Review Article

Systematic Literature Review and Meta-analysis: Real-World Mucosal Healing in Vedolizumab-Treated Patients with Crohn’s Disease

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Background. Vedolizumab is a gut-selective monoclonal anti-α4β7-integrin antibody approved for the treatment of adults with moderately to severely active Crohn’s disease (CD). Aim. To conduct a systematic literature review and meta-analysis of published real-world studies examining mucosal healing (MH) rates in patients with CD treated with vedolizumab in routine clinical practice. Methods. MEDLINE-, Cochrane-, and EMBASE-indexed publications from January 2014 to January 2020 and 2018-2019 conference abstracts were searched for real-world studies reporting MH-related outcomes in vedolizumab-treated adults with CD. A meta-analysis was conducted in R to generate pooled estimates of MH. The primary analysis included studies reporting point estimates of MH/endoscopic remission as absence of ulcers/erosions and/or Simple Endoscopic Score for CD (SES-CD) < 4, and 6 and 12 months. Results. The systematic literature review included 36 studies, predominantly of antitumour necrosis factor-experienced patients. MH and endoscopic remission were the most frequently reported endpoints. MH rates were 10.1%-46.0% at 6 months (ten studies) and 21.2%-62.5% at 12 months (eight studies). Fifteen studies defining MH as absence of ulcers/erosions and/or SES-CD < 4 were included for meta-analysis. Pooled MH rates for the primary analysis were 31.8% at 6 months (95% confidence interval (CI): 25.6-38.3; five studies, N = 223) and 33.4% at 12 months (95% CI: 25.9-41.4; three studies, N = 151). Conclusion. Approximately one-third of vedolizumab-treated patients with CD achieved MH at both 6 and 12 months in real-world clinical settings, despite utilisation in largely biologic-refractory patients. These findings confirm the effectiveness of vedolizumab for achieving MH in patients with CD.

1. Introduction

Crohn’s disease (CD) is a chronic and progressive inflammatory bowel disease in which uncontrolled inflammation can lead to structural bowel damage, causing long-term debilitating complications that often require surgery [1–3]. Treatment goals have recently evolved from symptom-based management toward control of inflammation to prevent bowel damage and promote mucosal healing (MH; as assessed by objective measures such as endoscopy) [4–6]. MH is generally referred to as endoscopic remission, describing the absence of ulceration; however, instruments
used to assess MH and measurable parameters used in definitions of MH-related endpoints are reported using variable nomenclature and are incompletely validated [7, 8]. Endoscopic evaluations of MH commonly utilise the Simple Endoscopic Score for CD (SES-CD), CD Endoscopic Index of Severity score, or absence of ulceration/deep ulceration with/without aphthae [5, 9]. Achievement of MH is associated with improved long-term outcomes, including reduced risk of relapse, decreased hospitalisations, increased rates of steroid-free remission, and longer resection-free intervals [5, 10–15]. Thus, consensus guidelines for CD management, including STRIDE II, consider MH to be an important therapeutic goal that may help patients achieve meaningful and sustained improvements in quality of life [8, 16, 17].

Although MH is associated with better long-term outcomes for patients, it is hard to achieve compared with other clinical treatment targets in CD [18]. For example, in the SONIC trial (biologic- and immunomodulator-naïve patients treated with either infliximab or azathioprine or both), only 53% of patients in clinical remission (CD Activity Index (CDAI) score < 150) achieved MH (absence of ulceration) [19]. In addition, clinical indices like CDAI, long used to evaluate CD treatment efficacy, have been criticised for being less reliable as indicators of mucosal inflammation [8, 20, 21]. CDAI scores analysed from three placebo-controlled trials of adalimumab, upadacitinib, and risankizumab were only moderately correlated with mucosal inflammation of the bowel assessed endoscopically using SES-CD scoring [22]. Vedolizumab is a gut-selective monoclonal anti-a4β7-integrin antibody approved for the treatment of adults with moderate to severe CD [23–25]. The GEMINI 2 and GEMINI 3 phase 3 clinical trials established the efficacy of vedolizumab for achieving clinical remission in patients with moderately to severely active CD [26, 27]. Several studies have established the effectiveness of vedolizumab as an induction and maintenance treatment for CD in real-world settings [28–32].

