Journal of Crohn's and Colitis, 2017, 245–257
doi:10.1093/ecco-jcc/jjx143
Advance Access publication October 25, 2017
Review Article

Review Article

Vedolizumab in IBD–Lessons From Real-world Experience; A Systematic Review and Pooled Analysis

Tal Engel,[a] Bella Ungar,[a] Diana E. Yung,[b] Shomron Ben-Horin,[a] Rami Eliakim,[a] Uri Kopylov[a]

[a]Gastroenterology Institute, Sheba Medical Center Tel Hashomer, Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel [b]Centre for Liver and Digestive Disorders, Royal Infirmary of Edinburgh, Edinburgh, UK

Corresponding author: Uri Kopylov, MD, Department of Gastroenterology, Sheba Medical Center, Derech Sheba 2, Ramat-Gan, Israel, 5262100. Tel.: 972-3-530-2060; fax: 972-3-530-3160; email: ukopylov@gmail.com

Abstract

Background: Vedolizumab [VDZ] is an anti-integrin monoclonal antibody effective in ulcerative colitis [UC] and Crohn's disease [CD]. Several real-world experience [RWE] studies with VDZ have been published to date. The aim of this systematic review was to summarise the available real-life experience with VDZ.

Methods: We performed a systematic review of the available RWE studies of VDZ in CD and UC. We performed a pooled analysis of the available efficacy and safety data for induction and maintenance treatment in adult cohorts. A narrative review of VDZ use in special clinical settings was also performed.

Results: Nine studies including 1565 [571 UC, 994 CD] adult patients were identified. In CD, clinical response and remission were achieved in 54% (95% confidence interval [CI] 41–66%) and 22% [95% CI 13–35%] by Week 6 and in 49% [95% CI 37–51%] and 32% [95% CI 23–42%] by Week 14; at Week 52, 45% [95% CI 28–64%] and 32% [95% CI 12–62] of the patients responded, and were in clinical remission, respectively. In UC, clinical response and remission were achieved in 43% [95% CI 37–49] and 25% [95% CI 12–45] by Week 6, respectively, and in 51% [95% CI 43–61%]and 30% [95% CI 24–36%] by Week 14/22, respectively; at week 52, clinical response and remission were achieved in 48% and 39% of the patients, respectively. Adverse effects were mostly minor and occurred in 30.6% of the patients; infections were reported in 3.4% of the patients.

Conclusions: VDZ is efficacious in CD and UC and has a favourable safety profile in RWE studies.

Key Words: Vedolizumab; Crohn's disease; ulcerative colitis.

1. Introduction

Although medical treatment options in inflammatory bowel disease [IBD] have improved dramatically over recent decades with the introduction of anti-tumour necrosis factor [TNF] antibodies, refractory disease still poses a major challenge, with primary non- response occurring in 20–30% of Crohn's disease [CD] and up to 40% of ulcerative colitis [UC] patients.[1] A substantial number of primary responders [as high as 46%] relapse despite continued treatment or dose escalation, with quite a substantial rate of early discontinuation of anti-TNF therapy.[2,3] Vedolizumab [VDZ] is a humanised monoclonal antibody that exclusively targets the alpha 4 beta 7 integrin, characteristically expressed by gut-homing lymphocytes, and modulates gut inflammation by limiting lymphocyte recruitment from the blood to the intestinal lamina propria.

Vedolizumab [VDZ] demonstrated efficacy in Crohn's disease and ulcerative colitis in the pivotal GEMINI trials.[4–7] In the GEMINI

I study [UC], the response rate to VDZ was significantly higher than to placebo at both Weeks 6 (47.1% compared with 25.5% to placebo arm [47.1% vs 25.5%, $p < 0.001$]) and 52 (41.8% for patients continuing VDZ every 8 weeks and or 44.8% for those receiving VDZ every 4 weeks vs 15.9% for placebo [$p < 0.001$]).[8] Notably, VDZ was more effective in anti-TNF naive patients [53% vs 39% at Week 6]. In moderate to severe CD [GEMINI II], clinical remission was significantly more frequent in patients treated with VDZ at Week 6 (14.5% vs 6.8% for placebo [$p = 0.02$]) and 52 (39.0% [q8w]/36.4[q4w] vs 21.6% for placebo).[6] The Gemini III study included CD patients who previously failed anti-TNF therapy. The rates of remission at Week 6 were not significantly different from with placebo (15.2% vs 12.1% [$p = 0.4$]), although clinical superiority over placebo was detectable at Week 10 (26.6% vs 12.1% [$p = 0.001$]).[7] Long-term follow-up data from the GEMINI LTS [long-term safety] open-label extension trial are also becoming available. Among UC patients who responded to VDZ induction and had available data, 88% and 96% were in clinical remission after 104 and 152 weeks, respectively; for CD patients, 83% and 89% were in clinical remission at the same time points.[9] Safety data from all GEMINI trials demonstrated an overall rate of adverse events that was similar to that with placebo. There was no increased risk of malignancy. A Cochrane systematic review of VDZ for UC reported no significant differences between VDZ and placebo for any adverse event or serious adverse event. Serious clostridial infections, sepsis and tuberculosis were reported infrequently [≤ 0.6% of patients], with upper respiratory tract infections accounting for more than half of the total infections reported.[10]

