Efficacy of intravenous cyclosporin in moderately severe ulcerative colitis refractory to steroids

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SUMMARY

Objective — The efficacy of intravenous cyclosporin (CSA) in acute severe ulcerative colitis (UC) is well established. The aim of this study was to evaluate its efficacy in moderately severe colitis refractory to steroids.

Methods — Twenty-six patients (17 men, mean age 41 ± 14 yr) with UC refractory to steroids treated with CSA were included in this study. Severity was defined according to Truelove criteria. A clinical activity score below 10 during 2 consecutive days defined clinical response.

Results — According to Truelove criteria, all patients had moderate UC. CSA was administered IV at a mean daily dose of 3.7 ± 0.5 mg/kg until response and then orally for 3.5 ± 2.6 months. A clinical response was achieved in 20/26 patients (76.9%) within 5.7 ± 2.8 days (5/6 failures were treated by proctocolectomy). During a follow-up of 27.8 ± 20.8 months, relapse rate was 60% (12/20). 7 patients underwent proctocolectomy and 5 had clinical remission with CSA retreatment (N = 4) and steroids (N = 1). At the end of follow-up, 12 patients (46%) were in clinical remission, 12 (46%) required colectomy, and 1 had chronic active UC and 1 was lost of follow-up. The probability to avoid surgery was 52% at 78 months. The only factor associated with avoidance of surgery was concomitant treatment with azathioprine (P = 0.007). Ten reversible adverse events occurred in 9 patients.

Conclusion — This study shows that CSA is safe and effective in moderately severe steroid resistant UC. Concomitant treatment with azathioprine significantly decreases the rate of subsequent surgery. CSA may act as a “bridge” until the therapeutic action of azathioprine is achieved for maintenance treatment. These results should be further confirmed by a prospective controlled study.

RÉSUMÉ

Efficacité de la ciclosporine intraveineuse dans le traitement des poussées modérées de recto-colite hémorragique cortico-résistante

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L’efficacité de la ciclosporine dans le traitement des poussées aiguës sévères de recto-colite hémorragique (RCH) est bien établie. Le but de cette étude était d’évaluer son efficacité dans les poussées modérées de RCH cortico-résistantes.

Patients et méthodes — 26 malades avec RCH cortico-résistante (17 hommes, âge moyen 41 ± 14 ans) traités par ciclosporine IV ont été inclus dans cette étude rétrospective. La sévérité des poussées était évaluée selon les critères de Truelove. La réponse au traitement était définie par un score d’activité clinique inférieur à 10 au moins 2 jours de suite.

Résultats — Les 26 malades présentaient une poussée modérée selon Truelove. La ciclosporine IV (dose moyenne 3,7 ± 0,5 mg/kg, puis relais oral pendant 3,5 ± 2,6 mois) a induit une réponse clinique initiale (décalé 5,7 ± 2,8 jours) chez 20/26 (76,9 %) malades ; parmi les 6 échecs il y a eu 5 colectomies. Après un suivi moyen de 27,8 ± 20,8 mois, le taux de rechute était de 60 % (12/20) : 7 colectomies, 5 remissions obtenues par une corticothérapie et 4 retraitements par ciclosporine. Au terme du suivi, 12 malades (46 %) étaient en rémission prolongée et 12 (46 %) malades avaient dû être colectomisés (1 en poussée chronique active, 1 perdu de vue). À long terme, la probabilité d’éviter une colectomie était de 52 % à 78 mois. Parmi tous les facteurs étudiés, seul un traitement par azathioprine était associé à un taux plus faible de colectomies (P = 0,007). Dix effets secondaires réversibles non graves ont été observés chez 9 malades.

Conclusion — Cette étude montre l’efficacité et la bonne tolérance de la ciclosporine dans la RCH cortico-résistante en poussée modérée. Un traitement par azathioprine diminue significativement le taux de colectomies. Ces résultats mériteraient d’être confirmés par une étude prospective contrôlée.

Introduction

Conventional treatment for acute episodes of ulcerative colitis (UC) includes 5-aminosalicylates and corticosteroids. However, many patients are either refractory or intolerant to these treatments and colectomy is considered as an alternative, especially in patients with severe attacks. Since 1994, cyclosporin A (CSA) has been shown to be effective to reduce the need for surgery in 60 to 86% of patients with severe attacks of UC refractory to steroids [1-5]. However, up to 70% of patients who initially responded to CSA undergo colectomy within 6 to 12 months [1, 4]. In these patients, CSA offers the opportunity to avoid emergency colectomy and provides time for “elective” colectomy.

