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The effectiveness and safety of rescue treatments in 108 patients with steroid-refractory ulcerative colitis with sequential rescue therapies in a subgroup of patients

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Abstract

Background: Among patients with steroid-refractory ulcerative colitis (UC) in whom a first rescue therapy has failed, a second line salvage treatment can be considered to avoid colectomy.

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Infliximab;
Inflammatory bowel disease

Aim: To evaluate the efficacy and safety of second or third line rescue therapy over a one-year period.

Methods: Response to single or sequential rescue treatments with infliximab (5 mg/kg intravenously (iv) at week 0, 2, 6 and then every 8 weeks), ciclosporin (iv 2 mg/kg/daily and then oral 5 mg/kg/daily) or tacrolimus (0.05 mg/kg divided in 2 doses) in steroid-refractory moderate to severe UC patients from 7 Swiss and 1 Serbian tertiary IBD centers was retrospectively studied. The primary endpoint was the one year colectomy rate.

Results: 60% of patients responded to the first rescue therapy, 10% went to colectomy and 30% non-responders were switched to a 2nd line rescue treatment. 66% of patients responded to the 2nd line treatment whereas 34% failed, of which 15% went to colectomy and 19% received a 3rd line rescue treatment. Among those, 50% patients went to colectomy. Overall colectomy rate of the whole cohort was 18%. Steroid-free remission rate was 39%. The adverse event rates were 33%, 37.5% and 30% for the first, second and third line treatment respectively.

Conclusion: Our data show that medical intervention even with 2nd and 3rd rescue treatments decreased colectomy frequency within one year of follow up. A longer follow-up will be necessary to investigate whether sequential therapy will only postpone colectomy and what percentage of patients will remain in long-term remission.

1. Introduction

Ulcerative colitis (UC) is a lifelong disease arising from an interaction between genetic and environmental risk factors. Mild or moderate disease is effectively treated with systemic and/or topical 5-ASA preparations.[1] Steroids are still the main stay of therapy for the induction of remission in severe forms of UC. However, almost 40% of patients with a severe flare of UC do not respond sufficiently to systemic steroids.[2,3] Calcineurin inhibitors, such as ciclosporin and tacrolimus (Tcl) as well as anti-TNF-antibodies, such as infliximab (IFX) (or adalimumab and golimumab as evident from recent clinical studies) are current therapeutic options in steroid-refractory UC. The optimal choice remains controversial despite the results of a randomized study of ciclosporin versus IFX in severe UC failing to respond to steroids.[4] Short term response rates with avoidance of colectomy reached 85% for both drugs without significant difference. Data from randomized trials and clinical experience regarding Tcl in steroid refractory UC are limited so far.[5,6]

Among patients with steroid-refractory UC in whom first rescue therapy has failed, a second line salvage treatment can be considered to avoid colectomy. Although this approach may be beneficial, sequential use of rescue treatments is potentially risky because of the cumulative immunosuppressive effects.[7] This is especially important when IFX is given as the first line therapy. Serum levels of IFX typically remain increased for at least 8 weeks.[8] Therefore, if ciclosporin (or Tcl) is initiated in IFX resistant cases, within less than 8 weeks after the last infusion, the risk for infectious complications may increase.

There are only limited data concerning the efficacy of second line rescue treatment in case of failure of the first line therapy. Maser et al. published a small retrospective study presenting the efficacy rates of IFX after ciclosporin failure and ciclosporin after IFX failure. These treatment options reached 40% and 33% respectively.[9] Chaparro and colleagues [7] showed that second line treatment with IFX was effective in avoiding colectomy in the short term in two thirds of patients with steroid-refractory UC in whom ciclosporin failed. Still, the authors emphasized the association with a high rate of adverse events and even mortality. The GETAID group reported in 2011 the largest series of patients treated with a second line salvage therapy[10] with one year colectomy free survival of 41%.

Both, the European Crohn's and Colitis Organization (ECCO) and the American College of Gastroenterology (ACG) recommend the use of a second line rescue therapy only in expert centers and colectomy after failure of a second-line therapy with either ciclosporin or IFX.[2,11]

Our goal was to assess the effectiveness and safety of a second or third line rescue therapy in a cohort of 108 corticosteroid refractory patients.

2. Methods

2.1. Patients

108 patients with steroid refractory UC from 7 Swiss (91 patients) and 1 Serbian centers (17 patients) were enrolled in the cohort. Patients with confirmed UC diagnosis treated with Tcl, ciclosporin or IFX were identified from the Swiss national inflammatory bowel disease (IBD) cohort database and the IBD register of the Department of Gastroenterology in University Hospital "Zvezdara", Belgrade, Serbia. MP (IBD specialist from University Hospital Zvezdara, Belgrade, Serbia) currently works in Switzerland. Therefore we had the opportunity to obtain and integrate the data from the Serbian center, which follows exactly the same therapeutic strategy for IBD treatment like the other Swiss tertiary centers.

In all patients, disease diagnosis had been achieved according to standard clinical, endoscopic, radiologic and histologic criteria.[12] Disease location was categorized according to the Montreal classification[13] (ulcerative proctitis, left-sided and extensive colitis). Steroid resistance was defined as a lack of