

Early Versus Late Use of Vedolizumab in Ulcerative Colitis: Clinical, Endoscopic, and Histological Outcomes

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Abstract

Background and Aims: We explored the potential for differential efficacy of vedolizumab between early and late ulcerative colitis [UC] with evaluation of clinical, endoscopic, and histological endpoints.

Methods: This was a multicentre, multinational, open-label study in patients with moderately-to-severely active UC, defining early UC by a disease duration <4 years and bio-naïve and late UC by a disease duration >4 years and additional exposure to tumour necrosis factor antagonists. Patients received standard treatment with intravenous vedolizumab for 52 weeks [300 mg Weeks 0, 2, 6, every 8 weeks thereafter without escalation]. The primary endpoint was corticosteroid-free clinical remission with endoscopic improvement [total Mayo score ≤2 with no subscore >1] at both Weeks 26 and 52.

Results: A total of 121 patients were included: in the “early” group, 25/59 [42.4%] achieved the primary endpoint versus 19/62 [30.6%] in the “late” group [$p = 0.18$]. There were no significant differences between the two groups in endoscopic improvement [Week 26: “early” 32/59 [54.2%] versus “late” 29/62 [46.8%]; $p = 0.412$; Week 52: 27/59 [45.8%] versus 25/62 [40.3%]; $p = 0.546$] or in histological remission [Robarts Histopathology Index <3 without neutrophils in the epithelium and lamina propria] [Week 26: 24/59 [40.7%] versus 21/62 [33.9%]; $p = 0.439$; Week 52: 22/59 [37.3%] versus 22/62 [35.5%]; $p = 0.837$].

Conclusions: No significant differences in clinical, endoscopic, and histological outcomes were observed between “early” and “late” disease.

Key Words: LOVE-UC Trial; inflammatory bowel disease; biologic; anti-integrin

1. Introduction

Ulcerative colitis [UC] is an inflammatory bowel disease [IBD] defined by chronic mucosal inflammation of the colon with a relapsing-remitting course.¹ Treatment goals in UC are stepwise with symptomatic response as the immediate treatment goal, symptomatic remission as the intermediate goal,

and combined symptomatic and endoscopic remission as the long-term goal.² Histological remission currently serves as an adjunct to endoscopic remission in UC, reflecting a deeper level of healing.

Vedolizumab is a humanised monoclonal antibody that interferes with the interaction between the $\alpha 4\beta 7$ integrin

on the surface of leukocytes and the corresponding mucosal addressin cell adhesion molecule-1 [MAdCAM-1] ligand on the vascular endothelium of the gut.³ It is effective in inducing and maintaining remission in moderate-to-severe UC.⁴ An almost universal observation with advanced therapies in UC is that remission rates are lower in patients with prior exposure to biologics compared with bio-naïve patients.^{4–8} Unlike Crohn's disease [CD] which is widely accepted to be a chronically progressive disease leading to bowel damage,⁹ it is less apparent for UC whether it has the same progressive nature and whether early and intensive therapy could result in better treatment outcomes.¹⁰ There is evidence to suggest that UC is indeed also a progressive disease: significant sub-mucosal fibrosis may develop in parallel with active inflammation, which results in increased wall stiffness and may lead to motility abnormalities¹¹; ultimately, strictures may also develop in UC, albeit less frequently than in CD.^{12,13} In a sense proximal disease extension, which occurs in up to 50% of patients with proctitis or left-sided colitis during the course of their disease,^{14,15} can also be considered disease progression. Finally, uncontrolled inflammation may lead to the development of dysplasia and colorectal cancer.¹⁶

Taken together, we hypothesised that an intervention early in the course of UC could also lead to better treatment outcomes compared with an intervention in long-standing disease where structural abnormalities may already have developed. We therefore designed an investigator-initiated, open-label study of vedolizumab in two distinct populations of patients with moderately-to-severely active UC: an “early” population within 4 years of diagnosis only exposed to conventional therapy and a “late” population more than 4 years after diagnosis and exposed to tumour necrosis factor [TNF] antagonists in addition to conventional therapy.

The primary objective of the present study was to explore the impact of vedolizumab on clinical and endoscopic outcomes after 52 weeks of treatment in “early” and “late” patients with UC. As a secondary objective, we explored histological outcomes.

