Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease

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Abstract

Background Selective patient recruitment can produce discrepancies between clinical trial results and real-world effectiveness.

Methods A systematic literature review and meta-analysis were conducted to assess vedolizumab real-world effectiveness and safety in patients with ulcerative colitis (UC) or Crohn’s disease (CD). MEDLINE, MEDLINE In-Process, EMBASE, and Cochrane databases were searched for real-world studies of vedolizumab in adult patients with UC/CD reporting clinical response, remission, corticosteroid-free remission, UC/CD-related surgery or hospitalization, mucosal healing, or safety published from May 1, 2014–June 22, 2017. Response and remission rates were combined in random-effects meta-analyses.

Results At treatment week 14, 32% of UC patients [95% confidence interval (CI) 27–39%] and 30% of CD patients (95% CI 25–34%) were in remission; and at month 12, 46% for UC (95% CI 37–56%) and 30% for CD (95% CI 20–42%). For UC, the rates of corticosteroid-free remission were 26% at week 14 (95% CI 20–34%) and 42% at month 12 (95% CI 31–53%); for CD they were 25% at week 14 (95%, CI 20–31%) and 31% at month 12 (95%, CI 20–45%). At month 12, 33–77% of UC and 6–63% of CD patients had mucosal healing. Nine percent of patients reported serious adverse events.

Conclusions Vedolizumab demonstrated real-world effectiveness in patients with moderate-to-severely active UC or CD, with approximately one-half and one-third of patients, respectively, in remission at treatment month 12. These findings are consistent with clinical trial data and support the long-term benefit–risk profile of vedolizumab.

Keywords Vedolizumab • Inflammatory bowel disease • Ulcerative colitis • Crohn’s disease • Real-world effectiveness

This study was previously presented as a poster at the 2016 Advances in Inflammatory Bowel Diseases Congress (AIBD) and the 2017 European Crohn’s and Colitis Organisation Congress (ECCO).

Rebecca Curtis was an employee of Takeda at the time of manuscript development.

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Introduction

Current treatment options for inflammatory bowel diseases (IBD) include aminosalicylates, corticosteroids (CS), thiopurines, calcineurin inhibitors, anti-cytokines, and anti-integrins [1, 2]. Vedolizumab is a gut-selective, humanized, monoclonal antibody that binds to \( \alpha_4 \beta_7 \) integrins, selectively blocking gut-selective lymphocyte trafficking [3, 4]. Vedolizumab efficacy and safety in moderate-to-severely active ulcerative colitis (UC) and Crohn’s disease (CD) were established by the GEMINI clinical trials [5–7], with marketing approval granted in May 2014 in the USA and later in Europe [8, 9]. Clinical guidelines recommend vedolizumab for UC not previously treated with biologic therapy [10], and for UC or CD that is refractory to conventional or anti-tumor necrosis factor-alpha (TNF\( \alpha \)) treatment [1, 2].

Strict inclusion criteria used in randomized controlled trials (RCTs) can limit the patient population and generalizability of trial results to clinical practice, with the latter further compromised by IBD patient heterogeneity [11, 12]. Indeed, up to two-thirds of patients with IBD might be ineligible to participate in RCTs of biologics [11, 13]. An additional hindrance is the increasing unwillingness of patients to accept placebo control. Randomized controlled trials are, therefore, unlikely to fully represent the real-world IBD population. However, physicians require real-world effectiveness data to complement clinical trial results and inform treatment decisions. Assessing the treatment quality and effect size in clinical practice and evaluating the strength of this evidence through systematic literature reviews and meta-analyses can provide such data. Summation can overcome potential bias associated with individual studies and address challenges associated with the transferability of RCT findings; systematic literature reviews are, therefore, at the top of the evidence hierarchy as defined by the Oxford Centre for Evidence-Based Medicine [14, 15].

Data from the GEMINI 3 trial suggest that the full effect of vedolizumab-induced clinical remission in patients with CD may not be apparent before treatment week 10 [7]. The European Summary of Product Characteristics and US Prescribing Information both recommend that vedolizumab treatment of UC and CD should be discontinued if a therapeutic benefit is not observed by week 14 (by week 10 in UC in Europe) [8, 9]. Real-world data allow evaluation of the optimal time points for assessing clinical effectiveness and when concomitant therapies should be adjusted based on therapeutic response outside of RCT protocol-defined assessments.

Given that vedolizumab is relatively new and the number of treated patients is increasing, ongoing safety monitoring is essential. Real-world data from large cohorts can further characterize a drug’s safety profile not fully elucidated in clinical trials [16, 17]. We sought to systematically review and summarize published literature on real-world effectiveness and safety of vedolizumab studies and conduct a meta-analysis of effectiveness data.

Materials and methods

Study selection

A systematic review of MEDLINE, MEDLINE In-Process, EMBASE and Cochrane (May 1, 2014–June 22, 2017), and searches of clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform were completed. Conference proceedings from 2015 to June 2017 were searched. Two researchers reviewed relevant publications independently, with disagreements resolved by discussion or a third reviewer. Studies were eligible if they included real-world evidence (e.g., medical record review, database, registry) and an adult patient population (\( \geq 18 \) years when initiating vedolizumab) receiving vedolizumab (Takeda Pharmaceuticals International, Inc., Deerfield, IL) for IBD (UC, CD, or unspecified/indeterminate colitis) and if outcomes reported were of interest. English and non-English language studies were eligible for inclusion. Studies were excluded if the total patient population was < 10, if vedolizumab was used off-label, or if safety data were reported at event level only (no denominator). Investigators were contacted for unpublished data (unpublished clinical data provided courtesy of Dr. Mark A. Samaan and Dr. Peter Irving from their UK study, 2016) and conference abstracts, and manual backward citation tracking of references (including studies) were performed to identify additional relevant studies [18–22].

Data extraction and outcome measures

One researcher used predefined parameters to extract all data using a piloted form and, after this, a second researcher performed data checks for accuracy. Information obtained for each eligible study included author, year of publication, geographic location, and clinical outcomes reported. Patient characteristics included disease duration, age, sex, prior medication history, and IBD-related surgeries. The primary outcome measure was clinical remission; secondary outcome measures were clinical response, CS-free clinical remission, mucosal healing, endoscopic improvement, surgery and hospitalization rates, dose escalation rates, and safety. Clinical response, clinical remission, and CS-free clinical remission rates (classified
according to summarized measures in Table S1) (Samaan and Irving, 2016) [13, 23–48] were collected at weeks 6, 14, 26–30 (month 6), and 46–54 (month 12), where available. Subanalyses were performed to determine clinical remission rates by geographic region and in patients who were anti-TNFα-naive.

### Grading of evidence

Studies were assessed using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence, which evaluates the strength of evidence (including quality and bias) based on study design [15, 49]. One reviewer appraised each study and assigned a level from 1 (high quality or low risk of bias) to 5 (low quality or high risk of bias) (Table S2) [15, 49], with uncertainty resolved by discussion with a second reviewer.

