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Characterisation of Mucosal Healing with Adalimumab Treatment in Patients with Moderately to Severely Active Crohn's Disease: Results from the EXTEND Trial

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Abstract

Background and Aims: Mucosal healing [MH] is an important goal for patients with Crohn's disease [CD], yet is incompletely characterised. We investigated whether MH differed by segments across the colon and ileum in patients who received adalimumab maintenance treatment in the EXTEND study.

Methods: In this double-blind study in adults with moderate to severe ileocolonic CD and mucosal ulceration, all patients received adalimumab induction [Week 0, 160 mg; Week 2, 80 mg]. At Week 4, patients were randomised to 40 mg adalimumab or placebo every other week until Week 52. In this post-hoc analysis, MH was assessed by CD Endoscopic Index of Severity [CDEIS], Simple Endoscopic Score for CD [SES-CD], and Colonic and Ileal Global Histologic Disease Activity Scores [CGHAS/IGHAS].

Results: Baseline endoscopic severity was similar across segments. At Week 52, mean changes in CDEIS surface involved and ulcerated surface were –68.5% to –90.6% in the rectum, sigmoid/left colon, and transverse colon compared with –22.3% to –50.0% in the right colon and ileum. Favourable shifts by Week 52 in ulcer size and ulcerated surfaces per SES-CD were more pronounced in the rectum, sigmoid/left colon, and transverse colon vs the right colon and ileum. At Week 52, CGHAS and IGHAS healing was more common in the colon [28.3%] vs the ileum [21.2%].

Conclusions: This analysis suggests differing propensities of the ileocolonic segments to heal endoscopically during adalimumab treatment. In the sigmoid/left and transverse colon, higher MH rates may be achieved, compared with the ileum, in patients with moderate to severe CD.

Key Words: Endoscopy; mucosal ulceration; inflammatory bowel disease

1. Introduction

Until recently, the main objective when treating patients with Crohn's disease [CD] was to alleviate disease-related symptoms.[1] However, improvement of symptoms does not always indicate control of objectively assessed underlying inflammation.[2,3] In contrast, the presence of deep, extensive ulcers strongly increases the chance of future colectomy.[4] Newer, more highly effective therapies have shifted the treatment goals for patients with CD to achieving outcomes such as mucosal healing which potentially lead to disease modification in parallel with clinical remission.[5,6] Mucosal healing has been associated with positive long-term clinical and surgical outcomes.[7–9]

Treatment with the anti–tumour necrosis factor [TNF] monoclonal antibodies adalimumab and infliximab may allow mucosal healing to be a realistic treatment target for patients with CD. The Extend the Safety and Efficacy of Adalimumab through Endoscopic Healing [EXTEND; NCT00348283] study was the first randomised, placebo-controlled study in patients with CD to use mucosal healing as the primary endpoint.[5] In EXTEND, maintenance adalimumab treatment [ie, induction and subsequent active therapy] resulted in greater mucosal healing rates compared with induction-only adalimumab treatment [ie, randomisation to placebo after adalimumab induction] in patients with moderate to severe ileocolonic CD and documented mucosal ulcers.[5]

To date, no data are available regarding the characterisation of mucosal lesions across the different colonic segments and ileum [ie, the rectum, sigmoid/left colon, transverse colon, right colon, and ileum] during the course of anti–TNF alpha treatment. This has clinical implications because it remains an open question whether mucosal healing observed by colonoscopy in the more easily accessed distal colonic segments is likely to indicate healing in the ileum as well. If the pattern of mucosal healing is found to vary among the segments [in particular, between ileal and colonic mucosa], it could suggest differences in the resolution mechanisms induced by anti-TNF alpha agents along the inflamed intestinal tract. These findings offer possibilities of adjusting treatment strategies for response enhancement based on specific locations of involvement. Using data from patients enrolled in the EXTEND study, we assessed the potential of adalimumab maintenance treatment [including an induction period] to achieve mucosal healing at five different specific ileocolonic segments.

2. Methods

2.1. Study design and patients

Detailed information regarding the design and patient disposition of EXTEND has been reported previously.[5] Briefly, EXTEND was a multicentre, randomised, double-blind, placebo-controlled clinical trial that assessed adalimumab safety and efficacy in inducing and maintaining mucosal healing in adults with moderately to severely active ileocolonic CD for > 4 months and a Crohn's Disease Activity Index [CDAI] value of 220 to 450 with documented mucosal ulceration by recorded ileocolonoscopy at screening.

All patients received open-label adalimumab induction [160 mg at Week 0 and 80 mg at Week 2]. At Week 4, patients were randomised to receive adalimumab [40 mg every other week] or placebo until Week 52. Beginning at Week 8, patients experiencing flare/non-response could move to open-label adalimumab every other week, followed by weekly adalimumab for continued flare/non-response.

2.2. Study assessments

To better establish patterns of healing, multiple scoring systems derived from endoscopy (Crohn's Disease Endoscopic Index of Severity [CDEIS][10] and Simple Endoscopic Score for Crohn's Disease [SES-CD][11]) and histology (Colonic and Ileal Global Histologic Disease Activity Scores [CGHAS and IGHAS], respectively)[12,13]] were used. All analyses presented here used data from blinded central readings.

In EXTEND, patients underwent a maximum of four endoscopies, conducted at screening, Week 12, the time of moving to open-label every-other-week dosing [if after Week 12], and Week 52. For the endoscopies, the five segments were recorded sequentially for approximately 1 min each on withdrawal of the endoscope and read centrally by one of the authors [PR].

The presence and extent of ulcers in the ileocolonic segments were derived from the CDEIS.[10] The CDEIS scores six endoscopic variables [presence of deep ulcers, superficial ulcers, nonulcerated stenosis, and ulcerated stenosis; proportion of ulcerated surfaces; and surface involved by disease] that are assessed in each of five ileocolonic segments [rectum, sigmoid/left colon, transverse colon, right colon, and ileum].[10] When present in a segment, deep ulcers received a score of 12, whereas superficial ulcers received a score of 6; the absence of ulcers was scored as 0.[10] Overall CDEIS values range from 0 to 44, with higher values indicating more severe disease.[14] In this analysis, the two stenosis-related subscores were not evaluated. Few patients had stenosis at baseline.

