Cyclosporine in Acute Severe Ulcerative Colitis - Effective Rescue for the Economically Challenged

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ABSTRACT *Ulcerative colitis (UC) is a chronic inflammatory bowel disease with upto one fourth patients suffering from acute exacerbation of their disease. Steroids have been the mainstay of therapy but 30-40% patients are resistant to steroids, requiring either infliximab or cyclosporine. We describe three cases of severe acute UC managed with cyclosporine (parenteral followed by oral) in patients who were refractory to steroids and one patient was even refractory to infliximab. These three patients responded well to cyclosporine and were in clinical and endoscopic remission on follow up. The management of severe UC with cyclosporine highlights a viable, cost effective alternative to biological therapy in such cases*
KEYWORDS: *Acute Severe Ulcerative colitis, Cyclosporine, Infliximab, Steroids*

I. Introduction

Ulcerative Colitis (UC) is a chronic debilitating inflammatory bowel disease with varied presentations. 25% patients with UC suffer from a severe flare during their lifetime requiring hospitalization with a response rate of about 80%. Colectomy is curative but has a trade off in the form of increased stool frequency and pouchitis and thus colon rescue therapy is now in vogue. Cyclosporine and anti tumor necrosis factor-alpha therapy have emerged as an effective colon rescue therapy. Recent data suggests equal efficacy of cyclosporine and infliximab in steroid refractory severe UC. Despite evidence, cyclosporine is underused because it requires monitoring.

We present three cases of severe UC, treated with cyclosporine, achieving remission and were colectomy free till last follow up.

II. Case Series (Table 1)

Three patients of Ulcerative colitis were admitted over a period of three months to our centre. At presentation they had bloody diarrhea and significant weight loss, Evaluation showed anemia, raised ESR, Gd IV disease on sigmoidoscopy and the biopsy of each was consistent with ulcerative colitis. One of the patients had toxic megacolon. They were diagnosed as a case of acute severe ulcerative colitis based on True-Love and Witts criteria and managed initially with injectable hydrocortisone, antibiotics and component support. Two of the patients had previous exposure to azathioprine and one had been managed with infliximab. Two patients had a poor compliance to medication. They had minimal response to steroids and continued to have more than 10 stools daily with high of CRP levels at day three of steroids. They were managed with injectable cyclosporine (2 mg/kg/day) along with cotrimoxazole, injectable antibiotics, steroids and nutritional support. Steroids were continued for 01 month and then tapered at 05 mg/week and cyclosporine was given for a total duration of three months. Azathioprine was started on day 28 of cyclosporine. All three patients achieved remission and have been in remission till last follow up. Cyclosporine therapy was well tolerated and no side effects were noted in any patient. On follow up, the patients were in clinical and endoscopic remission.

Table 1: Patients Demography and case details

	Characteristics	Case 1	Case 2	Case 3
1.	Age (yrs)/Sex	32/Male	24/Male	37/Male
2.	Weight (kg)/Weight loss (Kg)	48/12	52/18	51/08
3.	Duration of illness prior to index illness (months)	23	06	96
4.	Number of exacerbation prior to index illness	02	01	5
5.	Previous exposure to Infliximab/Azathioprine	No/No	No/Yes	Yes/Yes

6.	Compliance to medication		Yes	No	No
7.	Steroids used before (number of times)		Yes (01)	No	Yes (04)
8.	Symptom duration of flare (weeks)		06	04	05
9.	Investigations at presentation				
	(a)	ESR (mm in 1st hour)/CRP	64/82	62/109	48/65
	(b)	Hemoglobin	6.4	7.2	6.8
	(c)	Potassium	4.8	2.4	3.5
	(d)	Sigmoidoscopy	Gd IV	Gd IV	Gd IV
	(e)	Biopsy	Active UC	Active UC	Active UC
	(f)	CRP at day three of steroids (ng/ml)	73	NA	62
10.	Requirement of dose escalation to 4 mg/kg/day		Yes	No	No
11.	Response to therapy (days)		03	04	03
12.	Total duration of IV cyclosporine (days)		10	08	08
13.	Total duration of full dose steroids (IV + oral) (weeks)		6	4	4
14.	Steroids tapered over (weeks)		8	7	7
15.	Total duration of cyclosporine (IV + oral) (weeks)		14	12	14
16.	Started on azathioprine (days after starting cyclosporine)		28	30	28
17.	Follow up after cyclosporine therapy (months)		30	24	24

III. Discussion

Global prevalence of UC varies from 7.6 to 246.0 cases per 100,000 people. In India, the prevalence data are scant and studies have estimated it to be 6.02 cases per 100000 people in India. Acute severe UC is an acute exacerbation characterized by presence of daily passage of at least six bloody stools, along with any other sign of systemic disease (ESR > 30 mm/h, temperature > 37.8° C, pulse > 90/min and hemoglobin < 10.5 g/dL) according to True-love and Witt's criteria. It affects up to 25% of patients, either on initial presentation or later requiring hospitalization [1].