Despite the abundance of randomized controlled trial [RCT]-originated data, multiple knowledge gaps still remain. Primarily, all RCTs have stringent inclusion criteria and tend to exclude certain groups of patients such as patients with isolated small bowel disease inaccessible to ileocolonoscopy, patients with multiple comorbidities, and other special populations such as pregnant women, those with organ transplant, and paediatric and elderly patients.[11,12] A substantial proportion of the patients treated with biologics could not have been included in a clinical trial due to these limitations. In addition, multiple secondary outcomes such as postoperative recurrence, healing of perianal fistula and response of extra-intestinal manifestations frequently remain beyond the scope of major RCTs. Real-world experience series may shed light on those and additional issues, including previously undetected safety signals [primarily infections and malignancies]. To date, several real-world data series have been published demonstrating efficacy and safety comparable to those reported in the randomised controlled trials. In addition, several case reports and case series addressing specific clinical conditions and subpopulations are available..[4,13–26] The aim of our review was to summarise the currently available knowledge and to perform a pooled analysis of the efficacy and safety of VDZ in IBD patients, as reported by the real- world studies.

2. Methods

A structured search of the Pubmed and Embase database was performed to identify all studies that describe real-world experience with VDZ. For the purposes of the pooled analysis of efficacy and safety, only reports published in complete form in peer-reviewed literature were included. We extracted the baseline characteristics, efficacy, and safety data from the manuscripts. We addressed induction data as results at Weeks 6 and 12/14/22, depending on the study definition. Efficacy data for week 52/54 were defined as maintenance results.

For several topics covered in a narrative form, key conference abstracts presented at the European Crohn's and Colitis Organisation [ECCO], Digestive Disease Week [DDW], United European Gastroenterology Week [UEGW], and American College of Gastroenterology [ACG] congresses were included.

2.1. Statistical methods

The outcome measures were calculated as pooled proportions of patients [with 95% confidence intervals] responding VDZ treatment at various points in time, and the pooled proportions of patients with complications of interest. The fixed effects [Mantel-Haenszel] and random effects [DerSimonian-Laird] models were used for pooling, depending on heterogeneity. Heterogeneity was determined using the Q statistic of I^2 which describes the percentage of total variation across studies attributable to heterogeneity rather than chance. An I^2 value greater than 50% was taken to represent significant statistical heterogeneity, in which case the random effects model was applied; if studies were relatively homogeneous, the fixed effects model was used.[27] A minimum of three studies were required for each analysis. Statistical analyses were carried out using the 'meta' and 'metafor' packages[28] in R statistical software version 3.3.1 [R Foundation for Statistical Computing, Vienna, Austria].

Significant statistical heterogeneity was assessed by examining the forest plots for obvious outliers and by conducting subgroup analyses, chiefly differentiating patients with CD from those with UC. Although outlier studies could not always be eliminated due to the small numbers of studies in some subgroup analyses, this would be representative of 'real-world' experience where responses may vary widely across centres and patient groups. When quantitative analysis was impossible due to a small number of patients, we performed a systematic narrative review of the available data for special conditions and populations [postoperative, pregnant, and elderly patients, paediatric patients].

3. Results

Through the literature search, 297 publications were obtained. Nine adult (1565 [571 UC, 994 CD] patients)[13–19,26,29] and two pediatric studies (73 [27 UC, 46 CD patients])[20,30] were identified [Figure 1]. An additional study was excluded from the pooled analysis, which described the efficacy of VDZ at Week 54 including only Week 14 responders.[31] Only adult studies were included in the pooled analysis, as the number of paediatric studies was too small.

3.1. Clinical characteristics of patients included in RWE studies

Of the CD population 37%, and of the UC/inflammatory bowel disease unclassified [IBD-U] 48%, were male. Among the pooled cohort, 667 [40.6%] patients were on concomitant systemic steroids and 975 [59.5%] were on concomitant immunomodulators at the beginning of VDZ course. Additional details on the patients enrolled in the included studies appear in Table 1.

3.2. Clinical response and remission assessment

The definitions of clinical remission and response differed between the adult studies. Some authors used established clinical scores, and others used physician's global assessment [PGA] or a combination of both [Table 1].[4,13–19,31,32]

3.3. CD: efficacy

Figures 2 and 3 summarise results.

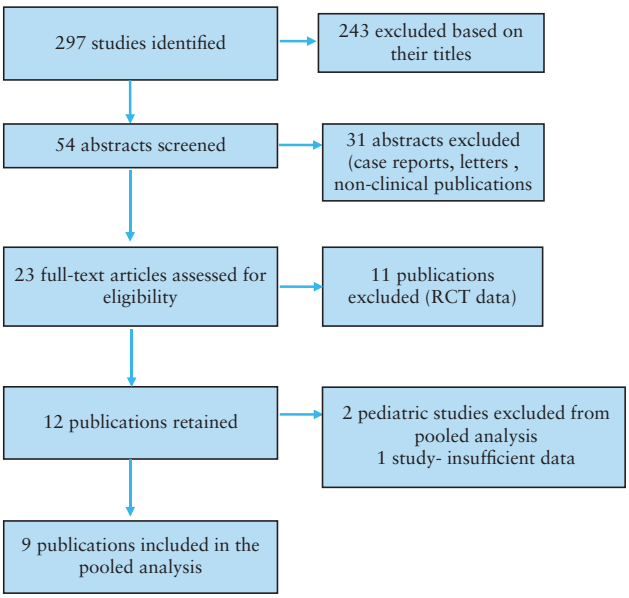

Figure 1. Inclusion of the studies for pooled analysis of vedolizumab efficacy and safety. RCT, randomised controlled trial.

