A prospective 52 week mucosal healing assessment of small bowel Crohn's disease as detected by capsule endoscopy

Barry Hall, Grainne Holleran, Jun-Liong Chin, Sinead Smith, Barbara Ryan, Nasir Mahmud, Deirdre McNamara

Department of Gastroenterology, Adelaide and Meath Hospital, Dublin 24, Ireland
Department of Gastroenterology, St James's Hospital, Dublin 24, Ireland

Received 9 July 2014; received in revised form 6 September 2014; accepted 9 September 2014

KEYWORDS
Capsule endoscopy; Small bowel Crohn's disease; Mucosal healing; Deep remission

Abstract

Background: Mucosal healing is increasingly recognised as an important treatment goal in Crohn's disease (CD). Data from colonic disease shows improved long-term outcomes in patients achieving complete mucosal healing. Little is currently known of this with regard to ileitis which is increasingly diagnosed using capsule endoscopy (SBCE). This is the first study to prospectively assess mucosal healing and deep remission rates following 52 weeks of therapy in a cohort of symptomatic small bowel CD patients commencing immunomodulator or biologic therapy.

Methods: Baseline demographics, quality of life questionnaires and Harvey-Bradshaw Index were collected along with C-reactive protein & calprotectin. Capsule endoscopy Crohn’s disease activity (CECDAI) index was used to assess ileitis severity. All parameters were reassessed at week 52. Results at baseline & week 52 were compared using univariate analysis, p < 0.05 considered significant.

Results: In total, 108 capsule procedures were performed on 43 patients. Based on the CECDAI, 39 (90%) demonstrated active small bowel CD at baseline with 28 (65%) undergoing 52 week assessment. In total, 12 (42%) participants achieved complete mucosal healing and deep remission by 52 week assessment (p < 0.0001 95% CI −0.62 to −0.22). Despite overall impressive mucosal healing rates, patients with strictures were less likely to demonstrate a decrease in CECDAI and were more likely to have symptoms.

Conclusion: In patients with active small bowel CD symptomatic and biochemical response to treatment appears to be mirrored by endoscopic remission in 42% of individuals. Strictures identified prior to therapy appear to be a poor indicator for success of treatment.

© 2014 European Crohn's and Colitis Organisation. Published by Elsevier B.V. All rights reserved.
1. Introduction

Crohn's disease (CD), as a disease entity, tends to commence as an inflammatory process with around 80% of individuals initially diagnosed with this disease sub-type [1]. If left unchecked, over time this inflammatory process can lead to the complications commonly associated with CD. In the past, the treatment of CD was largely dictated by clinical indices alone. With a greater understanding of the disease process, newer treatment objectives have emerged. One such treatment goal, mucosal healing, has been shown to increase steroid-free remission and decrease surgical and hospitalisation rates in patients with CD [2–5]. Indeed studies have shown that the correlation between clinical and endoscopic measures of disease activity is poor [6–8]. Rates of mucosal healing vary from 24–50% but importantly patients that did achieve sustained, complete mucosal remission were more likely to avoid hospitalisation and the need for surgical interventions. Deep remission, as defined by combined endoscopic, biochemical and clinical remission may become an increasingly important treatment end-point in CD [9].

The majority of studies have focused on mucosal healing rates in the colon and/or terminal ileum. However, little is currently known of this with regard to ileitis, active small bowel CD. Epidemiologically, small bowel involvement is expected in up-to 69% of CD patients and is considered a poor prognostic indicator in CD [10]. Newer dedicated small bowel imaging modalities such as small bowel capsule endoscopy (SBCE) and MR/CT enterography have improved the detection of this particular disease location [11,12]. To date, only a handful of studies assessing small bowel mucosal healing rates have been performed using dedicated small bowel imaging techniques. Three studies used MR/CT enterography to compare the imaging modality against endoscopy in the detection of therapeutic response [13–15]. One study, using SBCE, included only patients with inflammatory disease and only re-assessed patients in whom a clinical response was achieved [16]. A recently published study with a similar design to our own with 19 participants undergoing sequential SBCE after 12 weeks of therapy suggested it was an effective tool to monitor small bowel mucosal therapeutic response [17]. Overall the data focusing on mucosal healing of active small bowel CD is not as positive as colonic studies. Indeed in our own study, at week 12, no patient had achieved complete mucosal healing with only 27% of participants demonstrating a partial mucosal response [Hall et al, EJGH]. Studies have demonstrated the ability of SBCE to accurately diagnose small bowel CD [18,19], and along with the development of a validated capsule endoscopic scoring system [20], SBCE should be capable of accurately monitoring treatment response similarly to MR technology [13]. To our knowledge, this is the first study of its kind to undertake a 52 week mucosal healing assessment.