### Statistical analyses

Meta-analyses were performed to combine clinical response, clinical remission, and CS-free clinical remission rates using R statistical software (version 3.2.2; R Foundation; Vienna, Austria) with the “meta” package (version 4.3-2). When multiple publications were available for a study, data from the most recent cohort were used for the combined analyses. Weighted mean clinical response, clinical remission, and CS-free clinical remission rates and corresponding 95% confidence intervals (CIs) were calculated using the DerSimonian–Laird random-effects model to account for between-study heterogeneity [50]. Where mean/median values and 95% CIs were reported, data were used as stated (calculated using the binomial distribution if 95% CIs were not reported). For studies reporting safety, IBD-related surgery or hospitalization, and dose escalation, the proportion of events was calculated. For mucosal healing or endoscopic improvement, analyses were based on either a cumulative incidence approach or as a proportion of those receiving endoscopy.

Study heterogeneity was determined using the \( I^2 \) statistic (which describes the variability in the effect estimate that results from heterogeneity rather than sampling error [51]) and the Q-statistic \( (P < 0.05 \) was considered significant and suggested statistical heterogeneity). When ≥10 studies reporting the same outcome were available, publication bias was assessed using Egger’s weighted regression statistic, with \( P < 0.05 \) suggesting a higher likelihood of bias [52].

### Results

#### Study and patient characteristics

Of 1542 publications identified, 89 publications \( (N = 9486; n = 4532 \text{ CD}; n = 3216 \text{ UC}; n = 1738 \text{ IBD unspecified/indeterminate/other}) \) were eligible to be included in this review (Figure S1). Eleven studies \( (n = 1692) \) did not report separate UC and CD rates [18, 20, 22, 53–60]. Six studies focused on CD, 5 focused on UC, and 61 examined both conditions. Eighteen studies were full-text articles and 73 were conference proceedings. Most studies [40] were conducted in the USA, followed by Europe [30]. The grading of quality of evidence of the studies (Table S2) [15, 49] ranged from 3 (12 publications) to 4 (77 publications; Table S3) (Samaan and Irving 2016) [13, 18, 20, 22–48, 53–110].

The meta-analysis included 21 studies reporting clinical response \( (n = 2310) \) and 23 reporting clinical remission rates \( (n = 2298) \) (18 studies included an analyses of both outcomes; Table S1) (Samaan and Irving, 2016) [13, 23–34, 36–48]. Ten studies reported CS-free clinical remission rates (Table S1) (Samaan and Irving, 2016) [13, 23, 24, 28, 29, 31, 36, 38, 42, 46] and 10 reported mucosal healing or endoscopic improvement (Fig. 5; Figure S2) [34, 40, 60, 69]. Of 46 studies reporting safety outcomes, most were for UC/CD combined, rather than by separate indication (Table S4) [13, 18, 20, 24, 26, 27, 31, 32, 37, 38, 40–42, 44–46, 53, 55, 56, 58, 59, 61, 64–68, 70–74, 78–80, 84, 89, 91–95, 97, 98, 102, 104–109].

Patient demographics are described in Table S3 (Samaan and Irving, 2016) [13, 18, 20, 22–48, 53–110]. The mean patient age was 40.9 years (range 34.3–67.1; 39 studies); the mean disease duration was 9.8 years (range 2.9–18; 22 studies); and the mean percentage of patients with prior anti-TNFα therapy was 80.4% (range 0–100%; 42 studies).

#### Primary outcome

##### Clinical remission

Clinical remission was assessed in 18 studies in UC, 18 in CD, and 13 in both populations (Table S1) (Samaan and Irving, 2016) [13, 23–25, 27–34, 36, 38–40, 42–48]. In UC, clinical remission was achieved in 24% of patients at week 6 (95% CI 13–41%) and 32% at week 14 (95% CI 27–39%), which increased to 39% at 6 months (95% CI 30–48%) and 46% at 12 months (95% CI 37–56%) (Fig. 1) (Samaan and Irving, 2016) [13, 24, 25, 27–30, 32–34, 36, 38–40, 42, 65, 86]. In CD, clinical remission was achieved in 24% of patients at week 6 (95% CI...
a

| Study                | Patients in remission | Patients assessed | Week 6 remission rate (%) | Rate (%) | 95% CI     |
|----------------------|-----------------------|-------------------|---------------------------|----------|------------|
| Amiot et al.         | 39                    | 121               |                           | 32       | (24–41)    |
| Baungart et al.      | 13                    | 115               |                           | 11       | (6–19)     |
| Mankongpaisarnrungrung et al. | 5      | 7                 |                           | 71       | (29–96)    |
| Shelton et al.       | 6                     | 40                |                           | 15       | (6–30)     |
| Ungar et al.         | 6                     | 25                |                           | 24       | (9–45)     |

Random-effects model
Heterogeneity: $P < .0001$

b

| Study                | Patients in remission | Patients assessed | Week 14 remission rate (%) | Rate (%) | 95% CI     |
|----------------------|-----------------------|-------------------|---------------------------|----------|------------|
| Amiot et al.         | 47                    | 121               |                           | 39       | (30–48)    |
| Baungart et al.      | 27                    | 115               |                           | 23       | (16–32)    |
| Chaparro et al.      | 13                    | 42                |                           | 31       | (18–47)    |
| Christensen et al.   | 8                     | 20                |                           | 40       | (19–64)    |
| Kopylov et al.       | 20                    | 39                |                           | 27       | (17–39)    |
| Samaan et al.        | 7                     | 18                |                           | 39       | (17–64)    |
| Shelton et al.       | 17                    | 58                |                           | 29       | (18–43)    |
| Vivio et al.         | 8                     | 15                |                           | 53       | (27–79)    |

Random-effects model
Heterogeneity: $P = .13$

c

| Study                | Patients in remission | Patients assessed | Month 6 remission rate (%) | Rate (%) | 95% CI     |
|----------------------|-----------------------|-------------------|---------------------------|----------|------------|
| Amiot et al.         | 51                    | 121               |                           | 42       | (33–51)    |
| Dulai et al.         | 67                    | 180               |                           | 37       | (30–45)    |
| Hoog et al.          | 8                     | 16                |                           | 50       | (25–75)    |
| Samaan et al.        | 5                     | 10                |                           | 50       | (19–81)    |
| Stallmach et al.     | 11                    | 60                |                           | 18       | (10–30)    |
| Zezos et al.         | 28                    | 57                |                           | 49       | (36–63)    |

Random-effects model
Heterogeneity: $P = .01$

d

| Study                | Patients in remission | Patients assessed | Month 12 remission rate (%) | Rate (%) | 95% CI     |
|----------------------|-----------------------|-------------------|---------------------------|----------|------------|
| Amiot et al.         | 51                    | 121               |                           | 42       | (33–51)    |
| Dulai et al.         | 92                    | 180               |                           | 51       | (44–59)    |
| Eriksson et al.      | 25                    | 39                |                           | 64       | (47–79)    |
| Lenti et al.         | 16                    | 36                |                           | 44       | (28–62)    |
| Pauwels et al.       | 3                     | 6                 |                           | 50       | (12–88)    |
| Samaan et al.*       | 7                     | 12                |                           | 58       | (28–85)    |
| Stallmach et al.     | 15                    | 60                |                           | 25       | (15–38)    |

Random-effects model
Heterogeneity: $P < .01$
I included in UC and CD remission analyses (and Irving, 2016) [13, 23, 24, 29, 31, 36, 38, 46].

