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EDITORIAL

Role of Cyclosporine for the Treatment of IBD in the Biological Era

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ABSTRACT

About 30% of the patients with acute, severe ulcerative colitis (UC) do not respond to corticosteroids and require surgery or alternative medical therapy. Cyclosporine (CsA) and infliximab (IFX) are two potential choices as rescue therapies in the treatment of acute, severe UC. CsA is one of the most effective therapeutic choices in patients with severe UC; however, long term colectomy rate still varies between 60-88% among patients in whom CsA initially induced remission. IFX also proved to reduce short and long-term colectomy rates among steroid-refractory UC patients. This aim of this review is to summarize the results of the published studies examining the long-term results of CsA and IFX as rescue therapies, comparing their efficacy in steroid refractory UC and assessing the benefit of switching the drugs in case of therapeutic failure.

Key words: Acute ulcerative colitis; Cyclosporine; Infliximab; Rescue therapy

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INTRODUCTION

The main goal of treatment of ulcerative colitis (UC), a chronic idiopathic inflammatory condition, is to induce and maintain steroid-free remission, to achieve complete mucosal healing, to improve the quality of life, and to reduce the risks of colectomy. Corticosteroids have been the primary therapies in moderate to severe UC for years. Those who fail to respond to treatment with corticosteroids, or who present with severely active UC, should be considered as candidates for rescue treatment[1].

Cyclosporine (CsA), a calcineurin inhibitor selectively inhibiting T-cell mediated IL-2 production, and infliximab (IFX), a monoclonal antibody blocking tumor necrosis factor (TNF)-α are potential therapeutic choices to save the bowel[2,3]. Although CsA has been used effectively for the treatment of corticosteroid-refractory UC since the 1990's, it is also well-known that high number of the initially responders relapse and about 50-70% of them will undergo colectomy in the following 3-7 years[4,5]. IFX became a new therapeutic option to avoid surgery in steroid-refractory UC, though its benefit was queried by the initial results. Not only the single IFX infusion used in the study of Sands *et al* for the treatment of severe UC, but infusions given at week 0 and 2 for moderately active steroid resistant UC patients in the Probert's study did not meet the expectations[6,7]. However, later on, a randomized controlled trial of Järnerot *et al* found single infusion effective for moderate to severe, steroid-refractory UC[3] and the efficacy of IFX in moderate to severe UC had also been demonstrated in the ACT 1 and 2 studies[8].

This review aims to summarize the results of the published studies examining the long-term results of CsA and IFX as rescue therapies, comparing their efficacy in steroid refractory UC and assessing the benefit of switching the drugs in case of therapeutic failure.

LONG TERM EFFICACY OF CYCLOSPORINE

Cyclosporine is one of the most effective therapeutic choice in patients with severe UC, however, long term colectomy rate still varies between 60-88% among patients in whom cyclosporine initially induced remission[4]. The published data about the short and long term results of cyclosporine therapy are various and controversial–maybe due to the small patient numbers and the difference in the structure of the trials and the duration of therapy. Recently some studies tried to obtain a coherent view and examined the long-term outcome of CsA therapy. In the study of Mocciaro *et al*[9] the colectomy rate was 28.5% at 3 months and 48% at 12 months in 35 CsA-treated UC patients. The 2-3 year cumulative colectomy

rates were 54% and 57%. In this study, CsA was administered for a maximum of 3 months. Data from the UK revealed 42% of CsA-treated UC patients undergoing colectomy during a median follow-up of 3.8 years[10]. In a Japanese study, the overall percentages of patients who had not required surgery were 71.8% at 1 year, 61.5% at 2 years, 57.7% at 3 years and 48.4% at 5 years[11]. Unfortunately, these papers do not clarify the duration of CsA therapy. Cheifetz *et al*[12] treated 71 patients with CsA and followed them up for a mean of 3 years. Cumulative colectomy rates were 39% at 1 year, 42% at 2 years, and 46% at 5 years. CsA was discontinued in most patients by 6 months. In a recent paper of Sjöberg *et al*[13] CsA was given for a mean of 4.5 months. At 12 months 77% of the patients remained colectomy-free. However, this study was not followed up for more than 1 year. Our retrospective study confirmed that CsA is effective in the treatment of acute, severe UC during the long term follow-up. Colectomy-free survival was 53.4% during the more than 4 year follow-up period and significantly increased in case of longer duration of CsA therapy. If patients were treated for a year, the probability to avoid colectomy proved to be 66%. In the study of Sharkey et al. 84% remained colectomy-free over a median follow-up of 3.8 years among responders of oral CsA therapy[10]. Walch *et al* revealed a 29.7% colectomy rate in patients treated with iv CsA over a median follow-up period of 65 months[14]. Cacheux *et al* reported that 56% of 135 patients underwent colectomy after 3 years[15], whereas others reported a colectomy frequency after 5.5 years of 42%[16]. After 7 years, colectomy frequencies of 58%[5], 65%[17], and 88%[4] were reported.