2. Aims

To prospectively assess mucosal healing and deep remission rates in a cohort of symptomatic patients with small bowel CD commencing immunomodulator or biologic therapy following 52 weeks of treatment.

2.1. Primary endpoints

i) Using the capsule endoscopy Crohn’s disease activity index (CECDAI), identify rates of complete mucosal healing (absence of ulcers) at 52 weeks.

ii) Determine rates of deep remission as defined by complete mucosal healing and clinical/biochemical remission (Harvey–Bradshaw Index ≤ 5, absent disease activity on imaging, and calprotectin ≤ 50 µg/g) at 52 weeks.

2.2. Secondary endpoints

i) Assess partial response to therapy at 52 weeks as defined by a change in grade of CECDAI severity (mild-moderate CECDAI ≥ 3.5 and moderate-severe CECDAI ≥ 5.8).

ii) Determine clinical remission at 52 weeks as defined by Harvey–Bradshaw Index < 5

iii) Assess improvements in quality of life at 52 weeks in response to therapy.

3. Methods

3.1. Population

Following appropriate ethical approval, symptomatic patients with established CD were prospectively recruited from our inflammatory bowel disease services at the Adelaide and Meath hospital and St James's hospital, Dublin over a 15 month period. Major inclusion criteria included a pre-treatment Harvey–Bradshaw Index (HBI) ≥ 5, definitive CD for at least 6 months duration and demonstration of a patent small bowel. Any patient, including both treatment naïve and treatment experienced patients, requiring thiopurine or biologic therapy was considered suitable for the study and invited to participate. Appropriate medical therapy was decided by the treating physician prior to study entry based on available symptomatic, endoscopic, radiologic and histologic findings. A recent colono-scopy or imaging technique prior to study entry was not an essential requirement. The main exclusion criteria included any contraindication to the use of thiopurine or biologic therapies, known small bowel stricture, recent gastrointestinal surgery (within 3 months of study recruitment), steroid titration up-to 6 weeks prior to study entry, chronic NSAID use or NSAIDS within 6 weeks of study recruitment (apart from 5-ASA therapy), dysphagia, implanted cardiac devices, pregnancy, inability to give informed consent, severe concomitant illness and active infection.

3.2. Study design

3.2.1. Capsule protocol

Prior to baseline SBCE, all participants underwent a patency examination. Patency capsules were administered by specialist gastrointestinal physiologists. Patients were instructed to return 28 h after ingestion of the patency device to undergo a plain X-ray of their abdomen to ensure successful passage of the capsule. Any study participant who failed to pass their patency capsule (i.e. visible on X-ray performed 28 h after ingestion) was excluded from the study. SBCE investigations were performed using PillCam SB2
technology (Given Imaging, Yoqneam, Israel) on patients in whom a patent small bowel had been identified. Capsules were administered following an overnight fast with no bowel preparation. After swallowing the capsule, patients were permitted to leave the hospital with the portable recorder for the duration of the 8 hour study. Data from the recorder was downloaded on site within the department of gastroenterology and analysed by three clinical SBCE experts blinded to patient clinical information using Rapid Reader software (Version 6.5). All reports were made available to the treating consultants. Patients without evidence of ileitis on SBCE were excluded from the study. The degree of severity of small bowel CD was classified as follows; mild disease activity CEDDAI $\geq 3.5$, moderate to severe disease activity CEDDAI $\geq 5.8$. The CEDDAI values representing mild/moderate–severe disease activity are based on previously published work which attempted to define threshold levels of disease activity using the CEDDAI and an alternated capsule endoscopic scoring system, the Lewis score. A CEDDAI $\geq 3.5$ and $\geq 5.8$ correlated with a Lewis score $\geq 135$ and $\geq 750$, respectively [21]. Following 12 and 52 weeks of treatment, patients underwent a repeat SBCE. All patients underwent a repeat patency examination prior to SBCE following 52 weeks of therapy. Absence of ulcers on follow-up SBCE was considered to represent complete mucosal remission at week 52. A CEDDAI score $< 3.5$ not reaching the definition of complete mucosal healing was considered as a “normalisation” of CEDDAI without being considered complete mucosal healing. Partial response to therapy was defined by a decrease in grade of severity of the CEDDAI score from baseline.