2. Methods

2.1. Patients

Eligible patients were 18 to 80 years of age and had moderately-to-severely active UC, defined as a total four-component Mayo score ≥ 6 with an endoscopy sub-score of ≥ 2 . The “early” disease group was defined by a disease duration of <4 years with demonstrated failure or intolerance to aminosalicylates and topical and/or systemic corticosteroids or steroid dependency at any dose and additionally, but not mandatory, lack of efficacy of thiopurines or intolerance to thiopurines [any duration]. Previous exposure to any TNF antagonist was not allowed in the “early” disease group.

The “late” disease group was defined as a disease duration >4 years with demonstrated failure to respond to or intolerance to aminosalicylates, thiopurines, and TNF antagonists. Continuation of stable doses of aminosalicylates, thiopurines, and corticosteroids was allowed during the study, whereas TNF antagonists had to be discontinued for >4 weeks prior to vedolizumab initiation. The full enrolment criteria are provided in Supplementary Appendix A.

Steroids had to be tapered per protocol by Week 26: for patients with a clinical response at Week 6, the dose had to be reduced at a rate of 3 mg [budesonide] or 5 mg [prednisone]

per week. If patients experienced worsening of symptoms during tapering, the dose could be increased again to a maximum of 9 mg budesonide or maximally 40 mg prednisone equivalent for up to 3 weeks, followed by a new tapering course. For patients with no clinical response at Week 6 [per the investigator's discretion] or on and after Week 14, the dosage of oral corticosteroids could be increased to or initiated at 9 mg budesonide or ≤ 40 mg prednisone [or equivalent], with tapering to commence 3 weeks later. Once clinical response was attained, steroid tapering had to begin. A corticosteroid dose initiation or increase could only be done once during the study.

2.2. Study design and assessments

This was a multicentre, multinational, open-label study in 20 participating hospitals in Belgium, The Netherlands, and Hungary, conducted between July 2015 and May 2020. After a screening period of up to 14 days, patients underwent standard induction and maintenance dosing with vedolizumab for 1 year [with 300 mg vedolizumab intravenous administration at Weeks 0, 2, 6, and every 8 weeks thereafter]. No randomisation or blinding was performed. All authors had access to the study data and reviewed and approved the final manuscript. The study protocol was approved by the institutional review board at every study centre.

Assessments included physical examination, monitoring laboratory results, and recording adverse events at baseline and before every infusion. Treatment discontinuation was recorded together with the reason for discontinuation. Endoscopy was performed at baseline, Week 26, and Week 52. The procedure was recorded and evaluated by the local endoscopist using the Mayo endoscopic score.¹⁷ Recordings were centrally reviewed by an expert central reader [ML] who was unaware of the study visit sequence or clinical information. In case of any discrepancy between the local and central reader, the recording was sent for adjudication to the second central reader [GD], whose final score was used for further analysis.

Mucosal biopsies were obtained at baseline, Week 26, and Week 52. Two mucosal biopsies were taken from the most severely affected area within each of the explored colonic segments. If the colon was endoscopically normal, two biopsies were taken at random. Biopsies were scored centrally by two blinded, expert histopathologists [AM, GDHe] using the Geboes score¹⁸ and the Robarts Histopathology Index.¹⁹ The Geboes score is a seven-item scale [with four levels of severity for each item] that categorises inflammation as grade 0 [architectural change only], grade 1 [chronic inflammation], grade 2 [2A, lamina propria eosinophils, and 2B, lamina propria neutrophils], grade 3 [neutrophils in the epithelium], grade 4 [crypt destruction], or grade 5 [erosion or ulceration]. The score ranges from 0 to 5.4. The Robarts Histopathology Index is a four-item index [with four levels for each item] that evaluates chronic inflammation, lamina propria neutrophils, neutrophils in the epithelium, and erosion or ulceration. The total score ranges from 0 to 33, where higher scores denote more severe inflammation. The highest segmental score for each patient was used for further analysis.