In patients with UC, CS-free clinical remission was reported both in UC and CD; CS-free clinical remission involved a confidence interval. Data from Amiot et al. [65], Baumgart et al. [24], Mankongpaisarrung et al. [33], Shelton et al. [13], Ungar et al. [39], Chaparro et al. [25], Christensen et al. [27], Kopylov et al. [86], Samaan et al. [36], Vivio et al. [40], Dulai et al. [28], Hoog et al. [30], Stallmach et al. [38], Zeezos et al. [42], Eriksson et al. [29], Lenti et al. [32], Paauwels et al. [34], Samaan et al. 

Between-study heterogeneity was evident for all analyses (P = 0.01). For CD, between-study heterogeneity was evident for all groups included in UC CS-free clinical remission analyses. Between-study heterogeneity was evident for all groups included in UC CS-free clinical remission analyses.

Corticosteroid-free clinical remission was achieved in 14% at week 6 (95% CI 6–32%), 26% at week 14 (95% CI 20–34%), and 32% at 6 months (95% CI 21–45%), with the rate increasing to 42% at 12 months (95% CI 31–53%) (Fig. 3) (Samaan and Irving, 2016) [13, 24, 28, 29, 35, 36, 38, 42, 65, 86].

In CD, CS-free clinical remission was achieved by 13% at week 6 (95% CI 8–21%), 25% at week 14 (95% CI 20–31%), and 22% at 6 months (95% CI 15–32%) and was maintained at 31% to 12 months (95% CI 20–45%) (Fig. 4) (Samaan and Irving, 2016) [13, 23, 24, 29, 36, 38, 46, 86]. Between-study heterogeneity was evident for all groups included in UC CS-free clinical remission analyses (P ≤ 0.03 for all) and for all groups in the CD CS-free clinical remission analyses, other than week 14 (P = 0.14). Corticosteroid-free response results are summarized in Table S5.

Mucosal healing and endoscopic improvement

Twelve studies reported mucosal healing (Fig. 5) [23, 26, 28, 34, 35, 40, 46, 47, 69, 77, 83, 103], and 4 studies reported endoscopic improvement (Figure S2) [34, 40, 60, 69]. Mucosal healing rates ranged from 24 to 55% in patients with UC and 19–30% in patients with CD at month 6. At month 12, mucosal healing rates ranged from 33 to 77% in patients with UC and 6–63% in patients with CD. In a study of patients with UC or CD, endoscopic improvement was observed in 76 and 52% of patients, respectively, at a median time point of 22 weeks (Figure S2) [40]. In patients with CD, rates of endoscopic improvement were consistent over time with 53 and 50% of patients experiencing an improvement at week 16 and week 52, respectively (Figure S2) [34].

IBD-related surgery and hospitalization rates

Three real-world IBD studies [62, 99, 110] included in our systematic review (Table S6) [13, 22, 23, 26, 31, 35, 36, 40–42, 44–46, 54–56, 62–64, 67, 69, 71, 74, 76, 80–82, 85–88, 90, 91, 93, 96–102, 110] demonstrated reductions in hospitalization rates in the post-treatment versus pre-treatment period.

Vedolizumab dose-escalation rates

Rates of vedolizumab dose escalation ranging from 4 to 60% up to week 54 were reported in 8 real-world studies (Table S7) [23, 33, 37, 41, 46, 57, 75, 108]. Dose-escalation rates were lower in biologic-naive (4–20%) versus biologic-experienced patients (6–29%) [57, 75]. Among 4 studies reporting dose-escalation outcomes, 31–81% of patients recaptured response (Table S7) [33, 37, 46, 108].
Vedolizumab safety

Safety outcomes were reported in 46 studies (Table S4) [13, 18, 20, 26, 27, 31, 32, 37, 38, 41, 42, 45, 46, 55, 56, 59, 61, 64, 65, 68, 70–74, 78–80, 84, 89, 94, 97, 102, 104, 105, 107, 109] over a vedolizumab exposure/follow-up period of 0.5–12 months (exposure/follow-up data available for 27 studies). Overall adverse event (AE) rates were reported in 23 studies (0–67% of patients; n = 2358) and infections in 12 studies (range 5–24%; n = 1176). Serious AEs (range 0–13%) were reported in 4 studies (n = 857), and serious infections (range 4–10%) were reported in 3 studies (n = 832). Postoperative AEs were reported in 4 studies (range 8–65%) and serious postoperative AEs in 1 study (43%). The most common AEs were upper respiratory tract infections including nasopharyngitis (range 1–21%), arthralgia (range < 1–20%), *Clostridium difficile* infection (range < 1–20%), and fatigue (range 1–19%). Infusion-related reactions were uncommon, as were flu/flu-like infections, pruritus, and paresthesia (≤ 7% for all).

Subgroup analysis

Clinical remission rates by geographic location

A subgroup analysis by geographic location showed variable combined remission rates among patients with UC at week 14 [range 24% (Germany) to 39% (France and UK)] and month 12 [range 25% (Germany) to 64% (Sweden)] (Fig. 6a). Among studies conducted in the USA, remission rates were 38% (95% CI 25–52%) at week 14 and 51% at month 12. Remission rates among patients with CD also varied by geographic location (week 14: range, 19% [Spain] to 37% [UK]; month 12: range, 6% [Netherlands] to 60% [Sweden]) (Fig. 6b). Among studies conducted in the USA, remission rates were 27% (95% CI 20–35%) at week 14 and 35% at month 12.

Effectiveness in biologic-naïve patients

In biologic-naïve patients with UC, clinical remission was achieved in 51% of patients at week 14 (95% CI 40–62%) and 61% of patients at 12 months (95% CI 48–72%) (Figure S3) [24, 28, 31, 36, 38]. In biologic-naïve patients with CD, clinical remission was achieved in 48% of patients at week 14 (95% CI 28–68%) and 44% of patients at 12 months (95% CI 18–75%) (Figure S4) [24, 31, 36, 38].

Discussion

To the best of our knowledge, to date this is the most comprehensive meta-analysis of real-world clinical response and remission rates for vedolizumab over 12 months of treatment, incorporating data from both peer-reviewed full-text manuscripts and abstracts. Real-world effectiveness data provide valuable evidence to support the efficacy observed in RCTs, because trial patients may not be representative of the real-world IBD population [11].

In UC, clinical remission was achieved in approximately one-third of patients at 14 weeks and in approximately one-half of patients at 12 months. In CD, clinical remission was achieved by approximately one-third of patients at both 14 weeks and 12 months. An important treatment goal in the management of patients with IBD is the achievement and maintenance of sustained CS-free clinical remission [1, 2, 111]. Approximately, one-quarter of patients with UC or CD achieved CS-free clinical remission at 14 weeks and 42% of patients with UC and 31% of patients with CD at 12 months. As patients comprising the 12-month cohort likely represent the earliest vedolizumab users, they could represent a more severe, treatment-refractory cohort (most are likely to have failed anti-TNFα treatment). According to RCT experiences, greater effectiveness should be achieved in biologic-naïve patients. In a real-world setting, this trend could induce higher efficacy rates with continued and earlier use of the drug. Also, in our study, up to approximately one-third of patients with CD achieved clinical remission after week 14, suggesting potential benefits of therapeutic monitoring beyond this time point. Despite including patients with more complex disease versus RCTs, real-world clinical and CS-free clinical remission rates in UC and CD reported here are consistent with, and in some cases exceed, vedolizumab efficacy reported in the GEMINI trials [5–7]. Moreover, the findings suggest a similar treatment effect in UC and CD, despite including patients with more complex disease versus RCTs.