3.2.2. Data and sample collection

All study visits were conducted by a member of the study team. A baseline visit was conducted at time of initial SBCE. Patient demographics along with a Harvey–Bradshaw index (HBI), work productivity activity index (WPAI) and European Quality of Life score (EQ-5D) were recorded. A HBI $\geq 5$ was considered positive for disease activity at baseline. The WPAI is a 10 point scale completed by the patient relating to the degree their condition has affected them over the previous 7 days (0—no affect, 10—worst affected). The EQ-5D was also completed by each study patient and relates to their overall general well being over the previous 24 h (0—no affect, 100—worst affected). Blood ($\times 1$ serum tube) and one stool sample were also collected at baseline assessment. Serum samples were sent for C-reactive protein (CRP) analysis locally in the hospital laboratory. A CRP $\geq 5$ mg/dl was considered positive. Stool collection for calprotectin was performed on the same day as the baseline assessment and stored anonymously in a locked –80 °C freezer for batch analysis. A calprotectin value $\geq 50$ μg/g was considered positive. At weeks 12 and 52 of treatment, a repeat study visit was initiated for all enrolled participants. All clinical and biochemical indices including HBI, WPAI, EQ-5D, CRP and calprotectin levels were repeated at follow up visits. All collected data and samples were accessible to members of the study team only. A decrease in HBI below 5 was considered as clinical remission at week 52. A drop in the WPAI score at week 52 was considered a response to treatment. An improvement in EQ-5D at week 52 was considered a response to treatment. A decrease in CRP below 5 mg/l and/or calprotectin below 50 μg/g was considered to indicate biochemical remission at week 52.

3.2.3. Laboratory methods

Calprotectin analysis was performed using a commercially available ELISA technique (Oxford Biosystems, Oxford, England). Assay standards, controls and patient samples were added directly to wells of a microtitre plate coated with antibody to calprotectin. The plate was washed and horseradish peroxidase (HRP) conjugated human calprotectin specific monoclonal antibody was added to each well forming a “sandwich” of solid phase antibody human calprotectin-HRP conjugated monoclonal antibody was formed. For the detection of the immunocomplex, the well was then incubated with a substrate solution in a timed reaction and then measured in a spectrophotometric microplate reader which was directly proportional to the amount of human calprotectin in the test sample.

3.2.4. Statistical analysis

All statistics were performed using SPSS 19. All continuous data is described using medians with interquartile range. Results at baseline & week 12 were compared using two-tailed Wilcoxon analysis and Student’s $t$-test, a p value of $<0.05$ was considered significant.

4. Results

4.1. Study population

In total, 71 patients were screened for possible recruitment into the study. In all, 28 (39%) screened patients were deemed unsuitable due to either a failed patency {11 (39%)}, declined study protocol {14 (50%)} or no step-up in treatment required {3 (11%)}. Of the 43 (61%) patients entered into the treatment arm of the study, the median age was 38 years (range 19–63) and 22 (51%) were female. Within this cohort, 16 (37%) were smokers. The majority of patients {37, (86%)} had ileo-colonic disease with the remaining 6 (14%) having ileal only disease. Disease phenotype demonstrated the following; 16 (37%) inflammatory, 22 (51%) strictureting and 5 (12%) penetrating subtypes. In total, 19 (44%) of the study participants had required a previous surgical resection. Baseline patient characteristics are summarised in Table 1. All patients had already undergone a colonoscopy as part of their disease assessment prior to study participation. In total, 20 (47%) patients had undergone small bowel imaging in the 6 months prior to study participation. Importantly, no patient had dedicated CT/MR enterography performed in the 6 months prior to study entry. Of note, only distal small bowel abnormalities were detected on any of the imaging studies performed. Importantly, no patient had been on a titrating dose of steroids in the 6 week period preceding study inclusion. In all, 36 patients (84%) were commenced on adalimumab. The majority of these patients {31, (86%)} were treatment naïve in terms of a previous biologic therapy. All of these patients were given the standard dose initiation (160 mg/80 mg) followed by 40 mg every other week. The remaining 7 (16%) participants commenced azathioprine (titrated to 2–2.5 mg/kg). No therapeutic drug monitoring (anti-drug
antibodies/TPMT levels) was performed during the course of the study. In total, 39 (91%) were naïve to the prescribed treatment.

