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RESEARCH ARTICLE

ORAL CYCLOSPORINE IN PATIENTS WITH SEVERE ACUTE ULCERATIVE COLITIS

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by intermittent exacerbations and remissions. About 15% of patients with UC will have a severe flare of their disease requiring hospitalization. Unfortunately, approximately 30% of patients admitted with severe ulcerative colitis fail intravenous steroids and require surgery or a second-line therapy. Oral cyclosporine has been reported to be useful in inducing remission in patients with corticoreistant severe UC. We present our experience of its use in fourteen patients.

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Introduction:-

Ulcerative colitis is a chronic debilitating inflammatory bowel disease with varied presentations. 15% of patients will suffer a severe flare during their lifetime requiring hospitalization. Corticosteroids have been the mainstay for inducing remission in patients with severe flare; however this therapy is not successful in all cases and those failing to respond usually undergo colectomy or a second-line treatment. Lichtiger et al [1] were the first to show benefit of parental cyclosporine in fulminant ulcerative colitis. Subsequently oral cyclosporine became available in microemulsion form and was found to be useful in acute ulcerative colitis [2].

We report here our experience with the use of oral cyclosporine in fourteen patients with severe ulcerative colitis not responding to steroids.

Results:-

We treated fourteen patients with severe ulcerative colitis (aged 25-62 years; sex ratio M/F : 1,8) with oral cyclosporine between June 2012 and January 2019. All the patients had severe disease according to Truelove and Witt's criteria. The diagnosis of ulcerative colitis was established on the basis of clinical presentation, endoscopy findings and supportive histology. Four patients (28,5%) were diagnosed for the first time. Twelve patients (85,7%) had pancolitis and two patients (14,3%) had left-sided disease. A lower gastrointestinal endoscopy was performed for all the patients showing signs of severe inflammation in six patients (42,8%). All fourteen patients had failed to respond to 5-7 days of intravenous steroid therapy (Truelove regimen).

Baseline investigations like hemogram , renal and liver profiles , serum calcium , magnesium and cholesterol were repeated prior to starting oral cyclosporine. None of the patients had perforation , megacolon or life-threatening hemorrhage initially.

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Oral Cyclosporine (5mg/kg/day; Neoral*) was added in a divided daily dose and steroids were continued in the usual tapering-off regimen associated with Cotrimoxazole. The clinical activity score was determined daily during hospital stay (Lichtiger score).

Clinical response was achieved in eleven patients (78,5%) . the main time to response was 5 days. The cyclosporine blood level was in the range (between 150 and 250 ng/ml) in two patients (14,2%) and was low in twelve patients (85,7%) in whom a dose of 1mg/kg has been added. Our eleven patients were started on oral azathioprine in the 7th day and Neoral* was continued for an average of 55,4 days (7-90 days). The main side effects were : tingling (n=2 , 14,2%) ; hypomagnesemia (n= 3 , 21,4%) ; hypocholesterolemia (n=1 , 7,1%) ; and a regressive acne with hirsutism (n=1 , 7,1%).

The three patients (22,4%) who didn't respond to cyclosporine went to surgery because of the unavailability of other alternatives.

After a median follow-up of 50 months (range 4 to 72 months), 9 responders were colectomy-free (64,2%) and treated with azathioprine (n=5) or 6-Mercaptopurine (n=2). Two of these 9 patients relapsed 10 and 18 months, respectively, after Neoral had been discontinued. They responded to corticosteroids and went back into remission again on azathioprine. As for the patients who had a subtotal colectomy, the evolution was favorable with restoration of intestinal continuity.

Discussion:-

Medical control of severe attack of UC using steroids is not feasible in a considerable number of cases, and 30% to 50% of patients finally need colectomy [11]. Initial uncontrolled studies in the early 1990s showed that 80% of patients with acute severe colitis refractory to intravenous steroid therapy responded to Cyclosporine given as an intravenous infusion of 4mg/kg². A further small (n=20) randomised comparison of Cyclosporine (4 mg/kg/day continuous intravenous infusion) versus placebo for 14 days in steroid-refractory patients confirmed a response rate of 82% in the Cyclosporine group compared to 0% in the placebo group. This study was terminated early due to the obvious difference between the treatment and placebo groups [1].

