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Endoscopic and histologic response to cyclosporine in ulcerative colitis and their impact on disease outcome: a cohort study

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Maylis Capdepont: statistical analysis and manuscript review.

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ABSTRACT

Introduction: Cyclosporine (CsA) is an effective agent for treating patients with acute steroid-refractory ulcerative colitis (UC). The aim was to assess endoscopic and histologic responses to CsA and to determine their predictive value on UC outcome.

Patients & methods: Consecutive UC patients who received intravenous CsA for an acute refractory UC were included when they had endoscopic assessments with biopsies at entry and, at CsA interruption in responders. Mucosal healing (MH) was defined by Mayo endoscopic subscore $\leq 1$ and, histologic response (HR) by the absence of basal plasmocytosis or a Geboes score $< 3.1$.

Results: Among 21 patients who responded to CsA, MH was achieved in 81%. Survival rates without relapse at 2 years were 79% and 25% in patients with MH and without MH, respectively (p=0.04). HR was observed in 84% of patients according to basal plasmocytosis and in 68% according to Geboes score. Multivariate analysis revealed that a Mayo endoscopic subscore of 0 was the only prognostic factor associated with absence of relapse (RR=12; 95%CI: 1.05–136.79).

Conclusion: CsA provides MH and HR in most of UC patients responding to this drug. As suggested with other UC treatments, a complete MH with CsA has a good prognostic value.
INTRODUCTION

Ulcerative colitis (UC) is a lifelong inflammatory bowel disease involving the colorectal mucosa. Disease evolution is characterized by periods of flares, alternating with remission phases. During the last years, therapeutic goals in UC have dramatically evolved, moving from control of symptoms with steroid weaning and prevention of relapse to clinical remission associated with improvement of the endoscopic lesions. Indeed, UC patients achieving mucosal healing (MH) under treatment will have less disease relapse, related hospitalisations\(^1\) and colectomy compared to those with a clinical remission only\(^2,3\). Consequently, the most recent guidelines and experts’ consensus considered mucosal healing as a major therapeutic objective in UC\(^4,5\). It is now under debate if a complete mucosal healing - meaning recovery of a normal gut mucosa - should be reached rather than the persistence of mild endoscopic lesions, such as erythema and decreased vascular pattern.

Furthermore, and beyond mucosal healing, histologic healing (HH) has recently emerged as possible therapeutic objective. Few studies have examined the relationship between microscopic inflammation and long term outcome in UC. The analysis of the data suggest that histologic healing may be associated with more favourable disease course, with less disease relapse and risk for developing colorectal neoplasia\(^6,7\).

Despite these new therapeutic goals and significant improvements regarding medical treatment, UC still has a poorly predictable evolution. Even if most patients with UC have a benign disease course, at least 20% will develop an acute severe UC attack during their life\(^8,9\). Acute severe flare of UC is a life-threatening condition which assessment is based on simple criteria combining stool frequency, general symptoms and biologic inflammation\(^10,11\). Such patients should be admitted for receiving intravenous steroids that remain the mainstay
of treatment in acute severe UC. In case of steroid failure, occurring in 40% of patients, cyclosporine (CsA) and infliximab are rescue therapies with high and similar efficacy to avoid emergent colectomy together with an acceptable safety profile.

CsA has been used for more than twenty years in patients with acute steroid-refractory UC, but little is known about the efficacy of this drug on endoscopic and histologic lesions. The aim of the present study was to assess endoscopic and histologic responses to CsA and to determine their predictive value on UC course.
PATIENTS AND METHODS

Study design and settings

This was a retrospective study carried out in two academic referential centers from the Bordeaux University hospital (Hôpital Haut-Lévêque, Hôpital Saint-André). Patients were recruited consecutively and prospectively from January 2008 to April 2014. Their charts were reviewed retrospectively through the databases of the two departments. Inclusion date was defined as the day of starting CsA.

All inpatients who received CsA intravenously for steroid-refractory UC in the two recruiting centres during the study period were eligible. They were analysed if they responded to the treatment and have had two endoscopic examinations: one before starting CsA and the other at drug interruption. Consequently, patients with no response to CsA or without these two endoscopic assessments were excluded from the analysis.