### 4.2. Baseline assessment

At baseline assessment, all 43 patients had clinically active disease. In total, 16 (37%) had moderate clinical disease (HBI ≥ 8) and 27 (63%) had mild disease (HBI ≥ 5) at baseline assessment. No patient had severe clinical disease (HBI ≥ 16) at baseline assessment. In total, 39 (91%) subjects who underwent baseline assessment demonstrated active small bowel CD (CECDAI ≥ 3.5) on SBCE. Patients without active small bowel disease were excluded from the study at this time-point. Overall, 26 (67%) had moderate-severe disease (CECDAI ≥ 5.8) with the remaining 13 (33%) having mild disease (CECDAI ≥ 3.5) activity on initial, pre-treatment SBCE. The median CECDAI at baseline was similar for both adalimumab and azathioprine groups, 7 (range 4–27) in the overall cohort.

### 4.3. Week 52 assessment

#### 4.3.1. Mucosal response

Of the initial 43 participants who underwent baseline assessment, 28 (65%) had a 52 week assessment. Overall study recruitment and drop-out rates are shown in Fig. 1. Importantly, 8 (29%) participants who underwent 52 week assessment had at least one inflammatory stricture identified on SBCE. All patients with a stricture were on adalimumab. Overall, 20 (71%) participants had demonstrated an improvement in CECDAI as defined by a change in the grade of severity from baseline. Interestingly, 12 (42%) participants had achieved complete mucosal healing at 52 week assessment which was statistically significant (p < 0.0001 95% CI 0.62 to 0.72). Table 3 compares baseline and week 52 median CECDAI results between participants that achieved complete mucosal healing and those without a full mucosal response. Of the remaining patients not achieving complete mucosal healing, 8 (29%) still had moderate–severe disease (CECDAI ≥ 5.8) with a further 8 (29%) demonstrating mild disease (CECDAI ≥ 3.5) activity. Fig. 2 demonstrates the overall decrease in CECDAI from treatment baseline through 12 weeks to the final 52 week assessment. The median CECDAI at week 52 decreased from 6 at baseline to 3.5 (range 0–27) in the overall cohort. Somewhat surprisingly, despite seemingly impressive overall mucosal healing rates, this median decrease in CECDAI did not reach statistical significance. However, when participants with a stricture identified on SBCE were removed from the data, the median CECDAI at 52 weeks was 0 and this was found to be a statistically significant decrease in CECDAI from baseline (p < 0.0033 95% CI 1.85 to 8.48). Fig. 3 demonstrates the median CECDAI in all participants at baseline with the difference in CECDAI between strictureting and non-stricturing participants at week 52. Of note, no parameters from our 12 week data appeared to predict 52 week response. There was no statistically significant correlation between patient gender, disease duration of greater than 5 and 10 years or age at diagnosis and change in grade of CECDAI score. There was a trend towards less mucosal healing in older study patients (OR 2.0 p < 0.52) and in those that smoked (OR 2.5 p < 0.31) although neither parameter reached statistical significance. Of note, there was also a trend towards an improved mucosal response with adalimumab compared to azathioprine although this did not reach statistical significance (OR 2.8 p < 0.374).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of study patients (n = 43).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (range)</td>
<td>38 (17–69)</td>
</tr>
<tr>
<td>Female [n (%)]</td>
<td>22 (51)</td>
</tr>
<tr>
<td>Smoker</td>
<td>16 (37)</td>
</tr>
<tr>
<td>Disease extent</td>
<td></td>
</tr>
<tr>
<td>Ileo-colonic</td>
<td>37 (86)</td>
</tr>
<tr>
<td>Ileal only</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Disease subtype</td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>16 (37)</td>
</tr>
<tr>
<td>Strictureing</td>
<td>22 (51)</td>
</tr>
<tr>
<td>Penetrating</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Previous surgery</td>
<td></td>
</tr>
<tr>
<td>Ileo-colonic resection</td>
<td>14 (32)</td>
</tr>
<tr>
<td>Ileal resection</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Colonic resection</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Previous medications</td>
<td></td>
</tr>
<tr>
<td>No previous treatment</td>
<td>7 (16)</td>
</tr>
<tr>
<td>5-ASA</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>25 (58)</td>
</tr>
<tr>
<td>Biologic</td>
<td>5 (11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Baseline disease activity scores (endoscopic/clinical/biochemical) for study cohort (n = 43).</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Capsule endoscopy Crohn’s disease activity index (CECDAI)</td>
<td></td>
</tr>
<tr>
<td>No disease (CECDAI = 0)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Mild disease (CECDAI ≥ 3.5)</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Moderate to severe disease (CECDAI ≥ 5.8)</td>
<td>26 (61%)</td>
</tr>
<tr>
<td>b. Harvey Bradshaw Index (HBI)</td>
<td></td>
</tr>
<tr>
<td>Mild disease (5 ≥ HBI ≥ 7)</td>
<td>27 (63%)</td>
</tr>
<tr>
<td>Moderate disease (8 ≥ HBI ≥ 16)</td>
<td>16 (37%)</td>
</tr>
<tr>
<td>c. Quality of life indices</td>
<td></td>
</tr>
<tr>
<td>Median Work productivity activity index</td>
<td>3 (1–8)</td>
</tr>
<tr>
<td>Median European quality of life score</td>
<td>60 (40–100)</td>
</tr>
<tr>
<td>e. Calprotectin (µg/g)</td>
<td>195 (30–1600)</td>
</tr>
<tr>
<td>Median calprotectin</td>
<td></td>
</tr>
</tbody>
</table>
4.3.2. Clinical response
Of the 28 participants who underwent a 52 week assessment, 15 (54%) had achieved clinical remission (HBI < 5). Of the remainder, 8 (29%) had moderate clinical disease (8 < HBI < 16) and 5 (18%) had mild disease (5 < HBI < 7) activity at 52 week assessment. No patient had severe disease (HBI ≥ 16) at either baseline or 52 week assessment.