In cases of moderately severe acute episodes of UC refractory to steroids, colectomy can be performed without emergency in

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relatively fit patients. However, colectomy may sometimes appear excessive in patients with chronic active disease and/or mild distal left-sided colitis. Azathioprine and 6-mercaptopurine are used as long-term therapy in chronic active UC but the delay in response [6], from 3 to 6 months, limits their use in patients with altered quality-of-life. Therefore, the possibility of rapidly achieving remission could be of interest in this subgroup of patients. The aim of this study was to evaluate the efficacy of CSA in patients with moderately severe attacks of UC refractory to steroids.

Patients and methods

This study was conducted between January 1996 and July 2002 in two departments of Gastroenterology (Saint-André University Hospital, Bordeaux and Hôtel-Dieu University Hospital, Nantes, France). All patients treated with IV CSA for moderately severe UC resistant to steroids were included in the study.

All patients had a diagnosis of UC based on clinical, endoscopic and histological findings. To be included, patients had to present with a moderately severe attack of UC according to Truelove criteria [7] and to have not responded to conventional treatment with steroids, i.e., at least 1 mg/kg per day either intravenously (IV) or orally administered for one week.

Patients initially received IV CSA as a continuous infusion at the dose of 4 mg/kg per day, which was subsequently adapted to maintain plasma CSA levels between 100 and 400 ng/ml.

Disease activity was assessed using the clinical activity score ranging from 0 (no symptom) to 21 (severe symptoms) described by Lichtiger et al. [3]. The clinical activity score was calculated every day from the start of CSA. A score under 10 points during two consecutive days defined initial response and patients were then switched to oral CSA (Neoral®). Clinical remission was defined as the absence of diarrhea, bloody stools, and abdominal pain. Once remission was achieved, steroids were progressively tapered until complete discontinuation. Azathioprine (2-2.5 mg/kg per day) was introduced either simultaneously to CSA or 6 to 8 weeks after remission. Antibiotic prophylaxis was not systematically prescribed. Non-responders were proposed for colectomy.

Non-surgical patients were contacted at the end of study to collect the following elements: number of stools, pain, general well-being, and type of current treatment.

Parameters involved in the induction of initial response and subsequent need for colectomy were analyzed. Statistical analysis was performed using Fisher’s test for qualitative variables. The Student’s t test was used for quantitative variables with normal distribution, and the Kolmogorov-Smirnov’s test was used for quantitative variables with uneven distribution. The Kaplan-Meier method was used to determine the probability to avoid colectomy (non-colectomy survival rate). A P value < 0.05 was considered as statistically significant (software: Stata™ 7.0). All results are expressed as means ± standard deviation (SD).

Results

Patient demographics

We identified 26 patients treated with IV CSA for moderately severe UC resistant to steroids: 22 patients treated once, 3 treated twice, and one treated three times. The characteristics of the study population are reported in table I. The mean age was 41 years when CSA therapy was started, 65% were male. CSA therapy was initiated for resistance to oral (N = 11) or IV (N = 13) steroids, and for steroids intolerance in 2 patients (due to diabetes mellitus and osteoporosis, respectively). The mean duration of active disease before CSA therapy was 2.8 ± 2.4 months. Only 4 patients (15%) were treated for a first acute episode of UC. Fifty-four percent of patients had left-sided UC, 31% had pancolitis. According to Truelove criteria, all patients had moderately severe colitis: all patients had 0 to 3 disease activity index (maximum 21) and severe lesions, respectively. Azathioprine was commenced in 16/20 (80%) patients who initially responded to IV CSA. Among the 4 patients who did not receive azathioprine, one was previously known to be intolerant to this drug, and 3 had relapsed within the first 2 months, i.e., before introduction of azathioprine.

In 6 patients, IV CSA failed to achieve remission: 2 resistant to IV steroids and 3 to oral steroids. Five of them had an adequate CSA plasma levels (not performed in 1). Five patients underwent colectomy and one preferred to maintain steroid treatment. The five colectomies were performed during the first month following CSA treatment.

