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Abstract
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Reference

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Low-dose oral microemulsion ciclosporin for severe, refractory ulcerative colitis

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SUMMARY
Background: The optimal modalities of treatment with oral microemulsion ciclosporin in patients with severe, steroid-refractory ulcerative colitis are uncertain.
Aim: To assess the applicability, in terms of efficacy and tolerability, of a standard oral microemulsion ciclosporin treatment protocol targeting relatively low blood ciclosporin concentrations, in patients with severe, steroid-resistant ulcerative colitis.
Patients and methods: Patients with a severe attack of ulcerative colitis and no satisfactory response to intravenous corticosteroids were started on oral microemulsion ciclosporin. Dosages were adapted according to a standard protocol, targeting a blood predose ciclosporin concentration ($C_0$) of 100–200 ng/mL. Patients without a clinical response on day 8 were scheduled for colectomy.
Results: Sixteen patients were enrolled. A clinical response was observed in 14/16 (88%). The mean clinical activity index scores and concentrations of C-reactive protein on days 0, 4 and 8 were 11.8, 6.7 and 4.1, and 50.3, 19.3 and 9.7 mg/L respectively. The mean $C_0$ (days 0–8) was 149 pg/mL. The mean creatinine clearance rates on days 0 and 8 were 88 and 96 mL/min. One patient had an acute elevation of transaminases that resulted in discontinuing ciclosporin.
Conclusions: Even when dosed for a target $C_0$ of 100–200 ng/mL, oral microemulsion ciclosporin for severe, steroid-refractory ulcerative colitis achieves an efficacy similar to that attained with higher, potentially more toxic levels. The oral route should replace intravenous treatment in this clinical setting.

INTRODUCTION
Severe attacks of ulcerative colitis (UC) are steroid-refractory in 40% of cases.1–4 In 1994, Lichtiger et al.5 showed that intravenous ciclosporin afforded a response rate of 82%, compared with none in the placebo group, for patients with severe, steroid-refractory UC. A mean acute response rate of 75% was confirmed in subsequent open series6–11 and 78% of successfully treated patients have avoided colectomy in the follow-up if azathioprine (AZA) or mercaptopurine was added.9, 11 Two further randomized controlled trials (RCTs) showed a similar efficacy of intravenous ciclosporin monotherapy when compared with ciclosporin combined with corticosteroids12 and a similar efficacy of low-dose intravenous ciclosporin (2 mg/kg) when compared with 4 mg/kg.13 Although the three RCTs designed to assess ciclosporin efficacy in UC have not been powered to detect low-frequency side-effects, a number of case studies emerged, showing that considerable toxicity may be associated with intravenous ciclosporin treatment, particularly opportunistic infections such as fatal Pneumocystis carinii and Aspergillus fumigatus pneumonias,11, 14, 15 and seizures.16 In addition, the transplantation community

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has the experience of severe renal and neurological toxicity associated with the use of intravenous ciclosporin therapy.\textsuperscript{17} Thus, the introduction of oral microemulsion ciclosporin (Neoral, Novartis Pharma, Bern, Switzerland) that has a better bioavailability and lower variations of blood concentration than the older, lipophilic (Sandimmun, Novartis Pharma) preparation\textsuperscript{18, 19} and has allowed to abandon in many cases the use of intravenous ciclosporin early after organ transplantation.\textsuperscript{20, 21} has been a major progress in organ transplantation.

In steroid-refractory UC, oral ciclosporin has not been compared with intravenous ciclosporin, probably because of the large sample size required by a properly designed equivalence study. However, oral ciclosporin has been used to treat steroid-refractory UC in three open-label studies\textsuperscript{22–24} based on a total of 31 patients, with success rates of 85–100%. The chosen target ciclosporin concentrations varied markedly,\textsuperscript{22, 23} hence the optimal modalities of ciclosporin administration in this setting are still uncertain.