2.3. Endpoints

The primary endpoint was clinical remission and endoscopic improvement at both Weeks 26 and 52, defined by a total four-component Mayo score of ≤ 2 with no subscore >1 . Secondary

endpoints included endoscopic improvement [Mayo endoscopic subscore ≤ 1], endoscopic remission [Mayo endoscopic subscore 0], histological remission by the Geboes score [grade $< 2A.0$], histological remission by the Robarts Histopathology Index [< 3 without neutrophils in the epithelium or lamina propria], and histo-endoscopic mucosal improvement [histological remission by the Robarts Histopathology Index and endoscopic improvement], corticosteroid-free clinical remission [Mayo score ≤ 2 with no subscore > 1 without concomitant corticosteroids in patients using corticosteroids at screening]. The names and definitions of endpoints were modified compared with the initial version of the study protocol drafted in 2014 to reflect contemporary nomenclature: distinguishing endoscopic improvement from endoscopic remission, and the histological endpoints to align with contemporary consensus definitions and publications.^{20,21} Other prespecified secondary endpoints are listed in [Supplementary Table 1](#).

2.4. Statistical analysis

Patient characteristics were summarised descriptively. All patients who received at least one dose of vedolizumab were included in the analysis as the intention-to-treat population. All patients with missing data for determination of endpoint status and patients who withdrew from the trial early were imputed as non-responders in the analysis. Differences in categorical outcomes between the “early” and “late” groups were analysed with Fisher’s exact test. To reduce the risk of multiple testing, a hierarchical testing order was applied, whereby subsequent p -values could only be interpreted if the preceding test was significant. In the event of a non-significant result, all subsequent p -values should be regarded as nominal. The order was: primary endpoint, endoscopic improvement, histological remission by both definitions, and histo-endoscopic mucosal improvement. For other endpoints, no p -values were computed and only 95 % confidence intervals [CI] for the difference between groups are reported. We calculated that a sample size of 120 patients [60 in each arm] would provide the trial with 80% power to detect a between-group difference of 25 percentage points in the primary endpoint [60% in the “early” group, 35% in the “late” group]. All statistical testing was performed at the 0.05 significance level using SPSS, version 25 [IBM].

3. Results

3.1. Patients

Of the 156 patients who underwent screening, 121 patients were enrolled in the trial and received at least one infusion of vedolizumab [intention-to-treat population]: 59 were included in the “early” UC group and 62 in the “late” UC group [[Table 1](#)]. During the study, early withdrawal occurred in 25 patients in the “early” group and 24 in the “late” group, mainly for insufficient clinical response or worsening of UC [[Figure 1](#)].

3.2. Effectiveness

Clinical remission with endoscopic improvement at both Week 26 and Week 52 was achieved in 25/59 [42.4%] patients in the “early” group versus 19/62 [30.7%] in the “late” group [$p = 0.18$] [[Figure 2](#)].

At Week 26, 32/59 [54.2%] patients in the “early” group had endoscopic improvement versus 29/62 [46.8%] in the “late” group [$p = 0.412$] [[Figure 3A](#)]. At Week 52, the corresponding rates of endoscopic improvement were 27/59 [45.8%]

Table 1. Demographic and clinical characteristics of patients.

Characteristic	Early ulcerative colitis [n = 59]	Late ulcerative colitis [n = 62]
Male gender, n [%]	30 [51]	31 [50]
Age [years], median [IQR]	35 [27–49]	43 [32–54]
Body weight [kg], median [IQR]	71 [62–79]	76 [66–88]
Disease duration [years], median [IQR]	1 [1–3]	9 [5–14]
Extensive colitis, n [%]	15 [25]	11 [18]
Baseline Mayo endoscopic subscore 3, n [%]	24 [41]	43 [69]
Baseline albumin [g/L], median [IQR]	42 [37–44]	40 [36–44]
Baseline total Mayo score, median [IQR]	8 [7–10]	9 [8–10]
Concomitant corticosteroids at baseline, n [%]	27 [46]	30 [48]
Prior TNF antagonist use, n [%]	0	62 [100]

IQR, interquartile range.

and 25/62 [40.3%], respectively [$p = 0.546$] [[Figure 3B](#)]. At Week 26, 16/59 [27.1%] patients in the “early” group were in endoscopic remission versus 14/62 [22.6%] in the “late” group [$p = 0.563$] [[Figure 3A](#)]. At Week 52, the corresponding rates of endoscopic remission were 14/59 [23.7%] and 14/62 [22.6%], respectively [$p = 0.881$] [[Figure 3B](#)]. At Week 26, 10/27 [37.0%] patients who had been using corticosteroids at screening in the “early” group were in corticosteroid-free clinical remission versus 13/30 [43.3%] [95% CI for difference: -35.2%–22.6%]. At Week 52, 11/27 [40.7%] patients who had been using corticosteroids at screening in the “early” group were in corticosteroid-free clinical remission versus 12/30 [40.0%] [95% CI for difference: -25.5%–27.0%].