The SES-CD is a simple scoring system based on four endoscopic variables [presence and size of ulcers, proportion of surface covered by ulcers, proportion of affected surface, and presence and severity of stenosis] measured in the same five ileocolonic segments as the CDEIS.[11] Overall values on the SES-CD range from 0 to 56, with higher values indicating more severe disease.[14] The value for each variable ranges from 0 to 3, so that the score in each segment can range from 0 to 15; however, the maximum stenosis score in a segment distal to another evaluable segment cannot exceed 2, so that the stenosis scores cannot exceed a total of 11.

For the histological analysis, performed by one of the authors [KG], up to 10 biopsy specimens [two from each segment] were collected at each endoscopy; if involved areas were present, the samples were taken from those locations. Healing based on histology was assessed using the CGHAS and IGHAS [Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online] and was defined as CGHAS or IGHAS ≤ 2 at Weeks 12 and 52.[12,13] These measures assessed: the extent of epithelial damage and architectural changes; the presence of mononuclear and polymorphonuclear cells in the lamina propria, polymorphonuclear cells [ie, neutrophils] in the epithelium, erosions or ulcers, and granuloma; and the

proportion of ≥ 6 biopsy samples that were affected. Each total score could range from 0 [least severe] to 16 [most severe] when segments were summed either in the entire colon or in the ileum specifically.

2.3. Statistical analyses

2.3.1. CDEIS endoscopy data

In this report, CDEIS endoscopy analyses included only patients randomised at Week 4 who had CDEIS values at all three endoscopy visits [baseline, Week 12, and Week 52]. Patients who moved to open-label adalimumab before Week 12 were excluded. Patients were analysed according to their randomised treatment group, regardless of whether they moved to open-label adalimumab at Week 12 or later. However, if a patient moved to open-label adalimumab after Week 12, the observation at the time of moving to the open-label treatment was imputed as the Week 52 data point. In the ileocolon as a whole, for the CDEIS, the absence or presence of deep mucosal ulcers [originally scored as 0 or 12, respectively, and coded for this analysis as 'no' or 'yes'] was calculated at Weeks 12 and 52; the same analysis was repeated for superficial ulcers [originally scored as 6 when present and coded for this analysis as 'yes']. In individual ileocolonic segments, mean changes from baseline in the CDEIS subscores of percentage surface involved and ulcerated surfaces were determined at Weeks 12 and 52; improvement was indicated by a decrease in the CDEIS subscores.

2.3.2. SES-CD endoscopy data

In this report, SES-CD endoscopy analyses included only patients randomised at Week 4 who had SES-CD values at all three endoscopy visits [baseline, Week 12, and Week 52]. As with CDEIS analyses, patients who moved to open-label adalimumab before Week 12 were excluded, patients were analysed according to their randomised treatment group, and patients who moved to open-label adalimumab after Week 12 had the assessment at that time imputed as the Week 52 data. For SES-CD analysis, two subscores were evaluated: size of ulcers (0 = no ulcers, 1 = aphthous ulcers [> 0.1–0.5 cm], 2 = large ulcers [> 0.5–2 cm], and 3 = very large ulcers [> 2 cm]) and ulcerated surfaces [0 = none, 1 = < 10%, 2 = 10%–30%, and 3 = > 30%].[11] Shifts from baseline in these SES-CD subscores were determined in each ileocolonic segment at Weeks 12 and 52. In patients with subscores of 1, 2, or 3 at baseline, the percentages who improved [ie, decreased by at least 1 point] at Weeks 12 and 52 were also determined. No data were imputed for missing values in shift analyses.

2.3.3. CGHAS and IGHAS histology data

For histological analyses, all randomised patients who had CGHAS or IGHAS scores ≥ 3 at the baseline colonoscopy, indicating an ulcer, and who received at least one dose of blinded therapy, were included. Patients with missing data at Weeks 12 and 52 [and those who moved to open-label adalimumab at any time] were counted as not having achieved a response for these endpoints (ie, imputed as

Table 1. Demographic and baseline disease characteristics.

Characteristic	ADA/ADA [*n* = 28]	ADA/PBO [*n* = 21]	All patients [*N* = 49]	*P*-value[a]
Women, *n* [%]	18 [64.3]	13 [61.9]	31 [63.3]	1.00
White, *n* [%]	25 [89.3]	19 [90.5]	44 [89.8]	1.00
Age, years, mean [SD]	33.9 [11.7]	40.5 [14.0]	36.7 [13.0]	0.08
Body weight, kg, mean [SD]	67.7 [17.2]	73.6 [18.5]	70.2 [17.8]	0.26
CRP ≥ 1 mg/dl, *n* [%]	14 [51.9][b]	7 [33.3]	21 [43.8][b]	0.25
CD location, *n* [%]				NC
Colon	23 [82.1]	20 [95.2]	43 [87.8]	
Ileum	22 [78.6]	13 [61.9]	35 [71.4]	
Rectum	8 [28.6]	9 [42.9]	17 [34.7]	
Anal/perianal	7 [25.0]	7 [33.3]	14 [28.6]	
Gastroduodenum	3 [10.7]	2 [9.5]	5 [10.2]	
Other	1 [3.6]	1 [4.8]	2 [4.1]	
Jejunum	0	1 [4.8]	1 [2.0]	
CD duration, years, mean [SD]	8.8 [6.3]	8.8 [7.1]	8.8 [6.6]	1.00
CDAI, mean [SD]	300.4 [63.3]	301.6 [60.4]	300.9 [61.4]	0.95
CDEIS, mean [SD]	9.1 [6.8]	11.3 [6.1]	10.1 [6.5]	0.26
SES-CD, mean [SD]	11.3 [8.0]	14.0 [8.0]	12.4 [8.0]	0.25
Current smoker, *n* [%]	10 [35.7]	6 [28.6]	16 [32.7]	0.76
Previous anti-TNF agent, *n* [%]	11 [39.3]	10 [47.6]	21 [42.9]	0.58
Concomitant medication[s], *n* [%]				
Mesalazine	2 [7.1]	5 [23.8]	7 [14.3]	0.12
Immunomodulators[c]	9 [32.1]	9 [42.9]	18 [36.7]	0.55
Corticosteroids[d]	6 [21.4]	8 [38.1]	14 [28.6]	0.22
CD-related antibiotics[e]	2 [7.1]	1 [4.8]	3 [6.1]	1.00

ADA, adalimumab; ADA/ADA, ADA induction and maintenance; ADA/PBO, ADA induction only; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein; ITT, intent to treat; NC, not calculated; PBO, placebo; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumour necrosis factor.