3.3.1. Induction

Data for clinical response and remission at Week 6 for CD patients were available from five studies enrolling a total of 552 CD patients.[14–16,18,29]Clinical response and remission were achieved in 54% (95% confidence interval [CI] 41–66%; I^2 = 78.2%) and 22% of CD [95% CI 13–35%; I^2 = 86.8%] patients, respectively. Clinical response and remission at Week 14 were reported by five studies[13–16,26] enrolling 621 CD patients. Clinical response and remission were achieved in 49% [95% CI 37–51%; I^2 = 89.1%] and 32% [95% CI 23–42%; I^2 = 78.5%] patients, respectively. Steroid-free remission by Week 14 was assessed in five studies[13–16,26] that included 621 patients, and were achieved in 29% [95% CI 25–32%; I^2 = 93.2%] of them.

3.3.2. Maintenance

Clinical response and remission at week 52 were available from three studies enrolling a total of 347 CD patients.[18,19,32] Clinical response and remission were achieved in 45% [95% CI 28–64%; I^2 = 90%] and 32% [95% CI 12–62%; I^2 = 95.1%] of patients, respectively.

3.4. UC: efficacy

Figures 3 and 4 summarise results.

3.4.1. Induction

Data for clinical response and remission at Week 6 for UC patients were available from four studies enrolling a total of 288 UC/IBD-U patients.[14–16,29] Clinical response was achieved in 43% [95% CI 37–49%; I^2 = 0%], and clinical remission was achieved in 25% [95% CI 12–45%; I^2 = 87.2%] of the patients. Data for clinical response at Week 14, 12, or 22 were available from five studies including a total of 432 patients.[13–16,29] Clinical response and remission were achieved in 51% [95% CI 43–61%; I^2 = 61.7%] and 30% [95% CI 24–36%; I^2 = 44.5%] of the patients, respectively. Steroid-free remission by Week 14 was assessed in five studies[13–16,26] including 454 patients, and was achieved in 25% [95% CI 19–32%; I^2 = 59.1%].

3.4.2. Maintenance

Data for clinical response and remission at Week 52 or 54 were available from two real-world studies enrolling a total of 99 patients.[19,26] Clinical response and remission were achieved in 48% and 39% of the patients, respectively [CI was not calculated due to the low number of studies].[19,32]

3.5. Discontinuation of treatment

Rate of discontinuation was assessed in two studies. Eriksson *et al.* reported that 42% of patients discontinued VDZ after median follow-up of 17 months. Main reasons for discontinuation were lack or loss of response, and intolerance.[32] Allegretti *et al.* reported VDZ discontinuation by Week 54 in 39% of initial responders [28% due to flare; 11% due to adverse events].[31]

3.6. Clinical efficacy in anti-TNF naive patients

The percentage of anti-TNF naıve patients was very small [138/8.5%]. Two studies evaluated the effect in anti-TNF naıve patients.[15,19] Baumgart *et al.* reported that VDZ was significantly more effective for the induction of clinical remission in inflammatory bowel diseases at Week 14 in biologic-naive patients. More anti-TNF naıve CD [60%] and UC [39.3%] patients achieved clinical remission compared with anti-TNF exposed CD [21.7%] and UC [18.5%] patients.[15] Stallmach *et al.* reported on the maintenance results in the same patient cohort; in UC, clinical remission at Week 54 was significantly more frequent in anti-TNF naive patients (6/11, 55% vs 9/49, 18% in anti-TNF experienced patients [p = 0.02]). For CD, only six patients were anti-TNF naive; 2/6 [33%] achieved clinical remission at Week 54 as compared with 12/61 [19.7%] in anti-TNF experienced patients.[19]

3.7. Endoscopic response and mucosal healing

Two studies reported endoscopic response and mucosal healing to VDZ, enrolling together 148 CD patients and 29 UC patients.[17,18] Mucosal healing for CD was defined as absence of mucosal ulcerations or erosions in both studies. Mucosal disease activity in UC was determined using the endoscopic Mayo score.[33] Dulai *et al.* reported cumulative rates of mucosal healing of 21% and 67% after 6 and 12 months of therapy, respectively.[18] Vivio *et al.* reported mucosal healing in 30% and 69% in CD and UC, respectively, by 52 weeks.[17]

3.8. Biomarker response during vedolizumab treatment

Decrease in C-reactive protein [CRP] levels in patients achieving clinical remission with VDZ treatment was reported by most studies; however the change was frequently not statistically significant.[15,16,32,34] Steady decline and improvement of faecal calprotectin in responders was demonstrated in all studies reporting calprotectin values for both CD and UC.[15,19,32]

3.9. Predictors of clinical response

Eight studies assessed predictors of initial response to VDZ.[14–16,18,19,29,31,32] Smoking history, perianal disease, and previous anti-TNF exposure were associated with a lower likelihood of achieving remission.[18,19] Higher baseline disease severity and high CRP levels at treatment onset were associated with a lower likelihood of remission later in several studies.[13,15,16,19,31] Allegretti *et al.*[31] aimed to identify specific clinical predictors of long-term [Week 54] clinical response to VDZ in patients with initial response; in CD, concomitant immunomodulator treatment (odds ratio [OR] 8.33, 95% CI 2.15–32.26) was significantly associated with long-term

Table 1. Characteristics of the real world evidence studies of vedolizumab in IBD. PGA-physician's general assessment

