Safety and Feasibility of Using the Second-Generation Pillcam Colon Capsule to Assess Active Colonic Crohn's Disease

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BACKGROUND & AIMS: **The second-generation Pillcam Colon Capsule Endoscope (PCCE-2; Given Imaging Ltd, Yoqneam, Israel) is an ingestible capsule for visualization of the colon. We performed a multicenter pilot study to assess its safety and feasibility in evaluating the severity of Crohn's disease (CD).**

METHODS: **In a prospective study, 40 patients with active colonic CD underwent PCCE-2 and optical colonoscopy procedures. Using both techniques, we generated values for the Crohn's Disease Endoscopic Index of Severity (CDEIS), the Simple Endoscopic Score for CD, and global evaluation of lesion severity. In the first stage of the study, we calculated the correlation between PCCE-2 and optical colonoscopy scores. In the second stage, we performed interobserver agreement analysis for a random subset of 20 PCCE-2 recordings, graded in duplicate by 2 independent readers.**

RESULTS: **There was substantial agreement between PCCE-2 and optical colonoscopy in the measurement of the CDEIS (intraclass correlation coefficient [ICC], 0.65; 95% confidence interval [CI], 0.43–0.80). There was substantial interobserver agreement between 2 independent PCCE-2 readers for the CDEIS (ICC, 0.67; 95% CI, 0.35–0.86) and the Simple Endoscopic Score for CD (ICC, 0.66; 95% CI, 0.32–0.85). However, the PCCE-2 scoring systematically underestimated the severity of disease compared with optical colonoscopy; based on our results, PCCE-2 detected colonic ulcerations with 86% sensitivity and 40% specificity. No adverse events were observed and PCCE-2 was better tolerated than colonoscopy.**

CONCLUSIONS: **PCCE-2 is feasible, safe, and well tolerated for the assessment of mucosal CD activity in selected populations. Larger studies are needed to assess its operating characteristics further. European clinical trials database number: 2014-003854-15.**

Keywords: Inflammatory Bowel Disease; Diagnostic; Imaging; Monitoring.

The goals of treatment in Crohn's disease (CD) have evolved in recent years from symptom control to the healing of mucosal lesions visualized at endoscopy. Potent treatment combinations, such as anti–tumor necrosis factor (TNF) agents with immunomodulators, have made restoration of mucosal integrity achievable in a significant proportion of patients.[1,2] Importantly, mucosal healing has been associated with improved clinical outcomes including sustained steroid-free clinical remission, decreased rates of surgery and hospitalization, reduced occurrence of new perianal complications, as well as improvement in quality of life and increased work productivity.[3,4] Moreover, anti-TNF therapies have been shown to be more efficacious in patients with visible ulcers at endoscopy than in patients without such lesions.[2] It is recommended that clinicians check for the presence of ulcers before commencing anti-TNF therapy, and to repeat the endoscopy for the evaluation of mucosal healing after a period of treatment.

The generally poor correlation between symptoms and endoscopic appearance[5] recently has given rise to the concept of treating to a predefined endoscopic target

Abbreviations used in this paper: **CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CI, confidence interval; GELS, Global Evaluation of Lesion; ICC, intraclass correlation coefficient; OC, optical colonoscopy; PCCE-2, second-generation Pillcam Colon Capsule Endoscope; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor; UC, ulcerative colitis; VAS, visual analogue scale.**

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2015.01.031

rather than symptom resolution alone.[6,7] The emergence of endoscopy-driven treatment algorithms is likely to require more frequent endoscopies with treatment optimization until the goal of mucosal healing and disease control is met.

