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Tailoring Crohn's disease treatment: The impact of small bowel capsule endoscopy

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Abstract

Background and aims: Small bowel capsule endoscopy (SBCE) may detect proximal small bowel lesions that have been previously missed by ileocolonoscopy and small bowel imaging in patients with known ileal and/or colonic Crohn's disease (CD). We aimed to evaluate whether the therapeutic management is influenced by SBCE findings.
Methods: Retrospective single center study. Inclusion of consecutive patients with known non-stricturing and non-penetrating ileal and/or colonic CD, submitted to SBCE to evaluate disease extension and activity, with ≥ 1 year follow-up. Lesions were classified with the Lewis score (LS) as non-significant (LS < 135), mild (135 ≤ LS ≤ 790), or moderate-to-severe (LS > 790). Therapeutic changes were assessed three months after SBCE.
Results: Fifty consecutive patients (35 ± 13 years, 52% females) were included. At ileocolonoscopy, disease location was ileal (L1) in 60%, colonic (L2) in 10% and ileocolonic (L3) in 30% of the patients. In 33 patients (66%) SBCE detected significant proximal lesions previously missed by other modalities. The proportion of patients on thiopurines and/or biologics before SBCE was 2/50 (4%); this was significantly higher three months after SBCE, 15/50 (30%), p = 0.023. Treatment with thiopurines and/or biologics was started more often in patients with proximal small bowel lesions [13/33 (39%) vs. 1/17 (6%), p = 0.011, relative risk (RR) 6.5], particularly when severe (6%, 36% and 45% of patients with non-significant, mild and moderate-to-severe inflammation, respectively).
Conclusions: SBCE diagnoses previously undetected lesions and it influences therapeutic management of CD, triggering an earlier introduction of immunomodulators and/or biological therapy.

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1. Introduction

Crohn's disease (CD) is a chronic idiopathic inflammatory bowel disease that may affect any segment of the digestive tract and often involves the small bowel.[1] Ileocolonoscopy remains the first endoscopic procedure to establish the diagnosis in patients with suspected CD. Irrespective of the findings at ileocolonoscopy, further investigation is advisable to determine the location and extent of CD in the upper gastrointestinal tract and the small bowel.[1] The evaluation of the small bowel often relies on cross-sectional imaging with magnetic resonance enterography (MRE) or computed tomography enterography (CTE), for the assessment of the transmural nature of the disease and its anatomical distribution, characterization of strictures and detection of extraluminal disease. In this setting, the role of small bowel capsule endoscopy (SBCE) is still evolving.[2] SBCE has been shown to improve the detection of proximal small bowel lesions when compared to both CTE and MRE, while the diagnostic yield seems to be equivalent when lesions are limited to the terminal ileum.[3,4] The clinical implications of this incremental yield, mainly for mild proximal lesions, in patients with known CD remain to be clarified, although it is currently recognized that the finding of extensive and/or proximal lesions may influence therapeutic decisions towards an earlier introduction of immunomodulators and/or biological therapy, with the aim of reducing long term complications and disabling disease.[5–7] Nonetheless, data regarding the impact of SBCE findings on therapeutic decisions are scarce,[8,9] and the burden of proximal lesions in patients with known CD has not been extensively investigated.

The aim of this study was to determine whether new lesions detected by SBCE in the proximal small bowel and/or not previously recognized at the index ileocolonoscopy influenced the therapeutic management of patients with known ileal and/or colonic CD.