Subgroup analyses in UC and CD biologic-naïve patients receiving vedolizumab demonstrated substantially
### Week 6 CS-free remission rate (%)

| Study         | Patients in remission | Patients assessed | Week 6 CS-free remission rate (%) | Rate (%) | 95% CI    |
|---------------|-----------------------|-------------------|-----------------------------------|----------|-----------|
| Amiot et al.  | 26                    | 121               |                                   | 21       | (15–30)   |
| Baumgart et al. | 10                   | 115               |                                   | 9        | (4–15)    |
|               |                       |                   | Total:                            | 236      |           |
|               |                       |                   | Random-effects model              |          |           |
|               |                       |                   | Heterogeneity: $P < .01$           |          |           |

### Week 14 CS-free remission rate (%)

| Study         | Patients in remission | Patients assessed | Week 14 CS-free remission rate (%) | Rate (%) | 95% CI    |
|---------------|-----------------------|-------------------|-----------------------------------|----------|-----------|
| Amiot et al.  | 43                    | 121               |                                   | 36       | (27–45)   |
| Baumgart et al. | 22                   | 115               |                                   | 19       | (12–28)   |
| Kopylov et al. | 18                    | 74                |                                   | 24       | (15–36)   |
| Samaan et al. | 6                     | 18                |                                   | 33       | (13–59)   |
| Shelton et al. | 12                    | 52                |                                   | 23       | (13–37)   |
|               |                       |                   | Total:                            | 380      |           |
|               |                       |                   | Random-effects model              |          |           |
|               |                       |                   | Heterogeneity: $P = .06$           |          |           |

### Month 6 CS-free remission rate (%)

| Study         | Patients in remission | Patients assessed | Month 6 CS-free remission rate (%) | Rate (%) | 95% CI    |
|---------------|-----------------------|-------------------|-----------------------------------|----------|-----------|
| Amiot et al.  | 49                    | 121               |                                   | 41       | (32–50)   |
| Peerani et al. | 40                   | 180               |                                   | 22       | (16–29)   |
| Samaan et al.* | 5                     | 10                |                                   | 50       | (19–81)   |
| Stallmach et al. | 9                     | 60                |                                   | 15       | (7–27)    |
| Zezos et al.  | 25                    | 57                |                                   | 44       | (31–58)   |
|               |                       |                   | Total:                            | 428      |           |
|               |                       |                   | Random-effects model              |          |           |
|               |                       |                   | Heterogeneity: $P < .01$           |          |           |

### Month 12 CS-free remission rate (%)

| Study         | Patients in remission | Patients assessed | Month 12 CS-free remission rate (%) | Rate (%) | 95% CI    |
|---------------|-----------------------|-------------------|-----------------------------------|----------|-----------|
| Amiot et al.  | 49                    | 121               |                                   | 40       | (32–50)   |
| Dulai et al.  | 74                    | 180               |                                   | 41       | (34–49)   |
| Eriksson et al. | 23                   | 39                |                                   | 59       | (42–74)   |
| Samaan et al.* | 7                     | 12                |                                   | 58       | (28–85)   |
| Stallmach et al. | 13                  | 60                |                                   | 22       | (12–34)   |
|               |                       |                   | Total:                            | 412      |           |
|               |                       |                   | Random-effects model              |          |           |
|               |                       |                   | Heterogeneity: $P < .01$           |          |           |
improved remission rates versus the overall patient population. These results further strengthen evidence that vedolizumab demonstrates greater effectiveness in anti-TNF-α-naive patients. Post hoc analyses of GEMINI data indicated greater 12-month remission rates in anti-TNF-α-naive patients versus anti-TNF-α therapy failures (GEMINI 2 [CD] 49 versus 28%) [112] or versus anti-TNF-α-experienced patients (GEMINI 1 [UC] 47 versus 36%) [113]. Several real-world studies have demonstrated better outcomes with vedolizumab in anti-TNF-α-naive versus anti-TNF-α-experienced patients [24, 36, 38, 46, 114–116]. The results from the current study are consistent with these findings.

In the current study in both UC and CD, Swedish cohorts had higher clinical remission rates, whereas cohorts in Germany and Spain had lower remission rates. The differences in remission rates based on geography need to be interpreted with caution, however, because of the small number of studies in this analysis. Several characteristics of IBD patients, including epidemiology, phenotype, and genotype, are known to vary with geography [117]. Geographic differences in study population baseline characteristics [e.g., disease severity at vedolizumab initiation, disease duration, prior anti-TNF-α use (and number of prior therapies)], national treatment guidelines, and IBD management patterns may also account for variations in remission rates across geographic locations in our study. This is an area worthy of further investigation, but is beyond the current analysis.

Five publications included in the current review reported on hospitalization rates both pre-vedolizumab (6–12 months before initiation) and post-vedolizumab (6 months after initiation); 4 studies [63, 100, 101, 110] reported a reduction in post-treatment hospitalization rates, whereas 1 study [99] reported no change in hospitalization rates. Furthermore, a recent study in biologic-naive patients (published after the prespecified date range for this review) reported lower rates of IBD-related surgery and hospitalizations at 6 and 12 months after the first infusion of vedolizumab compared with infliximab [62]. Additional studies on the long-term effects of vedolizumab treatment on hospitalization rates are warranted.

Mucosal healing is an important IBD therapy goal associated with sustained clinical remission, CS-free clinical remission, and reduced hospitalization and surgery rates [118, 119]. Recent “treat-to-target” draft clinical guidelines state that only patients with mucosal healing (absence of macroscopic signs of active inflammation) and no/very mild signs or symptoms should be considered as remitted [120]. Among larger studies (sample size ≥ 100) in our systematic review, more than half of patients with UC or CD achieved mucosal healing at 12 months; results for UC were better than reported in GEMINI 1 [5]. Although data were limited to 12 studies, the observed rates of mucosal healing over 12 months were greater than the combined rates of clinical remission, supporting previous reports of a lack of clear correlation between clinical symptom measures and bowel damage assessed by endoscopy/colonoscopy or diagnostic imaging modalities [121, 122]. Interim results from the LOVE-CD trial demonstrated that, of 74 patients who underwent endoscopy, endoscopic remission (defined as Simple Endoscopic Score for CD ≤ 3) was observed in 30% of patients at week 26 [123]. Patients with endoscopic response were shown to have higher median vedolizumab concentrations compared with endoscopic nonresponders [123]. Results from the phase 3b, open-label, VERSIFY study (NCT02425111) will provide additional insights into rates of mucosal healing in CD patients receiving vedolizumab (manuscript in progress) [124].