Author	Year	Country of origin	Data collection	Single/ multicenter	Assessment of response	UC [n]	CD [n]	Male [n,%]- UC	Male [n,%]- CD	Previous surgery, CD [n,%]	anti-TNF naïve UC [n,%]	anti-TNF naïve CD [n,%]	Concomitant immuno-modulator -UC [n,%]	Concomitant immuno-modulator- CD [n,%]	Systemic cortico-steroids - CD [n,%]
Shelton[28]	2015	USA	Clinical scores	Multicenter	prospective	65	107	19 [29.2%]	54 [50.5%]	63/107 [58.9%]	5 [2.9%] for both UC and CD		17/59 [28.8%]	34/107 [31.8%]	39/107 [36.4%]
Williet[41]	2016	France	Clinical scores	Multicenter	prospective	16	31			NA	NA	NA	5/16 [31.3%]	15/31 [48.4%]	31/31 [100%]
Amiot[26]	2016	France	Clinical scores	Multicenter	prospective	121	173	67 [55.4%]	64 [37.0%]		3/120 [2.5%]	1/172 [0.6%]	115/121 [95%]	99/173 [57.2%]	59/173 [34.1%]
Stallmach[31]	2016	Germany	Clinical scores	Multicenter	prospective	60	67	35 [58.3%]	31 [46.3%]	35/67 [52.2%]	11/67 [16.4%]	6/60 [10%]	19/60 [31.7%]	52/67 [31.1%]	32/67 [47.8%]
Baumgart[27]	2016	Germany	Clinical scores	Multicenter	prospective	115	97	49 [42.6%]	28 [28.9%]	41/97 [42.3%]	28/115 [24.3%]	5/97 [5.2%]	88/115 [76.5%]	78/97 [81.4%]	82/97 [84.5%]
Kopylov[25]	2016	Israel	Clinical scores/ PGA	Multicenter	prospective	74	130	42 [56.8%]	68 [52.3%]	46/130 [35.4%]	11/69 [15.9%]	4/130 [3.1%]	16/69 [23.2%]	32/116 [27.6%]	53/130 [40.8%]
Vivio[29]	2016	USA	Clinical scores	Single center	prospective	21	30	8 [38.1]	14 [46.7%]	14/30 [46.7%]	5/21 [23.8%]	1/30 [3.3%]	10/21 [47.6%]	21/30 [70%]	8/30 [26.7%]
Dulai[30]	2016	USA	PGA	Multicenter	retrospective	-	212	-	85 [40.1%]	117/212 [55.2%]		19/212 [9.0%]		156/212 [73.6%]	71/212 [33.5%]
Eriksson[38]	2017	Sweden	Clinical scores	Multicenter	prospective	99	147	38 [38.4%]	64 [43.5%]	70/147 [47.6]	13/99 [13.1%]	21/147 [14.3%]	44/99 [44.4%]	50/147 [34.0%]	41/147 [27.9%]
Total						571	994	258 [48.7]	408 [42.3%]	386/790 [47.9%]	71 [14.5%]	58 [6.7%]	314 [56.1%]	537 [49.7%]	416 [41.9%]

Table 1. *Continued*

Systemic cortico-steroids-UC [n,%]	Clinical response week 6 - CD	Clinical response week 6 - UC	Clinical remission week 6 - CD	Clinical remission week 6 - UC	Clinical response week 14 - CD	Clinical response week 14 - UC	Clinical remission week 14 - CD	Clinical remission week 14 -UC	Steroid-free remission by week 14-CD	Steroid-free remission by week 14 UC	Clinical response week 52-CD	Clinical remission week 52-CD	Clinical remission week 52-UC
37/59 [62.7%]	25/42 [58.5%]	18/40 [45%]	15/42 [37.5%]	6/40 [15.0%]	43/88 [48.9%]	31/58 [53.4%]	21/88 [23.9%]	17/58 [29.3%]	16/88 [18.2%]	12/58 [20.7%]			
16/16 [100%]	8/31 [25.8%]	9/16 [56.3%]	8/31 [34.6%]	9/16 [34.6%]									
41/121 [33.9%]	98/173 [56.6%]	50/121 [41.3%]	54/173 [32.2%]	39/121 [32.2%]	110/173 [63.6%]	69/121 [57.0%]	47/121 [38.8%]	63/173 [36.4%]	53/173 [30.6%]	43/121 [35.5%]			
42/60 [70%]											17/67 [25.4%]	15/60 [25%]	14/67 [20.9%]
96/115 [83.5%]	62/94 [66.0%]	47/111 [42.3%]	14/94 [10.8%]	12/111 [10.8%]	50/83 [60.2%]	58/102 [56.9%]	19/83 [22.9%]	24/102 [23.5%]	16/83 [19.3%]	19/102 [18.6%]			
36/69 [52.2%]					45/130 [34.6%]				38/130 [29.2%]	18/74 [24.3%]			
3/21 [14.3%]						8/15 [53.3%]							
			23/212 [10.8%]								123/212 [58%]	74/212 [34.9%]	
25/99 [25.3%]					55/147 [37.4%]	37/99 [37.4%]	62/147 [42.2%]	28/99 [28.3%]	51/147 [34.7%]	23/99 [23.2%]	36/68 [52.9%]	41/68 [59%]	25/39 [64.1%]
296 [59.2%]	54% [41–66%]	43% [37–49%]	22% [13–35%]	25% [12–45%]	49% [37–61%]	51% [43–60%]	32% [23–42%]	31% [27–35%]	29% [25–32%]	25% [19–32%]	45% [28–64%]	39% [23–59%]	