MH was not assessed as a main endpoint in CD in the GEMINI clinical trial programme; clinical studies of MH have been conducted in smaller, selected patient cohorts (e.g., the prospective, phase 3b, open-label VERSIFY trial of patients with active CD [18] and a retrospective study of a subset of patients enrolled in the open-label extension phase of GEMINI studies (GEMINI LTS) [33]). Real-world studies assessing MH endpoints in vedolizumab-treated patients may achieve a larger sample size by including a broader range of patients and thus may provide a better understanding of the clinical effectiveness of vedolizumab among diverse patient populations treated in routine clinical practice.

This systematic literature review (SLR) and meta-analysis of real-world studies published in the last 7 years was conducted to examine and provide pooled estimates of the rates of MH in vedolizumab-treated patients with CD.

2. Methods

2.1. Study Selection. This SLR was conducted according to the general recommendations of the Cochrane handbook for Systematic Reviews of Interventions and PRISMA guidelines [34, 35]. MEDLINE-, Cochrane-, and EMBASE-indexed publications in English from January 2014 to January 2020 (Supplementary Tables 1–3) and conference abstracts from 2018 to 2019 (Supplementary Table 4) were searched for real-world studies reporting MH and related outcomes in vedolizumab-treated patients with CD. Bibliographies of identified relevant SLRs and network meta-analyses were reviewed for additional studies. No contact with authors was made to identify additional studies.

Search terms included combinations of free text and medical subject headings used to denote CD, inflammatory bowel disease, vedolizumab, and real-world studies (e.g., observational, real-world, case-control, cohort, and registry studies) (Supplementary Tables 1–4). The identified records were reviewed according to prespecified inclusion/exclusion criteria (Table 1) by one researcher, and 50% of the search results were reviewed by a second independent researcher. Studies with < 10 patients and patients aged < 18 years were excluded.

2.2. Data Extraction and Quality Assessment. One researcher used predefined parameters to extract all data, which were quality checked by a second researcher for accuracy. Key information obtained for each eligible study included author, year of publication, country/region, study design, sample size, study duration, vedolizumab dosing, and patient inclusion/exclusion criteria. Patient characteristics included age, sex, smoking status, disease duration, disease behaviour and location, and prior treatment history. Detailed study data on MH-related outcomes were also collected. Quality assessment of studies was undertaken using the National Institutes of Health Quality Assurance tools for cohort and case-control studies (Supplementary Table 5) [36].

2.3. Statistical Analyses. Studies identified during the SLR were assessed for inclusion in a meta-analysis. Studies that reported results on overlapping patient populations or used median time for the endpoint data, as well as studies that did not report on timepoints or an endpoint of interest, were excluded. A random effects meta-analysis was conducted using the meta package in R, using the method of restricted maximum likelihood and double arc sine transformation to generate pooled estimates of the proportion of patients achieving MH out of the total number treated with vedolizumab, with 95% confidence intervals (CIs). A sensitivity analysis was performed using the logit transformation. Heterogeneity was considered using Higgins’s I², providing an estimate of the percentage of variation across studies that was due to heterogeneity. All analyses used the endpoint of MH or endoscopic remission, defined as absence of ulcers and/or erosions or SES-CD cut – points < 4. The primary analysis included studies reporting point estimates at approximately 6 months and separately at approximately 12 months; the secondary analysis also included cumulative rates at 6 months and separately at approximately 12 months, and the tertiary analysis expanded the evidence base further to include point estimates, cumulative rates, and studies reporting data up to 12 months.
3. Results

3.1. Qualitative Summary: MH-Related Outcomes. Screening of 1751 potentially relevant records identified 36 vedolizumab real-world studies for inclusion in the SLR for qualitative evaluation (PRISMA flowchart in Figure 1 details publication screening and the reasons for exclusion). Most studies in the SLR were single-arm, retrospective cohort studies conducted in a single country (10/36 from the United States). Population size ranged from 13 to 650 patients, median patient age from 29.0 to 49.5 years, and median disease duration from 2.4 to 19.5 years (Supplementary Table 6). Most studies included a mix of both antitumour necrosis factor (TNF-) naïve and -experienced patients (23/36).