Dose escalation is used to address secondary loss of response to biologics in the clinical management of IBD [125]. The studies included here (n = 8) [23, 33, 37, 41, 46, 57, 75, 108] reported that 4–60% of patients required dose escalation up to week 54, with lower rates reported in biologic-naive patients (n = 2; range 0–20%). However, the highest rates of dose escalation (47–60%) were observed in more complex, treatment-refractory UC and CD patients who were included as part of a compassionate-use program [23] and thus are unlikely to be representative of the general IBD population receiving biologics. In 2 studies, dose-escalation rates were lower with vedolizumab than with anti-TNF-α agents [57, 75]. Of the few studies reporting dose-escalation outcomes (N = 4), at least one-third of patients were able to recapture response [33, 37, 46, 108].

A meta-analysis of 9 studies comprising 1565 adult patients with UC or CD was recently published by Engel and colleagues [126]. Investigation of rates of clinical remission, clinical response, CS-free clinical remission, and safety demonstrated that vedolizumab is efficacious in UC and CD and has a favorable safety profile. Our study results corroborate their findings. The overall AE rate
**Week 6 CS-free remission rate (%)**

| Study                  | Patients in remission | Patients assessed | Week 6 CS-free remission rate (%) | Rate (%) | 95% CI  |
|------------------------|-----------------------|-------------------|-----------------------------------|----------|---------|
| Amiot et al.           | 33                    | 173               |                                   | 19       | (14–26) |
| Baumgart et al.        | 11                    | 97                |                                   | 11       | (6–19)  |
| Dulai et al.           | 10                    | 117               |                                   | 9        | (4–15)  |
|                        |                       |                   |                                   | 387      |         |
| **Random-effects model** |                       |                   |                                   | 13       | (8–21)  |
| **Heterogeneity:** P = .03 |                       |                   |                                   |          |         |

**Week 14 CS-free remission rate (%)**

| Study                  | Patients in remission | Patients assessed | Week 14 CS-free remission rate (%) | Rate (%) | 95% CI  |
|------------------------|-----------------------|-------------------|-----------------------------------|----------|---------|
| Amiot et al.           | 53                    | 173               |                                   | 31       | (24–38) |
| Baumgart et al.        | 19                    | 97                |                                   | 20       | (12–29) |
| Kopylov et al.         | 38                    | 130               |                                   | 29       | (22–38) |
| Samaan et al.          | 5                     | 19                |                                   | 26       | (9–51)  |
| Shelton et al.         | 16                    | 85                |                                   | 19       | (11–29) |
|                        |                       |                   |                                   | 504      |         |
| **Random-effects model** |                       |                   |                                   | 25       | (20–31) |
| **Heterogeneity:** P = .14 |                       |                   |                                   |          |         |

**Month 6 CS-free remission rate (%)**

| Study                  | Patients in remission | Patients assessed | Month 6 CS-free remission rate (%) | Rate (%) | 95% CI  |
|------------------------|-----------------------|-------------------|-----------------------------------|----------|---------|
| Amiot et al.           | 48                    | 173               |                                   | 28       | (21–35) |
| Dulai et al.           | 21                    | 117               |                                   | 18       | (11–26) |
| Samaan et al.*         | 4                     | 10                |                                   | 40       | (12–74) |
| Stallmach et al.       | 9                     | 67                |                                   | 13       | (6–24)  |
|                        |                       |                   |                                   | 367      |         |
| **Random-effects model** |                       |                   |                                   | 22       | (15–32) |
| **Heterogeneity:** P = .03 |                       |                   |                                   |          |         |

**Month 12 CS-free remission rate (%)**

| Study                  | Patients in remission | Patients assessed | Month 12 CS-free remission rate (%) | Rate (%) | 95% CI  |
|------------------------|-----------------------|-------------------|-----------------------------------|----------|---------|
| Amiot et al.           | 47                    | 173               |                                   | 27       | (21–34) |
| Dulai et al.           | 40                    | 117               |                                   | 34       | (26–44) |
| Eriksson et al.        | 37                    | 68                |                                   | 54       | (42–67) |
| Samaan et al.*         | 3                     | 10                |                                   | 30       | (7–65)  |
| Stallmach et al.       | 10                    | 67                |                                   | 15       | (7–26)  |
|                        |                       |                   |                                   | 435      |         |
| **Random-effects model** |                       |                   |                                   | 31       | (20–45) |
| **Heterogeneity:** P = .05 |                       |                   |                                   |          |         |
Fig. 4 Meta-analysis of CS-free clinical remission rates among patients with Crohn’s disease receiving vedolizumab at the time points: a week 6; b week 14; c 6 months; and d 12 months. The size of each square represents the weight given to each study based on sample size. Error bars represent 95% CIs. Diamonds represent the point estimate of the averaged study rates; the lateral tips of the squares represent 95% CIs. CI confidence interval. Christensen et al. [23], Chaudrey et al. [24], Dulai et al. [46], Kopylov et al. [86], Samaan et al. [36], Shelton et al. [13], Dulai et al. [46], Samaan et al. [36], Samaan et al. a, Stallmach et al. [38], Eriksson et al. [29]. *Unpublished clinical data provided courtesy of Dr. Mark A. Samaan and Dr. Peter Irving from their UK study, 2016.

Fig. 5 Mucosal healing rates among patients with ulcerative colitis (a) or Crohn’s disease (b) receiving vedolizumab. Square size represents the weight given to each study, based on sample size. Error bars represent 95% CIs. CI confidence interval. Christensen et al. [69], Chaudrey et al. [26], Schmidt et al. [103], Gils et al. (a) [47], Gils et al. (b) [77], Pauwels et al. [34], Vivio et al. [40], Peerani et al. [35], Kochhar et al. [83], Dulai et al. (a) [28], Amiot et al. [23], Dulai et al. (b) [46]. *Median time point. *Only patients with ≥ 1 follow-up assessment at the specified time point were included in the analyses. Data from the VICTORY Consortium, which contributed the majority of mucosal healing data, used a cumulative incidence analysis, and remaining studies employed a “complete” case approach.
additional subgroup analyses by geographic location and in patients with no prior therapy with biologics. The current analysis also reports outcomes not assessed by Engel and colleagues, including hospitalization, surgical rates post-Vedolizumab initiation, dose-escalation rates, and subsequent outcomes.

Vedolizumab is a gut-selective integrin antagonist with no identified systemic immunosuppressive activity.
Real-world safety data reported here are consistent with those from the GEMINI trials, with no new or unexpected safety signals [128]. This tolerability profile may help to improve treatment persistence [115, 116], thereby potentially positively affecting long-term outcomes. Postoperative complication rates in the current analysis ranged from 13 to 65% [89, 102, 131–133]. A recent meta-analysis assessing the impact of preoperative vedolizumab treatment on the rate of postoperative complications in real-world patients with IBD demonstrated no increased risk of postoperative infectious or total overall postoperative complications compared with either preoperative anti-TNF-α therapy or no biologic therapy [134].