The diagnosis of UC was based on usual clinical, endoscopic and histological criteria. CsA was started at 2mg/kg/day, administered by a continuous intravenous infusion (electrical syringe). CsA blood levels were closely monitored during the first week in order to adapt the dosage, targeting concentrations between 150 and 250ng/mL. In patients with clinical response, intravenous CsA was switched orally (Neoral®) twice daily and adapted to blood levels; azathioprine was started with a dosage adapted to thiopurine methyl-transferase genotypes (2.5mg/kg/d in patients without any of the three common variants and 1mg/kg/d in those with one variant). In case of prior intolerance to azathioprine, mercaptopurine was given at 1-1.5mg/kg/d. CsA was given for several weeks as a bridge therapy for azathioprine/mercaptopurine. Steroids were tapered within one month and all patients received also pneumocystosis prophylaxis by cotrimoxazole until CsA interruption.
Initial response to CsA was assessed within the first week of treatment. It corresponded to a significant clinical improvement, defined by decrease of the partial Mayo score of at least 3 points and 30% in patients with acute non-severe refractory UC (patients with Lichtiger score \( \leq 10 \) at inclusion) or by decrease of the Lichtiger score at least 3 points and total score <10 points in patients with acute severe UC (patients with Lichtiger score >10 at inclusion) \(^{13}^{15} \). In patients responding initially, clinical relapse, absence of steroid withdrawal and colectomy under oral CsA were considered as failure.

Patients responding to CsA were followed until disease relapse, defined by occurrence of clinical symptoms of UC associated with significant endoscopic lesions (Mayo endoscopic sub-score \( \geq 2 \)) leading to systemic therapeutic change (steroids, immunosuppressant or biologic agent) or colectomy, or until azathioprine withdrawal because of toxicity or patient’s wish. For patients under follow-up still receiving azathioprine without relapse, data were collected until July 2014.

All patients received treatment according to clinical need. Drugs used were those normally employed in UC, according to licensed or published doses and frequency. All patients received treatment and had endoscopic examinations after informed consent.

**Data collection**

Medical records of included patients were reviewed and the following data at inclusion were collected: date of birth, gender, disease duration, disease extent according to Montreal classification \(^{16} \), indication of starting CsA (acute non-severe refractory UC or acute severe UC - defined above), number of previous flare, prior treatment exposure - including 5-ASA, steroids, thiopurines, methotrexate, anti-TNF - and main reason for drug interruption (withdrawal, failure or intolerance), disease activity according to partial Mayo score in patients with acute non-severe refractory UC or to Lichtiger score in patients with acute...
severe, concomitant treatments, haemoglobin level (in g/dL), C-reactive protein (CRP) (in mg/L) and albumin (in g/L).

Endoscopic assessments were performed by experienced gastroenterologists (E.C. and D.L.) at inclusion and at CsA interruption. Endoscopic UC activity was assessed by flexible recto-sigmoidoscopy using the Mayo endoscopic sub-score, grading mucosal lesions in four stages, from 0 to 3. Endoscopic assessments were categorized into mucosal healing, defined by sub-scores 0 or 1, and absence of mucosal healing, defined by sub-scores 2 or 3.

During endoscopic assessments, at least two biopsy samples were taken on colorectal mucosa. All were retrospectively reread by two pathologists with expertise in inflammatory bowel disease (C.P. and G.B.). Histologic activity was graded according to Geboes histologic score\(^\text{17}\) and presence of basal plasmocytosis\(^\text{18}\). The most severe lesions were retained for scoring. For each assessment, patients were categorized into histologic response, defined by Geboes score <3.1 or absence of basal plasmocytosis, and absence of histologic response, defined by Geboes score \(\geq 3.1\) or presence of basal plasmocytosis.

During the follow-up period and until CsA interruption, the following data were collected: disease relapse (defined above), changes of UC treatment, colectomy, side effects and date of the last visit.

**Objectives**

The objectives of the present study were the following: i) to determine the proportion of patients with short-term mucosal healing under CsA; ii) to determine the proportion of patients with short-term histologic response under CsA; iii) to determine the long-term relapse-free survival rate according to the level of endoscopic response to CsA; iv) to identify predictors of relapse-free survival after CsA withdrawal.
Statistical analysis

Continuous variables are presented as medians and range; categorical variables are presented as percentages with their 95% confidence intervals (95% CI). Continuous data were analysed using Mann-Whitney’s test. Categorical data were analysed using the Pearson’s chi-squared test, or Fisher’s exact test if any cell number was <5, for frequencies. Evolution of variable studied from inclusion to CsA interruption was compared using the McNemmar test. Relapse-free survival curve was calculated for each subgroup from inclusion to end of the follow-up using Kaplan-Meier method and compared using log-rank test.