MH was assessed by various instruments across studies, including endoscopy, magnetic resonance imaging, and computed tomography. For MH-related endpoints, 22 studies reported MH, nine endoscopic remission, six endoscopic response, four endoscopic improvement, four deep remission, and two endoscopic healing, and a single study each reported endoscopic remission/response, radiologic improvement, radiologic remission, objective response, and objective remission based on endoscopic/radiographic assessment. Although definitions applied to these endpoints varied across studies, the majority defined MH/endoscopic remission as the absence of ulcers or erosions (17 studies) and/or a SES-CD score of ≤ 4 (six studies).

Real-world MH rate ranges were 20.0%-22.2% at 3 months (mean ± SD, 21.3% ± 1.2%; three studies [37–39]), 10.1%-46.0% at 6 months (mean ± SD, 30.4% ± 11.8%; ten studies [29, 30, 39–46]), and 21.2%-62.5% at 12 months (mean ± SD, 37.8% ± 14.6%; eight studies [28, 37, 39, 43, 47–51]). Cumulative 12-month MH rates were 54%-62.5% in anti-TNF-naïve patients (two studies [28, 49]) and 47%-59.7% in anti-TNF-experienced patients [28, 49].

Rates of endoscopic remission (absence of ulcers/erosions and SES-CD scores of < 4) were reported in seven studies [52–58]. Rates of endoscopic remission in vedolizumab-treated patients were 15%-33% at/within 6 months (two studies [54, 57, 58]) and 27%-38% at or within 12 months (four studies [53, 56–58]), with two studies contributing cumulative data over 6 months [54] and 6-12 months [58], respectively. The first of these [54] reported a significantly higher
cumulative rate of endoscopic remission with early- versus late-stage CD at 6 months: 29% (n = 62) in patients with a disease duration of ≤ 2 years, versus 13% (n = 588) for disease duration of >2 years. A prospective cohort study, stratifying endoscopic remission rates by disease duration, reported a similar trend for higher rates of endoscopic remission in patients with shorter CD duration, which was more pronounced at week 52 versus week 26 of vedolizumab treatment [57]. This study also reported higher rates of endoscopic remission at 26 weeks in anti-TNF-naïve (62% (95% CI: 32%-85%); n = 13) versus anti-TNF-experienced patients (29% (95% CI: 20%-39%); n = 97). Also, at 52 weeks, rates were 62% (95% CI: 32%-85%) versus 33% (95% CI: 24%-43%) for anti-TNF-naive versus anti-TNF-experienced patients, respectively [57].

3.2. Meta-analysis: MH Outcomes. Data from 15 separate real-world studies defining MH using absence of ulcers/erosions and/or SES-CD cut–points < 4 were included for meta-analysis (Table 2); 21 publications were excluded primarily because of irrelevant time of measurement and not defining MH by absence of ulcers/erosions and/or SES-CD score of ≤ 4 (Figure 1 and Supplementary Table 7). Most (nine) of the 15 included studies were retrospective, five were prospective, and one was a registry-based study. All studies included a mix of anti-TNF-naïve and -experienced patients, apart from Kopylov [41], which included only anti-TNF-naïve patients, and two studies for which this information was not available. Among studies with a mix of anti-TNF- naïve and -experienced patients, prior use of anti-TNF agents ranged from 68.9% to 99.4%. Most studies used absence of ulcers and/or erosions (10 studies) or resolution of deep ulcers (one study) and/or SES-CD score of < 4 (three studies), SES-CD score of < 2 (one study), and SES-CD score of 0 (one study) (Table 2). The number of patients with endpoint data varied across the studies from 11 to 650; baseline

Figure 1: PRISMA flow diagram showing studies included in the systematic literature review (SLR) and meta-analysis (MA). PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Table 2: Details of 15 study publications included for meta-analysis.