Long-term response

During a mean follow-up of 27.8 ± 20.8 months (range: 6-78), 8 patients had long-term remission without relapse: 7 were long-term responders after 17.6 ± 9.2 months (range: 6-32), 1 was in remission with no steroids but still received oral CSA 13 months after inclusion. All of these patients received azathioprine...
prine once remission was achieved. Seven patients were able to interrupt steroids and one patient had maintenance steroids < 5 mg per day but about to discontinue at the end of study.

Twelve patients with an initial response relapsed after IV CSA. Seven patients relapsed while on oral CSA and underwent colectomy at 2.4 ± 1.7 months after initial therapy: 5 in the first 3 months, 1 at 7 months, and 1 at 12 months. Five patients relapsed after they had stopped oral CSA for 11.5 ± 2.3 months; 3 were treated with azathioprine, 2 had stopped azathioprine for 6 months. All of them were successfully treated with either oral steroids (N = 1) or with another course if IV CSA (N = 4) at 2.4 ± 1.7 months after initial therapy: 5 in the first 3 months, 1 at 7 months, and 1 at 12 months. Five patients relapsed after they had stopped oral CSA for 11.5 ± 2.3 months; 3 were treated with azathioprine, 2 had stopped azathioprine for 6 months. All of them were successfully treated with either oral steroids (N = 1) or with another course if IV CSA (N = 4) with long-term remission achieved in all but 1 patient who experienced another relapse and was treated with a third course of IV CSA, and remained in remission 4 years later.

To summarize (figure 1), 20/26 patients (77%) had an initial response to IV CSA. Eight experienced long-term remission and 12 relapsed. Seven patients underwent colectomy after relapse, 5 responded to medical treatment. Thirteen patients experienced long-term response after one (N = 8), two (N = 4), three (N = 1) courses of IV CSA. Twelve patients underwent colectomy: 5 because of initial failure of IV CSA, 7 because they relapsed while on oral CSA. All colectomies were performed during the first year following initial treatment with IV CSA. Life table analysis of “non colectomy” is show in figure 2. The probability of not requiring colectomy was 62% at 6 months (CI 0.40-0.77), and 52% at 6.5 years (CI 0.31-0.70).

Predictive factors of long-term response

According to long-term response, 2 groups of patients were defined: Group I consisted of patients (N = 13) with long-term remission without colectomy, including those with one or several relapses and one patient in remission but lost to follow-up at 6 months; Group II (N = 13) included all the patients who underwent colectomy and the patient who failed to respond to CSA but who declined surgery. As indicated in table II, there was no significant differences between the 2 groups in terms of demographics, clinical characteristics of disease, and dose of CSA initially administered to achieve remission.

Outcome of patients with initial response to IV CSA according to azathioprine therapy was evaluated: while azathioprine did not significantly influence the relapse rate (50% vs. 100%, P = 0.117), it significantly decreased the need for colectomy (18.8% vs. 100%, P = 0.007).

Tolerability

Nine patients experienced 10 adverse events. Six events occurred during the IV CSA treatment: arterial hypertension (N = 3), transient ischemia attacks due to hypertension (N = 1), paresthesia (N = 1), and Streptococcus faecalis septicemia from central venous catheter (N = 1). No case of opportunistic infection was observed. The case of transient ischemia attacks and 2 cases of hypertension occurred in patients with plasma CSA levels above normal range (674 and 744 ng/mL, respectively). CSA was discontinued in the patient with transient ischemia attacks who entirely recovered in 24 hours. Since a clinical response had been obtained, oral CSA was started without any further compli-
cation. However, this patient relapsed 4 weeks later and underwent colectomy. One case of reversible neutropenia and 1 case of hypertrichosis occurred during treatment with oral CSA.

**Discussion**

This study shows that IV CSA rapidly achieves remission in approximately 80% of patients with moderately severe UC refractory to steroids. Long-term remission without steroids was observed in 50% of patients, especially when azathioprine was initiated once clinical response was obtained. Treatment with azathioprine was the only factor significantly associated with avoidance of colectomy. The results of CSA in moderately severe UC are very similar to those reported in severe acute colitis refractory to steroids.

As in many other studies designed to evaluate the efficacy of CSA in refractory acute exacerbations of UC [3, 8, 9], the disease severity in the present study was determined according to clinical and biological criteria (Truelove and Witts criteria) [7]. The mean duration of the attacks (2.8 months) clearly indicates that the patients included in our study had chronically active steroid-resistant UC.