At Week 26, 24/59 [40.7%] patients in the “early” group were in histological remission by the Robarts Histopathology Index versus 21/62 [33.9%] in the “late” group [$p = 0.439$] [[Figure 3A](#)]. At Week 52, the corresponding rates of histological remission by the Robarts Histopathology Index were 22/59 [37.3%] and 22/62 [35.5%], respectively [$p = 0.837$] [[Figure 3B](#)]. At Week 26, 17/59 [28.8%] patients in the “early” group were in histological remission by the Geboes score versus 12/62 [19.3%] in the “late” group [$p = 0.223$] [[Figure 3A](#)]. At Week 52, the corresponding rates of histological remission by the Geboes score were 17/59 [28.8%] and 19/62 [30.6%], respectively [$p = 0.826$] [[Figure 3B](#)]. At Week 26, 24/59 [40.7%] patients in the “early” group had histo-endoscopic mucosal improvement versus 19/62 [30.6%] in the “late” group [$p = 0.249$] [[Figure 3A](#)]. At Week 52, the corresponding rates of histo-endoscopic mucosal improvement were 22/59 [37.3%] versus 18/62 [29.0%], respectively [$p = 0.335$] [[Figure 3B](#)]. Other secondary efficacy endpoints are reported in [Supplementary Table 2](#).

3.3. Safety

Adverse events were reported by 101/121 [83.5%] patients receiving vedolizumab; adverse events that occurred in at