[a]*P*-values for ADA/PBO vs ADA/ADA groups, based on one-way analysis of variance [continuous variables] or Fisher's exact test [categorical variables].

[b]One patient did not have a value for CRP at baseline.

[c]Includes azathioprine, mercaptopurine, and methotrexate.

[d]Includes budesonide, prednisolone, and prednisone.

[e]Includes levofloxacin, metronidazole, and rifaximin.

Patients were from the ITT population and had CDEIS or SES-CD data at baseline, Week 12, and Week 52, including data imputed when moving to open-label therapy after Week 12.

non-responders [NRI]). The different population for the histological analyses [ie, including patients with missing data at some time points, whereas endoscopic analysis included only patients without missing data] was dictated by the timing of study assessments. For patients who moved to adalimumab treatment because of disease flare after Week 12, endoscopy data from the visit at the time of the move to the open-label treatment was used as the last assessment for colonoscopy endpoints and did not include tissue samples for histology analysis.

P-values for continuous variables [eg, mean changes from baseline] were from an analysis of covariance model with treatment as independent variable and the baseline value of the variable under analysis as covariate. *P*-values for categorical variables [eg, percentages of patients achieving an endpoint] were derived from Fisher's exact test. Due to small sample sizes, *p*-values were not calculated for some categorical variables.

3. Results

3.1. Patient characteristics

Demographic and baseline disease characteristics of patients with ulcers at baseline and CDEIS or SES-CD values at baseline, Week 12, and Week 52 are shown in Table 1. Characteristics in the two randomised treatment groups were well balanced; the characteristics of this subanalysis population were similar to those of the overall EXTEND population. The majority of patients had disease in the colon [87.8%] and ileum [71.4%]. CDEIS subscores at baseline showed that ulcers and involved surfaces were evenly distributed across the different ileocolonic segments [Table 2].

3.2. CDEIS endoscopy data

3.2.1. CDEIS deep and superficial ulcers in the entire ileocolon

The proportions of patients whose baseline ulcers, analysed separately for deep ulcers [Figure 1A] and for superficial ulcers [Figure 1B], persisted at Week 12 were similar for patients receiving maintenance adalimumab treatment and those receiving induction adalimumab only. By Week 52, lower percentages of patients receiving maintenance adalimumab treatment compared with those receiving induction adalimumab followed by placebo had deep or superficial ulcers; the absolute difference between the two treatment groups ranged from 36 to 40 percentage points [Figure 1A and B]. Given that the effects of adalimumab induction in this and other analyses were still apparent at Week 12 in patients randomised to placebo at Week 4, the remainder of the results section will mainly focus on the data from Week 52.

Table 2. CDEIS subscores at baseline by ileocolonic segment.

Baseline value, mean	ADA/ADA [*n* = 28]	ADA/PBO [*n* = 21]
CDEIS surface involved		
Rectum	3.9 [*n* = 12]	5.0 [*n* = 14]
Sigmoid/left colon	3.6 [*n* = 15]	5.5 [*n* = 14]
Transverse colon	4.9 [*n* = 12]	4.0 [*n* = 10]
Right colon	3.7 [*n* = 7]	4.8 [*n* = 9]
Ileum	4.0 [*n* = 13]	5.2 [*n* = 8]
CDEIS ulcerated surface		
Rectum	1.2 [*n* = 12]	1.2 [*n* = 13]
Sigmoid/left colon	1.3 [*n* = 15]	1.3 [*n* = 13]
Transverse colon	1.9 [*n* = 12]	0.9 [*n* = 10]
Right colon	0.9 [*n* = 7]	1.1 [*n* = 9]
Ileum	1.3 [*n* = 13]	1.5 [*n* = 8]

ADA, adalimumab; ADA/ADA, ADA induction and maintenance; ADA/PBO, ADA induction only; CDEIS, Crohn's Disease Endoscopic Index of Severity; ITT, intent to treat; PBO, placebo.

Patients were from the ITT population and had CDEIS data at baseline, Week 12, and Week 52 [including data imputed when moving to open-label therapy after Week 12].

3.2.2. CDEIS Surface Involved by Ileocolonic Segment

In patients randomised to receive maintenance adalimumab treatment, the mean percentage change from baseline in CDEIS surface involved indicated large improvements at Week 52 in the rectum, sigmoid/left colon, and transverse colon, and smaller improvements in the right colon and ileum [Figure 2A]. The same pattern was observed for mean percentage changes from baseline to Week 12 [Supplementary Figure 1A, available as Supplementary data at *ECCO-JCC* online].

3.2.3 CDEIS ulcerated surface by ileocolonic segment

In patients receiving maintenance adalimumab treatment, the mean percentage change from baseline in CDEIS ulcerated surface indicated large improvements at Week 52 in the rectum, sigmoid/left colon, and transverse colon, and smaller improvements in the right