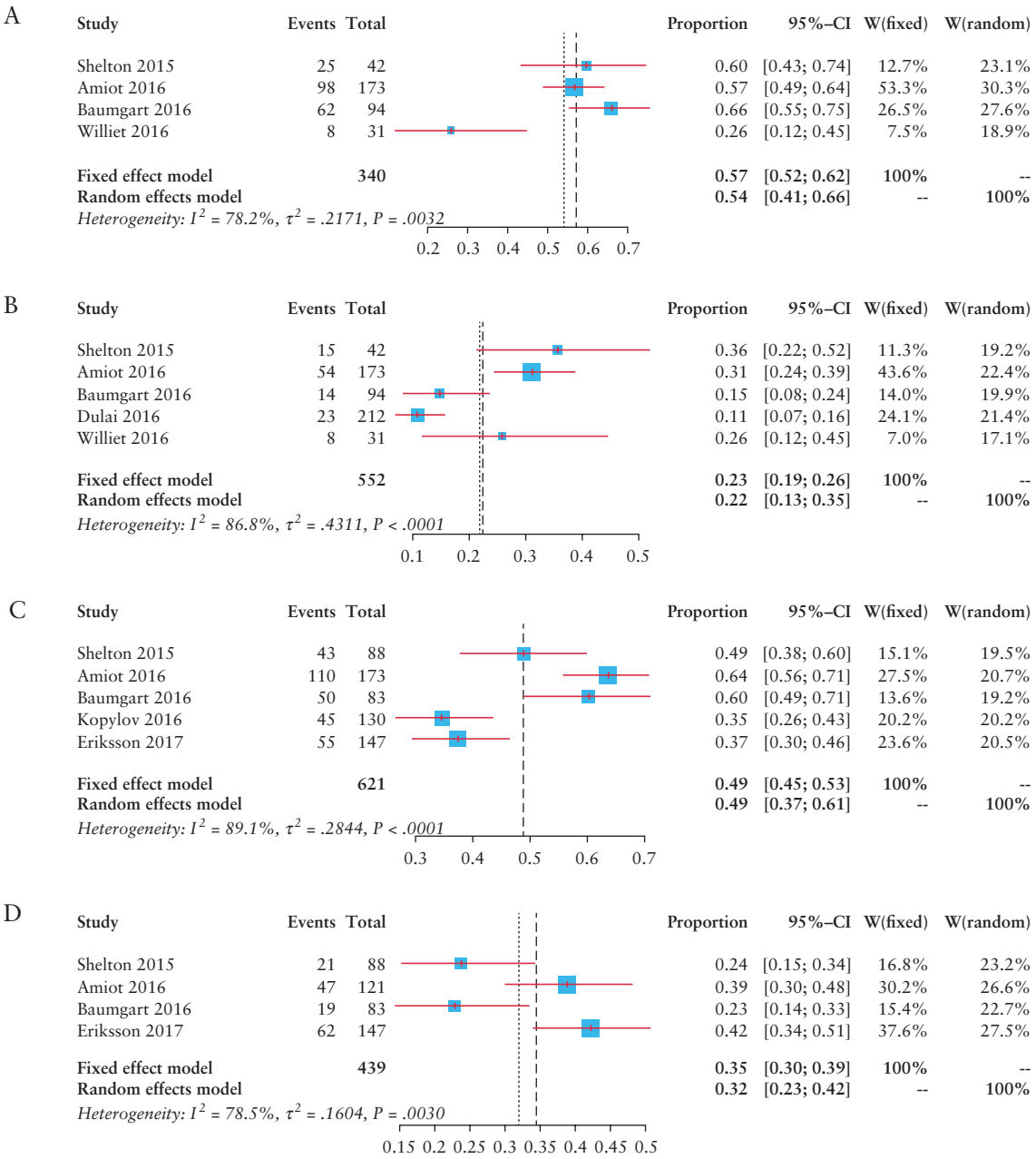

Figure 2. Pooled efficacy of vedolizumab in Crohn's disease [CD]. A: clinical response, 6 weeks; B: clinical remission, 6 weeks; C: clinical response, 14 weeks; D: clinical remission, 14 weeks; E: steroid-free remission, 14 weeks; F: clinical response, 52 weeks; G: clinical remission, 52 weeks.

response on multivariate analysis; for UC, no such predictors could be identified.

4. Extra-intestinal manifestations

There are very limited data on the efficacy of VDZ in treatment of extra-intestinal manifestations [EIM]. Results from the GETAID cohort presented in an abstract form addressed the efficacy of VDZ for EIMs. Among the 294 patients with IBD, 50 [17.2%] presented with EIM at baseline, including 46 [15.6%] with arthropathies and five [1.7%] with skin manifestations. At Week 14, complete remission was observed in 24 [52.2%] patients with arthropathies and in four [80%] patients with skin manifestations. At Week 54, 21 [45.7%] and three [60%] were still in complete remission for athropathies and skin manifestations, respectively.[35]

5. Safety

A total of 390 [30.6%] adverse events [AEs] were reported in the real-world studies. The three most common adverse events in real-world data were myalgia and arthralgia, followed by nasopharyngitis, infection, and skin eruption [Table 2]. Infections were reported in 43 [3.4%] patients. Among serious infections that were reported in the RWE series there were four cases of *Clostridium difficile* infections,[13,15] one case of tuberculosis,[14] one case of encephalitis of unidentified aetiology,[13] and two cases of severe sepsis.[13,17] One