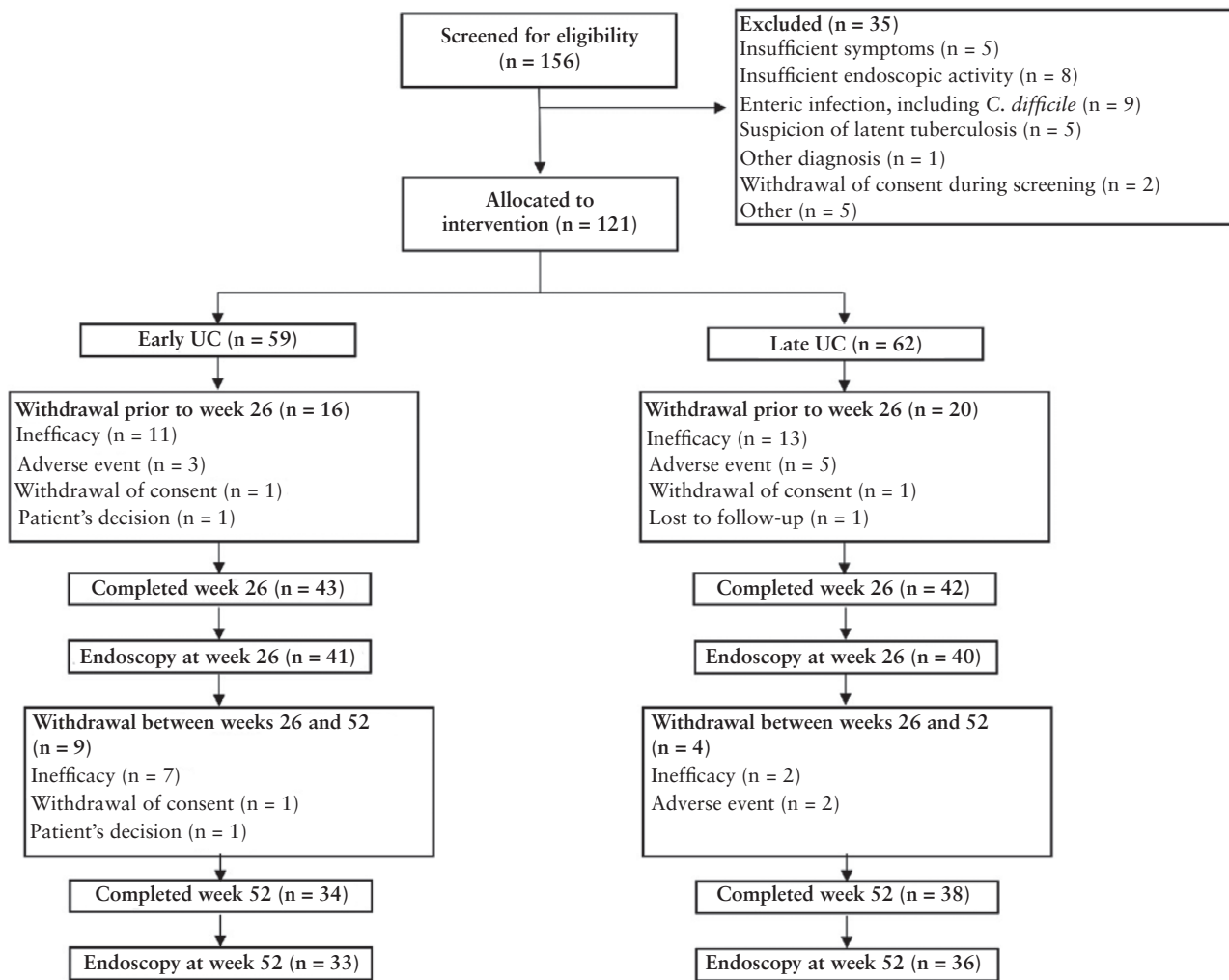


Figure 1. Patient disposition during the study.

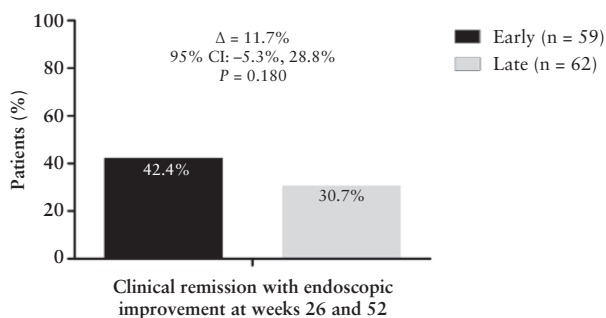


Figure 2. The proportion of patients achieving the primary endpoint of clinical remission [Mayo score ≤ 2 with no subscore > 1] with endoscopic improvement [Mayo endoscopic subscore ≤ 1] at Weeks 26 and 52. CI, confidence interval.

least 5% of patients are reported in [Supplementary Table 3](#). Arthralgia was reported by 18/121 [14.9%] patients and other events that could have been extraintestinal manifestations were reported by 3/121 [2.5%] [one case each of iridocyclitis, uveitis, and aphthous stomatitis].

A total of 19 serious adverse events in 15 patients [15/121; 12.4%] were reported, the commonest [$n = 9$] being worsening of UC. Other adverse events included umbilical

hernia requiring surgery in one patient, acute kidney injury in two patients, surgery for inguinal hernia in one patient, gastroenteritis in one patient, transitory ischaemic attack in one patient, lower extremity deep vein thrombosis in one patient, pregnancy in one patient, internal carotid artery stenosis in one patient, and urothelial carcinoma in one patient. No patient required UC-related surgery. There were no deaths. Thirteen out of 121 [10.7%] patients were hospitalised during the study, nine of the hospitalizations being related to UC. There were no differences in the incidence of serious adverse events (4/59 [6.8%] versus 11/62 [17.7%]; $p = 0.067$) or hospitalizations (3/59 [5.1%] versus 10/62 [16.1%]; $p = 0.050$) between the two groups.

4. Discussion

LOVE-UC was the first prospective study to assess the potential for differential efficacy of vedolizumab in patients with “early” and “late” UC. Patients in the “early” group had a disease duration shorter than 4 years and were bio-naïve, and patients in the “late” group had a disease duration greater than 4 years and had been exposed to TNF antagonists. There were no statistically significant differences in the rates of clinical remission and endoscopic improvement by the full Mayo score at both Weeks 26 and 52 between the two groups. There