| Study author (year) | Study design | Patient age at baseline, mean (SD), years | Anti-TNF-naïve and/or-experienced, % | Measure used |
|---------------------|--------------|------------------------------------------|--------------------------------------|--------------|
| Dreesen (2018) [30]† | Retrospective cohort study | Median (IQR), 40 (29-52) | Mixed (previous biologics, 89%) | The complete absence of ulcerations |
| Löwenberg (2019) [57]† | Prospective cohort study | Median (IQR), 36 (28-46) | Mixed (prior anti-TNF, 88%) | SES-CD score of < 4 |
| Kotze (2018) [39]† | Retrospective cohort study | 50.1 (16.4) | Mixed (prior anti-TNF, 68.9%) | An improvement in mucosal inflammation compared with baseline, with resolution of deep ulcers |
| Ylisaukko-Oja (2018) [46]† | Retrospective cohort study | 40.3 (13.5) | Mixed | SES-CD score of < 2 |
| Kopylov (2018) [41]† | Retrospective cohort study | Median (IQR), 49 (33-67) | Naïve (prior anti-TNF, 0%) | The absence of ulceration at follow-up endoscopy in patients who had ulceration at baseline ileocolonoscopy |
| Bertani (2019) [47]† | Prospective cohort study | NR | NR | The absence of any ulcerations |
| Plevris (2019) [43] | Retrospective cohort study | Median (IQR), 39 (29-54) | Mixed (prior anti-TNF, 86.9%) | The absence of mucosal ulceration/erosion on ileocolonoscopy and complete tapering of steroids; in patients for whom ileocolonoscopy was not possible, MH was assessed by MRI and defined according to local site radiologist or capsule endoscopy (defined according to local site physician) |
| Koliani-Pace (2019) [49] (ERA 1)‡ | Retrospective cohort study | Median (IQR), 35 (26-50) | Mixed (prior anti-TNF, 94%) | The absence of ulcers and/or erosions |
| Koliani-Pace (2019) (ERA 2)‡ | Retrospective cohort study | Median (IQR), 38 (28-55) | Mixed (prior anti-TNF, 88%) | The absence of ulcers and/or erosions |
| Faleck (2019) [54] | Registry study | 36 (pooled estimate from subgroups) | Mixed (prior anti-TNF, 91%) | The absence of ulcers and/or erosions |
| Amiot (2017) [70]§ | Prospective cohort study | Median (IQR), 35.6 (29.4-46.8) | Mixed (previous anti-TNF: 1 anti-TNF agent, 99.4%; ≥2 anti-TNF agents, 90.7%) | The absence of any ulcer |
| Perin (2019) [42]§ | Retrospective cohort study | 42.76 (17.27) | Mixed (previous anti-TNF, 88.46%) | The complete absence of ulcers |
| Hanžel (2019) [40]§ | Prospective cohort study | Median (IQR), 42 (28-50) | Mixed (previous biologics, 82%) | SES-CD score of < 4 and the absence of any mucosal ulceration |
| Reinglas (2019) [58]§ | Retrospective cohort study | 48.5 (15.1) | Bioexperienced | SES-CD score of < 4 |
| Wang (2019) [71]§ | Retrospective cohort study | Median (range), 43 (23-75) | Mixed | SES-CD score of 0 |
| Yacoub (2018) [45]§ | Prospective cohort study | NR | NR | The absence of significant intestinal inflammation on MRI as judged by an experienced radiologist and/or the absence of any ulcerations during endoscopy |

anti-TNF: antitumour necrosis factor; IQR: interquartile range; MH: mucosal healing; MRI: magnetic resonance imaging; NR: not reported; SES-CD: Simple Endoscopic Score for Crohn’s Disease. †Studies included in the primary analysis. ‡Data from two separate timepoints, ERA 1 and ERA 2, from a single registry study (VICTORY). §Studies that were only included in the tertiary analysis, including point estimates, cumulative rates, and data up to 12 months.
characteristics are summarised in Table 3. For the 6-month meta-analysis, sex ratios differed slightly across studies, from 30% to 54% of males, and median age ranged from 30 to 56.1 years.

3.3. Pooled Estimates for Rates of MH from Meta-analysis. In the primary analysis, pooled MH rates considering point estimates were 31.8% at 6 months \((n = 223, \text{five studies})\) (Figure 2(a)) and 33.4% at 12 months \((n = 151, \text{three studies})\) (Figure 2(b)). There was no evidence of heterogeneity: \(I^2 = 0\%\) in both the 6- and 12-month analyses.

In the secondary analysis, which combined point estimates and cumulative rates in a single analysis, pooled MH rates were 24.5% within 6 months \((n = 1,013, \text{seven studies})\) (Figure 3(a)) and 40.5% within 12 months \((n = 941, \text{five studies})\) (Figure 3(b)). There was considerable heterogeneity in the 6-month \(I^2 = 85\%\) and 12-month results \(I^2 = 86\%\).

