Digestive and Liver Disease 48 (2016) 734–739

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

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

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ARTICLE INFO

*Article history:*
Received 4 February 2016
Accepted 7 March 2016
Available online 11 March 2016

*Keywords:*
Cyclosporine
Histologic remission
Mucosal healing
Ulcerative colitis

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 and 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 ≤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.


## 1. 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

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http://dx.doi.org/10.1016/j.dld.2016.03.007
1590-8658/

[10,11]. Such patients should be admitted for receiving intravenous steroids that remain the mainstay of treatment in acute severe UC [12]. 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 [12–14].

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.

## 2. Patients and methods

### 2.1. Study design and settings

This was a retrospective study carried out in two academic referential centres 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 analyzed 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 [12]. CsA was started at 2 mg/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 250 ng/mL [13]. 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 (2.5 mg/kg/d in patients without any of the three common variants and 1 mg/kg/d in those with one variant). In case of prior intolerance to azathioprine, mercaptopurine was given at 1–1.5 mg/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.

### 2.2. 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 rectosigmoidoscopy 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 [17] and presence of basal plasmocytosis [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.

### 2.3. 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.

### 2.4. 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 analyzed using Mann–Whitney's test. Categorical data were analyzed 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 analyzed were the following: gender, age at