2. Methods

We conducted a single center retrospective study, from January 2008 to December 2012, with an inclusion of consecutive patients with established non-stricturing and non-penetrating ileal and/or colonic CD, submitted to SBCE to assess disease extent and activity. All patients had an ileocolonoscopy as the first endoscopic diagnostic procedure. Patients with unsuccessful ileoscopy at colonoscopy were not included in this study. Patients with obstructive symptoms and/or those with evidence of ileal stenosis at ileocolonoscopy and/or radiological features of stricturing or penetrating disease did not undergo subsequent SBCE. Small bowel radiological imaging was not mandatory prior to SBCE. Thus, patients with no clinical features of stricturing or penetrating disease and no stricture at the index ileocolonoscopy were allowed to undergo SBCE without previous small bowel imaging. Patients taking aspirin or nonsteroidal anti-inflammatory drugs discontinued the medication at least four weeks before the SBCE. Baseline variables assessed at the time of SBCE included age, Montreal classification, serum inflammatory biomarkers, history of abdominal surgery related to Crohn's disease and current medication. All patients followed a clear liquid diet for 24 h and 12 h fasting prior to SBCE (PillCam® SB2, Given® Imaging Ltd Yoqneam, Israel). All SBCE were reviewed by two experienced physicians (>200 SBCE examinations) using RAPID Reader®, and in case of no interobserver agreement the findings were reviewed until a consensus report was achieved. Small bowel inflammatory activity was systematically assessed with the Lewis score[10] (LS) for each tertile of the small bowel, using the calculator included in the RAPID® software. The length of each tertile was determined by equally dividing the small bowel transit time of the capsule in three parts. Following a widely accepted methodology,[10] a LS <135 was assumed to correspond to normal examination or clinical insignificant lesions, a LS of 135 to 790 corresponded to mild inflammatory activity, and a LS >790 corresponded to moderate or severe inflammatory activity. Small bowel lesions were considered to have proximal location if they were located in the upper two thirds of the small bowel (first two tertiles of the SBCE) and/or located in the third tertile proximal to the terminal ileum, out of the reach of the colonoscope. For the purpose of the study, the terminal ileum was considered to correspond to the last 10 min of the passage of the capsule in the small bowel before entering the cecum, which translates to a length of approximately 15 cm, assuming an average velocity of 1.5 cm/min for the passage of the capsule, as described elsewhere.[11] In those cases where the capsule did not reach the cecum, small bowel tertiles were determined based on the last small bowel image available; in those cases, the relative position of the capsule to the ileocecal valve was estimated using topographic landmarks with the localization track of RAPID® software, as well as the estimated distance from the duodenum at the time of battery exhaustion. Any changes in CD medication within three months after the SBCE were assessed.

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois). Baseline and SBCE data were summarized using descriptive statistics. Categorical data were analyzed with Pearson's chi-squared or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed considering the start of thiopurines and/or biologics within three months of the SBCE as the dependent variable. A p-value <0.05 was considered statistically significant.

3. Results

Fifty consecutive patients (mean age 35 ± 13 years, 52% females) with known non-stricturing and non-penetrating ileal and/or colonic CD, submitted to SBCE to assess disease extent and activity, were included in the study. Baseline characteristics, interventions and outcomes of the population are summarized in Table 1. SBCE was performed shortly after (less than 3 months) the diagnosis of CD in 70% of patients (n = 35) and within the first year after the initial diagnosis in 84% (n = 42). The location of the disease at the index ileocolonoscopy was ileal (L1) in 60% (n = 30), colonic (L2) in 10% (n = 5) and ileocolonic in 30% (n = 15) of patients. Seven patients (14%) had perianal fistulae and/or abscesses. Seven patients (14%) had previous history of abdominal surgery related to CD. Small bowel imaging was performed in 32 patients (64%), either with CT enterography/enteroclysis (n = 13), CT with no oral contrast intake (n = 10), MR enterography (n = 4) or small bowel follow through (n = 5). Small bowel imaging was unremarkable in 56% (n = 18) and

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Table 1 Population baseline characteristics, interventions and outcomes.

Age	35 ± 13 years
Gender (% female)	52% females
CD location	
Ileal (L1)	60% (n = 30)
Colonic (L2)	10% (n = 5)
Ileocolonic (L3)	30% (n = 15)
Complex perianal disease	14% (n = 7)
Abdominal surgery related to CD	14% (n = 7)
Patients with anemia and/or raised inflammatory biomarkers at the time of SBCE	58% (n = 29)
Small bowel imaging	64% (n = 32)
Time from diagnosis to SBCE (months)	
Within 3 months	70% (n = 35)
Within 1 year	84% (n = 42)
Proximal small bowel lesions on SBCE (SL $\geq$ 135)	66% (n = 33)
Proximal moderate-to-severe inflammation on SBCE (SL > 790)	22% (n = 11)
Patients on thiopurines and/or biologics at the time of SBCE (%)	4% (n = 2)
Patients on thiopurines and/or biologics within 3 months after SBCE (%)	30% (n = 15)
Mean follow-up after SBCE (years)	2.9 ± 1.3 [1–5] years