The aim of this study was to assess the applicability, in terms of efficacy and tolerability, of a standard oral microemulsion ciclosporin treatment protocol targeting relatively low blood ciclosporin concentrations, in patients with severe, steroid-resistant UC. We report here the results obtained with this approach in the first 16 patients.

**PATIENTS AND METHODS**

All patients had severe, refractory UC, defined according to the following criteria: (i) they had suffered a severe flare according to the modified ‘Oxford’ criteria of Truelove and Witts;\textsuperscript{4, 25} (ii) they had received intravenous corticosteroids (methylprednisolone 0.8 mg/kg or equivalent) for seven or more days, along with low-fibre diet, adequate intravenous fluid and electrolyte replacement and low molecular-weight heparin (LMWH); (iii) they still had five or more bloody bowel movements per day and, additionally, a general wellbeing rated as ‘average’ or worse by the doctor, or abdominal tenderness rated as ‘mild/localized’ or worse; (iv) a lower endoscopy at least until the splenic flexure had been performed between the sixth and eighth day of intravenous corticosteroid treatment to confirm the presence of active inflammatory lesions.

Eligible patients were checked for the following exclusion criteria: perforation of the bowel; megacolon as defined by a colonic dilatation of at least 6 cm associated with systemic toxicity;\textsuperscript{26} uncontrolled local or systemic infection; presence of bacterial pathogens or *Clostridium difficile* toxin in stool samples collected between the sixth and eighth day of intravenous corticosteroid treatment; uncontrolled hypertension; renal failure as defined by a creatinine clearance (estimated with the Cockroft formula) of <20% of the normal rate; serum transaminases or alkaline phosphatase activities more than 1.5 times the normal value and a serum cholesterol concentration of <3.1 mmol/L.

In addition, patients were excluded if the medicosurgical team judged that continuation of medical treatment was unsafe, on the basis of general and nutritional status. The presence of cytomegalovirus (CMV) inclusions in rectal or colonic biopsies was not an exclusion criterion but warranted an antiviral treatment, as detailed below.

Based on previous personal observations of ciclosporin efficacy even at low *C*\textsubscript{0} in steroid-refractory UC, we chose a target predose trough (*C*\textsubscript{0}) ciclosporin concentration of 100–200 \(\mu\)g/L. This target *C*\textsubscript{0} is slightly lower than the 150–250 \(\mu\)g/L *C*\textsubscript{0} used in the low-dose arm of a comparative trial of intravenous ciclosporin.\textsuperscript{13}

The *C*\textsubscript{0} were measured using a radioimmunoassay with a monoclonal antibody, daily after the third dose until the target *C*\textsubscript{0} was attained and every 2nd day thereafter. For patients enrolled after 2002, the concentration of ciclosporin 2 h postdose (*C*\textsubscript{2}) was determined in addition to *C*\textsubscript{0}. Neoral was started at 3 mg/kg b.d. *C*\textsubscript{0}-based dose adjustments were performed according to a standard protocol (Table 1).

Intravenous corticosteroids were continued at the same dosage throughout the ciclosporin treatment. Azathioprine or mercaptopurine, when already taken on inclusion, was continued. Patients with CMV inclusions in rectal or colonic biopsies collected before ciclosporin treatment were given oral valganciclovir, 450 mg b.d., for 14 days.