In addition to the limitations of real-world studies, the limitations of this meta-analysis include potential publication bias. Egger's weighted regression statistic was calculated for only 1 analysis (CD at week 14) and in this case the P value suggested that bias was unlikely. The remaining analyses did not include enough studies (≥10) to allow an assessment of publication bias [52]. However, the inclusion of studies published as abstracts as in the current analysis may help minimize the risk of publication bias. A moderate to high degree of between-study statistical heterogeneity was detected in some analyses. Major contributory factors to this heterogeneity may include the different disease activity measures and variable thresholds used to assess clinical response and remission, which may impact the extrapolation of these findings to clinical practice. Nevertheless, the current meta-analysis attempted to address bias by combining study data using a weighted average based on sample size. Moreover, the consistency of evidence levels (i.e., most studies were level 4) did not allow for sensitivity analysis to be conducted by study quality. Finally, real-world data may be less stringent than RCT data, which are obtained by rigorous data collection and quality control of data integrity. However, real-world data provide greater insight into the effectiveness of vedolizumab in heterogenous and more complex patient populations that are more representative of clinical practice.

Conclusions

The results from this meta-analysis of real-world data confirm the effectiveness of vedolizumab in inducing long-term clinical response, clinical remission, CS-free clinical remission, and mucosal healing in patients with moderate-to-severely active UC or CD. The safety data presented here support the positive long-term benefit–risk profile of vedolizumab in the treatment of IBD.

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Compliance with ethical standards

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References

1. Gomollón F, Dignass A, Annes V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn’s disease 2016: part 1: diagnosis and medical management. J Crohns Colitis. 2017;11(1):3–25.
2. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. J Crohns Colitis. 2017;11(7):769–84.
3. Soler D, Chapman T, Yang LL, et al. The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7
integrin therapeutic antibody in development for inflammatory bowel diseases. J Pharmcol Exp Ther. 2009;330(3):864–75.
4. Wyant T, Fedyk E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab. J Crohns Colitis. 2016;10(12):1437–44.
5. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699–710.
6. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn’s disease. N Engl J Med. 2013;369(8):711–21.
7. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn’s disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147(3):618–27.
8. ENTYVIO® [Summary of Product Characteristics]. Taastrup, Denmark: Takeda Pharma A/S; 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002782/WC500168528.pdf. Accessed 20 September 2017.
9. ENTYVIO® [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America Inc; 2018. https://general.takeda.pharm.com/ENTYVIOPI. Accessed 14 May 2018.
10. Dassopoulos T, Cohen R, Schert E, et al. Identification, assessment and initial medical treatment of ulcerative colitis. Clinical Care Pathway. 2015. http://campaigns.gastro.org/algorithm/UlcerativeColitis/pdf/Ulcerative_Colitis_Care_Pathway.pdf. Accessed 14 May 2018.
11. Ha C, Ullman TA, Siegel CA, et al. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. Clin Gastroenterol Hepatol. 2012;10(9):1002–7.
12. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence — what is it and what can it tell us? N Engl J Med. 2016;375(23):2293–7.
13. Shelton E, Allegretti JR, Stevens B, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients: a multicenter cohort. Inflamm Bowel Dis. 2015;21(12):2879–85.
14. Green S. Systematic reviews and meta-analysis. Singapore Med J. 2005;46(6):270–3 (quiz 274).
15. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence. http://www.cebm.net/wp-content/uploads/2017/03/OCEBM-Levels-of-Evidence-2.1.pdf. Accessed 15 March 2017.
16. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn’s disease: TREAT™ registry. Clin Gastroenterol Hepatol. 2006;4(5):621–30.
17. D’Haens G, Reinisch W, Colombel JF, et al. Five-year safety data from ENCORE, a Europeanobservational safetysafetyregistry for adults with Crohn’s disease treated with infliximab(Remicade®) or conventional therapy. J Crohns Colitis. 2017;11(6):680–9.
18. Chaudrey K, Whitehead D, Dulai PS, et al. Safety of vedolizumab in inflammatory bowel disease in a multi-center real world consortium. Gastroenterology. 2016;150(4 suppl 1):S974.
19. Mendoza Ladd AH, Scott FI, Grace R, et al. Tuti1918. Safety of vedolizumab in inflammatory bowel disease patients: real world experience from a large university practice. Gastroenterology. 2016;150(4 suppl 1):S977.
20. Stringfield S, Parry L, Sandborn W, et al. Patients on vedolizumab have a high rate of postoperative complications. Dis Colon Rectum. 2016;59(5):e96.
21. Bhayat F, England D, Blake A. P1187. Post-marketing safety experience with vedolizumab: skin reactions (psoriasiform and eczematous). Presented at: American College of Gastroenterology; October 14–19, 2016; Las Vegas, NV.
22. Bhayat F, Blake A, Travis S, P668. Post-marketing experience of vedolizumab in inflammatory bowel disease: analysis of pneumonia and other respiratory tract infections. J Crohns Colitis. 2017;11(suppl 1):s421–22.
23. Amiot A, Serrero M, Peyrin-Biroulet L, et al. One-year effectiveness and safety of vedolizumab therapy for inflammatory bowel disease: a prospective multicentre cohort study. Aliment Pharmacol Ther. 2017;46(3):310–21.
24. Baumgart DC, Bokemeyer B, Drabik A, et al. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice—a nationwide consecutive German cohort study. Aliment Pharmacol Ther. 2016;43(10):1090–102.
25. Chaparro M, Sierra-Ausín M, Mesonero F, et al. Effectiveness and safety of vedolizumab for the induction of remission in inflammatory bowel disease. J Crohns Colitis. 2016;10(suppl 1):S416–7.
26. Chaudrey K, Lightner A, Singh S, et al. Efficacy and safety of vedolizumab for inflammatory bowel disease in clinical practice. Inflamm Bowel Dis. 2016;22(suppl 1):S19–20.
27. Christensen B, Goeppinger SR, Colman RJ, et al. Vedolizumab in the treatment of IBD: the University of Chicago experience. Gastroenterology. 2015;148(4 suppl 1):S866.
28. Dulai P, Meserve J, Hartke J, et al. DOP023. Predictors of clinical and endoscopic response with vedolizumab for the treatment of moderately-severely active ulcerative colitis: results from the US VICTORY consortium. J Crohns Colitis. 2017;11(suppl 1):S392–3.
29. Eriksson C, Rundquist S, Lykiardopoulos B, et al. P364. A Swedish observational study (SVEAH) on vedolizumab assessing effectiveness and healthcare resource utilization in patients with inflammatory bowel disease. J Crohns Colitis. 2017;11(suppl 1):S262–3.
30. Höög C, Eberhardsson M, Almer S. P419. Efficacy of vedolizumab in patients with inflammatory bowel disease and failure of anti-TNF-antibodies. Presented at: European Crohn’s and Colitis Organisation Congress. March 16–19, 2016; Amsterdam, The Netherlands.
31. Kopylov U, Ron Y, Avni-Biron I, et al. Efficacy and safety of vedolizumab for induction of remission in inflammatory bowel disease—the Israeli real-world experience. Inflamm Bowel Dis. 2017;11(suppl 1):S40–1.
32. Lenti MV, Levison S, Eliadou E, et al. P525. Effectiveness and safety of vedolizumab in IBD patients: a multicentre experience of “real world data” from the UK. J Crohns Colitis. 2017;11(suppl 1):S347.
33. Mankongpaisarnrung C, Mattar M, Charabaty A. Single-center experience: vedolizumab in patients with Crohn’s disease and ulcerative colitis at Georgetown University Hospital. Inflamm Bowel Dis. 2016;22(suppl 1):S32.
34. Pauwels RWM, De Vries AC, Van der Woude CJ. P447. Vedolizumab induces significantly higher endoscopic remission rates at week 16 in ulcerative colitis as compared to Crohn’s disease. J Crohns Colitis. 2017;11(suppl 1):S305.
35. Peerani F, Narula N, Dulai PS, et al. Efficacy and predictors of outcomes of vedolizumab for ulcerative colitis in clinical practice. Gastroenterology. 2016;150(4 suppl 1):S392–3.
36. Samaan MA, Pavlidis P, Johnston E, et al. Vedolizumab: early experience and medium-term outcomes from two UK tertiary IBD centres. Frontline Gastroenterol. 2017;8(3):196–202.
37. Shivashankar R, Mendoza Ladd AH, Grace R, et al. Effect of vedolizumab dose escalation on recapturing response in patients with inflammatory bowel disease. Gastroenterology. 2017;152(5 suppl 1):S77.
71. Crowell KT, Tinsley A, Williams ED, et al. PD7. Vedolizumab as rescue therapy in Crohn’s Disease: results from a tertiary care center. Presented at: Annual Scientific Meeting of the American Society of Colon and Rectal Surgeons; April 30–May 4, 2016; Los Angeles, CA.