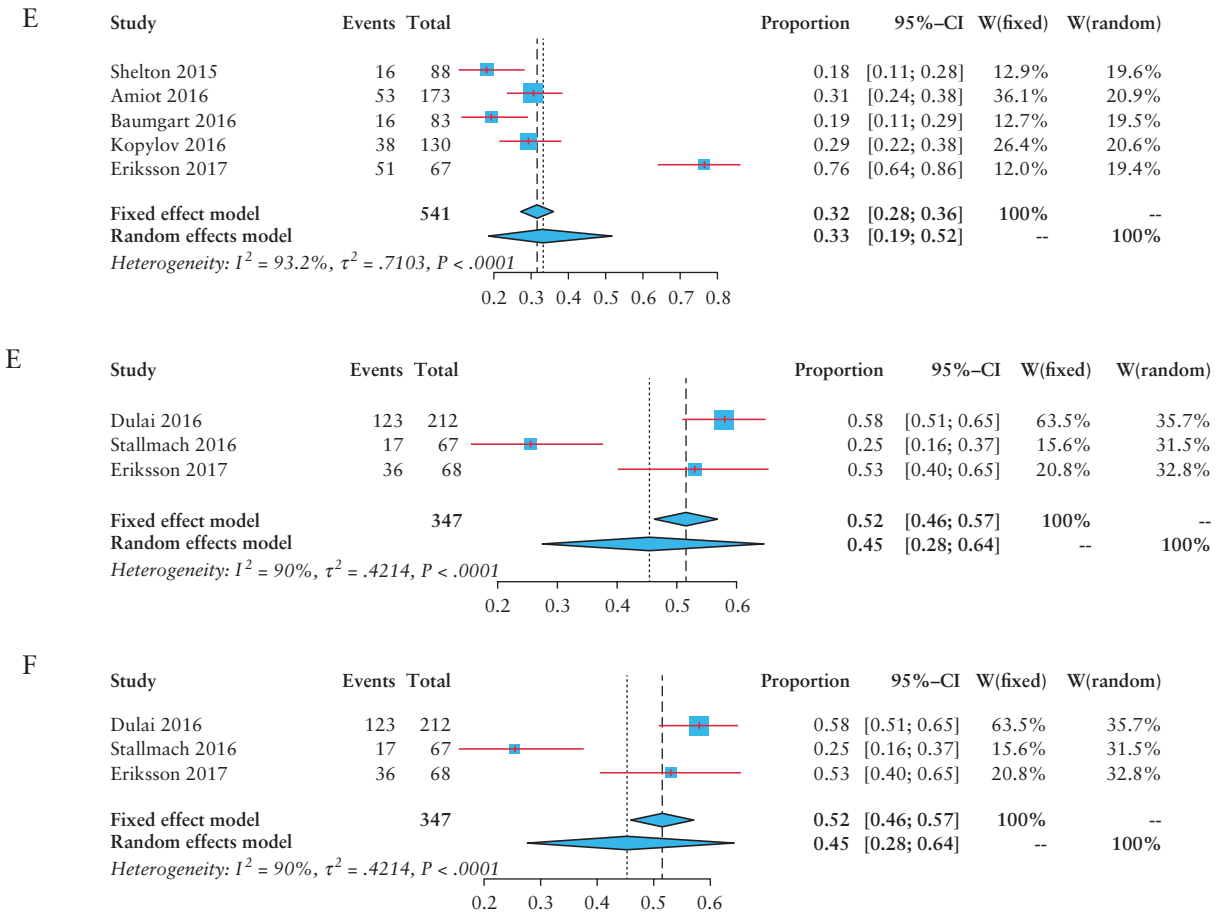

Figure 2. Continued.

case of severe disseminated histoplasmosis was reported in a patient treated concomitantly with VDZ and methotrexate [MTX]. The patient recovered with antifungal treatment and required prolonged hospitalisation.[17] One case of pseudomonas meningitis in a young CD patient treated concomitantly with azathioprine [AZA] and budesonide was reported as a separate case.[36] Neurological AEs included paraesthesias in 15 [1.4%] patients[37] and a transient hearing loss in one patient.[13] Infusion reactions occurred in eight [0.006%] patients.

Death was reported in 3/1640 [0.001%] patients. In one case, a 69-year-old patient with severe pancolitis, who received VDZ with full dose of corticosteroids, died from complications of necrotising fasciitis and colonic perforation during colonoscopy.[13] The other one was a 72-year-old patient who developed cytomegalovirus [CMV] colitis 14 weeks after VDZ first exposure, and died from complications of sepsis and acute kidney injury.[17] The third was a 39-year-old female with severe penetrating ileocolonic CD, who developed postoperative septic shock.[18]

6. Special situations

6.1. Postoperative complications

Four studies that evaluated the risk of perioperative complications in patients treated with VDZ were published in complete form to date,[38–41] with equivocal results. A study from the Mayo clinic included 90 patients who received VDZ within 12 weeks of an abdominal operation; 50 experienced postoperative complications [53%], 35 of which were surgical site infections [SSI] [36%]. The VDZ group experienced significantly higher rates of any postoperative infection [53% vs 33% compared with anti-TNF, and 28% with non-biologics; $p < 0.001$] and surgical site infections [37% vs 10% compared with with anti-TNF and 13% with non-biologics; $p < 0.001$].