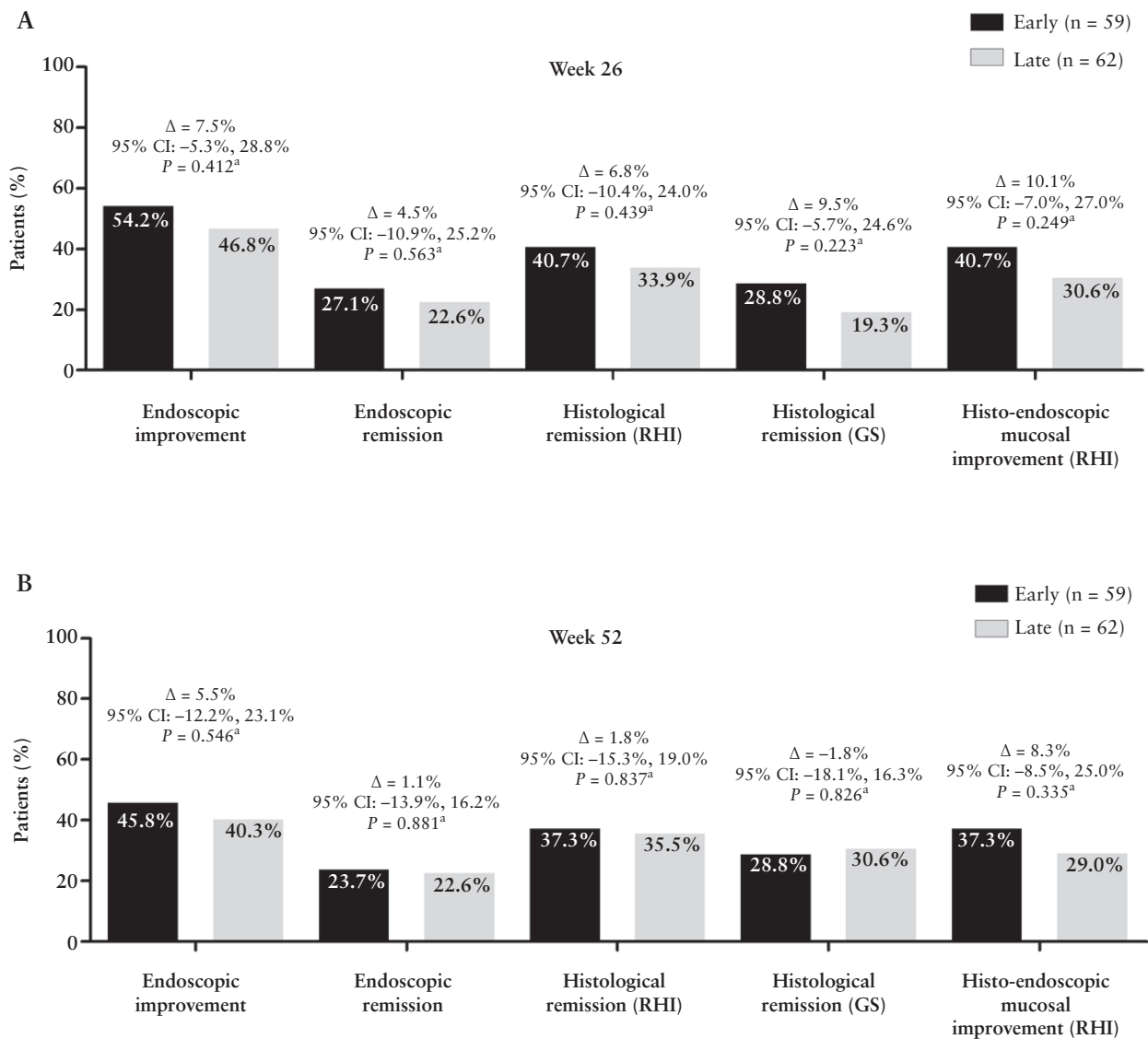


Figure 3. Proportion of patients achieving secondary endpoints of endoscopic improvement [Mayo endoscopic subscore ≤ 1], endoscopic remission [Mayo endoscopic subscore 0], histological remission by the Roberts Histopathology Index [Roberts Histopathology Index < 3 without neutrophils in the epithelium and lamina propria], histological remission by the Geboes score [Geboes grade $< 2A.0$], and histo-endoscopic mucosal improvement [histological remission by the Roberts Histopathology Index with endoscopic improvement] at Weeks 26 [A] and 52 [B]. CI, confidence interval; GS, Geboes Score; RHI, Roberts Histopathology Index. ^aThe *p*-values are nominal.

were also no significant differences in secondary endoscopic and histological endpoints. Overall, vedolizumab was well tolerated and no new safety signals were seen.