Median HBI decreased from 7 at baseline to 5 (range 0–15) at 52 week assessment which reached statistical significance (p < 0.0001 95% CI −0.74 to −0.34). Interestingly, despite this seeming clinical improvement, patients with a stricture on SBCE were 6 times more likely to complain of symptoms although this didn't quite reach statistical significance (OR 6.000 p = 0.0613 95% CI 0.9187 to 39.1859). Fig. 4 demonstrates the median HBI in all participants at baseline and 52 weeks with separation of stricturing and non-stricturing participants at week 52. Quality of life scores also improved over the duration of the study, particularly in patients with no evidence of stricturing disease. Median WPAI decreased from 3 to 2 (range 0–7) which was statistically significant (p < 0.0001 95% CI −1.61 to −0.86). There was a similar improvement in EQ-5D with an increase from 60 at baseline to 70 (range 30–90) at 52 weeks (p < 0.0001 95% CI −0.74 to −0.34). Similarly to HBI, patients with strictures were 5 times more likely to express poorer quality of life scores although again this did not reach statistical significance (OR 4.8 p = 0.13 95% CI 0.6168 to 37.3519).

4.3.3. Biochemical and deep remission
Biochemical response to treatment mirrored both endoscopic and clinical response. Median CRP decreased from 5 to 1 (0–120 mg/l) over the duration of the study. This didn't reach statistical significance although it is important to note that the majority of patients (64%) had a normal CRP at baseline assessment. The median decrease in calprotectin...
from 195 μg/g at baseline to 25 μg/g at 52 week assessment did not reach statistical significance \( (p < 0.0224 \text{ CI } 0.05 \text{ to } 0.57) \). Deep remission was defined as combined clinical and biochemical remission. All patients had active endoscopic, clinical and biochemical disease at baseline. Following 12 weeks of treatment, 54% of patients had achieved clinical remission although no patient had achieved complete endoscopic remission. At 52 week assessment, 12 (42%) patients had achieved deep remission which was statistically significant \( (p < 0.0001 \text{ CI } -0.62 \text{ to } -0.22) \). Table 4 summarises rates of endoscopic, clinical and deep remission at baseline, 12-week and 52-week assessment.