Before intravenous steroids and colectomy, mortality rate was 70% in severe UC which now is less than 1% due to medical therapy, timely initiation of rescue therapy and availability of colectomy. Steroids reduce mortality as compared to placebo and form the mainstay of treatment of acute severe UC. Despite these, colectomy rates continue to be about 30% [2].

Presently for severe UC steroids are given for a period of 07 days with limited benefit beyond that with 30 – 40% patients being resistant to steroids and may need to go on to rescue medication or colectomy [3]. As the armamentarium grows, with novel targets of therapy, the treatment becomes more individualized and heterogeneous.

Cyclosporine, a calcineurin inhibitor with rapid onset of action, has been shown to be efficacious in severe UC enabling the physician to assess the response timely.

Lichtiger et al showed marked response to cyclosporine as compared to placebo (82% vs 0%) with crossover to cyclosporine showing 100 % response [4]. On comparing cyclosporine with infliximab, Sjöberg showed similar efficacy of the two agents but a lower rate of colectomy in the cyclosporine group in a retrospective review [5]. CYSIF trial randomized thiopurine naïve patients to cyclosporine or infliximab with azathioprine which was started on day 7 and steroids were tapered off. Approximately 85% patients had a positive response in both groups. On a 100 day follow up, colectomy rates (18% vs 21%) and treatment failures (60% vs 54%) were also similar [6].

In CONSTRUCT trial [7] 270 patients of acute severe UC were randomized to receive either Infliximab or cyclosporine and found that the rate of colectomy (41% vs 48%) and mean time to colectomy (811 vs 744 days) were similar.

Lowenberg et al in their study found that the median length of stay was significantly higher in the cyclosporine group (11 days vs 04 days) with higher initial hospitalization cost, but this difference reversed over three months. No significant differences were noted in colectomy rates at 6 months (23% vs 31%) [8]. Giovanni et al showed a colectomy-free rate of 61% at 1 year with better response in patients concurrently on azathioprine (80%) as compared to azathioprine untreated group (47%) [9].

Moskovitz et al showed that treatment with cyclosporine avoided colectomy in 83% of patients during initial hospitalization but most (54%) of these patients ultimately required colectomy (over a 7 year period) [10]. The colectomy rate was higher in thiopurine experienced patients as compared to patients who were concurrently started on thiopurines (59% vs 31%). Moccario et al also showed higher colectomy rates with cyclosporine as compared to infliximab with higher risk in patients with raised C Reactive Protein, extensive disease and non concurrent azathioprine use [11].

Cyclosporine administration protocol is with 2 mg/kg/day if the patient fails to show any response to parenteral steroids within 07 days (for severe colitis) or 03 days (for fulminant colitis) in absence of any contraindication to cyclosporine [12]. Cyclosporine levels should be done on the second day and repeated every three days with target trough levels of 150 – 250 ng/ml in whole blood. On establishing a response oral

cyclosporine should be started at 4 mg/kg/day and tapering of steroids should be initiated along with introduction of azathioprine. Cyclosporine should be continued for a total of three months (with a whole blood level of 100 – 200 mg/ml) and then tapered off. Subsequently the patients should be maintained on 5ASA and azathioprine for maintenance.

The potential limitations in the usage of cyclosporine vary from a higher cost of therapy, frequent monitoring of biochemical parameters, incidence of adverse effects and apparently higher colectomy rates.

Minor side-effects including tremor, paraesthesia, malaise, headache, abnormal liver function, gingival hyperplasia and hirsutism occur in 31% to 51% [13]. Nephrotoxicity due to dose dependant side effect can be reversed by concomitant use of calcium channel blockers. None of our patients developed renal dysfunction. With low dose of cyclosporine co-trimoxazole prophylaxis may not be necessary but may be required in the early phase when the dose is high and is usually given along with full dose steroids.

IV. Conclusion

Cyclosporine is an effective and potent member in the management of acute severe UC. It is as efficacious and potent as infliximab in terms of disease control and prevention of complications. It is comparable to infliximab to in short term prevention of colectomy. It proves to be useful and a more economically optimal alternative to other rescue medication especially in a developing country like India.

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