In the tertiary analysis, the pooled MH rate at 12 months was 41.5% \((95\% \text{ CI: 33.7\%-49.4\%})\); however, considerable heterogeneity was observed \(I^2 = 82\%\).

### 4. Discussion

This comprehensive review of the real-world effect of vedolizumab on MH in patients with CD identified 36 studies reporting MH-related outcomes published in the last 7 years. Rates for MH-related endpoints, including MH, endoscopic remission, endoscopic response, deep remission, and endoscopic healing, were frequently within the 26%-50% range. MH rates in vedolizumab-treated patients were similar, despite considerable cross-study variability, suggesting generalisability of the evidence. In the primary meta-analysis, rates of MH were consistent with pooled estimates of

| Baseline characteristics | No. of studies reporting data |
|--------------------------|-------------------------------|
| Age\(^\dagger\)          | 35-50.1 years                 | 14 |
| Age at diagnosis\(^\ddagger\) | 22-32 years                  | 6 |
| Male sex                | 30%-64%                       | 14 |
| Disease duration\(^\S\)  | 8-19.5 years                  | 10 |
| Active smokers          | 8.8%-30%                      | 12 |
| Disease location         |                               |    |
| (i) Ileal: 0%-35.9%      |                               |    |
| (ii) Colonic: 14%-31.9%  |                               |    |
| (iii) Ileocolonic: 46%-86%|                               |    |
| (iv) Upper GI: 1.3%-11.1%|                               |    |
| Disease behaviour        |                               |    |
| (i) Stricture: 21.3%-41.7%|                               |    |
| (ii) Penetrating: 12%-25% |                               |    |
| (iii) Perianal: 12%-45.3% |                               |    |
| Extraintestinal manifestations | 27%-31.9%                | 3 |
| Crohn’s disease-related surgery | 36%-49.1%               | 7 |
| Concomitant treatment    |                               |    |
| (i) Corticosteroids      |                               |    |
| (ii) Immunomodulators    |                               |    |
| Prior medication usage   |                               |    |
| Steroids\(^\S\)          | 34%-41%                       | 2 |
| Immunomodulators         | 76.2%-97.5%                   | 2 |
| (i) Infliximab \((n = 3): 54.0\%-75.0\%\) | | |
| (ii) Adalimumab \((n = 3): 52.0\%-68.0\%\) | | |
| Biologics                |                               |    |
| (i) Golimumab \((n = 2): 0\%\) |                               |    |
| (ii) Ustekinumab \((n = 1): 17\%\) |                               |    |
| (v) Anti-TNF agent \((n = 11): 0\%-100\%\) | | |
| Mixed anti-TNF-naïve and -experienced patients | Prior anti-TNF agents: 68.9%-99.4\% | 10 |
| Anti-TNF-experienced patients only |                               | 1 |
| Anti-TNF-naïve patients only |                               | 1 |
| Mucosal healing definitions | Absence of ulcers/erosions | 10 |
| Resolution of deep ulcers |                               | 1 |
| And/or SES-CD score of <4 |                               | 1 |
| And/or SES-CD score of <2 |                               | 1 |
| And/or SES-CD score of 0 |                               | 1 |

\(^\dagger\) Antitumour necrosis factor; GE: gastrointestinal; SES-CD: Simple Endoscopic Score for Crohn’s Disease. \(^\ddagger\) Four studies (Kotze et al. [39]; Ylisaukko-Oja et al. [46]; Perin et al. [42]; Reinglas et al. [58]) reported mean age and standard deviation. \(^\S\) Three studies (Kotze et al. [39]; Amiot et al. [70]; Wang et al. [71]) reported mean age at diagnosis and standard deviation. \(^\S\) Two studies (Kotze et al. [39]; Ylisaukko-Oja et al. [46]) reported mean disease duration and standard deviation. \(^\S\) Patients who were steroid dependent or steroid refractory at baseline.
approximately one-third of vedolizumab-treated patients with CD achieving MH at 6 and 12 months.