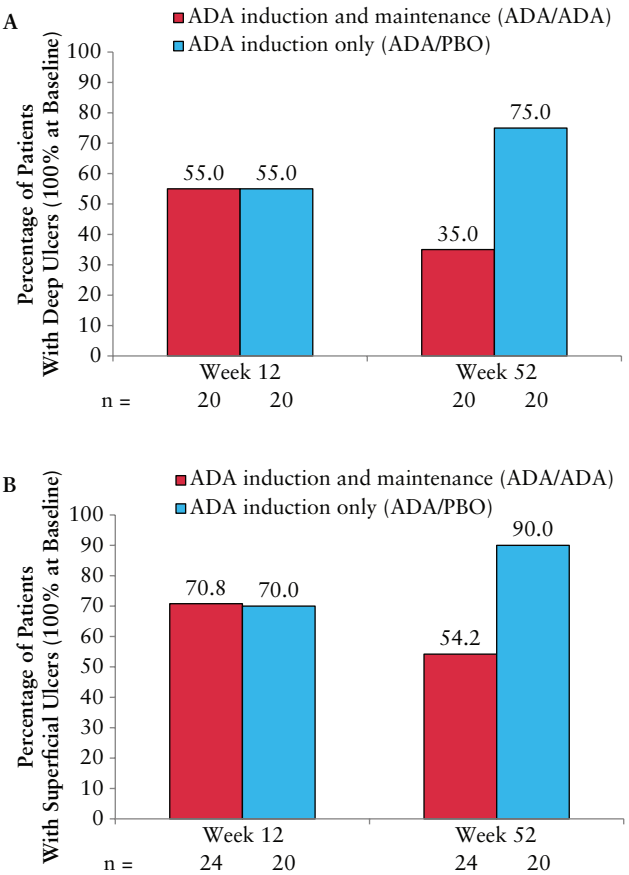

Figure 1. Percentage of patients with [A] deep and [B] superficial ulcers per CDEIS at Weeks 12 and 52. Patients were from the ITT population and had at least one [A] deep or [B] superficial ulcer per CDEIS at baseline and also had data at Week 12 and Week 52 [including data imputed when moving to open-label therapy after Week 12]. ADA, adalimumab; CDEIS, Crohn's Disease Endoscopic Index of Severity; ITT, intent to treat; PBO, placebo.

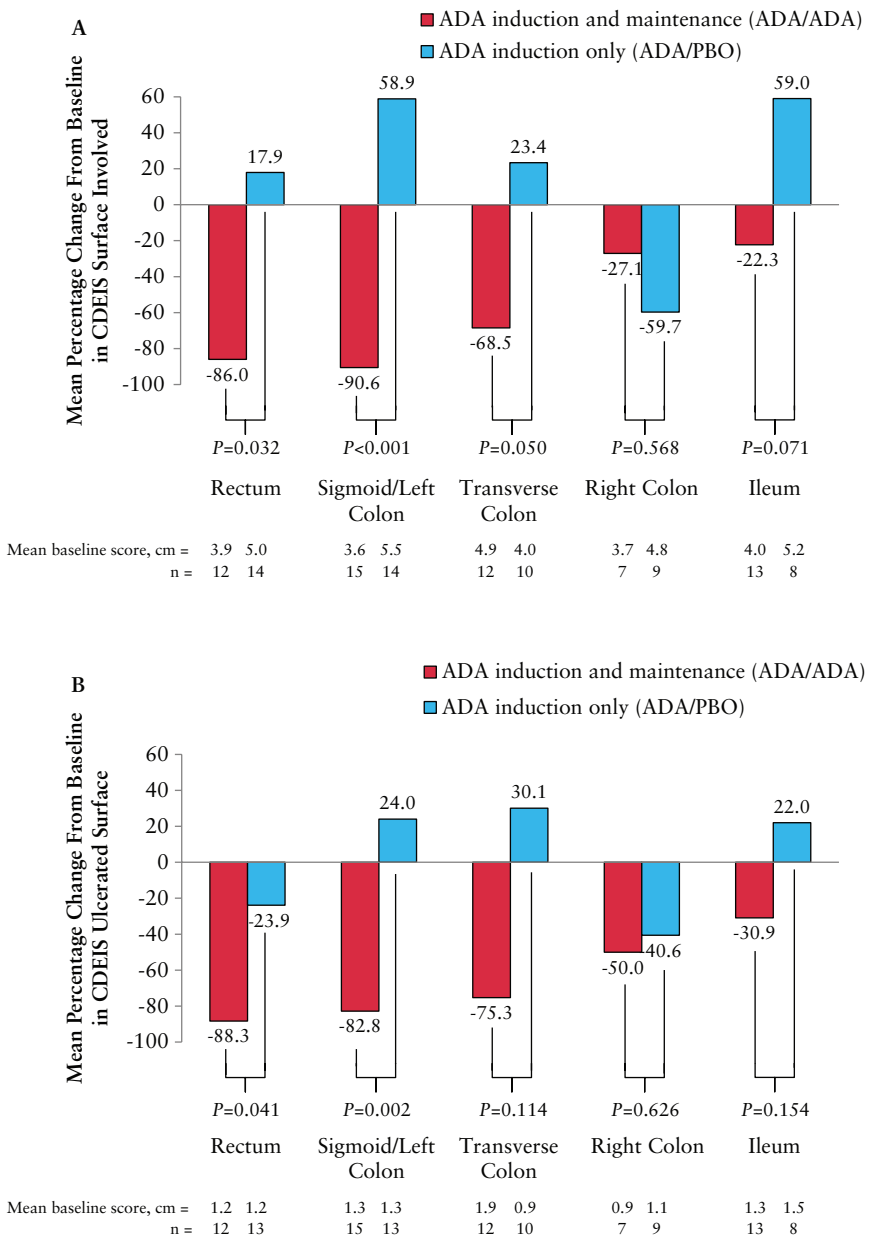

Figure 2. Mean percentage change from baseline in [A] surface involved and [B] ulcerated surface CDEIS subscores by segment at Week 52. Patients were from the ITT population, had measurable [A] surface involved or [B] ulcerated surface CDEIS subscores in the relevant segment at baseline, and had data at Week 12 and Week 52 [including data imputed when moving to open-label therapy after Week 12]. ADA, adalimumab; CDEIS, Crohn's Disease Endoscopic Index of Severity; ITT, intent to treat; PBO, placebo. *P*-value is from an analysis of covariance model with treatment as independent variable and baseline value as covariate.

colon and ileum [Figure 2B]. The same pattern was observed for mean percentage changes from baseline to Week 12 [Supplementary Figure 1B, available as Supplementary data at *ECCO-JCC* online].

3.3. SES-CD endoscopy data

3.3.1. SES-CD ulcer size subscore by ileocolonic segment

Shifts from baseline to Week 52 in SES-CD ulcer size subscore are shown in Table 3. In patients with ulcers in a given segment at baseline [ie, had a score of 1, 2, or 3], the percentage with improvement was also determined at Week 52 [Figure 3A]. Improvements were greatest in the sigmoid/left colon, rectum, transverse colon, and right colon, and less pronounced in the ileum. Shifts from baseline to Week 12 in SES-CD ulcer size subscore are shown in Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online. Among patients who were randomised to receive maintenance adalimumab, the patterns of shifts from baseline in SES-CD ulcer size subscore at Week 12 were similar to those observed at Week 52.