72. Drvarov O, AbuHashem R, Schunk N, et al. Skin and joint side effects in a subpopulation of anti-TNF experienced IBD patients, who respond to a treatment with vedolizumab, a humanized a4b7 integrin antibody. Gastroenterology. 2015;148(4 suppl 1):S865.

73. Dulai PS, Singh S, Narula N, et al. Vedolizumab for moderate to severely active inflammatory bowel disease: a multi-center U.S. consortium. Am J Gastroenterol. 2015;110(suppl 1):S809–10.

74. Eksteen B, Heatherington J, Oshiomogho JL, et al. Efficacy and safety of induction dosing of vedolizumab for reducing biliary inflammation in primary sclerosing cholangitis (PSC) in individuals with inflammatory bowel disease. Gastroenterology. 2016;150(4 suppl 1):S1268.

75. Ehehalt R, Schubert S, Stein D, et al. Treatment patterns of vedolizumab and anti-TNF-α use among patients with UC and CD in Germany: a multicenter retrospective chart review. Presented at: Advances in Inflammatory Bowel Diseases (AIBD) Annual Conference. December 8–10, 2016; Orlando, FL.

76. Gabriëls RY, de Graaf APJ, Meijssen MAC, et al. In a Dutch real-life inflammatory bowel disease score cohort with 90% prior anti-tumour necrosis factor failure, vedolizumab showed a 25% remission rate: a retrospective multicentre study. J Crohns Colitis. 2016;10(suppl 1):S416.

77. Gils A, Dreesen E, Compernolle G, et al. OP020. Recent anti-TNF exposure predicts lower vedolizumab trough concentrations in patients with Crohn’s disease. J Crohns Colitis. 2017;11(suppl 1):S12.

78. Grace R, Bownik H, Scott F, et al. Infectious complications in IBD patients on immunomodulators, corticosteroids, and vedolizumab: is older age a predictor of higher complication rates or worsened response? Am J Gastroenterol. 2015;110(suppl 1):S823.

79. Gudsoorkar V, Chaikriangkrai K, Abraham B. Vitamin D deficiency is associated with persistent CRP elevation and a lower clinical response to vedolizumab treatment in Crohn’s disease patients. Am J Gastroenterol. 2015;110(suppl 1):S844–5.

80. Kaimakliotis P, Lazarev M, Bayless T, et al. Side effects related to vedolizumab use in inflammatory bowel disease—The Leeds experience. J Crohns Colitis. 2017;11(suppl 1):S192–3.

81. Kopylov U, Sebastian S, Ron Y, et al. P366. The efficacy of vedolizumab for induction of clinical response and remission in anti-TNF naïve patients with inflammatory bowel disease—a multicenter European real world experience. J Crohns Colitis. 2017;11(suppl 1):S264–5.

82. Lenti MV, Johnston A, O’Connor A, et al. P227. Outcomes of anti-TNF versus vedolizumab therapy for ulcerative colitis: the Leeds experience. J Crohns Colitis. 2017;11(suppl 1):S192–3.

83. Lightner AL, Raffals LE, Mathis KL, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. J Crohns Colitis. 2017;11(2):185–90.

84. Lucci MB, Collins E, Cao B, et al. Sa1198. Initial vedolizumab cohort: patient characteristics and clinical response. Gastroenterology. 2015;148(4 suppl 1):S255.

85. Menon S, Makanyanga J, Mitchell T, et al. Results of vedolizumab use in the ‘real world.’ Presented at: Australian Gastroenterology Week. 10–12 October 2016; Adelaide, South Australia.

86. Morganstern B, Singh N, Targan S, et al. Single-center experience of vedolizumab in patients with inflammatory bowel disease: does age matter? Gastroenterology. 2015;148(4 suppl 1):S250.

87. Navaneethan U, Edminster T, Zhu X, et al. Vedolizumab is safe and effective in elderly patients with inflammatory bowel disease. Inflamm Bowel Dis. 2017;23(4):E17.

88. Plevris N, Manship TA, Deekae A, et al. P416. Real world data on the effectiveness and safety of vedolizumab in the treatment of Crohn’s disease and ulcerative colitis: the Edinburgh experience. J Crohns Colitis. 2017;11(suppl 1):S288–9.

89. Raluy-Callado M, Alam N, Wang R, et al. Hospitalisations and rehospitalisations among inflammatory bowel diseases patients treated with vedolizumab. Gastroenterology. 2015;148(4 suppl 1):S872.

90. Papamichail K, Rivals O, Billiet T, et al. Long-term outcome of IBD patients with primary non-response to anti-TNF therapy. J Crohns Colitis. 2015;9(suppl 1):S58–9.

91. Patel RJ, Grimes I. Vedolizumab in inflammatory bowel disease: a retrospective review of clinical efficacy, extra-intestinal manifestations and adverse reactions. Am J Gastroenterol. 2016;111(suppl 1):S317–8.

92. Plevris N, Manship TA, Deckae A, et al. P416. Real world data on the effectiveness and safety of vedolizumab in the treatment of Crohn’s disease and ulcerative colitis: the Edinburgh experience. J Crohns Colitis. 2017;11(suppl 1):S288–9.

93. Rahlay-Calleado M, Alam N, Donaldson R, et al. A real-world study of outcomes in biologic-naïve patients with Crohn’s disease and ulcerative colitis initiating vedolizumab. J Crohns Colitis. 2016;10(suppl 1):S238.

94. Rahlay-Calleado M, Alam N, Wang R, et al. Hospitalisations and treatment discontinuation among patients with ulcerative colitis and Crohn’s disease treated with vedolizumab compared with infliximab. United Eur Gastroenterol J. 2016;4(5 suppl):A634.