Exposure to VDZ was a significant predictor of postoperative SSI on multivariate analysis [$p < 0.001$].[38] An additional study from the same cohort addressed UC patients only and included 88 patients who received VDZ and 62 who received anti-TNFα within 12 weeks of surgery. More vedolizumab-treated patients had superficial surgical site infections [$p = 0.047$] and mucocutaneous separation at the ileostomy [$p = 0.047$], but there was no difference in the overall surgical infectious complication rate, deep space surgical site infections, or need for reoperation within 30 days.

After ileal pouch-anal anastomosis, there was a higher rate of intra-abdominal abscesses [31.3% vs 5.9%] and mucocutaneous separation [18.8% vs 0%] in the vedolizumab group compared with the anti-TNFα group, although the difference did not reach statistical significance.[39] Two other currently available series did not demonstrate an increased risk of postsurgical complications with preoperative VDZ treatment. Yadav *et al.* compared the rate of surgical complications in patients who received VDZ, anti-TNFs, and non-biological therapy within 4 weeks of surgery, using propensity score matching.[40] The study included 443 patients [64 on

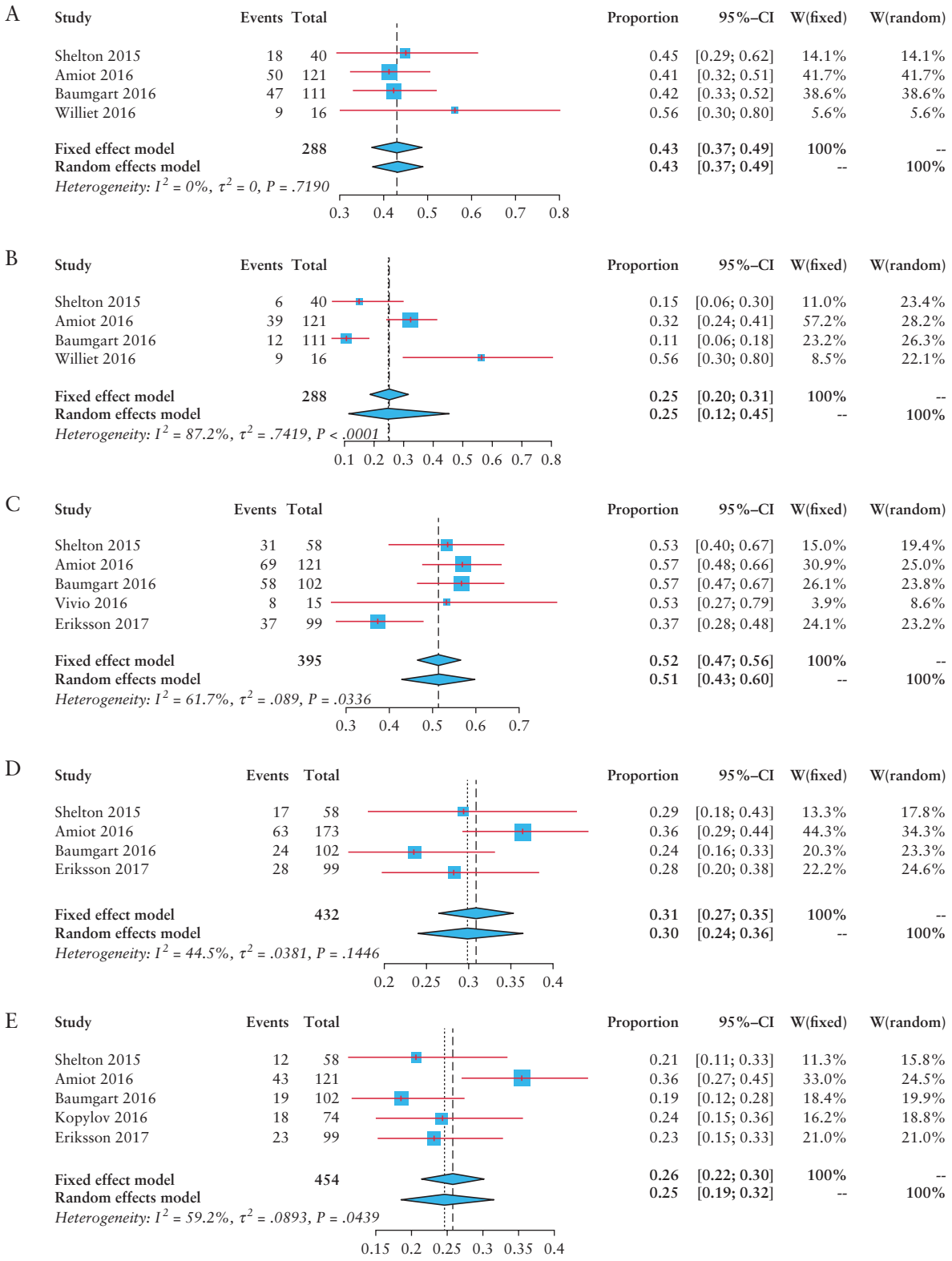

Figure 3. Pooled response and remission rates with vedolizumab treatment in inflammatory bowel disease [IBD].

vedolizumab, 129 on anti-TNF-α agents, and 250 on non-biological therapy]; 32% experienced postoperative complications. The risks of postoperative complications were not different among patients in either treatment group.[40] An additional recent large Belgian single-centre study included 170 UC patients; of these, 20% received VDZ and 35% anti-TNFs within 8 weeks before proctocolectomy with ileoanal pouch-anal anastomosis. No significant difference could be observed between different treatment categories in development of short-term postoperative complications.[41] It is possible that the discrepancy in the results stems from additional confounders such as