Univariate and multivariate analyses of prognosis factors of relapse-free survival were performed to assess impact of mucosal healing, histologic response, clinical, disease, and treatment variables. Continuous variables were dichotomised according to the median. Variables analysed were the following: gender, age at inclusion, disease duration, endoscopic activity at inclusion and at CsA withdrawal, histologic activity at inclusion and at CsA withdrawal according to the presence of basal plasmocytosis and the Geboes score. A logistic regression model was created using significantly associated variables (P<0.20), and the odds ratios (OR) for the variables that remained significant (P<0.05) in the model determined. All analyses were performed with SPSS software. Significance threshold was 0.05 for all analyses.
RESULTS

Patient characteristics at inclusion

Thirty-nine patients received CsA for steroid-refractory UC during the study period. Among them, 18 (46%) were excluded from the analysis: 14 (36%) patients underwent CsA failure and four (10%) due to the absence of second endoscopic evaluation at CsA interruption.

Therefore, twenty-one patients were analysed. Their main characteristics are displayed in the table 1. Eleven (52%) were female, median age was 36 years (range: 16-71) and median disease duration was 2 (0-17) years. Type of UC was E1 in 3 (14%) patients, E2 in 8 (38%) and E3 in 10 (48%) according to the Montreal classification. CsA was given because of acute non-severe refractory UC in 8 (38%) patients (median partial Mayo score at inclusion: 8 (7-9)) or for acute severe UC in 13 (62%) patients (median Lichtiger score at inclusion: 12 (11-15)).

All patients had active endoscopic UC lesions at inclusion, including 1 (5%) patient with Mayo endoscopic sub-score 1, 7 (33%) with sub-score 2 and 13 (62%) with sub-score 3 - including 6 patients with severe endoscopic lesions (figure 1).

Nineteen patients were available for both histologic assessment of UC activity at inclusion and at CsA withdrawal. Among them, 7 (37%) had basal plasmocytosis on colorectal biopsies taken at inclusion and 17 (89%) a Geboes score ≥3.1 (figures 2A and 2B).
**Endoscopic and histologic response to CsA**

Median duration of treatment with CsA was 103 (60-145) days and corresponded exactly to the median time for the second endoscopic assessment by flexible rectosigmoidoscopy.

At CsA interruption, Mayo endoscopic sub-score was 0 in 9 (43%) patients, 1 in 8 (38%) patients, 2 in 4 (19%) patients. No patient had Mayo endoscopic sub-score 3. Overall, CsA provided mucosal healing in 17/21 (81%) patients. When comparing mucosal healing rates at inclusion to those at CsA interruption, difference was significant (p<0.001) (figure 1).

Among the 19 patients with biopsies at both endoscopic examinations, 3 (16%) patients had basal plasmocytosis at CsA interruption and 6 (32%) had a Geboes score ≥3.1. Overall, CsA provided 68-84% of histologic response according to the definition used. When comparing rates of histologic response according to basal plasmocytosis and Geboes score at inclusion to those at CsA interruption, difference was only significant for the Geboes score (p=0.003) (figures 2A and 2B).

**Outcome after CsA interruption**

At CsA interruption, azathioprine was continued as maintenance therapy in all patients. Median follow-up duration since inclusion was 42 (0.3-66.1) months. During this period, 7 (33%) patients had ulcerative colitis relapse: six patients required systemic therapeutic change (steroids, immunosuppressant or biologic agent) and one underwent colectomy. Additionally, a 68 year-old woman died during follow-up, 25 months after inclusion, from acute diarrhoea not related to UC.

In patients with mucosal healing, relapse-free survival rates at 12 and 24 months were 79% and 79% respectively, while these figures were respectively 50% and 25% in those without mucosal healing (p=0.04) (figure 3). Moreover, when comparing patients with Mayo
endoscopic sub-score 0 to those with Mayo endoscopic sub-score 1, there was a trend towards better relapse-free survival (p=0.06).

In patients with histologic response defined by Geboes score <3.1, relapse-free survival rates at 12 and 24 months were 82% and 70%, respectively, as compared to 50% and 50% in those without histologic response (p=0.007) (figure 4A). When absence of basal plasmocytosis defined histologic response, relapse-free survival rates at 12 and 24 months were, 71% and 71%, respectively, and 67% and 33% in those without histologic response (p=0.057) (figure 4B).