Unfortunately, conventional optical colonoscopy (OC) is invasive, unpleasant, usually requires sedation or anesthesia, and carries the risk of significant complications.[8] Therefore, it is disliked by most patients and also is a costly and time-consuming endeavor for health care providers. In an attempt to limit the necessity for repeated endoscopic examinations, several surrogate markers of disease activity, such as fecal calprotectin[9] and magnetic resonance enterocolonography,[10] have been investigated. However, these have specific limitations and the increasing desire to visualize the mucosa directly to monitor inflammatory activity means that an accurate and simple alternative to OC would be of significant value. The utility of capsule endoscopy technology for this indication in the small bowel has been investigated and a growing body of evidence now supports its use.[11–13] Although capsule endoscopy is not free of complications and requires significant investment from endoscopy departments as well as the expertise and time of readers, attention now is turning to applying similar technology to colonic mucosal assessment. For this purpose, a second-generation Pillcam Colon Capsule Endoscope (PCCE-2; Given Imaging Ltd, Yoqneam, Israel) was designed based on technologic advances made on existing small-bowel capsules and the first-generation Pillcam Colon Capsule Endoscope (PCCE-1; Given Imaging Ltd). A detailed description of its properties and functions can be found in the Supplementary Materials and Methods section. The feasibility and safety of its use in colonic assessment has been investigated for polyps and cancer,[14,15] as well as for ulcerative colitis (UC), but the current study examines the utility of the PCCE-2 in the assessment of CD.

Patients and Methods

Study Design

This study was performed at 3 inflammatory bowel disease referral centers, 1 in The Netherlands and 2 in Belgium. Ethics committees at all participating sites approved the study protocol and written informed consent was obtained from all participating patients. Patients were enrolled between December 2011 and October 2013. Eligible patients were those with clinically and biochemically active CD and in whom OC was clinically indicated. Evidence of clinical disease activity was defined as a Crohn's Disease Activity Index (CDAI) of 150 or higher, in combination with biochemical evidence of inflammation, defined by a serum C-reactive protein level of 5 mg/L or greater, as well as a fecal calprotectin level greater than 200 μg/g. All patients had prior documentation of colonic involvement by CD, affecting at least 2 segments of the colon, and to a degree more severe than aphthous ulceration alone. CD could be limited to the colon alone or may affect both the large and small bowel.

Patients were excluded if they had any contraindication for OC or capsule endoscopy[16] such as known small-bowel strictures. A patency capsule examination could be arranged for patients with obstructive symptoms suggestive of possible small-bowel strictures.

Bowel Preparation, Second-Generation Pillcam Colon Capsule Endoscope, and Optical Colonoscopy Procedures

The regimen that was followed for bowel preparation as well as a description of the PCCE-2 and OC procedure protocol can be reviewed in the Supplementary Materials and Methods section. A description of the method used to assess the patients' subjective experience of the procedures also is included.

Assessment of Endoscopic Disease Activity

Immediately after the colonoscopies the estimates of endoscopic disease activity were recorded using the Simple Endoscopic Score for Crohn's Disease (SES-CD[17]) and the Crohn's Disease Endoscopic Index of Severity (CDEIS[18]). These scores reflect the presence and size of ulcers, ulcerated and affected surface area, stenoses, as well as depth of ulceration (only included in the CDEIS). Examples of typical lesions seen with OC and PCCE are shown in Figure 1. A score is given to each of the 5 ileocolonic segments individually that contributes to the total score. In addition, a global evaluation of lesion severity (GELS) was marked on a 10-cm visual analogue scale (VAS). PCCE-2 recordings were read at a later time point but without knowledge of colonoscopic scores by 2 investigators (G.D. and A.M.V.G.) using the same scoring system. Assessment of the entire small bowel also was made on PCCE-2 recordings.

Statistical Analyses and Validation of Second-Generation Pillcam Colon Capsule Endoscope Recordings in Assessing Disease Activity

The primary aim of this study was to investigate the relationship between colonoscopic assessments of mucosal disease activity and those made using the PCCE-2. To express the degree of agreement between the 2 modalities we calculated the intraclass correlation coefficient (ICC) as a measure of the conformity of the data sets.[19] Interpretation of ICCs was predefined based on the Landis and Koch[20] benchmarks whereby a negative value reflects poor reliability, 0 to 0.2 reflects slight reliability, 0.21 to 0.40 reflects fair reliability, 0.41 to