers. One to 6 patients were included in each center. All patients received at least one dose of adalimumab and were included in the intention-to-treat (ITT) population. The baseline characteristics of the patients are summarized in Table 1. The mean age of our population was 40.5 years (range 18-70; SD \pm 14.5), and the mean disease duration was 6.7 years (range 2-17; SD \pm 3.7). Twenty-one patients (70%) had extensive ulcerative colitis, and 9 (30%) left-sided colitis. All patients had received corticosteroids at some point in time. Twenty-six patients (86.7%) had been previously treated with at least one immunosuppressive agent (25 received azathioprine or mercaptopurine; 4, methotrexate; and 2, mycophenolate mofetil). Seven patients had previously received intravenous cyclosporine as rescue therapy in the management of corticosteroid-refractory severe ulcerative colitis, and were subsequently treated with thiopurinic agents in the long term.

All patients had previously received infliximab. The reason for infliximab discontinuation in 16 patients (53.3%) was loss of response. All of them had active disease despite an increase in infliximab dosage to 10 mg/kg (8 patients) or a decrease in the interval of infliximab administration to 6 weeks or fewer (8 patients). Twelve patients (40%) became intolerant to infliximab: 8 patients suffered an acute infusion reaction, three patients experienced a delayed hypersensitivity reaction, and one patient developed a lupus-like syndrome. Two patients showed primary non-response to infliximab induction doses (6.7%).

Nineteen patients (63.3%) were receiving corticosteroids at baseline, with a mean prednisone dose of 34.2 mg/day (range 10-60; SD \pm 17.4), while 15 (50%) were

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3 receiving some immunosuppressive agent (13 patients received azathioprine or
4 mercaptopurine; and 2, methotrexate).

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8 Twenty-six patients received adalimumab for outpatient refractory ulcerative colitis.

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10 Four patients received adalimumab as in-patients due to severe intravenous
11 corticosteroid-refractory disease, and none of them had been treated with cyclosporine
12 in the previous 6 months.
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17 The interval between the last infliximab infusion and week 0 ranged from 4-52 weeks
18 (median 6, IQR 4-11). All patients received a loading dose of 160 mg of adalimumab at
19 week 0 followed by an 80 mg dose at week 2. Subsequent 40 mg adalimumab doses
20 were given every other week.
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29 *Table 1. Baseline characteristics of patients (about here)*
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32 *Clinical efficacy*

33 Short-term clinical response

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36 Sixteen patients (53.3%) showed clinical response at week 4, and 18 patients (60%) at
37 week 12 (Figure 1). Thirteen patients achieved clinical response at both weeks. Three
38 patients (10%) and 8 patients (26.7%) showed clinical remission at weeks 4 and 12,
39 respectively.
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48 Seven patients underwent dose escalation between weeks 4 and 12 from 40 mg every
49 other week to 40 mg weekly. Three of the patients without response to the induction
50 doses subsequently underwent colectomy before week 12 (at weeks 3, 6 and 7,
51 respectively). The mean partial Mayo score was 6.5 (range 4-9; SD \pm 1.5) at baseline
52 versus 3.6 (range 0-9; SD \pm 2.1) at week 4 ($p < 0.001$; one datum carried forward) and
53 versus 3.03 (range 0-9; SD \pm 2.4) at week 12 ($p < 0.001$; three data carried forward).
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3 There were no differences in mean partial Mayo score at weeks 4 and 12 ($p=0.130$). At
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5 baseline, 25 patients (83%) presented C-reactive protein ≥ 5 mg/L. Thirteen patients
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7 (43%) presented C-reactive protein ≥ 5 mg/L at weeks 4 and 12 (one and three data
8
9 carried forward, respectively).

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12 The proportion of patients who achieved clinical response at week 12 was broadly
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14 similar in patients included after loss of response to infliximab (10 out of 16, 62.5%)
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16 and those with previous intolerance to the drug (8 out of 12, 66.6%) ($p=0.999$). Neither
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18 of the two primary non-responders to infliximab showed clinical response at week 12.
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20 Among the patients treated with corticosteroids at baseline, 10 out of 19 (52.6%)
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22 achieved clinical response at week 12. Eight out of 11 patients (72.7%) without
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24 corticosteroids at week 0 showed clinical response at week 12. Ten out of 15 patients
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26 (66.6%) at baseline on immunosuppressant developed clinical response at week 12,
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28 compared with 8 of 15 patients (53.3%) without immunosuppressant at entry ($p=ns$).

