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Alimentary Tract

Six year adalimumab efficacy in steroid-dependent Crohn's disease patients: A prospective real life study

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ABSTRACT

Background: Adalimumab is effective in the treatment of Crohn's disease. We have already reported data on the efficacy of adalimumab in 110 steroid-dependent patients. At the end of the study 90 patients (64.5%) maintained clinical remission.
Aims: To assess efficacy and safety of adalimumab after 6 years in patients of the original cohort who responded to treatment.
Methods: The present study is an extension of the published paper on 90/110 patients. We report results on clinical remission and safety of 6 year maintenance therapy with adalimumab.
Results: Of the original cohort 90 patients completed the study, 17 were lost to follow-up and 3 died. At the end of follow-up (74.16 ± 10.3 months) 37/90 patients (41%) maintained clinical remission. Of these, 32 (86%) continued adalimumab and 5 (13%) discontinued treatment due to clinical remission and mucosal healing. Of the remaining 53/90 patients, 47 (52%) discontinued adalimumab due to clinical failure and 6 (7%) to adverse events.

We obtained endoscopy data in 31/32 patients in clinical remission continuing adalimumab: 11 (36%) did not improve, 6 (19%) worsened, 14 (45%) improved. At univariable analysis no variables were related to treatment outcome.
Conclusions: This "real life" prospective study shows that adalimumab is a long-term effective and safe maintenance treatment in steroid-dependent Crohn's disease patients.

1. Introduction

According to the second European evidence-based consensus on diagnosis and management of Crohn's disease (CD) [1], steroid-dependent patients are defined as those 'unable to reduce steroids below the equivalent of prednisolone 10 mg daily (or budesonide below 3 mg daily) within 3 months of starting steroids, without recurrent active disease', and those who relapse within 3 months of stopping steroids. According to the Italian guidelines, patients treated with any dosage of steroids are considered steroid-dependent [2].

Prolonged steroid response has been reported in 44% of patients with CD, steroid dependency in 36% and steroid refractory in 20% of patients [3]. Despite the widespread use of immunosuppressive and biological treatment, corticosteroid dependency remains clinically challenging.

Immunosuppressant [4] and anti-TNFα therapies [5–7] are effective in steroid-dependent CD patients to maintain the steroid-free clinical remission [2]. Adalimumab (ADA) is effective for induction [8] and maintenance [6] therapy of patients with moderate to severe CD. In the CHARM study [6], the steroid-sparing effect of ADA was analyzed in a subgroup (44%) of patients treated with corticosteroids at the baseline visit. Lémann's study [9] evaluated prospectively the efficacy of infliximab plus azathioprine in steroid-dependent CD patients, although it must be noted that the mean baseline Crohn's Disease Activity Index (CDAI) score of the trial population was 240, corresponding to a moderate disease activity despite steroids.

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We have previously published data on efficacy and prognostic factors for response to ADA (80/40 mg or 160/80 mg every other week followed by 40 mg every other week) in 110 steroid-dependent patients [10]. At week 6, 91% of patients had clinical benefit (remission 45.5%, response 45.5%). After a mean follow-up of 14.6 months, 80.9% of responder patients maintained a clinical benefit (remission 64.5%, response 16.4%). Multivariable analysis showed that the highest induction regimen was the only variable significantly correlated to remission at week 6. To date, long-term efficacy data of ADA in steroid-dependent patients was reported only in the ADHERE studies, as a subgroup analysis of the CHARM trial at 2 and 4 years [11,12].

In the current study, we report the results on efficacy and safety of a 6-year maintenance therapy with ADA in 90 out of the original 110 steroid-dependent CD patients, including statistical analysis of prognostic factors for remission.

2. Materials and methods

2.1. Patients' characteristics

In this prospective observational analysis, we extended the follow-up of the previous study [10] until November 2015. As previously described in detail [10], patients who achieved clinical response or remission after prednisone treatment but subsequently developed steroid-dependency, according to the definition of the second European evidence-based consensus [2], were treated with ADA in order to achieve and maintain a steroid-free clinical remission. Patients included in the original cohort were followed up prospectively in the outpatient clinic at 3–4 monthly intervals, to evaluate maintenance of steroid-free remission (CDAI score less than 150). At each visit, we recorded general wellbeing and physical examination. We did not evaluate the C-reactive protein as serologic marker because all included patients were steroid-dependant and most of them had normal CRP values under steroids.