3.3.2. SES-CD ulcerated surfaces subscore by ileocolonic segment

Shifts from baseline to Week 52 in SES-CD ulcerated surfaces subscore are shown in Table 4. In patients with ulcers in a given segment at baseline [ie, had a score of 1, 2, or 3], the percentage with improvement was also determined at Week 52 [Figure 3B]. Improvements were seen most clearly in the sigmoid/left colon and rectum, followed in declining order by the transverse colon, right

Table 3. Shifts from baseline to Week 52 in SES-CD ulcer size subscores by segment.

ADA/ADA [*n*]	Subscore at baseline	Subscore at Week 52, *n* [%]			
Rectum		0	1	2	3
16	0	14 [87.5]	–	2 [12.5]	–
5	1	4 [80.0]	1 [20.0]	–	–
7	2	7 [100]	–	–	–
0	3	–	–	–	–
Sigmoid/left colon		0	1	2	3
13	0	13 [100]	–	–	–
5	1	5 [100]	–	–	–
8	2	7 [87.5]	–	1 [12.5]	–
2	3	1 [50.0]	1 [50.0]	–	–
Transverse colon		0	1	2	3
14	0	14 [100]	–	–	–
4	1	3 [75.0]	–	1 [25.0]	–
6	2	4 [66.7]	1 [16.7]	1 [16.7]	–
3	3	1 [33.3]	–	2 [66.7]	–
Right colon		0	1	2	3
18	0	18 [100]	–	–	–
2	1	1 [50.0]	–	1 [50.0]	–
4	2	3 [75.0]	1 [25.0]	–	–
0	3	–	–	–	–
Ileum		0	1	2	3
8	0	6 [75.0]	2 [25.0]	–	–
2	1	–	1 [50.0]	1 [50.0]	–
10	2	6 [60.0]	1 [10.0]	1 [10.0]	2 [20.0]
1	3	–	–	1 [100]	–
ADA/PBO [*n*]	Subscore at Baseline	Subscore at Week 52, n [%]			
Rectum		0	1	2	3
7	0	5 [71.4]	2 [28.6]	–	–
3	1	2 [66.7]	–	1 [33.3]	–
8	2	3 [37.5]	1 [12.5]	4 [50.0]	–
2	3	–	–	1 [50.0]	1 [50.0]
Sigmoid/left colon		0	1	2	3
7	0	5 [71.4]	–	2 [28.6]	–
2	1	1 [50.0]	–	1 [50.0]	–
10	2	–	–	9 [90.0]	1 [10.0]
1	3	–	–	1 [100]	–
Transverse colon		0	1	2	3
10	0	6 [60.0]	–	4 [40.0]	–
4	1	1 [25.0]	1 [25.0]	2 [50.0]	–
6	2	2 [33.3]	1 [16.7]	3 [50.0]	–
0	3	–	–	–	–
Right colon		0	1	2	3
10	0	7 [70.0]	1 [10.0]	2 [20.0]	–
2	1	1 [50.0]	1 [50.0]	–	–
7	2	2 [28.6]	3 [42.9]	2 [28.6]	–
0	3	–	–	–	–
Ileum		0	1	2	3
9	0	7 [77.8]	1 [11.1]	1 [11.1]	–
0	1	–	–	–	–
7	2	1 [14.3]	–	6 [85.7]	–
1	3	–	–	1 [100]	–

ADA, adalimumab; ADA/ADA, ADA induction and maintenance; ADA/PBO, ADA induction only; ITT, intent to treat; PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's Disease.

Patients were from the ITT population and had data at baseline, Week 12, and Week 52 [including data imputed when moving to open-label therapy after Week 12].

colon, and ileum. Shifts from baseline to Week 12 in SES-CD ulcerated surfaces subscore are shown in Supplementary Table 3, available as Supplementary data at *ECCO-JCC* online. Among patients who received maintenance adalimumab, the patterns of shifts from baseline in SES-CD ulcerated surfaces subscore at Week 12 were similar to those observed at Week 52, although the differences among segments were small at Week 12.

3.4. CGHAS and IGHAS histology data

Among patients receiving maintenance adalimumab treatment who had a CGHAS or IGHAS ≥ 3 at baseline, a slightly greater percentage had a score of 0, 1, or 2 at Week 52 in the colon as compared with the ileum [Figure 4]. The same pattern was observed for changes from baseline to Week 12 [Supplementary Figure 2, available as Supplementary data at *ECCO-JCC* online].

4. Discussion

Identifying the pattern of mucosal healing following treatment may be important for indicating whether patients with positive changes in a distal region [eg, the colon] are likely to experience corresponding improvements in proximal regions [eg, the ileum]. It has generally been thought that disease involvement in CD is more severe in the rectum and ileum, and that healing of mucosal ulceration with systemic therapy proceeds in a mostly uniform way among segments of the colon and ileum. However, no research has been done specifically to support these beliefs. The EXTEND study provided an opportunity to examine these questions in patients with moderately to severely active CD and ulcers at baseline, who were treated for 52 weeks. In this post-hoc analysis, our findings based on EXTEND data challenge both of the prior assumptions. The severity of disease before initiation of adalimumab treatment was similar across segments [range of mean values in patients who later received maintenance adalimumab: CDEIS surface involved, 3.6–4.9; CDEIS ulcerated surface, 0.9–1.9], and was no greater in the rectum and ileum compared with other locations. However, healing of mucosal ulcers with maintenance adalimumab was not consistent across segments; multiple different assessments based on endoscopy demonstrated that the rectum, sigmoid/left colon, and transverse colon healed more readily than the right colon and ileum. Baseline ulceration was similar across segments; thus, the different patterns of healing among those segments at Week 52 cannot be explained by initial variation in the degree of involvement. Consistent with endoscopy results, healing according to histology was more frequent in the colon than the ileum. Our analyses indicate that healing in distal and proximal ileocolonic regions is not uniform, implying that colonoscopy of all segments may be important for a full assessment of disease activity. The difference in endoscopic healing among ileal and colonic segments could be correlated with recent genetic data, which separated ileal Crohn's disease and colonic Crohn's disease.[15]