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37 *Figure 1. Short-term clinical response: proportion of patients with clinical response and*
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39 *remission at weeks 4 and 12. Sustained clinical response or remission: clinical response*
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41 *or remission at both weeks (about here)*

42 43 44 45 Long-term outcomes

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48 During a median follow-up of 48 weeks (IQR 16-104), 15 patients (50%) discontinued
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50 adalimumab (Figure 1). The reason for discontinuation was a lack of response or loss of
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52 response in 13 patients (including 5 patients who needed colectomy within 2 weeks of
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54 being withdrawn) and serious adverse events in two patients. The median time to
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56 discontinuation was 19 weeks (IQR 12-32). Fifteen patients continued on adalimumab
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58 at the last follow-up visit (Figure 2). The probability of remaining on adalimumab
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3 therapy was 96.7%, 90%, 71%, 63% and 50% at 4, 12, 20, 30 and 40 weeks,
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5 respectively. Eleven patients overall (36.7%) required dose escalation from 40 mg every
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7 other week to 40 mg weekly. The median time to escalation was 10 weeks (IQR 8-23.
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10 Of the 19 patients who were on corticosteroids at the time of first adalimumab
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12 administration, 13 (68%) discontinued these drugs during follow-up. All patients who
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14 were taking corticosteroids at week 0 and who continued on adalimumab at long-term
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16 (n=7) were able to stop corticosteroid treatment. All four patients who received
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18 adalimumab on an in-patient basis for severe intravenous corticosteroid-refractory
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20 disease discontinued adalimumab.
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24 Six patients needed colectomy (Figure 3). The probability of avoiding colectomy was
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26 96.7%, 90%, 90%, 83.3%, 83.3% and 80% at 4, 12, 20, 30, 40 and 60 weeks,
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28 respectively. The median time to colectomy was 16 weeks (IQR 5.2-40.5). Colectomies
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30 were performed at weeks 3, 6, 7, 25, 32 and 66, respectively. The 6 patients with
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32 colectomy showed no clinical response at week 12. All patients who achieved clinical
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34 response at week 12 (n=18) were colectomy-free at long-term. **Among the 11 patients**
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36 **who needed escalation of adalimumab 8 were colectomy free at long term.** Among the
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38 week 12 responders, twelve patients continued on adalimumab at the last follow-up
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40 visit, and 3 of them needed escalation to 40 mg weekly. Of the four patients who
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42 received adalimumab as in-patients for severe intravenous steroid-refractory disease,
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44 two (50%) underwent colectomy at weeks 3 and 32, respectively. The other two patients
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46 discontinued adalimumab but avoided colectomy in the long-term (36 and 62 weeks,
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48 respectively).
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58 *Figure 2. Cumulative probability of continuing on adalimumab during follow-up:*
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60 *Kaplan–Meier method (about here)*

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3 *Figure 3. Cumulative probability of avoiding colectomy during follow-up: Kaplan–*
4 *Meier method (about here)*
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10 *Predictive factors*

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12 We explored the factors associated with short-term response. There was a trend toward
13 an increased response rate at week 4 in patients on immunomodulators at baseline (OR
14 0.2, p0.063). Regarding long-term outcomes, survival curves showed that patients with
15 clinical response at week 12 had an increased probability of remaining on adalimumab
16 (Breslow p<0.001) (Figure 4a). The Cox proportional hazard survival regression
17 analysis indicated that patients with no response at week 12 had a significantly higher
18 adjusted rate of adalimumab withdrawal (HR 7.27, 95%CI 2.32-22.75; p=0.001).
19 Patients on immunomodulators at baseline showed a tendency toward a reduced
20 adjusted rate of adalimumab withdrawal (HR 0.392, 95%CI 0.124-1.238; p=0.100).
21 Evaluation of the survival curves showed that achieving clinical response at week 12
22 was associated with long-term colectomy-free survival (p<0.001) (Figure 4b). No
23 response at week 12 was identified as an independent predictor of colectomy (HR
24 undefined; p=0.001).
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46 *Figure 4. Cumulative probability of continuing on adalimumab during follow-up:*
47 *differences in the survival curves between patients with and without clinical response at*
48 *week 12 (top). Cumulative probability of avoiding colectomy during follow-up:*
49 *differences in the survival curves between patients with and without clinical response*
50 *at week 12 (bottom) (Breslow exact test) (about here)*
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Safety