revealed features of ileitis in 44% (n = 14) of patients. In one patient, CT additionally identified features of non-stricturing CD of the upper jejunum. Upper endoscopy was performed in 66% of patients (n = 33), revealing no features of CD in any of the patients. At the time of SBCE, patients were medicated with aminosalicylates (32%, n = 16), budesonide (36%, n = 18), oral prednisone (10%, n = 5), thiopurines (2%, n = 1) or biological therapy (2%, n = 1); nine patients (18%) had not initiated any medication. Twenty-nine patients (58%) had raised inflammatory biomarkers (C-reactive protein, erythrocyte sedimentation rate, ferritin, platelet count) and/or anemia at the time of capsule endoscopy. The rate of complete examinations, with the capsule reaching the cecum within the battery life, was 80% (n = 40). Overall, SBCE detected significant lesions (LS $\geq$ 135) in 84% of patients (n = 42), being mild (135 $\leq$ LS $\leq$ 790) in 44% (n = 22) and moderate to severe (LS > 790) in 40% (n = 20). In thirty-seven patients (74%) the capsule detected lesions in the terminal ileum, which had already been identified at index ileocolonoscopy. In patients with colonic disease (L2), SBCE detected previously unsuspected inflammatory activity of the terminal ileum in 3/5 (60%), that had not been detected at ileocolonoscopy. In 8 patients (16%) with ileal involvement at index ileocolonoscopy, lesions were not detected by the SBCE, although proximal lesions were identified in 2 of those patients. Overall, thirty-three patients (66%) had significant inflammatory activity in the small bowel proximal to the level reached by the colonoscope, and in 22% (n = 11) it was moderate or severe. These lesions had not been previously recognized at the index ileocolonoscopy or small bowel radiological imaging in all but one patient in whom small bowel CT scan identified jejunal disease.

Three months after the SBCE, patients' medication included aminosalicylates (22%, n = 11), budesonide (36%, n = 18), thiopurines (18%, n = 9), or biological therapy (12%, n = 6); three patients (6%) remained without any medication — Fig. 1. Overall, 44% of patients (n = 22) initiated a new IBD treatment within three months after the SBCE, as follows: 5 patients (10%) were started on budesonide, 9 patients (18%) started immunosuppression with thiopurines, 5 patients (10%) started biological therapy and 3 patients (6%) underwent surgery. The introduction of thiopurines and/or biologics occurred in 2/9 (22%) patients who were not taking any medication, 2/16 (13%) patients on aminosalicylates, 5/18 (28%) patients taking budesonide and 4/5 (80%) patients on prednisone at the time of SBCE. One other patient was escalated from azathioprine to infliximab. Patients were medicated with thiopurines and/or infliximab in 2/50 (4%) and 15/50 (30%) at the time of SBCE and three months after the SBCE, respectively (p = 0.023). Regarding baseline serum analysis, thiopurines and/or biologics were initiated in 8/29 (27.6%) patients with anemia and/or raised inflammatory biomarkers vs. 6/21 (28.6%) of patients who had normal serum analysis at the time on SBCE (p = 0.593). The start of treatment with thiopurines and/or biologics in patients who were previously naïve to those medications occurred in 13/33 (39%) vs. 1/17 (6%) patients with or without significant inflammatory activity in the proximal small bowel detected at the SBCE, respectively (p = 0.011). Additionally, there was a trend towards starting thiopurines and/or biologics when proximal small bowel lesions were more severe, occurring in 1/17 (6%), 8/22 (36%) and 5/11 (45%) of patients with non-significant, mild and moderate to severe proximal lesions, respectively — Fig. 2. On multivariate logistic regression, proximal involvement with significant inflammatory activity (LS $\geq$ 135) on SBCE was independently associated with the start of thiopurines and/or biologics, with a RR (relative risk) of 6.5 (p = 0.029). The other variables included in the multivariate logistic regression were not associated with such a therapeutic adjustment: anemia and/or raised serum analysis (p = 0.733), ileal involvement at the index ileocolonoscopy (p = 0.969), complex perianal disease (p = 0.194) or prior abdominal surgery (p = 0.817). The mean follow-up after SBCE was 2.9 ± 1.3 [1–5] years. The proportion of patients in corticosteroid-free remission at follow-up was 57.1% (8/14) in the immunosuppression group versus 61.1% (22/36) among patients who were not taking immunomodulators or biological therapy (p = 0.552).