The greatest improvements in CDEIS surface involved and ulcerated surfaces subscores at Week 52 following maintenance adalimumab treatment occurred in the rectum [–86% to –88%], sigmoid/left colon [–83% to –91%], and transverse colon [–69% to –75%], compared with the right colon [–27% to –50%] and ileum [–22% to –31%]. The differences in improvements were unrelated to CDEIS subscores at baseline, which were similar across segments, although mean baseline severity was worst in one of the segments [ie, the transverse colon] that later improved the most with treatment. Similarly, SES-CD shift analyses suggested a pattern of greater healing in the rectum, sigmoid/left colon, and transverse colon relative to the right colon and ileum. However, in these analyses, the CDEIS appeared to be more sensitive to changes in ulcerated surface than the SES-CD; this could be an important consideration

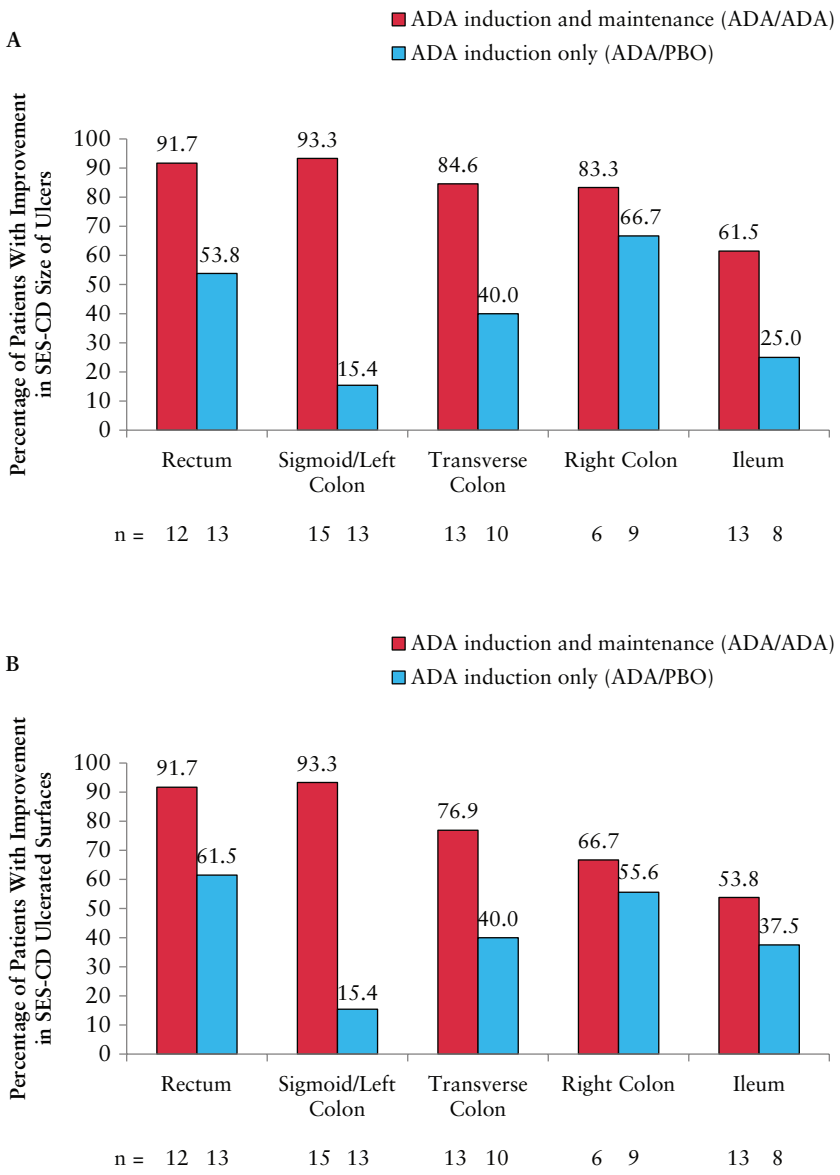

Figure 3. Improvements from baseline to Week 52 in [A] size of ulcers and [B] ulcerated surfaces SES-CD subscores by segment in patients with baseline subscores of 1, 2, or 3. Patients were from the ITT population and had data at baseline, Week 12, and Week 52 [including data imputed when moving to open-label therapy after Week 12]. ADA, adalimumab; ITT, intent to treat; SES-CD, Simple Endoscopic Score for Crohn's Disease; PBO, placebo.

when designing studies that aim to detect small efficacy signals. Finally, histological healing was more common in the colon compared with the ileum at Week 52 [28% vs 21%, respectively]. The natural course of CD in the patients who received adalimumab induction followed by placebo exhibited a different trajectory: surface involvement increased slightly at Week 52 in the rectum, but ulcerated surface decreased, which suggests spreading of mild effects of CD on the mucosa.

The improvements in the presence of ulcers and in the CDEIS surface involved and ulcerated surfaces observed following adalimumab maintenance in the different ileocolonic segments are consistent with the original findings from the EXTEND study, which showed that a greater percentage of patients receiving adalimumab maintenance compared with adalimumab induction only followed by placebo achieved complete mucosal healing.[5] The present findings suggest that adalimumab has efficacy across all segments but that some of those segments heal less readily than others. However, several differences from the original analyses should be noted when considering the implications of the segmental analyses. First, the mucosal healing results in the present analyses as compared with the original analyses could have been influenced by differences in the endpoints that were chosen and the imputation methods that were used. The original analysis included all patients with ulceration at screening, and patients with missing data at Weeks 12 and 52 were treated as non-responders at those time points. The present analysis included only patients who had data at baseline, Week 12, and Week 52 [or who moved to open-label adalimumab therapy after Week 12]; therefore, no imputation was needed. Selecting patients with data at all assessments could have biased the results. Finally, the original analysis examined all types of ulcers, whereas the present analysis explored deep and superficial ulcers separately.

This analysis that characterised CDEIS and SES-CD improvements by ileocolonic segments has several potential strengths. All analysed patients had at least one ulcer at baseline; therefore, any

Table 4. Shifts from baseline to Week 52 in SES-CD ulcerated surfaces subscores by segment.