The largest body of evidence on the efficacy of biologics by disease duration in UC is an individual-patient data meta-analysis of 25 trials, pooling 3227 patients treated with infliximab, adalimumab, golimumab, and vedolizumab.²² Following the consensus definition for early CD,²³ the threshold was set at 18 months, with sensitivity analyses performed for cut-offs at 3 years and 5 years. Unlike for CD, there was no impact on disease duration regardless of the cut-off used, on the efficacy of biologics in UC. There was no evidence for a class-specific effect of prior biologic exposure on subsequent treatment outcomes, although the meta-analysis had low power to detect it as only one non-TNF antagonist [vedolizumab] was included for UC. These findings align with observations from retrospective, real-world cohort studies where early UC was differently defined, with

the duration threshold ranging from 2 to 4 years.^{24–28} The majority of studies have evaluated TNF antagonists^{24–27}; in two of the cohorts, infliximab use early in the duration of the disease was associated with worse treatment outcomes, which probably reflected more severe disease in patients receiving infliximab soon after diagnosis of UC.^{24,26} In the cohort of patients treated with vedolizumab, early disease within 2 years of diagnosis was not associated with significantly better treatment outcomes, although rates of endoscopic remission were numerically higher [22% versus 16%].²⁸

Taken together, the findings of the LOVE-UC study in conjunction with earlier cohort studies suggest that treatment with vedolizumab in UC leads to favourable treatment outcomes, regardless of prior disease duration. The study was not designed, however, to separate the impact of disease duration from the impact of previous exposure to TNF antagonists. Although these two variables are understandably highly correlated, they may exert opposing effects on the probability

of response to treatment with vedolizumab. This notion was highlighted in the development of a clinical decision support tool to predict outcomes of vedolizumab therapy for UC.²⁹ Briefly, data from the GEMINI trial were used to develop the model, which was then validated in routine care and from other randomised trials.^{29,30} In this model, the absence of prior exposure to TNF antagonists and disease duration longer than 2 years were associated with a higher likelihood of corticosteroid-free remission after treatment with vedolizumab. The weight of these two variables in the model was equal. It appears that the association between longer disease duration and more favourable treatment outcomes is specific to vedolizumab,³⁰ although the underlying mechanisms remain unknown. These observations are also reflected in the findings of real-world studies where prior exposure to biologics, but not disease duration in its own right, was associated with a lower likelihood of remission.^{31,32}

In contrast to CD,²³ there is no consensus definition of early UC, and all pragmatic definitions, including the one used in LOVE-UC, are arbitrary and probably do not capture disease biology and do not accurately stratify patients. With the emerging concept that UC is also a progressive disease with the potential for bowel damage, clinical, endoscopic, and histological outcomes within 52 weeks of treatment may not necessarily fully capture the potential positive effects of early intervention in UC. Prospective disease-modification trials are an unmet need in IBD and their design is fraught with conceptual and practical challenges. The SPIRIT consensus within the International Organization for the Study of IBD proposed a framework of outcomes to be assessed at 2–5 years in such trials: health-related quality of life, disability, faecal incontinence, IBD-related surgery and hospitalisations, disease extension in UC, extraintestinal manifestations, development of dysplasia or cancer, and mortality.³³

Histological remission is an emerging treatment goal in UC,² currently not supported by prospective, randomised data,³⁴ with the ongoing randomised VERDICT trial [NCT04259138] expected to provide further information on the optimal treatment target in UC. Aside from VARSITY, a head-to-head trial comparing vedolizumab versus adalimumab in UC,²¹ LOVE-UC is the largest dataset on histological remission in patients with UC treated with vedolizumab, supported by two well-known and reliable histological scoring indices. In VARSITY, histological endpoints were assessed at Weeks 14 and 52 and the mean duration of disease in patients treated with vedolizumab was 7.3 years; 20.8% had been previously exposed to TNF antagonists. The definitions of histological remission were the same as in LOVE-UC, ie, Robarts Histology Index <3 without neutrophils in the epithelium or lamina propria and a Geboes grade <2. At Week 52, the rate of histological remission by the Robarts Histopathology Index in anti-TNF naïve patients in VARSITY was 39.8% and the corresponding rate for the Geboes score was 32.2%. Although not directly comparable, these patients resemble the “early” group in LOVE-UC, where similar rates of histological remission were observed with 37.3% and 28.8%, respectively. No formal statistical comparison was made between patients by prior anti-TNF exposure in VARSITY, but remission rates were numerically lower in bio-exposed patients at Week 52 [29.1% by the Robarts Histopathology Index, 17.7% by the Geboes score]. In LOVE-UC, histological remission rates were higher in the “early” patients at Week 26, with a blunted difference between the two groups at Week 52. There was