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3 Six patients experienced adverse events. Two adverse events led to the discontinuation
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5 of adalimumab: one patient suffered exacerbation of psoriasis, and one patient
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7 developed cough refractory to treatment. One patient developed fatigue and a mild skin
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9 rash. One patient had transient fever, and another suffered arthralgia. Exacerbation of
10
11 psoriasis, fever, arthralgia and rash were considered by the investigators to be probably
12
13 related to the study medication. Refractory cough subsided shortly after adalimumab
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15 withdrawal. One female was diagnosed with a dermoid ovarian cyst. Only the 6 patients
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17 who underwent colectomy required hospitalization to perform the procedure.
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3 DISCUSSION
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5 The present study describes our experience with adalimumab in the context of a
6 compassionate use program in patients with ulcerative colitis refractory to conventional
7 medical treatment, including infliximab. TNF is found in increased concentrations in the
8 blood, stools and colonic mucosa of patients with ulcerative colitis, but the role of this
9 cytokine in the pathogenesis of the disease is not as evident as in Crohn's disease.
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Infliximab is the only TNF antagonist offering confirmed efficacy in ulcerative colitis (5,6). No controlled studies assessing the efficacy of adalimumab in ulcerative colitis patients previously treated with infliximab have been published to date. The hypothesis is that pre-existing antibodies induced by infliximab, which is a hybrid human-murine antibody, would not affect adalimumab response in either Crohn's disease or in ulcerative colitis.

As regards the adverse effects profile, our results are similar to those of large controlled series in patients with Crohn's disease treated with adalimumab and with a similar duration of follow-up (3), as well as to two uncontrolled studies in patients with ulcerative colitis (9,10). Only two of the recorded adverse effects led to the suspension of adalimumab. No adverse effect was considered to be serious or required hospital admission. No patients developed serious infections that could be related to adalimumab. During follow-up, admission or surgery was only necessary in the 6 patients undergoing colectomy.

In our study over 50% of the patients showed short-term clinical response at weeks 4 and 12, thus leading the investigators to decided on long-term continuation of adalimumab in these subjects. The partial Mayo score provided evidence for clinical improvement as early as week 4. We consider this to be related to a rapid response to the adalimumab induction doses. The clinical response rates were broadly similar in

