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Alimentary Tract

Dose optimization is effective in ulcerative colitis patients losing response to infliximab: A collaborative multicentre retrospective study

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ABSTRACT

Background: Subjects maintained on infliximab scheduled therapy for inflammatory bowel disease may require dose optimization due to secondary loss of response. There are limited data on infliximab dose optimization for ulcerative colitis.
Aims: To investigate dose optimization in ulcerative colitis patients with secondary loss of response.
Methods: This was a retrospective multicentre study. Primary outcome was rapid clinical response assessed at the next administration of infliximab after dose intensification. Secondary outcomes were rapid clinical remission, and clinical response, remission and colectomy rate by week 52. Doubling the dose (10 mg/kg q8 weeks) vs. shortening the dose interval (5 mg/kg every 6 or 4 weeks) were compared.
Results: Forty-one patients from eight centres were enrolled (15 for double dose and 26 for interval shortening). Rapid response was achieved in 37/41 patients (90.2%), while 19/41 (46.3%) achieved rapid clinical remission. At week 52, 28/41 patients were maintained in clinical remission, but 4 (9.8%) underwent colectomy. No difference was found between the two optimization strategies. Subjects achieving rapid clinical response had a significantly higher colectomy-free rate at week 52 ($p = 0.002$).
Conclusion: Dose optimization of infliximab was effective to restore clinical response or remission and to prevent colectomy in ulcerative colitis patients with secondary loss of response.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease that usually affects the colonic mucosa from the rectum up to the cecum. The clinical management of UC aims to control symptoms and heal the mucosa, reducing the occurrence of flares, and avoiding total colectomy, which is indicated in case of refractory colitis [1]. Therapy aims to induce and maintain clinical remission, and heal the mucosa in order to prevent further flares, hospitalizations and colectomy.

Depending on the severity of the disease, 5-aminosalicylic acid (5-ASA) agents and corticosteroids are used for induction of remission of active UC [2]. However, although 5-ASA can effectively maintain remission, the long-term use of corticosteroids usually results in steroid-dependent or even refractory disease and is hampered by unwanted and serious adverse events [3]. Thiopurines are slow-acting agents with steroid-sparing effects, but their efficacy in maintaining long-term remission of colitis has been disputed [4,5].

Infliximab (IFX), a chimeric monoclonal antibody blocking tumour necrosis factor α (TNF-α) with high affinity [6], has been shown to induce and maintain remission in patients with moderate and moderate to severe active inflammatory bowel disease (IBD)

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[7,8]. Data from the ACT trials clearly show that IFX was superior to placebo in the induction and maintenance of remission in ambulatory patients with moderate-to-severe active UC [8]. It has also been shown that IFX is effective as 'rescue' (second line) therapy in hospitalized patients with severe colitis unresponsive to intensive intravenous corticosteroid regimen [9,10].

However, up to 40% of patients who respond initially to IFX will inevitably lose response over time during scheduled maintenance therapy [11]. The reasons underlying this secondary loss of response to IFX (sLoR) are not completely understood [12]. The contribution of several factors including the development of neutralizing antibodies, the immune status of the patient, genetic factors, alterations in metabolism of the drug, and concomitant medications that may interact with the activity of anti-TNF-α antibodies have been investigated [13]. In this case, a dose increase up to 10 mg/kg or shortening the interval every 4–6 weeks can help regain response. In the ACCENT 1 trial, double dosing determined a regain of response in 80–90% of patients [14]. A recent study by Kopylov and colleagues [15] showed that shortening the dosing interval to 6 weeks appears to be at least as effective as doubling the dose to 10 mg/kg or halving the infusion intervals to once every 4 weeks in patients with CD. Rapid response to dose intensification occurred in 69% of patients in the 6-week group and 67% in the double dose group. Response was maintained at 12 months in 40% and 29% of the patients, respectively, with no significant differences between the two strategies [15].

No clear data are available on UC. In the ACT trials, scheduled therapy with 10 mg/kg IFX i.v. every 8 weeks was equally effective to 5 mg/kg, with rates of sustained remission up to 35% at week 54. There is no data on the efficacy of shortening the dose interval to 6 or 4 weeks [8]. A study by Rostholder et al. showed that 54% of patients with UC treated with maintenance IFX required dose escalation over time. However, unlike in CD, dose escalation was associated with lower rates of remission and higher rates of colectomy (33% of cases, compared with 21% of non-escalation patients) [16].