95. Reynolds M, Raluy-Callado M, O’Hara D, et al. P-025. Hospitalisations and Crohn’s disease—the Israeli experience. United European Gastroenterol J. 2016;4(5 suppl):A449–50.

96. Raluy-Callado M, Alam N, O’Hara D, et al. P-025. Vedolizumab use among patients with UC and Crohn’s disease treated with vedolizumab compared with infliximab. United Eur Gastroenterol J. 2016;4(5 suppl):A449–50.
patients: results from a prospective German observational study. J Crohns Colitis. 2017;11(suppl 1):S242–3.

104. Shivashankar R, Mendoza Ladd AH, Grace R, et al. Safety of vedolizumab use in patients with inflammatory bowel disease. Gastroenterology. 2017;152(5 suppl 1):S585.

105. Stevens BW, Shelton E, Sauk J, et al. Efficacy of vedolizumab as induction therapy in refractory IBD patients following multiple anti-TNF therapy failures. Gastroenterology. 2015;148(4 suppl 1):S609.

106. Tadbiri S, Grimaud JC, Peyrin-Biroulet L, et al. DOP025. Efficacy of vedolizumab on extraintestinal manifestation in patients with inflammatory bowel disease: a post hoc analysis of the OBSERV-IBD cohort from the GETAID. J Crohns Colitis. 2017;11(suppl 1):S42.

107. Trefois Q, Descamps O, Coche JC, et al. Efficacy of vedolizumab as induction therapy for inflammatory bowel disease in a ‘real-life’ study. Acta Clinica Belgica. 2016;71(suppl 1):S7 (Abstract 0005).

108. Wice M, Oppenheim S, Miller H, et al. Efficacy and safety of vedolizumab in patients with inflammatory bowel disease in a large tertiary medical center. Am J Gastroenterol. 2016;111(suppl 1):S270.

109. Ylisaukko-oja T, Eberl A, Aaltoren J, et al. P515. Evaluation of treatment persistence of vedolizumab among Finnish inflammatory bowel disease patients in real-life clinical practice (FINVEDO). J Crohns Colitis. 2017;11(suppl 1):S342.

110. Reynolds M, Alam N, Raluy M, et al. Hospitalisations and characteristics of patients with ulcerative colitis and Crohn’s disease treated with vedolizumab in real-world clinical practice: results from a multicentre study. J Crohns Colitis. 2016;10(suppl 1):S214.

111. Manz M, Vavricka SR, Wanner R, et al. Therapy of steroid-resistant inflammatory bowel disease. Digestion. 2012;86(suppl 1):11–5.

112. Sands BE, Sandborn WJ, Van Assche G, et al. Vedolizumab as induction and maintenance therapy for Crohn’s disease in patients naïve to or who have failed tumor necrosis factor antagonist therapy. Inflamm Bowel Dis. 2017;23(1):97–106.

113. Feagan BG, Rubin DT, Danese S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. Clin Gastroenterol Hepatol. 2017;15(2):229–39.e5.

114. Kane SV, Brixner D, Rubin DT, et al. The challenge of compliance and persistence: focus on ulcerative colitis. J Manag Care Pharm. 2008;14(1 suppl A):S2–12.

115. Cummings F, Gay S, Irving P, et al. A retrospective United Kingdom chart review of early vedolizumab experience: real-world treatment, effectiveness and safety in inflammatory bowel disease (REVIVE). Inflamm Bowel Dis. 2017;23(suppl 1):S25–6.

116. Raluy-Callado M, Fraeman K, Donaldson R, et al. Real-world treatment persistence with vedolizumab in Crohn’s disease and ulcerative colitis patients. J Crohns Colitis. 2016;10(suppl 1):S173–4.

117. Ng SC, Bernstein CN, Vatn MH, et al. Geographical variability and environmental risk factors in inflammatory bowel disease. Gut. 2013;62(4):630–49.

118. Pineton de Chambrun G, Blanc P, Peyrin-Biroulet L. Current evidence supporting mucosal healing and deep remission as important treatment goals for inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2016;10(8):915–27.

119. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141(4):1194–201.

120. European Medicines Agency. Draft guideline on the development of new medicinal products for the treatment of Crohn’s disease. 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003265.pdf. Accessed 17 Feb 2017.

121. Peyrin-Biroulet L, Reinisch W, Colombel JF, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn’s disease in the SONIC trial. Gut. 2014;63(1):88–95.

122. Fiorino G, Bonifacio C, Allocca M, et al. Bowel damage as assessed by the Lémann Index is reversible on anti-TNF therapy for Crohn’s disease. J Crohns Colitis. 2015;9(8):633–9.

123. Berends S, Löwenberg M, Baert F, et al. DOP046. Higher serum concentrations of vedolizumab are associated with superior endoscopic outcomes in Crohn’s disease: data from the LOVE-CD trial. J Crohns Colitis. 2018;12(suppl 1):S063.

124. Danese S, Feagan B, Sandborn W, et al. OP023. A phase 3b open-label multicentre study (VERSIFY) of the efficacy of vedolizumab on endoscopic healing in moderately to severely active Crohn’s disease (CD) [abstract]. J Crohns Colitis. 2018;16(12 suppl 1):S016–7.

125. Dalal SR, Cohen RD. What to do when biologic agents are not working in inflammatory bowel disease patients. Gastroenterol Hepatol (N Y). 2015;11(10):657–65.

126. Engel T, Ungar B, Yung DE, et al. Vedolizumab in IBD—lessons from real-world experience; a systematic review and pooled analysis. J Crohns Colitis. 2018;12(2):245–57.

127. Parikh A, Fox I, Leach T, et al. Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2013;19(8):1691–9.

128. Vermeire S, Loftus EV Jr, Colombel JF, et al. Long-term efficacy of vedolizumab for Crohn’s disease. J Crohns Colitis. 2017;11(4):412–24.

129. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn’s disease. Gut. 2017;66(5):839–51.

130. Loftus EV Jr, Colombel JF, Feagan BG, et al. Long-term efficacy of vedolizumab for ulcerative colitis. J Crohns Colitis. 2017;11(4):400–11.

131. Ferrante M, Schils N, De Buck van Overstraeten A, et al. OP012. Perioperative use of vedolizumab is not associated with short-term postoperative infectious complications in patients with ulcerative colitis undergoing (procto)colectomy with ileal pouch-anal anastomosis. J Crohns Colitis. 2017;11(suppl 1):S7–8.

132. Shen B, Blake A, Lasch K, et al. P134. Vedolizumab use in patients with IBD undergoing surgery: a summary from clinical trials and post-marketing experience. Inflamm Bowel Dis. 2017;23(suppl 1):S47.

133. Yamada A, Komaki Y, Patel N, et al. Risk of postoperative complications among inflammatory bowel disease patients treated preoperatively with vedolizumab. Am J Gastroenterol. 2017;112(9):1423–9.

134. Law C, Narula A, Lightner A, et al. Pre-operative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease: a systematic review and meta-analysis. Presented at: 13th Congress of the European Crohn’s and Colitis Organisation (ECCO). 14–17 February 2018; Vienna, Austria. P453.