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3 patients included after loss of response to infliximab and in those with prior intolerance
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5 to the drug. There were no differences according to the use of corticosteroids at
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7 baseline. Patients on immunomodulators at baseline tended to respond better in the short
8
9 and long-term. The potential impact of combining immunosuppressant and anti-TNF
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11 agents for Crohn's disease remains the subject of debate (12,13). The efficacy and
12
13 safety results of adding or maintaining immunomodulators in patients with ulcerative
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15 colitis and treated with adalimumab should be studied in depth.
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19 Data from the open-label multicenter CARE study in patients with Crohn's disease
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21 showed that 36% of primary non-responders to infliximab showed a response to
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23 adalimumab at week 26 (14). In two open-label single-center studies, patients with
24
25 Crohn's disease who were classified as being refractory to infliximab were treated with
26
27 adalimumab: one of 4 patients and three of 6 entered remission, respectively (15,16).
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29 Based on these data, we included patients who had never responded to infliximab.
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31 Neither of the two patients showing no initial response to infliximab showed short-term
32
33 response to adalimumab. To our knowledge, these are the only ulcerative colitis patients
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35 refractory to infliximab who have received adalimumab as rescue therapy. This
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37 management option for patients with ulcerative colitis must be explored in large patient
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39 series.
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46 At week 12, a total of 8 patients (26.7%) presented a partial Mayo score of 1 or 0 and
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48 were considered to be in clinical remission. The definition of remission used in our
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50 study is weak, since no endoscopic evaluation was carried out. Given the nature of the
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52 compassionate use program, it was not possible to pre-establish explorations outside
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54 those contemplated in routine clinical practice. This explains why not all patients
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56 underwent endoscopic follow-up to assess mucosal healing, and why the endoscopic
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58 explorations were not performed in the same week of follow-up. Nevertheless, we
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3 observed complete mucosal healing (0 points on the Mayo endoscopic subscore) in two
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5 patients of our series after long-term treatment with adalimumab (17).
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8 Recently, a placebo-controlled multicenter study assessed the efficacy of adalimumab in
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10 anti-TNF naive patients with active ulcerative colitis (18). The study population is not
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12 similar to ours. Only two of the 30 patients in our series were primary non-responders to
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14 infliximab, so this is a more selected population in which the majority of patients
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16 responded to the first anti-TNF. **Another main difference is that in our study, but not in
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18 the Reinisch study, escalation of adalimumab dose was permitted. Seven patients
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20 underwent dose escalation to 40 mg weekly before assessment of response at week 12.**
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24 Despite the different treated populations, **the adalimumab dosing** and that the time when
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26 assessments are made were also different (eight weeks in the study of Reinisch and 12
27
28 weeks in ours) response rates were broadly similar: 54.6% (18) and 60%, respectively.
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30 Remission rates are not comparable because our study did not include endoscopic
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32 assessment.
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36 Data assessing the long-term efficacy and safety of adalimumab in patients with
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38 ulcerative colitis previously treated with infliximab are limited, with only one published
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40 study including 13 patients (8,9). In our series, half of the patients continued on
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42 adalimumab at the last follow-up visit. The decision to continue or interrupt
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44 adalimumab for the long term was clearly subjective, i.e., it was left to the discretion of
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46 the investigator, since no criteria were pre-specified to determine whether or not to
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48 proceed to adalimumab discontinuation. Nineteen patients were on corticosteroids at
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50 baseline, and 68% of these subjects reduced or discontinued such treatment during
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52 therapy with adalimumab. More remarkably, all patients who entered the trial on
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54 corticosteroids and continued on adalimumab at long-term were able to stop
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3 corticosteroid treatment. These results suggest that adalimumab, like infliximab (5),
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5 might be effective as a corticosteroid-sparing drug in ulcerative colitis
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8 The most relevant outcome of our study is the need for colectomy during follow-up. It
9
10 can be argued that total proctocolectomy heals ulcerative colitis. On the other hand,
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12 colectomy is not risk free: patients require frequent follow-up procedures, and
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14 complications are not uncommon (19). An ileoanal pouch is frequently associated with
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16 complications, which include pouchitis in approximately 40% of patients (20), pouch
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18 failure in around 8% of patients (21), and a marked reduction in female fertility (22).
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20 These complications and the potential impact of surgery on patient body image –
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22 including the possibility of requiring a permanent ileostomy – lead a considerable
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24 number of patients with a poor response to conventional treatment to demand other
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26 medical therapies, including the off-label use of adalimumab. *Post hoc* data from ACT
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28 studies showed infliximab to have a colectomy-sparing effect in ulcerative colitis
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30 outpatients (23). In our study, 80% of patients avoided colectomy during follow-up. The
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32 proportion of patients who needed colectomy in the long-term was similar to that
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34 reported with infliximab in an open-label study including 121 outpatients (17%
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36 subjected to colectomy) (24), and lower than that reported with adalimumab for a
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38 similar follow-up period in 13 outpatients (46% subjected to colectomy) (9). A recent
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40 open-label study with adalimumab in ulcerative colitis patients naïve to anti-TNF had a
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42 colectomy rate of 15% (3/20) (25). Our series included four in-patients with severe
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44 intravenous corticosteroid-refractory disease, and two of them (50%) required
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46 colectomy. Clinical response at week 12 was a predictor of better outcomes in the long-
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48 term, diminishing the rate of patients who discontinued adalimumab. The 6 patients
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50 who needed colectomy failed to achieve response at week 12. More importantly, none
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52 of the patients with short-term response needed colectomy at long-term. Thus, a
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3 response to adalimumab induction doses is a potent predictor of colectomy avoidance in
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5 the long-term.
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8 The main limitations of our study are the lack of a control group, the heterogeneity of
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10 the ulcerative colitis patients, and the weakness of the definition of remission without
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12 endoscopic assessment. Infliximab trough levels and human anti-chimeric antibodies
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14 were not measured at entry to the study. Recent evidence underscores the importance of
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16 these measurements in the clinical management of patients with inflammatory bowel
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18 disease who lose response to infliximab (26). In any case it does not seem reasonable to
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20 prematurely switch to another anti-TNF compound before considering the optimization
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22 of infliximab therapy by either increasing the dose or decreasing the dosing interval.
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27 In conclusion, adalimumab was well tolerated in our cohort and induced durable clinical
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29 response in many patients with otherwise medically refractory ulcerative colitis.
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31 Patients who achieved clinical response at week 12 avoided colectomy in the long-term.
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34 Despite the study limitations, our results suggest that patients with ulcerative colitis who
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36 have lost response to or are intolerant of infliximab may benefit from switching to
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38 adalimumab.
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Table 1.