LONG TERM EFFICACY OF INFLIXIMAB

Long-term benefit of IFX in severe, steroid-refractory UC may be still questionable. A review of Panaccione *et al*[18] revealed randomized controlled trials, which examined the efficacy of IFX for the treatment of severe steroid-refractory UC. Although the initial results of the studies were controversial, IFX proved to reduce short and long-term colectomy rates among steroid-refractory UC patients. In the paper of Gustavsson *et al*, the benefit of rescue therapy with IFX in steroid-refractory acute UC was shown to remain after 3 years. 50% of the patients receiving IFX *vs* 76% receiving placebo had colectomy after 3-year follow up in this study[19]. In the study of Kohn *et al* 15% of the enrolled patients with severe UC treated with IFX underwent colectomy within 2 months. Early colectomy rates were higher in patients receiving one IFX infusion, compared with those receiving two or more infusions. After a median time of 23 months 82.9% of the patients avoided late colectomy[20]. A retrospective study of 30 patients conducted at Oxford revealed that 53% of the patients required colectomy and only 17% achieved steroid-free remission after a median follow-up of 13 months[21].

It should be mentioned that IFX had a less pronounced effect in patients with more severe UC than in those with less severe UC in the Jarnerot study[3] and a detectable trough level of IFX was the strongest predictor of remission in the study of Seow *et al*[22].

COMPARISON BETWEEN CYCLOSPORINE AND INFLIXIMAB

The first head to head comparison of iv CsA and iv IFX was performed by Laharie *et al* In this parallel, open-label, randomised, controlled trial the Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID) compared the efficacy of CsA and IFX in acute, severe UC not responding to intravenous steroid therapy a minimum of 0.8 mg/kg per day for at least 5 days[23]. None of the patients had previously received rescue therapy. CsA and IFX were randomly given for 58 and 57 patients. Patients with a clinical response at day 7 were switched to oral 4 mg/kg CsA or received 2 additional IFX infusions on days 14 and 42. Treatment failure was noticed in 60% of the patients given CsA compared with 54% given IFX. Rate of colectomy did not differ between the groups. Odds ratio for treatment failure with CsA relative to IFX was 1.4, compared with 1.3 without adjustment. The clinical activity determined by Lichtiger scores between day 0 and day 7 decreased faster in patients who received IFX *vs* CsA; this difference was significant on days 3 and 4. The median time to clinical response was 5 days in the CsA group and 4 days in the IFX group. They concluded that CsA was not more effective than IFX in patients with acute severe UC refractory to intravenous steroids. The proportions of patients with serious adverse events were similar between the two groups. The high rate of treatment success with IFX was suggested to be due to a beneficial interaction between IFX and azathioprine in patients naive to both drugs.

In a retrospective review of inpatients with steroid-refractory UC the outcomes of 19-19 patients receiving CsA and IFX were examined[24]. At 12 months, colectomy rate was significantly higher in patients treated with CsA compared to IFX (68% for CsA, 37% for IFX, p=0.06), although CsA was used in a dose of 2 mg/kg and more patients received concomitant immunosuppressive drugs at the time of salvage therapy in the IFX-treated group. An Italian single center trial of 21 patients found no difference in 30-day remission rates achieved with IFX *vs* CsA, although, IFX was associated with more infective complications than CsA[25]. The observational study of Sjöberg[13] *et al* compared the efficacy of CsA and IFX as rescue therapies. Single IFX infusion proved to be more effective in preventing both early and late colectomy than CsA (93% *vs* 67% at 3 months and 77% *vs* 57% at 12 months). The superiority of CsA was seen exclusively during the first 15 days. It should be noted that first attack of the disease was significantly more common in IFX treated patients, and we previously confirmed that subsequent colectomy rate was 2.5 times higher in patient not responding to the first iv steroid therapy[26]. However, the CsA cohort had more severe disease activity as judged on higher CRP value, lower hemoglobin concentration, and higher fulminant colitis index after 3-4 days of steroid therapy. Kornbluth found that CsA may be better in hyperacute cases since its therapeutic level is achieved within 24 hours and the response to IFX on day 7 is equal to those with CsA[27]. A recently published paper[28] prospectively compared the clinical outcomes in patients treated with CsA or IFX in 83 steroid-refractory acute, severe UC. Of those patients who received ⩾72 h of CsA, 56% avoided colectomy at the time of discharge. However, colectomy free rate was 84% in patients receiving one IFX infusion (p=0.006). At 3 months, the colectomy-free rate was 53% for CsA *vs* 76% for IFX (p=0.04), and 42% *vs* 65% at 12 months (p=0.04).