ADA/ADA [*n*]	Subscore at baseline	Subscore at Week 52, *n* [%]			
Rectum		0	1	2	3
16	0	14 [87.5]	2 [12.5]	–	–
10	1	9 [90.0]	1 [10.0]	–	–
1	2	1 [100]	–	–	–
1	3	1 [100]	–	–	–
Sigmoid/left colon		0	1	2	3
13	0	13 [100]	–	–	–
11	1	10 [90.9]	1 [9.1]	–	–
3	2	3 [100]	–	–	–
1	3	–	1 [100]	–	–
Transverse colon		0	1	2	3
14	0	14 [100]	–	–	–
9	1	6 [66.7]	3 [33.3]	–	–
2	2	1 [50.0]	1 [50.0]	–	–
2	3	1 [50.0]	1 [50.0]	–	–
Right colon		0	1	2	3
18	0	18 [100]	–	–	–
5	1	3 [60.0]	2 [40.0]	–	–
1	2	1 [100]	–	–	–
0	3	–	–	–	–
Ileum		0	1	2	3
8	0	6 [75.0]	2 [25.0]	–	–
10	1	4 [40.0]	3 [30.0]	2 [20.0]	1 [10.0]
3	2	2 [66.7]	1 [33.3]	–	–
0	3	–	–	–	–
ADA/PBO [*n*]	Subscore at Baseline	Subscore at Week 52, n [%]			
Rectum		0	1	2	3
7	0	5 [71.4]	2 [28.6]	–	–
9	1	4 [44.4]	4 [44.4]	1 [11.1]	–
2	2	1 [50.0]	1 [50.0]	–	–
2	3	–	2 [100]	–	–
Sigmoid/left colon		0	1	2	3
7	0	5 [71.4]	1 [14.3]	1 [14.3]	–
11	1	1 [9.1]	7 [63.6]	3 [27.3]	–
2	2	–	1 [50.0]	1 [50.0]	–
0	3	–	–	–	–
Transverse colon		0	1	2	3
10	0	6 [60.0]	3 [30.0]	1 [10.0]	–
8	1	3 [37.5]	4 [50.0]	–	1 [12.5]
2	2	–	1 [50.0]	1 [50.0]	
0	3	–	–	–	–
Right colon		0	1	2	3
10	0	7 [70.0]	3 [30.0]	–	–
6	1	2 [33.3]	4 [66.7]	–	–
3	2	1 [33.3]	2 [66.7]	–	–
0	3	–	–	–	–
Ileum		0	1	2	3
9	0	7 [77.8]	2 [22.2]	–	–
3	1	–	2 [66.7]	1 [33.3]	–
4	2	–	2 [50.0]	2 [50.0]	–
1	3	1 [100]	–	–	–

ADA, adalimumab; ADA/ADA, ADA induction and maintenance; ADA/PBO, ADA induction only; ITT, intent to treat; PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's Disease.

Patients were from the ITT population and had data at baseline, Week 12, and Week 52 [including data imputed when moving to open-label therapy after Week 12].

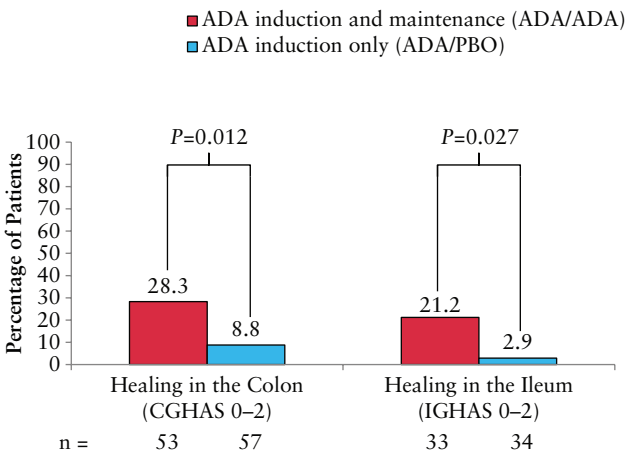

Figure 4. Histological analysis of mucosal disease activity, depicting patients with CGHAS or IGHAS values of 0, 1, or 2 at Week 52. Patients were from the ITT population and had a baseline score of ≥ 3. ADA, adalimumab; CGHAS, Colonic Global Histologic Disease Activity Score; IGHAS, Ileal Global Histologic Disease Activity Score; ITT, intent to treat; PBO, placebo.

improvements in those segments clearly constitute resolution of mucosal inflammation. The 52-week period of treatment allowed for evaluation of long-term effects, which may be important for robust healing, particularly of deep ulcers. Focusing on data from Week 52 also avoided complications at earlier times caused by lingering effects of the induction regimen in patients subsequently randomised to placebo.

The interpretation of the results is limited by several considerations beyond the potential bias that is inherent in post-hoc exploration of data. First, the overall number of patients available for analysis, compared with the original EXTEND study population, was limited by the necessary requirement that they have valid data at baseline, Week 12, and Week 52. Second, the sizes of some analysis groups were small, limiting the validity of comparisons, especially for the shifts in SES-CD ulcerated surfaces and ulcer size subscores. In particular, the numbers of patients with large or very large ulcers and with ulcerated surfaces ≥ 10% at baseline were very small, creating a 'ceiling effect' on possible improvement. More fundamentally, the endoscopic data did not track individual lesions over time. Therefore, a deep ulcer could have become a superficial ulcer or vice versa, and entirely new ulcers could have appeared. This limits the confidence with which it is possible to say that ulcers were completely healed. The consistent pattern of results among different endpoints increases confidence in the overall findings, which suggest that mucosal healing was common in the rectum, most frequent in the sigmoid/left colon and transverse colon, less common in the right colon, and least frequent in the ileum.

Whether some ileocolonic segments are inherently more resistant than others to healing is an intriguing question that cannot be definitively answered with the data from EXTEND. Genome-wide association study data have suggested that some genes involved in susceptibility to CD differ for colonic vs ileal involvement.[15,16] Arguing against the idea of resistance to healing in the ileum is that adalimumab suppressed recurrence of ulceration to a significantly greater degree than thiopurine treatment in the Post-Operative Crohn's Endoscopic Recurrence study; nearly all patients in that study had previous partial resection of the ileum.[17] However, greater healing according to the CDEIS ulcerated surface subscore was

observed previously in the rectum and right colon as compared with the transverse colon, sigmoid/left colon, and ileum in patients with CD who received infliximab.[18] Because of the small sample size of this study, we could not address whether baseline variables associated with differences in outcome to anti-TNF alpha agents [ie, disease duration, previous treatment history, concomitant treatment, and body weight] could further modulate differences in segment-specific resolution of inflammation. Larger prospective studies would be needed to confirm our descriptive findings on the locations and timing of mucosal healing among ileocolonic segments.