little change in histological remission from Weeks 26 to 52 in LOVE-UC, which indicates that 26 weeks is a sufficient time frame for achieving histological remission. An earlier time point at 14 weeks, as used in VARSITY, appears premature for assessment of histological remission, as a substantial increase in histological remission was observed between Weeks 14 and 52 in that trial.

The strengths of the trial included central reading for endoscopy and histology, together with a protocolised steroid-tapering schedule. Limitations of the study also have to be acknowledged. At the time of designing the trial, the 12-point Mayo score, including physician global assessment, was considered the standard and therefore used to define the primary endpoint. Subsequently, the Mayo score was modified to exclude this element; although it appears that both versions of the score perform similarly in the assessment of treatment effect sizes,³⁵ this should nonetheless be considered when interpreting the results of LOVE-UC. Accurate histological assessment of disease activity is dependent on mucosal biopsy sampling. Although two samples, as used in LOVE-UC, are the minimum requirement for reliable assessment, three may have been preferable, particularly for the Geboes score and in patients with endoscopically active disease.³⁶ Furthermore, the distinction between early and late disease at 4 years was arbitrary and based on expert opinion. The absence of a signal for differential efficacy by cut-off for defining early UC in a recent individual-patient meta-analysis,²² suggests that the definition did not affect the findings of the study. Unfortunately, we did not distinguish between failure and intolerance of TNF antagonists, which could potentially have impacted on the results. Finally, the observed difference between the two groups for the primary endpoint [11.8%] fell short of the expected difference used to calculate the sample size [25%]. The trial was therefore underpowered to detect differences lower than 25%, which are not necessarily clinically insignificant.

In conclusion, in this prospective study in patients with moderate-to-severe UC treated with vedolizumab, no significant differences in remission rates were found in the rate of clinical remission and endoscopic improvement by the full Mayo score at both Weeks 26 and 52 between “early” bio-naïve patients and “late” TNF-exposed patients. Despite numerical differences favouring the “early” group, no significant differences were observed for secondary endpoints based on endoscopy and histology either.

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Conflict of Interest

SV: received financial support for research from AbbVie, J&J, Pfizer, Takeda and Galapagos; speakers' and/or consultancy fees from AbbVie, Abivax, AbolerIS Pharma, AgomAb Therapeutics, Alimentiv Inc, Arena Pharmaceuticals, Astra Zeneca, BMS, Boehringer Ingelheim, Celgene, Cytokine Pharma, Dr Falk Pharma, Ferring, Galapagos, Genentech-Roche, Gilead, GSK, Hospira, Imidomics, Janssen, J&J, Lilly, Materia Prima, Mestag Therapeutics, MiroBio, Morphic, MrMHealth, Mundipharma, MSD, Pfizer, Prodigest, Progenity, Prometheus, Surrozen, Takeda, Theravance, Tillotts Pharma AG, VectivBio, Ventyx, Zealand Pharma. JH: received speaker's fees from

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Guarantor of the article: SV. Development of study concept and design: SV, GDHa. Study supervision: SV, GDHa. Acquisition, analysis, and interpretation of the data: SV, JH, ML, MF, PB, FH, DF, KP, HP, AM, GDHe, TM, WVM, TL, EC, MSH, FB, GDHa. Drafting of the manuscript: JH, MSH, SV, GDHa. Critical revision of the manuscript for important intellectual content: SV, JH, ML, MF, PB, FH, DF, KP, HP, AM, GDHe, TM, WVM, TL, EC, MSH, FB, GDHa.

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Data Availability

Data will be made available upon reasonable request to the corresponding author.

Supplementary Data

Supplementary data are available at ECCO-JCC online.

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