<table>
<thead>
<tr>
<th>Ciclosporin <em>C</em>\textsubscript{0} (ng/mL)</th>
<th>Dosage adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75</td>
<td>+1 mg/kg b.d.</td>
</tr>
<tr>
<td>76–99</td>
<td>+0.5 mg/kg b.d.</td>
</tr>
<tr>
<td>100–200</td>
<td>No change</td>
</tr>
<tr>
<td>201–300</td>
<td>−0.5 mg/kg b.d.</td>
</tr>
<tr>
<td>&gt;300</td>
<td>−1 mg/kg b.d.</td>
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Patients were evaluated on days 0, 4 and 8 of ciclosporin treatment using the Lichtiger clinical activity index (CAI). A clinical response was defined as a CAI of <10 on day 8, with a drop of ≥3 when compared with baseline. In case of clinical response, the patients were switched on oral prednisolone 1 mg/kg for 2 weeks, which was then tapered by weekly 10 mg decrements until half of the initial dosage was attained and thereafter by weekly 5 mg decrements. Ciclosporin was continued at the same dosage for a total of 8 weeks, with weekly controls of blood levels. Azathioprine 2–2.5 mg/kg was started within a week of treatment success, thus allowing for a 6–7 week overlap of ciclosporin and AZA. Although co-trimoxazole prophylaxis of pulmonary pneumocystosis was not an obligate part of the protocol, it was used during the triple immunosuppression phase in selected patients. Self-administered LMWH was continued after discharge for a total duration of 4 weeks, including the inpatient phase. When a clinical response was not obtained, subtotal colectomy was performed. In addition, subtotal colectomy was decided based on clinical judgement or in case of occurrence of an adverse event forcing to discontinue ciclosporin permanently.

RESULTS

The study period extended from October 1996 to February 2005. During this period, 36 patients were admitted for severe UC. Two had toxic megacolon and underwent immediate subtotal colectomy. Among the remaining 34, 17 had disease refractory to intravenous corticosteroids as defined above and were considered for the study. The team decided to perform subtotal colectomy for one of the 17 patients, for whom continuation of medical treatment appeared unsafe because of poor general condition and impending colonic perforation. No other exclusion criteria were met, leaving 16 patients (11 males and five females) enrolled in the study. The mean age was 41 years (range 19–69). Four had new-onset UC and 12 had had UC for 1 month to 9 years. At inclusion, the duration of the intravenous corticosteroid treatment was 8–14 days. Two patients had received 3 mg/kg/12 h. The target 100–200 μg/L was attained between days 1 and 4.

The mean CAI scores were: 11.8 (day 0), 6.7 (day 4) and 4.1 (day 8). The mean serum concentration of C-reactive protein (CRP) was: 50.3 mg/L (day 0), 19.3 mg/L (day 4) and 9.7 mg/L (day 8) (Figure 1). Dose adjustments were performed for most patients; however, the mean dosage used on day 8 was 2.85 mg/kg/12 h, a value close to the 3 mg/kg/12 h used initially. The target 100–200 μg/L was attained between days 1 and 4.

The mean C0 for all measurements was 149 μg/L (142 μg/L for responders, 199 μg/L for non-responders). For the five patients who had measurements of both C0 and C2, the mean values were 148 and 826 μg/L respectively. The non-responder patient had both values above the average.

The mean creatinine clearance rates on days 0 and 8, estimated with the Cockroft formula, were 88 and 96 mL/min respectively (P = 0.08, paired Student’s t-test). One patient developed acute renal failure on day 3, when he had refused to be adequately hydrated for 48 h. Ciclosporin administration was suspended for 2 days and then resumed after the patient had been rehydrated and renal function had normalized. For this reason, the patient did not qualify for treatment failure in the study. One patient had mild, chronic renal failure at the beginning of ciclosporin treatment (creatinine clearance rate 47 mL/min). The mean ciclosporin dose used between days 0 and 8 for this patient was 2.2 mg/kg/12 h; the creatinine clearance rate did not worsen on day 8 (51 mL/min) and thereafter. No cases of arterial hypertension were observed.
Two patients had acute psychiatric diagnoses during the ciclosporin treatment phase, one of them required referral to the psychiatric ward for a 6-week period. Three patients had mild tremor, one had simultaneous alopecia and face hirsutism that continued for 3 months after the ciclosporin treatment was over. Only one patient (described above) developed abnormal liver tests during ciclosporin treatment.

DISCUSSION

We describe a standardized protocol for oral microemulsion ciclosporin administration in patients with steroid-refractory UC, deliberately targeting $C_0$ concentrations of 100–200 ng/mL, lower than those used in previously published studies. In a series of 16 patients, we find that this regimen has a similar efficacy compared with those described so far and does not impair renal function.

