ORIGINAL ARTICLE

Prediction of clinical outcomes in Crohn's disease by using confocal laser endomicroscopy: results from a prospective multicenter study

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Background and Aims: Assessment of prognostic factors in patients with Crohn's disease (CD) is of pivotal importance for early intervention and "treat-to-target" strategies. Confocal laser endomicroscopy (CLE) enables on-demand in vivo characterization of mucosal inflammatory and architectural changes during endoscopy. We prospectively assessed the value of CLE for prediction of clinical outcome parameters in CD.

Methods: Consecutive patients with CD undergoing colonoscopy were included in a multicenter study. Confocal imaging focused on 2 highly reproducible histologic hallmarks of active colonic inflammation: focal cryptitis and crypt architectural abnormality. We evaluated whether CLE, CD endoscopic index of severity (CDEIS), serum C-reactive protein (CRP), and CD activity index (CDAI) were associated with the risk of medical treatment escalation, transmural adverse events, and CD-related hospitalization or surgery during a 4-year follow-up.

Results: Among 49 patients (53% men, median age, 39 years), baseline CRP was ≥5 mg/L in 47%, CDEIS ≥3 in 75%, and CDAI >150 in 51%. Focal cryptitis and crypt architectural abnormality were observed in 63% (CLE^+ group). CLE^+ patients showed an increased incidence of medical treatment escalation ($P < .001$; relative risk [RR] = 3.27) and transmural lesions ($P = .025$; RR = 1.70), whereas patients with CRP ≥5 mg/L had increased CD-related hospitalization and surgery ($P = .020$, RR = 2.71) at 1-year follow-up. No further association with prognostic clinical outcomes was found over the 1-year follow-up as well as for CDEIS and CDAI at any time.

Conclusions: CLE reveals CD-related features of mucosal inflammation and allows for early prediction of relevant clinical outcomes. Further studies should now address whether this promising prognostic tool could refine the timing of treatment strategies in patients with CD. (Gastrointest Endosc 2017;■:1-10.)

Abbreviations: CD, Crohn's disease; CDAI, CD activity index; CDEIS, CD endoscopic index of severity; CLE, confocal laser endomicroscopy; CRP, C-reactive protein; IBD, irritable bowel disease; IQR, interquartile range; RR, relative risk; UC, ulcerative colitis.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the GI tract characterized by inflammatory changes frequently resulting in clinical flares and progressive segmental bowel damage.[1,2] Early intervention in high-risk patients is emerging as a more effective approach for CD compared with step-wise therapy escalation mainly based on symptom control.[3] Furthermore, achieving mucosal healing with targeted therapies may change the natural course of the disease by decreasing relapse rates, hospitalization, and the need for surgery.[4]

However, white-light endoscopy and histopathology often reveal signs of active inflammation in many patients with CD in clinical remission.[4–7] In addition, microscopic features of disease activity may prevail even in patients showing endoscopic remission. Although in ulcerative colitis (UC) the persistence of histologic lesions indicates an increased likelihood of both relapse[8–10] and colitis-associated cancer,[11–14] the prognostic relevance of microscopic inflammation in CD is still a matter of intense debate.[9]

Confocal laser endomicroscopy (CLE) is a novel endoscopic imaging modality allowing in vivo characterization of microscopic tissue details during ongoing endoscopy in real time.[15] In patients with irritable bowel disease (IBD), CLE enables the detection of either inflammatory[16–18] or dysplastic[19] histopathologic mucosal changes. In patients with CD, this technique can distinguish patients from controls and active versus quiescent disease even in areas of macroscopically uneventful mucosa.[20] More recently, confocal imaging has shown promising results in differentiating CD and UC in vivo.[21] Moreover, the rate of epithelial-cell shedding as assessed by CLE in endoscopically normal mucosa of the terminal ileum has been used to predict clinical relapse rates[22] and major events such as hospitalization or surgery[23] in patients with IBD at 1-year follow-up.

Based on these findings, we hypothesized that the presence of CD-related histopathologic hallmarks of large-bowel mucosal active inflammation as observed by confocal imaging might predict the subsequent clinical course of the disease. Accordingly, the aim of this prospective study was to comparatively assess the value of CLE, CD endoscopic index of severity (CDEIS), serum C-reactive protein (CRP), and CD activity index (CDAI) for prediction of clinical outcome parameters in patients with CD.

METHODS

Patient enrollment

This was a prospective, multicenter observational study based on patients with CD undergoing colonoscopy for evaluation of disease activity. Patients were consecutively included between 2012 and 2015 at the University Hospitals of Erlangen, Germany, and Padua, Italy. All patients signed informed consent after the attending physician had explained the procedure in detail. The study was approved by the local ethics committee and government authorities and was conducted in accordance with the Declaration of Helsinki (NCT 01524120).

Patients were included if they met the following inclusion criteria: ≥18 years of age, not pregnant or breast-feeding, established diagnosis of CD with large-bowel involvement, documented clinical follow-up of at least 1 year, and Boston Bowel Preparation Scale score ≥2 in the 3 broad regions of the colon.[24] Patients with 1 or more of the following criteria were excluded from the study analysis: disease reclassification during the last 3 years, severe uncontrolled coagulopathy, impaired renal function, active gastrointestinal bleeding, known allergy to fluorescein, and residence in institutions.

At baseline, several clinical data, including CRP value, CDEIS, CDAI, disease phenotype and localization according to the Montreal classification, and ongoing treatments, were collected. CRP values ≥5 mg/L were defined as increased, whereas CD-related endoscopic and clinical activity were considered relevant for CDEIS ≥3 and CDAI >150 based on standard thresholds established in the literature.

Endoscopy and endomicroscopy assessment

All colonoscopies were performed after standard bowel preparation using either oral sodium phosphate or polyethylene glycol-electrolyte lavage solution. Intravenous sedation with constant monitoring of vital signs was performed (eg, midazolam hydrochloride and pethidine hydrochloride or propofol sedation).

CE-certified and Food and Drug Administration-approved CLE systems were used. One includes an endoscope with the confocal optic integrated into the distal tip of a standard high-resolution endoscope (iCLE; Pentax Medical, Tokyo, Japan); the other includes a probe-based endomicroscopy system capable of passage through the working channel of a standard endoscope (pCLE, Cellvizio, Mauna Kea Technologies, Paris, France). Technical details of the systems have been described in detail elsewhere.[15,21] Within this study, iCLE images were collected at a frame rate of 0.8/second at 1024 × 1024 pixels or 1.6/second at 1024 × 512 pixels.

All procedures were performed by 4 expert endoscopists (H.N., G.E.T., J.M., A.B.) who were aware of the patient's history, clinical disease activity, and endoscopic results. During withdrawal, all segments of the colon were carefully evaluated. Inflammatory endoscopic lesions were classified according to the CDEIS.[25] The CDEIS score ranges from 0 to 44, with a higher score indicating more severe disease.[25] After white-light endoscopic assessment, the mucosa was intensively washed with water to avoid CLE image artifacts according to residual stool contamination. Afterward, 3 to 5 mL of fluorescein sodium 10% was