Variable	
Patients, n (%)	30 (100%)
Male sex, n (%)	16 (53.3%)
Age -years, mean (SD)	40.5 (\pm 14.5)
Smoker status	
Non-smoker, n (%)	27 (90.0%)
Smoker, n (%)	3 (10.0%)
Extension	
Left-sided, n (%)	9 (30.0%)
Extensive, n (%)	21 (70.0%)
Duration of disease - years, mean (SD)	6.7 (\pm 3.7)
Partial Mayo score, mean (SD)	6.5 (\pm 1.5)
C-reactive protein \geq 5 mg/L, patients, n (%)	25 (83%)
Prior use of:	
IMM (AZA/6MP/MTX/MYC) – n (%)	26 (86.7%)
Cyclosporine – n (%)	7 (23.3%)
Use of infliximab, n (%)	30 (100%)
Reason for discontinuation:	
Loss of response, n (%)	16 (53.3%)
Intolerance, n (%)	12 (40.0%)
Acute infusion reaction, n	8
Delayed hypersensitivity reaction, n	3
Lupus-like syndrome, n	1
Primary non-responder, n (%)	2 (6.7%)
IFX infusions – n (SD)	7.6 (\pm 4.8)
IFX duration – weeks (SD)	41.3 (\pm 33.2)
Drugs used at inclusion	
Steroids – n (%)	19 (63.3%)
– mg/day (SD)	34.2 (\pm 17.4)
IMM – n (%)	15 (50.0%)

IMM, immunosuppressive agent; AZA, azathioprine; 6MP, 6-mercaptopurine; MYC, mephenolate mofetil; IFX, infliximab.

1

Figure 1.