Real-world effectiveness data for MH corroborate the findings from clinical trials reporting MH efficacy in vedolizumab-treated patients with CD [18, 33]. In the VERSIFY phase 3b clinical trial, rates of endoscopic remission (SES-CD score of ≤ 4) and endoscopic response (≥50% reduction in baseline SES-CD score) at 52 weeks (n = 101)
were 17.9% and 53.6%, respectively [18]. Additionally, a retrospective analysis of data from 24 patients from Leuven University Hospitals enrolled in the GEMINI LTS study (who received vedolizumab on a 4-weekly dosing schedule for ≥ 1 year) noted durable MH (absence of ulceration) in 29% of patients with CD (median [range] time on treatment 33 (6–59) months) [33]. The lower MH rates reported in clinical trials versus real-world settings might be due to protocol and patient population differences, endoscopic assessment by central reviewers, stricter definitions of MH applied to a smaller, selected patient sample, and protocol restrictions on treatment optimisation. The prospective, open-label LOVE-CD study of 110 patients (included in this meta-analysis of real-world evidence) used blinded evaluation of SES-CD scores by central reviewers (MH defined as SES-CD score of < 4) but reported higher rates of endoscopic remission (33% and 36%) and endoscopic responses (40% and 46%) at 6 and 12 months of treatment, respectively. The difference may be due, in part, to the additional vedolizumab infusion at week 10 permitted by the protocol in LOVE-CD [57].

The treat-to-target strategy of early immunosuppression combined with tight and frequent control of mucosal inflammation was developed with the aim of reducing the risk of development of debilitating comorbidities in CD [5, 8]. Complete MH (SES-CD score of 0) achieved 2 years after immunosuppressive therapy in treatment-naïve patients has been associated with higher rates of 4-year steroid-free remission [11, 59]. Consistent with these findings, real-world vedolizumab studies also indicated that patients with shorter versus longer disease durations had higher endoscopic remission rates [54, 57]. In real-world studies from this SLR [28, 49, 57] and in VERSIFY [18], rates for MH and endoscopic remission in vedolizumab-treated patients were also higher among anti-TNF-naïve patients versus those previously treated with anti-TNF agents. This clinical effect of prior anti-TNF treatment on the subsequent efficacy of vedolizumab could be explained by the observation that anti-TNF biologics downregulate the expression of the mucosal addressin cell adhesion molecule-1 (MAdCAM-1), the primary ligand of the α4β7 integrin heterodimer found on subsets of peripheral lymphocytes [60].

Considering vedolizumab treatment relative to other biologic treatments for CD, data from the EVOLVE study demonstrated comparable real-world MH rates in biologic-naïve patients with moderate to severe CD treated with vedolizumab or anti-TNF agents [28, 61]. Cumulative MH rates at 12 months (62.5% vs. 59.7%, respectively) and over 24 months (100.0% vs. 90.1%, respectively) included in this SLR were comparable between vedolizumab-treated and anti-TNF-treated patients [28]. These high rates were based on the cumulative number of at-risk patients in each treatment group, calculated by computing the probability of MH. As such, outcome rates of > 90% do not correspond to 90% or 100% of all CD patients achieving this outcome. Our study shows that most patients achieve MH within 6 months, and the rate is stable at 1 year without further significant increases. In the context of the treat-to-target strategy, this would support optimisation of treatment if MH is not achieved within 6 months with vedolizumab. The combined use of biomarkers and clinical indices, as well as the measurement of drug levels, could help improve clinical outcomes, including MH [62–64].

Real-world evidence can be used to validate clinical trials results [65]; the US Food and Drug Administration has created a framework for evaluating real-world evidence to help support study requirements after treatments have been approved [66]. Data from clinical practice are more reflective of the heterogeneity in patient characteristics and drug exposure/adherence than controlled trials [65, 67, 68]. However, the lack of standardised information across real-world studies is a limitation that can decrease comparability and potentially introduce bias. Here, we found high variability in terminology and specific definition/cut-off values for MH-related endpoints. Restricting the primary meta-analysis to studies that measured MH using absence of ulcers/erosions and/or SES-CD cut – points < 4 was designed to minimise this effect on pooled analysis of MH rates.

Three types of analysis for point estimates were conducted to assess the variability of treatment effect across different study subgroupings [69]. These analyses did not indicate a large variability in treatment effect size when selecting different subsets of patients based on length of follow-up or cumulative rates versus point estimates. For the primary analysis, no significant evidence of heterogeneity was observed in the results across studies, although few studies were included (five and three studies for the 6-month and 12-month analyses, respectively). One study included in the primary analysis had a low number of patients (n = 11). For the secondary meta-analysis of point estimates and cumulative rates, considerable heterogeneity measured by $I^2$ was observed, suggesting that the pooled estimates should be interpreted with caution.