4. Discussion

In patients with CD, the location and extent of the disease in the upper gastrointestinal tract and the small bowel should be assessed at diagnosis in order to establish the prognosis and define the therapeutic strategy.[1] In a recent meta-analysis,[12] SBCE was superior to push enteroscopy, small bowel follow through and CTE, but not to MRE, in the evaluation of patients with nonstricturing small bowel CD. SBCE has been shown to detect proximal small bowel lesions in up to 50% of patients with previously diagnosed ileal CD.[13] It has also been shown to improve the detection of proximal small bowel lesions when compared to both CTE and MRE, while the diagnostic yield seems to be equivalent when lesions are limited to the terminal ileum.[3,4] The clinical implications of this incremental yield is uncertain, although the finding of extensive and/or

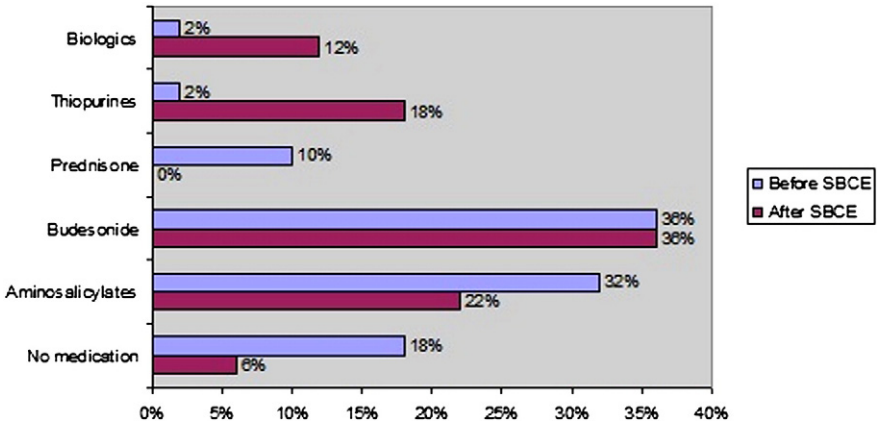

Figure 1 Baseline and post-SBCE medications for Crohn's disease.

proximal lesions have been considered to potentially trigger an earlier introduction of immunomodulators and/or biological therapy, with the aim of reducing long term complications of the disease[5–7]; this possibility was demonstrated herein. In a recent retrospective study of 108 patients, with a median follow-up of 24 months, including 32 patients with ileal disease, 25 patients with colonic disease, and 51 patients with ileocolonic disease, jejunal lesions at SBCE were detected in 56% of patients, mainly in those who also presented ileal involvement. The presence of jejunal lesions was the only independent factor significantly associated with an increased risk of relapse and could be regarded as a factor of severity.[14] Also in a large series of 1403 Korean patients with CD, jejunal involvement was independently associated with worse long-term prognosis, higher use of corticosteroids and thiopurines, and higher rates of strictureplasties and hospitalizations.[15] In 2011, Long et al.[9] reported a high rate of *positive* SBCE studies among CD patients, with only 22.2% of patients having normal examinations, and 47.6% presenting with severe mucosal inflammation. Our results are consistent with these data, reinforcing the importance of accurately establishing the extent and severity of CD. In our study, SBCE detected significant inflammatory activity (LS $\geq$ 135) in the vast majority of patients (84%), being mild (135 $\leq$ LS $\leq$ 790) in 44% and moderate to severe (LS $>$ 790) in 40% of cases. Rosa et al.[16] recently demonstrated that the use of the Lewis score to characterize and grade the inflammatory activity on SBCE may contribute to an earlier and more accurate diagnosis of CD. Also in this study, the Lewis score was useful to objectively grade and quantify small bowel inflammatory activity, and it was associated with the likelihood of escalating therapy after a follow-up of three months after the SBCE. The capsule detected significant inflammatory activity in the proximal small bowel, which had not been previously recognized either at ileocolonoscopy or small bowel imaging, in 66% of patients. Treatment with thiopurines and/or biologics was initiated more often in patients with significant inflammatory activity in the proximal small bowel (39% vs. 6%, p = 0.011). Additionally, we observed a trend towards starting immunosuppression and/or biologics when proximal small bowel lesions were more severe. In most cases, SBCE were requested by the attending GE physician shortly after the diagnosis of CD by ileocolonoscopy, with the aim of assessing disease extent and activity, as the finding of extensive small bowel disease has been increasingly regarded as a marker of severity and poorer outcomes in CD, which should trigger treatment escalation according to current recommendations.[7] From a practical point of view, physicians regarded the capsule information as crucial for treatment decision. As detailed above, thiopurines and/or biologics were initiated in 27.6% of patients with anemia and/or raised inflammatory biomarkers and in 28.6% of those with normal serum analysis (p = 0.593) at the time of SBCE, suggesting that serum analysis was not the key factor triggering treatment escalation.