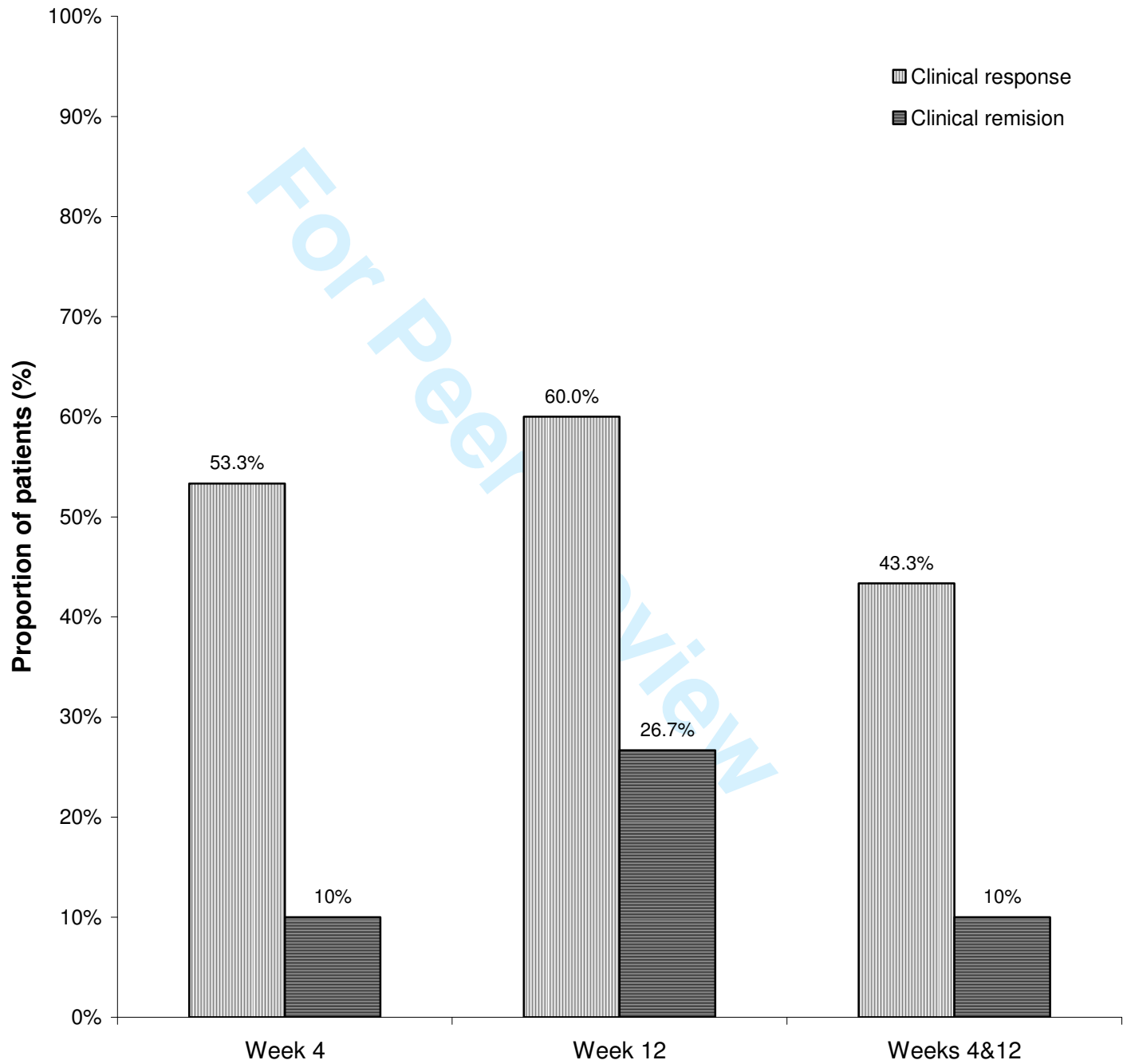
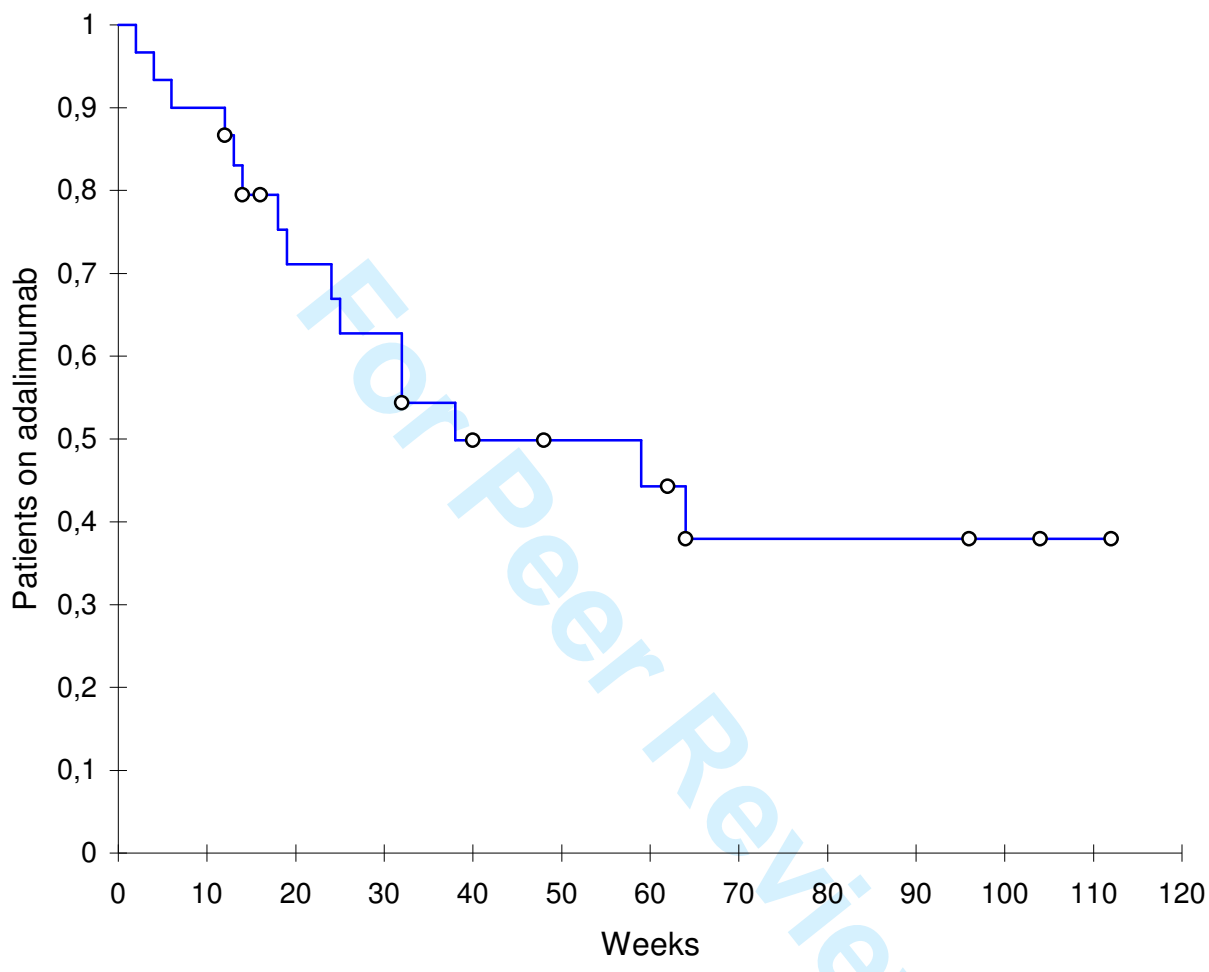