In the current study we collected data on 90 out of 110 patients. In patients with steroid-free maintained clinical remission, we reported data on endoscopic features in order to evaluate their relationship with clinical outcome. We defined endoscopic improvement or worsening according to the SES-CD score [13], compared to baseline features at the beginning of the previous study. We also evaluated the long-term safety of ADA during and at the end of the follow-up period.

2.2. Statistical analysis

Data were analyzed using the software package SPSS 15 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as means ± SD or range when appropriate. Categorical variables were summarized as frequency and percentage. Significant differences were calculated using a χ^2 test for categorical variables. Demographic and disease variables were related to the main outcome (maintenance of steroid-free clinical remission) using a univariable analysis. We considered the following variables: sex, age, smoking habit, disease duration, family history, previous surgery, pattern of disease, dosage of steroids at baseline, induction regimen, site of disease, previous biological therapies, ADA discontinuation, ADA dose escalation, switch to another biologic, surgical treatment in ADA failure, and side effects.

Differences were considered significant for p-value <0.05. We planned to carry out multivariable analysis if we obtained a p-value <0.05 at univariable analysis.

Table 1
Baseline characteristics of study population (*N.* 90).

Male/female, *N* (%)	47 (52.2)/43 (47.8)
Mean age, years ± sd	40 ± 13.1
Disease duration, months ± sd	10.3 ± 8.8
Smoking habit, *N* (%)	
• Non-smokers	40 (44.4)
• Current smokers	30 (33.3)
• Ex-smokers	20 (22.2)
Luminal disease location, *N* (%)	
• Ileo-Colitis (L3)	56 (62.2)
• Jejuno-ileitis (L1)	21 (23.3)
• Colitis (L2)	13 (14.4)
Mean CDAI score ± sd	165.8 ± 43.5
Previous abdominal surgery, *N* (%)	46 (51.1)
Patients with concomitant perianal disease, *N* (%)	5 (5.5)
Previous biologics treatment, *N* (%)	
• Infliximab	
- Intolerant	15 (16.7)
- Non-responders	12 (13.3)
- End of treatment	–
• Certolizumab pegol	
- Non-responders	5 (5.6)
- Intolerant	1 (1.1)
History of immunosuppressants, *N* (%)	63 (70)
Dosage of steroid at baseline, *N* (%)	
• 10–15 mg/die	47 (52.2)
• >15 mg/die	43 (47.8)

3. Results

Of the 110 patients included in the original study, we report long-term data on 90 patients, given that 17 (19%) were lost to follow up and 3 (0.3%) died for reasons not related to ADA treatment (myocardial infarction, car accident, post-surgical complication). Mean follow-up was 74.16 ± 10.3 months. Clinical characteristics of the evaluated patients are reported in Table 1. Patients who continued ADA were followed up every 3 months, the others every 4–6 months or according to clinical symptoms. At the end of follow-up, 37 patients (41%) maintained clinical remission, as showed in the Kaplan Meier curve (Fig. 1): 32 of these (87%) were still in maintenance treatment with ADA monotherapy, with 21 (66%) receiving ADA 40 mg every other week and 11 (34%) receiving ADA 40 mg weekly as maintenance treatment; 5 patients (13%) discontinued ADA due to clinical remission and mucosal healing, switching to immunosuppressants with clinical benefit until now. Of the remaining patients, 6 (7%) discontinued ADA due to adverse events and 47 (52%) due to clinical failure: 20 out of the latter 47 patients (43%) switched to other treatments (infliximab or immunosuppressants) while 27 (57%) underwent surgery. The flow chart of the evaluated patients is summarized in Fig. 2.

We obtained data on endoscopy at 2 years in 31 out of the 32 patients in steroid-free clinical remission and still in maintenance treatment: 11 (36%) showed no endoscopic improvement, 6 (19%) had an endoscopic worsening (SES-CD score 9 ± 1.5 vs. 11.2 ± 1.8), while 14 patients (45%) improved the endoscopic lesions, with complete mucosal healing in 8 cases. Patients who discontinued ADA due to treatment failure were switched to another therapy, taking into consideration the clinical condition without endoscopic evaluation.

At univariable analysis, we found no correlation between the evaluated variables and treatment outcomes at the end of follow-up.

ADA was well tolerated in the long-term. At the end of the previous study, 7 patients (6.3%) had developed side effects with treatment discontinuation (1 pneumonia, 1 severe mycosis, 2 fever, 1 severe cutaneous reaction, 2 abdominal abscesses). In the current analysis, no other discontinuation of ADA, due to side effects, was

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