In conclusion, in patients with moderate to severe CD, the baseline severity of disease involvement was similar across segments of the colon and ileum, yet mucosal healing at Week 52 with systemic treatment was not uniform among all segments. The greatest improvements in subscores for CDEIS surface involved in the disease, CDEIS ulcerated surface, SES-CD ulcer size, and SES-CD ulcerated surfaces subscores, were observed in the rectum, sigmoid/left colon, and transverse colon. Histological findings indicated that healing in the colon was more frequent than healing in the ileum. Together, our results suggest that the colon might heal more readily than the ileum during treatment with adalimumab and, potentially, other agents of the anti-TNF class. Thus, it cannot be presumed that healing of distal segments on imaging indicates that proximal segments have also healed; rather, direct inspection of all ileocolonic segments is necessary to determine to what extent ulceration in the entire tract has resolved.

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Conflict of Interest

WR has served as a speaker for Abbott Laboratories, AbbVie, Aesca, Aptalis, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult; as a consultant for Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, Astellas, AstraZeneca, Avaxia, BioClinica, Biogen Idec, Bristol-Myers Squibb, Cellerix, ChemoCentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millennium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trials, Schering-Plough, SetPoint Medical, Takeda, Therakos, TiGenix, UCB, Vifor, Zyngenia, and 4SC; as an advisory board member for Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, Astellas, AstraZeneca, Avaxia, Biogen Idec, Bristol-Myers Squibb, Cellerix, ChemoCentryx, Celgene, Centocor, Celltrion, Danone Austria, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millennium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Schering-Plough, SetPoint Medical, Takeda, Therakos, TiGenix, UCB, Zyngenia, and 4SC; and has received research funding from Abbott Laboratories, AbbVie, Aesca, Centocor, Falk Pharma GmbH, Immundiagnostik, and MSD. J-FC has received consulting and/or lecture fees from AbbVie, ActoGeniX, Albireo Pharma, Amgen, AstraZeneca, Bayer AG, Biogen Idec, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Cellerix, Centocor, ChemoCentryx, Cosmo Technologies, Danone Research, Elan Pharmaceuticals, Genentech, Giuliani SPA, Given Imaging, GlaxoSmithKline, Hutchison MediPharma, MSD, Neovacs, Ocera Therapeutics, Otsuka America Pharmaceutical, Pfizer, Prometheus Laboratories, Sanofi-Aventis, Schering-Plough, Shire, Synta Pharmaceuticals, Takeda, Teva, Therakos, Tillotts Pharma, UCB Pharma, and Wyeth, and has stock ownership in Intestinal Biotech Development. GD has received consulting and/or lecture fees from AbbVie, ActoGeniX, AIM, Boehringer Ingelheim GmbH, Centocor, ChemoCentryx, Cosmo Technologies, Elan Pharmaceuticals, enGene, Dr Falk Pharma, Ferring, Galapagos, Giuliani SpA, Given Imaging, GlaxoSmithKline, Janssen Biologics, MSD, Neovacs, Novo Nordisk, Otsuka, PDL BioPharma, Pfizer, Receptos, Salix, SetPoint, Shire Pharmaceuticals, Schering-Plough, Takeda, Tillotts Pharma, UCB Pharma, Versant, and Vifor Pharma; research grants from AbbVie, Janssen, Given Imaging, MSD, Dr Falk Pharma, and PhotoPill; and speaking honoraria from AbbVie, Tillotts, Tramedico, Ferring, MSD, UCB Pharma, Norgine, and Shire. WJS has received consulting fees from AbbVie, ActoGeniX NV, AGI Therapeutics, Alaven Pharmaceuticals, Alba Therapeutics, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas, Athersys, Atlantic Healthcare, Axcan Pharma, BioBalance, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Centocor, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine PharmaSciences, Eagle Pharmaceuticals, Eisai Medical Research, Elan, enGene, Eli Lilly, EnteroMedics, Exagen Diagnostics, Ferring, Flexion Therapeutics, Funxional Therapeutics, Genzyme, Genentech, Gilead Sciences, Given Imaging, GlaxoSmithKline, Human Genome Sciences, Ironwood Pharmaceuticals, KaloBios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera, Merck Research Laboratories, Merck Serono, Millennium, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics, PDL BioPharma, Pfizer, Procter & Gamble, Prometheus Laboratories, ProtAb Limited, PurGenesis Technologies, Receptos, Relypsa Inc, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus, Schering-Plough, Shire Pharmaceuticals, Sigmoid Pharma, Sirtris Pharmaceuticals, SLA Pharma [UK], Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG, TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics, Warner Chilcott, and Wyeth; lecture fees from AbbVie, Bristol-Myers Squibb, and Janssen; and research support from AbbVie, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen, Millennium, Novartis, Pfizer, Procter & Gamble, Shire, and UCB Pharma. PR has received consultancy fees from AbbVie, Bristol-Myers Squibb, Centocor, Merck, Takeda, and UCB Pharma; and speaker fees and research support from AbbVie, Centocor, MSD, and UCB Pharma. KG has no conflicts of interest to disclose. JP, SE, QZ, AMR, HAR, and RT are employees of AbbVie Inc. and may own AbbVie stock or stock options.

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Author Contributions

All authors made substantial contributions to each of the following: [1] the concept and design of the study, or acquisition of data, or analysis and interpretation of data; [2] drafting the article or revising it critically for important intellectual content; and [3] final approval of the version to be submitted. Specific contributions were: WR, J-FC, GD, WJS, PR, KG, JP, SE, QZ, AMR, HAR, and RT contributed to the conception and design of the study and analysis and interpretation of the data; WR, J-FC, GD, WJS, PR, and KG contributed to the acquisition of data; KG was responsible for the central reading of the histology and data analysis.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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