Figure 2.

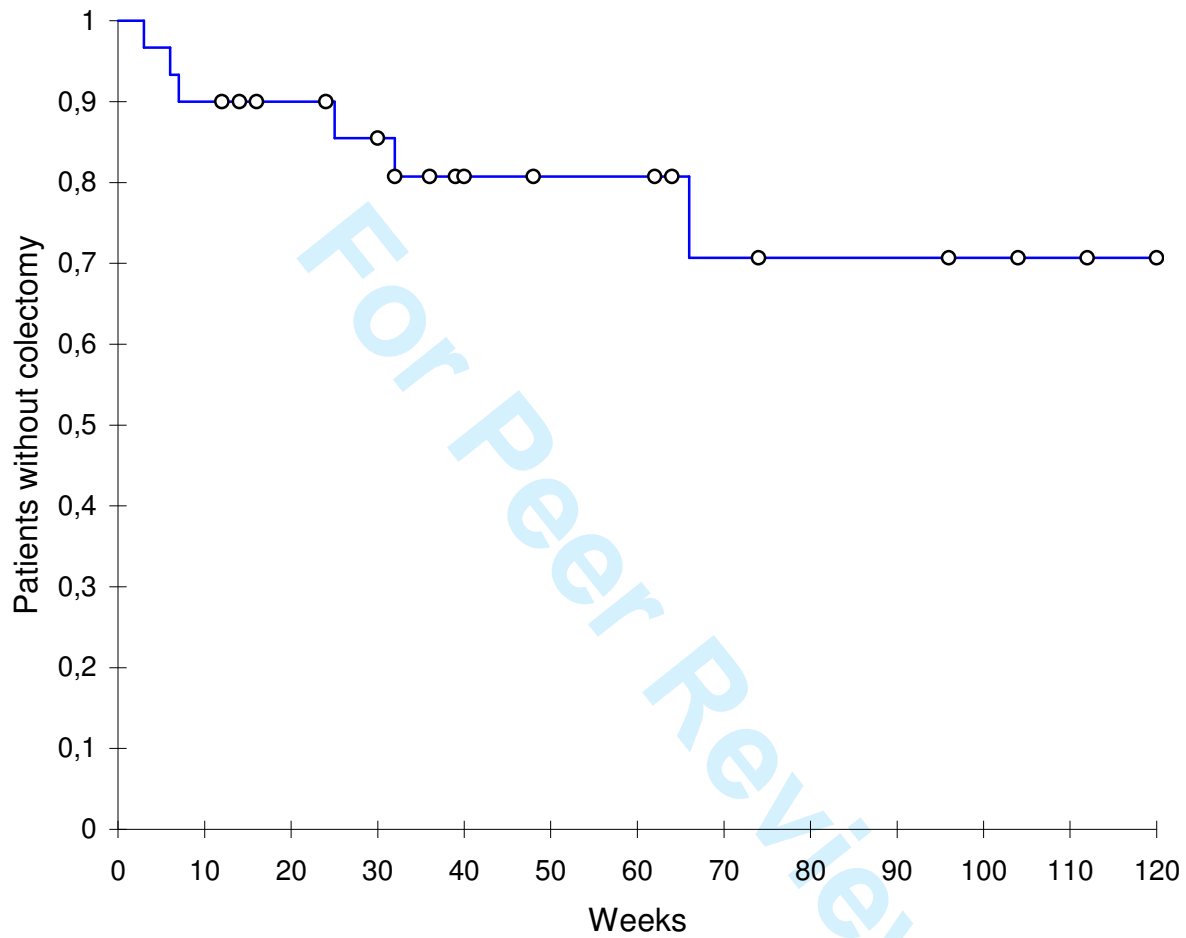


Number at risk:

Week:	0	12	20	30	40	60	80	100
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Figure 3..