The aim of this study was to assess and compare the outcome of dose optimization in UC patients with sLoR, and to compare efficacy and safety outcomes in subjects treated with dose increase or interval shortening.

2. Methods

This was an observational European retrospective multicentre collaborative study. The study population included all consecutive UC patients treated with IFX scheduled therapy (5 mg/kg q8 weeks) between 2009 and 2012, who needed dose optimization due to sLoR. Two strategies were compared: doubling the dose (DD, 10 mg/kg q8 weeks) vs. shortening the dose interval (IS, 5 mg/kg every 6 or 4 weeks). Optimization strategy was chosen on a clinical basis, according to the clinician's judgement.

To be eligible for this study, patients had to have an established diagnosis of UC confirmed by clinical evaluation, endoscopy and histology, indication to IFX therapy for steroid-dependant or steroid-refractory active disease, and clinical and serologic evidence of sLoR to the classical dose of IFX during scheduled maintenance therapy, leading to dose escalation. In order to fulfil the inclusion criteria, the dose escalation had to be continued for at least 2 consecutive infusions. Patients were followed continuously for at least 12 months after starting IFX. Data on clinical activity of disease were recorded at predefined time points (baseline, time of sLoR, first visit after dose optimization, and at week 52). In addition, endoscopy had to be available at week 52 after IFX dose optimization. Patients were excluded if available data were insufficient to calculate the Mayo score, including endoscopic activity [17].

Patients affected by unclassified colitis, microscopic colitis or colonic CD, active infectious colonic disease, as well as patients with a primary IFX failure or with follow-up shorter than 12 months after starting IFX were excluded from the study.

For each patient, data were reviewed by an investigator in the participating institution, and clinical and laboratory parameters were recorded, when available. All information was recorded anonymously according to local regulations. Clinical activity of the disease was assessed using the clinical Mayo subscore. Remission was defined as Mayo Subscore ≤ 1; response was defined as a decrease of 3 points of partial Mayo Score and of at least 30% from baseline. The extent of the disease was classified according to the Montreal Classification [18].

The primary outcome was rapid clinical response, defined as a decrease of at least 30% from baseline in the clinical Mayo subscore, with no partial score exceeding 2, assessed at the next administration of IFX after dose intensification. Secondary outcomes were rapid clinical remission (defined as a global Mayo Score <1), clinical response and remission at week 52, and colectomy rate at week 52 following IFX dose intensification. Adverse events due to dose intensification were also evaluated and compared.

Follow-up data on patients who returned to the standard regimen of IFX were also required and collected.

No sample size calculation was performed. Response and remission rates were compared by using the χ^2 test. Survival analysis at week 52 on the study outcomes was performed by using Kaplan–Meyer curves and log rank test. Predictive factors for colectomy were investigated by logistic regression analysis. Differences were considered statistically significant if $p < 0.05$.

The study was approved by the Local Ethical Committee in each participating Centre.

3. Results

Forty-one subjects (73.1% males, mean age 46.6 years) from eight referral centres in Europe and Israel met the inclusion criteria. Baseline characteristics are shown in Table 1. Fifteen subjects were treated by doubling the dose (DD group) to 10 mg/kg every 8 weeks and 26 were treated by interval shortening (IS group) every 4–6 weeks. Mean time of sLoR onset was 29 months (range 4–95 months) from the first infusion of IFX.

In the whole study population, rapid clinical response was achieved in 37/41 patients (90.2%), of whom 19/41 (46.3%) also achieved rapid clinical remission. Twenty-eight patients (68.3%) maintained clinical remission at week 52, but 4 (9.8%) underwent colectomy by this time point (Fig. 1).

In the DD group, 13/15 patients (86.7%) had rapid clinical response and 10/15 (66.7%) had rapid clinical remission, compared to 24/26 patients (92.3%) and 9/26 patients (34.6%) in the IS group, respectively (Fig. 2).

At week 52, 8/15 (53.3%) patients were in remission and 3/15 patients (20%) underwent colectomy in the DD group, compared to 20/26 (76.9%) and 1/26 patients (3.8%) in the IS group (Fig. 3).

No statistically significant difference was found between the DD and IS groups for all outcomes ($p = 0.14$ for remission, $p = 0.25$ for colectomy).

Survival analysis showed that subjects who achieved rapid clinical response had significantly higher colectomy-free rates at week 52 than patients who did not ($p = 0.002$, Fig. 4). None of the other possible predictors (sex, age, previous medications, smoking habits, concomitant use of thiopurines, and serum levels of CRP at baseline or at the time of LoR) correlated significantly with this outcome.