### 4.3.4. Strictures

In total, 14 (32%) participants had at least one stricture identified on SBCE. Of these, 9 were newly detected on initial SBCE at treatment baseline. Only one of these participants demonstrated an endoscopic stricture improvement throughout the course of the study in response to adalimumab. The remaining 13 participants all had apparent worsening of their stricture, both clinically and endoscopically. Indeed, 8 (57%) required surgical intervention during the study follow-up period. A further 3 are also likely to require surgical intervention in the near future to treat their stricture. There was no obvious correlation between clinical/demographic data and subsequent stricture formation. Importantly, smoking, young age at diagnosis or disease duration was not associated with stricture formation.

### 4.4. Side-effects

There were two transient capsule retentions at 12 week assessment. Both retentions were due to worsening of a previously identified stricture. One participant required hospitalisation for a 48 hour monitoring period although both capsules passed spontaneously without the need for rescue steroids or surgical intervention. There was also one true capsule retention at 52 week assessment which required surgical retrieval of the capsule with stricturoplasty. Of note, all three patients had successfully passed a repeat patency examination prior to SBCE. There was also one severe reaction to adalimumab which required discontinuation of the drug.

### 5. Discussion

Our primary goal was to assess mucosal healing in a small bowel CD cohort and correlate this with clinical response in order to identify rates of deep remission. Data from colonic studies would suggest that complete mucosal healing rates
can occur in up-to 50% of patients at long-term follow up. This in turn is associated with improved outcomes including decreased risk of surgery and hospitalisation over time. However, mucosal healing as an end-point is easier to monitor in colonic disease when compared to disease affecting the more hard to reach small bowel. From our data, at week 12 no patient had achieved complete mucosal healing although 27% of participants did demonstrate a statistically significant partial mucosal response as defined by normalisation of CECDAI score [Hall et al, EJGH]. No measured parameters at this time-point were capable of predicting patients whom ultimately achieved mucosal healing and deep remission. However, our 52-week data does demonstrate a similar rate of complete healing (42%) to that which has been seen in colonic studies. This is extremely encouraging data. Partial mucosal healing rates, as defined by a decrease in grade of CECDAI, of 37% were also similar to colonic data. It is important to note that this study was designed to assess firstly whether small bowel mucosal healing occurs and secondly if capsule endoscopy can be utilised to monitor small bowel therapeutic response. Thus, while there was a trend towards improved mucosal healing in the adalimumab group compared to the azathioprine group, the study was not designed or powered to compare treatment responses between different therapeutic agents. This is the first study to utilise the validated CECDAI scoring system to assess small bowel mucosal healing. As such, it is still unknown what numerical decrease in CECDAI can be considered indicative of a mucosal response to treatment. Furthermore, it is not apparent when exactly participants achieved a complete mucosal response to treatment. Future studies would be useful to try to ascertain at an earlier stage in therapy which patients are likely to achieve long-term response and whether a change in CECDAI can accurately predict this response.

Importantly this study has shown that SBCE appears capable of safely and accurately monitoring treatment response in patients with small bowel CD. There was only one capsule retention out of 108 SBCE performed despite a high prevalence of strictures (32%) and a high rate of previous surgery (44%). Previous studies have suggested that if a patency capsule has passed, without pain, through the bowel prior to dissolving that the risk of capsule retention is close to negligible [22] Our own experience over the course of the study would appear to correlate with current evidence that when utilised correctly, the risk of capsule retention is close to negligible.