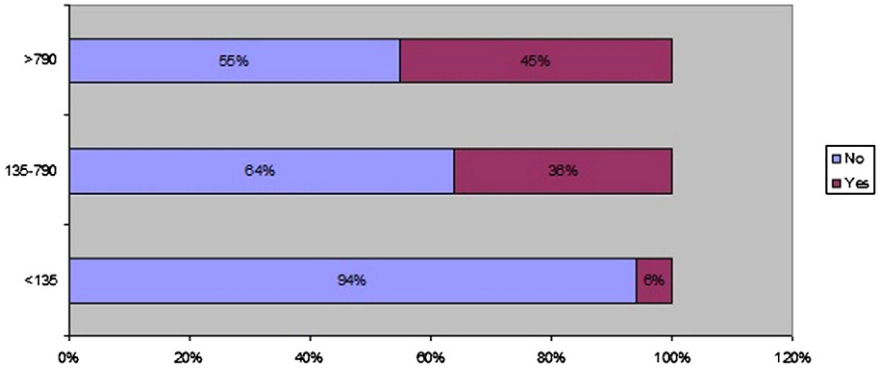

Figure 2 Start of thiopurines and/or biologics according to the degree of proximal inflammatory activity at SBCE (Lewis score).

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Conversely, on logistic regression, proximal involvement with significant inflammatory activity (LS $\geq$ 135) on SBCE was independently associated with the start of thiopurines and/or biologics, with a RR (relative risk) of 6.5 (p = 0.029).

The fact that a slightly larger proportion of patients not taking immunosuppressive therapy was doing better at follow-up (61.1% vs. 57.1% in corticosteroid-free remission, p = 0.552) is likely related to the fact that these patients had less severe disease from the beginning. As the methodology of our study did not contemplate an arm of patients with extensive small bowel involvement not being submitted to immunosuppression, we cannot extrapolate from our results that the therapeutic intervention that was triggered by the findings on capsule endoscopy resulted in an improved prognosis, however we can assume that it induced therapeutic escalation, which, based on data from the literature, can be expected to reduce the likelihood of clinical relapse and hospitalizations.

From another perspective, there is ongoing discussion on whether SBCE could be used to guide the decision of stopping drugs such as thiopurines and/or biologics when mucosal healing is documented.[5,6,17,18] In our study, none of the patients had a therapeutic *downgrade* based on SBCE findings, which could be explained by the fact that, at the time of SBCE, few patients were medicated with thiopurines and/or biological therapy, presumably because the staging of disease extension had not been concluded, or it had been performed with less sensitive small bowel radiological imaging. However, we should acknowledge the fact that only 32/50 patients (64%) were submitted to small bowel imaging prior to SBCE, including the use of small bowel follow through or CT scan with no oral contrast intake, less accurate than CT/MR enterography, which was performed in 34% of patients (n = 17). This could have eventually precluded the recognition of some of the lesions that in our study were only detected by the SBCE.

Regarding the risk of capsule retention, this has been shown to be increased in patients with known CD, particularly when there is a history of obstructive symptoms or known intestinal stenosis.[19–23] Cross-sectional imaging or Agile® patency capsule seem to be equally effective in identifying stenoses that may cause capsule retention.[24,25] In our hospital, we do not systematically use Agile® patency capsule, and during this study we did not perform small bowel imaging in all patients with known CD prior to SBCE, except for those with obstructive symptoms or known intestinal stenosis. Although capsule retention rate was relatively low (6%) when compared to data reported in the literature,[18] these patients developed obstructive symptoms and finally underwent abdominal surgery to retrieve the capsule and treat underlying disease, after unsuccessful medical management and attempt of endoscopic removal. All patients who had capsule retention had been submitted to small bowel cross-sectional imaging that did not identify any stenoses and had no previous history of obstructive symptoms.

To conclude, the role of SBCE in the evaluation of patients with known CD is still evolving, however there is growing evidence that it may significantly improve the detection of lesions within the small bowel. It may potentially contribute to influence therapeutic management, towards an earlier introduction of immunomodulators and/or biological therapy, particularly in patients with moderate to severe inflammatory activity in the proximal small bowel. Whether this approach will improve outcomes in CD will require further investigation.

Conflicts of interest

None.

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None.

Author contributions

Cotter J carried out the study, critically revised the manuscript and approved the final version to be submitted. Dias de Castro F reviewed the capsule endoscopy videos and performed data analysis. Moreira MJ reviewed the capsule endoscopy videos and participated in the design of the study. Rosa B reviewed the capsule endoscopy videos and drafted the manuscript; all the authors read and approved the final manuscript.

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