Although no specific factor has been identified to differentiate between the patients' probably responding to CsA or IFX, hypalbuminaemia, superinfection with Clostridium difficile and deep colonic ulcerations are seems to be bad prognostic factors of responding to either CsA or IFX[27]. Data of Fabro's review indicated that new-onset UC, shorter disease duration and more active disease are more frequent in non-responders to IFX therefore in these cases use of CsA is more beneficial than IFX[29].

Burger *et al* revealed that short-term adverse events are higher in patients receiving IFX and that thiopurine refractory patients respond less well to CsA[30]. However, the recently published meta-analysis of Chang *et al* including the data of 321 patients demonstrated that the

rates of colectomy at 3 and 12 months, adverse drug reactions, and postoperative complications are equivalent when using IFX or CsA as a rescue therapy in acute, severe UC[31].

The currently ongoing trial 'CONSTRUCT (COmparison of iNfliximab and ciclosporin in STeroid Resistant Ulcerative Colitis)' with the main goals to determine the clinical and cost effectiveness of IFX and CsA in acute severe steroid resistant UC may help in the decision of the two therapeutic choice.

SWITCHING BETWEEN THE TWO DRUGS

Shifting from CsA to IFX and vice versa after the failure of the other drug seems to be an obvious therapeutic method, although the risk of toxicity is supposed to increase in these cases. Deciding the order of the therapies should also be considered because of the different pharmacokinetic characteristics of the drugs. Only one study examined the outcomes of CsA and IFX treatment after the failure of the other drug in severe, steroid-refractory UC and achieved colectomy free remission in one third of the patients with the salvage therapy[32].

Chaparro *et al* examined the efficacy and safety of IFX after CsA failure in patients with steroid refractory UC in a retrospective review. They found that after the first IFX infusion, 13% of the 47 patients achieved remission, and 74% partial response. Of the 35 patients who received the third IFX infusion, 60% achieved remission, and 37% partial response. 30% underwent colectomy. They concluded that IFX might avoid colectomy in two-thirds of patients with corticosteroid-refractory UC after failure of CsA. However, the rate of adverse events was 23%[33].

Due to the potentially high rate of short- and long-term complications, second line medical therapy however should be considered very cautious.

CONCLUSION

The treatment of steroid-refractory UC has been a challenge for ages, and, despite the continuous therapeutic improvement, surgery still plays an important role in the management of these cases. About 30% of the UC patients do not respond to corticosteroids and require surgery or alternative medical therapy. Although CsA and IFX are similarly effective in patients with UC not responding to intravenous steroids, toxicity, lack of maintenance therapy and the need of regular monitoring requiring special centers limit the use of CsA and IFX seems to be more effective in less severe cases. Despite the relatively high number of patients requiring colectomy on long term follow-up, CsA still remains the most effective, accepted rescue therapeutic solution for acute UC and also enables to introduce immunomodulators for maintaining remission. After the uncertain initial results, IFX became a new and effective therapeutic option for rescue therapy in steroid refractory UC. However, less data exist on the use of IFX in case of acute steroid failure maybe because IFX has been available for fewer years for severe UC. It seems that CsA is better in hyperacute cases since its therapeutic level is achieved within 24 hours and the response to IFX on day 7 is equal to those with CsA. In case of hypocholesterolaemia using IFX is more beneficial than CsA to avoid seizures in the patients. New-onset UC, shorter disease duration and more active disease are seems to be predictors of non-responding to IFX therefore in these cases use of CsA is more beneficial than IFX.

In conclusion, both CsA and IFX are possible and effective therapeutic choices in case of acute UC. CsA may be preferred in more severe cases and switching to IFX may be beneficial in case of non responders to CsA. Identifying biomarkers as predictors would also be helpful to find the most appropriate and individual therapy for the patients.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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