Data concerning the efficacy of CSA in non-severe UC are limited, but consistent with the results of the present study: CSA can achieve remission rates of 65 to 100% when administered IV [10, 11]. Actis et al. have reported a small series of 9 patients treated with oral microemulsion CSA for chronic active steroid-dependent UC: 8 out of 9 (89%) patients had remission without steroids, 5 of them with a maintained response at 3 months. Our study, involving a significant number of patients with long-term follow-up, provides further evidence that CSA is as effective in moderately severe as in severe colitis [12].

The 52% probability of non-colectomy at 6.5 years in the present study is consistent with previous results of IV CSA used in severe acute colitis [1, 2, 4, 8]. We found no predictive factor of long-term remission apart from treatment with azathioprine. Azathioprine was associated with a lower rate of relapse (50 vs. 100%) although statistical level of significance was not reached probably because of a type 2 error. In contrast, treatment with azathioprine was significantly associated with avoidance of colectomy (18.8 vs. 100%). It has been previously suggested that responders to IV CSA in severe acute UC maintain a significantly longer remission when azathioprine (or 6-mercaptopurine) is given simultaneous to or after CSA [2]. Our results suggest that the same holds true for moderately severe UC but, considering the small number of patients not treated with azathioprine and the retrospective design of our study, this should be confirmed by adequate controlled studies. Indeed, among the 4 patients who did not receive azathioprine, 3 experienced an early relapse; it is therefore difficult to conclude that azathioprine would have been effective to prevent the relapse. Nevertheless, considering the high proportion of patients who underwent colectomy, the use of CSA alone because of intolerance or allergy to azathioprine is questionable, especially in patients with chronic active steroid-resistant colitis. In patients treated with azathioprine, relapses may eventually be retreated with IV CSA as was the case in 4 patients in the present study. In these patients, long-term response without colectomy was obtained. Re-treatment may be useful to allow for azathioprine to achieve efficacy which can sometimes take 6 to 9 months.

The overall tolerance to CSA was good and similar to previous studies, although it has been suggested that a lower dose (i.e., 2 mg/kg per day) may provide an improved toxicity profile [13]. The concomitant treatment with oral CSA and azathioprine was well tolerated, as previously reported [14].

In conclusion, this study shows that in UC refractory to steroids, IV CSA is as effective in chronic active disease as in severe acute attacks. Oral microemulsion CSA may be as effective and safer than IV CSA [12] and therefore represents a more ade-

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**Table II.** – Comparison of demographic and clinical characteristics of patients with long-term remission without colectomy after CSA therapy (group I) and patients who failed to respond to CSA (group II).

<table>
<thead>
<tr>
<th></th>
<th>Group I (N = 13)</th>
<th>Group II (N = 13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>8/5</td>
<td>9/4</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 ± 13</td>
<td>44 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.9 ± 5.8</td>
<td>5.8 ± 6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of the attacks (weeks)</td>
<td>1.9 ± 1.3</td>
<td>3.6 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Truelove score</td>
<td>1.9 ± 1.3</td>
<td>2.2 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical activity index</td>
<td>13.5 ± 2.7</td>
<td>12.9 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Localisation of colitis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left colon (N = 14)</td>
<td>8 (57%)</td>
<td>6 (43%)</td>
<td>NS</td>
</tr>
<tr>
<td>Sub total (N = 4)</td>
<td>2 (50%)</td>
<td>2 (50%)</td>
<td></td>
</tr>
<tr>
<td>Pancolitis (N = 8)</td>
<td>3 (38%)</td>
<td>5 (62%)</td>
<td></td>
</tr>
<tr>
<td>IV CSA in mg/kg/day</td>
<td>3.7 ± 0.6</td>
<td>3.8 ± 0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

CSA : cyclosporin A

* results expressed as mean ± SD.
Cyclosporin in moderately severe ulcerative colitis

An adequate formulation allowing treatment on an outpatient basis. CSA achieves remission rapidly in most patients, but long-term remission probably requires treatment with azathioprine. Oral CSA may act as a “bridge” until the therapeutic action of azathioprine is achieved for maintenance treatment, although recent data do not support this hypothesis [15]. Therefore, further randomized studies are needed to evaluate the efficacy of oral CSA in chronic active steroid-resistant colitis.

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