In univariate analysis, complete mucosal healing at CsA interruption, defined by Mayo endoscopic sub-score 0 (vs. Mayo endoscopic sub-scores 1 and 2) tended to be associated with a decreased relapse rate (p=0.067). Interestingly, neither the presence of basal plasmocytosis nor Geboes score ≥3.1 at CsA interruption was associated with disease relapse. In multivariate analysis, the only factor associated with disease relapse was the absence of complete mucosal healing, with a relative risk of 12.0 (90%CI: 1.05-136.79; p=0.045).
DISCUSSION

In the present cohort study, we found that most of the patients admitted for steroid-refractory UC who have been successfully treated by CsA achieved both mucosal healing and histologic response. By contrast to histologic response, we observed that only a complete endoscopic (Mayo score of 0) healing provided by CsA was associated long-term survival without disease relapse.

Mucosal healing has become a desirable goal in UC. If the efficacy of CsA has been demonstrated for treating patients with steroid-refractory acute severe UC more than 20 years ago, few studies explored so far the endoscopic response to this agent. In two randomised controlled trials, early endoscopic response to CsA has been assessed by flexible sigmoidoscopy, finding no significant changes after one week of intravenous therapy. However, such a short period of time for assessing the endoscopic response in patients with acute severe UC harbouring major mucosal lesions is probably insufficient for identifying any drug effect. More recently, a Japanese group evaluated the endoscopic response to CsA in UC after two weeks of treatment and reported an early improvement that was correlated with avoidance of colectomy at one year. When assessing endoscopic response to CsA later, after 98 days as it has been done in a randomised controlled trial, mucosal healing was observed in nearly half of patients. The results from the present retrospective cohort are concordant with 48% of patients with mucosal healing after a median duration of 103 days of treatment. These results further confirm the ability of CsA for inducing mucosal healing in UC.

Whatever the drug used in active UC (5-ASA, steroids or anti-TNF), patients who achieve clinical remission with mucosal healing under treatment have more favourable disease outcomes than those with persisting endoscopic activity. This predictive value of
mucosal healing seems related to the level of endoscopic improvement obtained under treatment. Indeed, it has been observed in several recent studies that patients who recovered a normal colorectal mucosa, corresponding to a Mayo endoscopic sub-score 0, experience less frequent disease relapses and colectomy than those with persistent mild endoscopic activity. Results from the present study are in the same line, showing that patients with Mayo endoscopic sub-score 0 experienced less disease relapse during follow-up compared to patients with Mayo endoscopic sub-score 1.

Beyond mucosal healing, accumulating data suggest that histologic healing could be a future therapeutic objective in UC. Indeed, histologic healing has been shown to be associated with more favourable disease course, with less disease relapse, related-hospitalisation, colectomy and colorectal adenocarcinoma. However, the results from the present study do not confirm the prognostic value of histologic response on relapse-free survival. This discrepancy could be related to the three-month interval from inclusion that may be too short for achieving significant histologic improvement in a population of patients with severe flare. A sample bias could be not excluded as most of patients had only two colonic biopsies. Another explanation is the absence of standardised definition for histologic response in UC despite using two of the most histologic scores used in UC, i.e. Geboes score and basal plasmocytosis. None of these scores have been validated yet and they have mild reproducibility. An active research is ongoing in order to better define and validate criteria for assessing UC histologic activity and healing.

We acknowledge that the present study has several limitations. First, there were a limited number of patients analysed, due to lower use of CsA during the last decade. However, management of patients from our cohort was homogeneous and standardised, providing comparable results to the literature. Second, endoscopic assessments were done locally and the Mayo endoscopic sub-score was the only score used as most of patients have
been treated before the development of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS)\textsuperscript{11}. Since endoscopic assessments were performed by two endoscopists experts in the field of inflammatory bowel disease and biopsies were reread by expert pathologists, we estimated that it was limiting the observation bias.

In conclusion, CsA is an effective drug for steroid-refractory UC providing mucosal and histologic healing within the first three months in most of responders. These data further confirm that CsA is a powerful treatment for inducing remission in UC when it is used as a bridge therapy for thiopurines. If achievement of histological healing is not associated with favourable clinical outcome, the disappearance of all endoscopic signs of disease activity is associated with less disease relapse. Prospective interventional studies are now required to confirm that complete endoscopic remission should be targeted in UC.
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Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe

Randomized, double-blind comparison of 4 vs. 2 mg/kg intravenous cyclosporine in severe

Rapid endoscopic improvement is important for 1-year avoidance of colectomy but not for the


Figure legends

Figure 1: Evolution of endoscopic ulcerative colitis activity according to the Mayo endoscopic sub-scores from inclusion to cyclosporine interruption (median interval duration between both examinations: 103 days) (n=21).