An oral microemulsion form of Cyclosporine (Neoral®) with high bioavailability was first used in the transplant population then subsequently tested in the setting of steroid refractory acute colitis following demonstrations that the pharmacokinetics were similar in patients with inflammatory bowel disease and controls. Additionally, a recent report from the Oxford group [15] suggests that Neoral was more effective than intravenous cyclosporine [12]

In 9 studies [2,3-10], all of them non-controlled, the efficacy of oral Cyclosporine was evaluated in patients with UC. In total, there were 94 patients, some with moderate flare-ups, although usually refractory to steroids. In several studies there were no specific details on the extent of the disease (at least in 23 patients the colitis was left-sided). The doses employed varied between 4 and 10 mg/kg; with 5 mg/kg being employed in 6 of the 9 studies. The rate of response was 71.2% , with response being obtained in 67 of the 94 patients included. The mean time-to-response, an aspect not specified in some studies, was a weighted mean of 5.19 days (range 3.8 to 7 days). Table I reflects the more relevant aspects of the articles evaluating oral Cyclosporine.

Table I:- Studies using oral cyclosporine for the treatment of severe ulcerative colitis attack.

Authors	Initial dose (mg/kg/day)	Patients (n)	Responders (%)	Response time (days)	Left-side colitis (patients,n)	Extensive colitis (patients, n)
Sood et al [3]	4	6	5 (83)	3,8	2	4
Daperno et al [4]	5	14	7 (50)	7	–	–
Falasco et al [5]	5	10	2 (20)	–	–	–
Navazo et al [6]	7	10	9 (90)	3	1	9

Ortiz et al [7]	5	5	4 (80)	5	1	4
Actis et al [8]	5	9	8 (88)	—	6	3
Van bodegraven et al [9]	10	12	9 (75)	—	1	11
Taylor et al [10]	5	13	9 (69)	—	5	4
Actis et al [2]	5	15	14 (93)	—	7	7
Our Study	5	14	11 (78)	5	2	12

Infliximab has been proposed in acute severe or corticosteroid-refractory active UC. Infliximab has a better safety profile than cyclosporine. Several open studies and two prospective randomized controlled trials have assessed the efficacy of infliximab in this setting [13, 14]. In 1 trial, the patients included were outpatients who had failed to respond to 40 mg of oral prednisone; the primary endpoint was remission at week 6. This trial showed no efficacy for infliximab [13]. In the other trial, patients included had failed to respond to intravenous methylprednisolone and were subdivided into fulminant and nonfulminant UC flares. The primary endpoint was colectomy or death. This trial showed a significant decrease in colectomy rate in patients treated with infliximab compared with those treated with a placebo [14]. The results of the latter trial are supported by those of the ACT I and II trials, which demonstrate the efficacy of infliximab compared with placebo [14]. These results do not abolish the use of cyclosporine in UC. Cyclosporine has a major advantage over infliximab in that it has a short half-life, and there is some evidence that inhibition of interleukin-2 production and NFAT-regulated gene expression by cyclosporine rapidly disappears after it has been stopped [15,16]. Consequently, if opportunistic infections occur, cyclosporine can be stopped and disappears rapidly from the serum after withdrawal, whereas infliximab remains for 8 weeks after infusion. For these reasons, cyclosporine remains a valuable option in active corticosteroid-refractory UC. The optimal therapy of severe or corticosteroid refractory UC (i.e., cyclosporine or infliximab) is an unresolved issue and should be tested in further studies. However, in patients who flare under azathioprine at therapeutic 6-TG levels, cyclosporine is not a valuable option because it is associated with high colectomy rates in the long term [17].

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