The value of our observation is limited by the absence of a randomized comparison with the reference treatment (intravenous ciclosporin) and by the small number of patients included. Nevertheless, the comparison retains some validity as our inclusion criteria exactly match those used in previous studies of intravenous ciclosporin, and the overall treatment success rate of 13 of 16 subjects (88%) in the acute phase is at least comparable with the previously published results.

Overall, ciclosporin was well-tolerated. The most severe adverse drug reaction was the occurrence of acute psychiatric conditions in two patients. Although corticosteroids might have contributed to these two episodes, the direct involvement of ciclosporin that might cause severe neuropsychiatric adverse effects is plausible. Potential severe psychiatric side-effects should be taken into account when considering ciclosporin treatment for severe UC.

No study has adequately determined whether there is a correlation between ciclosporin serum levels and response rates in steroid-refractory UC. In the original study with intravenous ciclosporin, dosages were adapted to achieve a broad range of $C_0$, from 100 to 400 ng/mL. In a later study, the response rate was identical whether patients were assigned to intravenous ciclosporin dosed for a $C_0$ of 150–250 ng/mL, or of 250–350 ng/mL.

In this regard, our results extend the information gained from the three previous reports of steroid-refractory severe UC treated with oral microemulsion ciclosporin. The largest of these studies included 15 patients and achieved $C_0$ spanning from 60 to 240 ng/mL, making it difficult to draw any conclusions about the optimal range. In another study based on 10 cases, the target $C_0$ ranged between 250 and 350 ng/mL; these levels are higher than the 150–250 ng/mL target $C_0$ that have been shown efficacious after intravenous administration. The third report provided only limited information as it was based on six observations only and achieved a wide range of ciclosporin $C_0$ (220–480 ng/mL). We have shown that a target $C_0$ of 100–200 ng/mL achieves an efficacy similar to that attained with higher, potentially more toxic levels. Individual dosages of ciclosporin required adaptation for most patients, a fact partially hidden by the finding that the mean ciclosporin dosages on day 8 were virtually identical to those used initially.

None of the previously published studies provided any data regarding the 2 h post-dose ($C_2$) ciclosporin.
concentration, a parameter now known to be critical.\textsuperscript{29, 30} In the present study, ciclosporin dosage adjustments were initially based on the $C_0$ level. Meanwhile, the use of $C_2$ has been advocated for in the early phase following renal,\textsuperscript{11} liver\textsuperscript{32} and heart\textsuperscript{33} transplantation, and therefore we have implemented $C_2$ dosage for the last five patients. $C_2$ correlates with drug exposure as defined by the area under the curve of ciclosporin concentration much better than does the $C_0$ ‘trough’ level.\textsuperscript{31} We observe that the mean $C_2$ level of 839 $\mu$g/L found in our patients is just below the typical target $C_2$ of 850–1400 $\mu$g/L used in a study of de novo liver recipients.\textsuperscript{32} More studies are required to determine the optimal target $C_2$ for patients with severe, steroid-refractory UC.

Historically, the rationale for using intravenous ciclosporin was the need to deliver effective blood levels of ciclosporin in de novo solid-organ transplant recipients, for whom the oral route was insufficient because of postoperative ileus and poor bioavailability of the older lipophilic formulation of ciclosporin. Since the advent of oral microemulsion ciclosporin, the use of intravenous ciclosporin in solid-organ transplant recipients has markedly decreased,\textsuperscript{20, 21} a practice widely adopted despite the absence of formal equivalence studies comparing the two regimens. Similarly, considering that microemulsion ciclosporin has pharmacological parameters in patients with UC similar to those previously measured in other populations,\textsuperscript{34} and its apparent efficiency in concording open studies\textsuperscript{22–24} including ours, we believe that it should now replace intravenous ciclosporin for the treatment of severe steroid-refractory UC.

REFERENCES