Figure 2: Evolution of histologic ulcerative colitis activity from inclusion to cyclosporine interruption (n=19) according to the Geboes score (2A) and basal plasmocytosis (2B).

Figure 3: Kaplan-Meier curves of survival without relapse according to endoscopic response to cyclosporine

Figure 4: Kaplan-Meier curves of survival without relapse according to histologic response to cyclosporine defined by a Geboes score <3.1 (A) or by the absence of basal plasmocytosis (B)
Conflicts of interest:

Clémence Fron, Clémence Pierry, Edouard Chabrun, Clément Subtil, Maylis Capdepont
Geneviève Belleannée: none.
Florian Poullenot, Frank Zerbib: lectures fees from AbbVie.
David Laharie: consulting and/or lecture fees from AbbVie, Ferring, Jansen, MSD, Pfizer, Takeda.
**Table 1**: Baseline characteristics of the 21 patients with steroid-refractory ulcerative colitis who responded to cyclosporine and have had two endoscopic examinations.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, in years (range)</td>
<td>36 (16-70)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Median disease duration, in months (range)</td>
<td>50 (0-524)</td>
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<tr>
<td>Active smoking</td>
<td>1 (5)</td>
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<tr>
<td>Disease location, n (%)</td>
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</tr>
<tr>
<td>E1</td>
<td>3 (14)</td>
</tr>
<tr>
<td>E2</td>
<td>8 (38)</td>
</tr>
<tr>
<td>E3</td>
<td>10 (48)</td>
</tr>
<tr>
<td>Median number of previous flare, n (range)</td>
<td>2 (0-10)</td>
</tr>
<tr>
<td>Previous treatment exposure, n (%)</td>
<td></td>
</tr>
<tr>
<td>Thiopurines</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>3 (14)</td>
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<tr>
<td>Indication for cyclosporine, n (%)</td>
<td></td>
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<tr>
<td>Acute non severe refractory UC</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Acute severe UC</td>
<td>13 (62)</td>
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<tr>
<td>Median CRP level, in mg/L (range)</td>
<td>27 (0-151)</td>
</tr>
<tr>
<td>Median hemoglobin level, in g/dL (range)*</td>
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</tr>
<tr>
<td>Median albumin level, in g/L (range)**</td>
<td>31 (23.2-44.0)</td>
</tr>
</tbody>
</table>

*: data available in 20 patients.

**: data available in 19 patients.
Figure 1

The bar chart shows a comparison between Baseline and End of CsA. The percentage values are represented by different shades of blue and purple for Mayo 3, Mayo 2, Mayo 1, and Mayo 0 categories.

At Baseline:
- Mayo 3: 80%
- Mayo 2: 40%
- Mayo 1: 20%
- Mayo 0: 0%

At End of CsA:
- Mayo 3: 40%
- Mayo 2: 60%
- Mayo 1: 0%
- Mayo 0: 0%

A significant difference is indicated by P<0.001.
Figure 2A

- **Inclusion**: 11 CsA interruption episodes, with 89 episodes above 3.1 and 32 episodes below 3.1.
- **CsA interruption**: 11 episodes above 3.1 and 68 episodes below 3.1.

Significance: $P=0.003$
Figure 2B

<table>
<thead>
<tr>
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<th>Present</th>
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<tr>
<td>Inclusion</td>
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<td>63</td>
</tr>
<tr>
<td>CsA interruption</td>
<td>16</td>
<td>84</td>
</tr>
</tbody>
</table>

P = 0.219
Figure 3

The figure shows the survival off relapse (% vs. Months) for patients categorized into two groups based on the Mayo Clinic stages: Mayo 0-1 and Mayo 2-3. The graph indicates a statistically significant difference between the two groups, with a p-value of 0.040.
Survival off relapse (%) vs Months

- Geboes score < 3.1
- Geboes score > 3.1

p = 0.007
Figure 4B

The graph shows the survival off relapse (%) over time (months) for two groups: Absence of plasmocytosis and Presence of plasmocytosis. The p-value for the difference between the two groups is 0.057.