In terms of clinical response, 54% of our patients were in clinical remission at week 52. Quality of life parameters had also improved from baseline with statistical significance. Furthermore, 42% of our participants were in deep remission as defined by endoscopic, clinical and biochemical remission at 52 weeks. No patient who had achieved mucosal healing required hospitalisation or surgical intervention over the duration of the 52 week follow-up. Unfortunately this was not mirrored in those patients who had a stricture identified on SBCE. In total, 32% had an inflammatory stricture. This particular cohort had poor outcomes. Not only were they more likely to feel unwell with high HBI and poor quality of life indicators but they also had a high chance of requiring surgery within 52 weeks of stricture diagnosis on SBCE. It is also important to consider that a further 11% of screened patients failed an initial patency examination and were excluded from the study. While some of these failures are likely due to delayed transit of the patency capsule, a proportion may indeed have had a severe stricture present. Exclusion of this potentially severe cohort may have actually exaggerated our already poor response rates for this particular phenotype. Interestingly, the majority of these strictures were newly diagnosed on SBCE at study baseline. However, no participant had undergone dedicated small bowel surgery.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Rates of clinical, endoscopic and deep remission over the course of the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical remission (%)</td>
</tr>
<tr>
<td>Week 0</td>
<td>0</td>
</tr>
<tr>
<td>Week 12</td>
<td>54</td>
</tr>
<tr>
<td>Week 52</td>
<td>54*</td>
</tr>
</tbody>
</table>

* p < 0.0001 95% CI −0.74 to −0.34.
** p < 0.0001 95% CI −0.62 to −0.22.
*** p < 0.0001 95% CI −0.62 to −0.22.
bowel imaging in the form of CT/MR enterography. Regardless of the technique utilised, the authors would suggest that early diagnosis and aggressive treatment of ileal disease should be considered as a treatment goal given the fact that by the time strictures develop it may be too late to prevent the need for surgery. Dedicated ileal assessment at baseline diagnosis with either SBCE or CT/MR enterography may be prudent.

There were a number of limitations to our study. Despite reaching statistical significance and being the largest study to date, the numbers in this study are relatively small. The relative heterogeneity of our study group may also be considered a weakness. Furthermore, the trend towards a worse outcome for older subjects and for smokers although not statistically significant suggests the requirement for larger studies to expand on these potential associations. While our study shows that mucosal healing does occur in a significant proportion of patients with small bowel CD, and while rates are similar to those reported in colonic studies, it is not possible with our design to assume the effect is directly related to the treatment given, as there was no control arm and the natural history of small bowel CD is unknown. However, we do intend to follow this cohort over a longer time scale to further assess treatment effect and the long term impact of small bowel mucosal healing on hospitalisation and surgery rates. It is important to note that only follow-up small bowel assessment was undertaken as part of the study protocol. No follow-up colonoscopies were undertaken to monitor large bowel mucosal response. This was not possible due to limited access to endoscopy and likely patient compliance to study protocol and does not affect our treatment end-points. Thus, it is impossible to gauge the effect that potential large bowel involvement may have had on therapeutic response. While the presence and treatment of large bowel disease were not end-points of this study, it would be interesting to correlate both small and large bowel mucosal response. In future practice, the authors would suggest that both ileo-colonoscopy and dedicated small bowel imaging should be used as tools to assess treatment response.

6. Conclusion

To our knowledge, this is the first study to assess partial and complete rates of small bowel mucosal healing and deep remission in a cohort of CD patients following 52 weeks of therapy. Our study shows capsule is a safe and effective means of assessing small bowel treatment response. Overall complete mucosal healing rates were similar to colonic data. The presence of/or development of a stricture during treatment was a poor prognostic indicator in terms of the success of therapy. Early diagnosis and treatment of small bowel CD may decrease the risk of stricture development and subsequent need for surgery.

Acknowledgements/conflicts of interest

B Hall and D McNamara received an Abbvie sponsored, investigator led grant to conduct this study (IMM-11-0108). Study sponsors had no role in the study design or collection, analysis and interpretation of data. Study sponsors also had no role in the writing of the manuscript or in the decision to submit the manuscript for publication.

This manuscript, including related data, figures and tables has not been previously published and is not under consideration elsewhere.

Study concept and design: DMcN; patient recruitment + study visits; BH, GH, BR NM, DMcN JLC; capsule analysis; BH, GH, DMcN; calprotectin analysis; BH, SS; statistical analysis; BH, SS, DMcN; manuscript write-up; BH, DMcN; manuscript review; BR, GH, NM, JLC

All authors are satisfied with final manuscript for submission. All authors declare no conflict of interest.

References