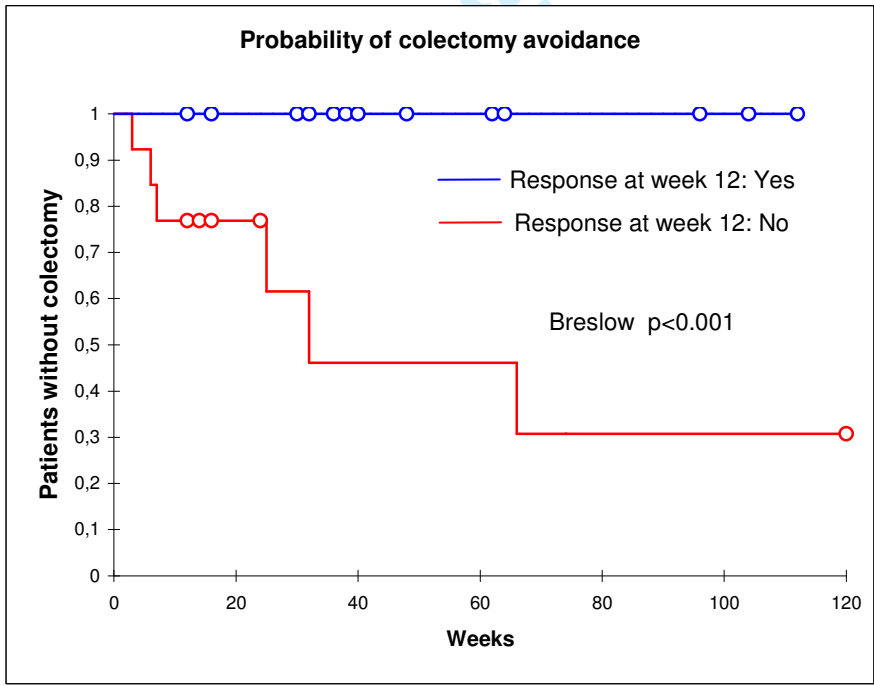
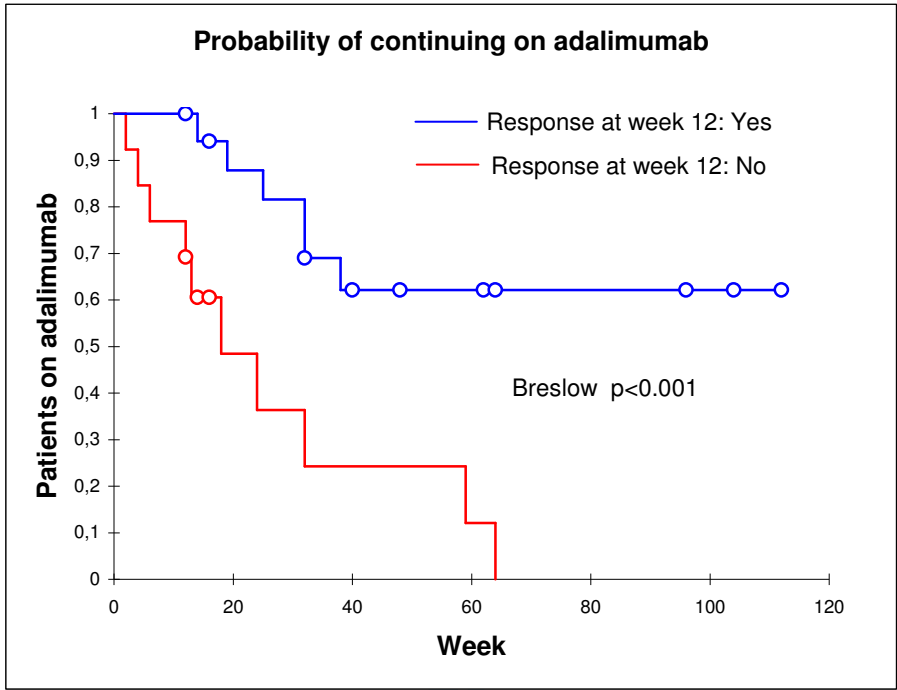


Number at risk:

Week:	0	12	20	30	40	60	80	100
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Figure 4.



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