The lack of central reading for endoscopy data is also a limitation of pooled MH rates from independent real-world studies; however, most studies were from well-known and expert institutions. The National Institutes of Health quality assessment indicated that all studies included in this SLR and meta-analysis were of fair quality (Supplementary Table 5). Many studies reported MH outcomes for only a portion of the total enrolled patients because of the lack of endoscopic assessment data; therefore, the sample sizes for MH and endoscopic remission results were small, and the baseline characteristics of these patients were mostly unavailable.

MH has been identified as an important treatment goal in recent CD management guidelines [8], associated with long-term benefits for patients [10–14]. More comparative treatment effectiveness data using standardised, well-validated MH endpoints would help inform risk-benefit evaluations for CD therapies [4]; however, a more pressing challenge for the management of CD may lie in maintaining sustainable treatment effects over the disease course.

5. Conclusions

The findings of this SLR support the effectiveness of vedolizumab for achieving MH in patients with CD treated in real-
world clinical settings. In a meta-analysis of pooled data from real-world studies, approximately one-third of vedolizumab-treated patients with CD achieved MH at 6 and 12 months, despite utilisation in largely biologic-refractory patients. Indications that MH rates may be higher in anti-TNF-naïve versus -experienced patients, and the potential benefit of early vedolizumab treatment, warrant further investigation.

Data Availability

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Data are available upon request via application at https://search.vivli.org.

Ethical Approval

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

Disclosure

This work is presented as an ePoster at Digestive Disease Week®Gastroenterology 2021:160:S-702-3.

Conflicts of Interest

S.D. reports lecture/consulting fees from AbbVie, Allergan, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Hospira, Johnson & Johnson, Merck, Merck Sharp & Dohme, Mundipharma, Pfizer, Sandoz, Takeda, TiGenix, UCB, and Vifor. P.K. and C.A. are employees of and hold stock/options in Takeda. SW is a former employee of UCB, and Vifor. P.M.I. reports lecture fees from AbbVie, Bristol Myers Squibb, Celgene, Falk Pharma, Ferring, Gilead, Jansen, Merck Sharp & Dohme, Pfizer, Sandoz, Sapphire Medical, Shire, Takeda, Tillotts, and Warner Chilcott; financial support for research from Merck Sharp & Dohme, Pfizer, and Takeda; and advisory fees from AbbVie, Arena, Genentech, Gilead, Hospira, Janssen, Lilly, Merck Sharp & Dohme, Pfizer, Pharmacosmos, Procise, Prometheus, Roche, Samsung Bioepis, Sandoz, Takeda, Topi-vert, VHI2, Vifor, and Warner Chilcott.

Authors’ Contributions

P.K., J.Y., J.-G.L.M., S.K., E.H., and S.W. contributed to the conception and design of the study. J.Y., J.-G.L.M., S.K., E.H., and C.A. contributed to the acquisition of the data. S.D., P.K., J.Y., J.-G.L.M., S.K., E.H., C.A., S.W., and P.M.I. contributed to the analysis and interpretation of the data. S.D., P.K., J.Y., J.-G.L.M., S.K., E.H., C.A., S.W., and P.M.I. were involved in drafting the article and/or revising it critically for intellectual content. All authors approved the final version of the article, including the authorship list.

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Supplementary Materials

Supplementary Table 1: MEDLINE literature search strategy for real-world evidence of mucosal healing with vedolizumab. Supplementary Table 2: EMBASE literature search strategy for real-world evidence of mucosal healing with vedolizumab. Supplementary Table 3: Cochrane literature search strategy for real-world evidence of mucosal healing with vedolizumab. Supplementary Table 4: EMBASE conference abstracts: literature search strategy for real-world evidence of mucosal healing with vedolizumab. Supplementary Table 5: Quality assessment of studies using NIH QA cohort study tool A. Supplementary Table 6: Patient baseline characteristics for the 36 studies identified in the systematic literature review. Supplementary Table 7: Studies excluded from MA. Supplementary materials references list. PRISMA Checklist. (Supplementary Materials)

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