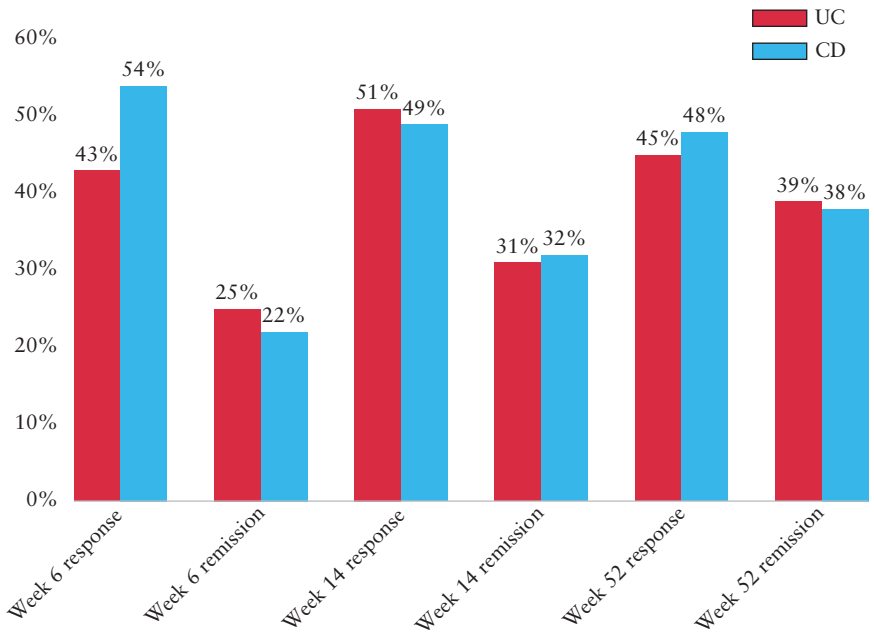

Figure 4. Pooled efficacy of vedolizumab in ulcerative colitis [UC]. A: clinical response, 6 weeks; B: clinical remission, 6 weeks; C: clinical response, 14 weeks; D: clinical remission, 14 weeks; E: steroid-free remission, 14 weeks.

disease severity, surgical technique, definitions of complications or patient selection. Further large studies are needed to clarify whether VDZ indeed poses any increased risk of postsurgical complications, and whether any additional caution in the management of perioperative IBD patients on VDZ should be required.

6.2. Pregnancy

Our knowledge pertaining to the safety of VDZ in pregnancy is currently very limited. A recent paper summarised the experience from the GEMINI programme. Across six studies, there were 27 pregnancies in female participants and 19 pregnancies in partners of male participants. Eleven live births, five elective terminations, four spontaneous abortions, and four undocumented outcomes were reported. A congenital corpus callosum agenesis anomaly was reported in one live birth from a healthy volunteer with extensive obstetric history, exposed to single-dose VDZ 79 days before estimated conception. Of 19 pregnancies in partners of male participants, there were 11 live births, two spontaneous abortions, three elective terminations, and three undocumented outcomes. Post-marketing reports recorded 81 pregnancies, resulting in four live births, 11 spontaneous abortions, and 66 pregnancies that were ongoing or reported undocumented outcomes.[42] In addition, three cases of uneventful pregnancies in patients treated with VDZ[21,24] were published so far. Importantly, VDZ crosses the placenta in similarity to other IgG1 antibodies, and can be detected in the cord as well as in the infant blood.[43] Results from the PIANO registry demonstrate that the serum level of VDZ in an infant at birth is approximately half of that detected in the maternal serum.[44] Although the role of alpha-4 beta 7 signalling in embryonic and infant development is unclear, animal studies using supratherapeutic doses of VDZ showed no signs of teratogenicity, stillbirth, impaired intrauterine growth, or postnatal physical development up to 6 months of age.[45]

Due to a scarcity of available safety data in pregnancy, VDZ should be used during pregnancy only if the benefits to the mother outweigh the risks to the mother/unborn child.[42] Importantly, no data regarding the safety of lactation or safety of vaccinations in a newborn exposed to VDZ in utero are currently available.

6.3. Ostomy and pouch patients

A single series reported the outcomes of VDZ patients with ileostomy and ileo-anal pouches.[16] Out of 12 stoma patients, five [41.7%] responded and two [16.7%] were in remission by Week 14. Out of eight patients with pouchitis or CD of the pouch, six [75.0%] responded and one [12.5%] was in remission by Week 14.[16]

6.4. Paediatric patients

To date, two paediatric case series were published in complete form. Conrad *et al*. described their experience with 21 patients with previous failure of anti-TNF treatment.[20] Clinical response was observed in 6/19 [31.6%] at Week 6 and in 11/19 [57.9%] by Week 22; steroid-free remission was achieved in 20% of the patients by Week 22.[20] A larger multicentre case series included 52 paediatric patients [58% CD and 42% UC]. Week 14 remission rates for UC and CD were 76% and 42%, respectively. At Week 22, anti-TNF naive patients had higher remission rates than TNF-exposed patients [100% versus 45%, $p = 0.04$].[30] The reported adverse events in both cohorts were minor and similar to those reported in the adult series.

6.5. Elderly patients

The evidence on the efficacy and safety of VDZ in the elderly was addressed in a single case series published in letter form. Navaneethan *et al*.[23] reported the experience in 29 patients above the age of 60; clinical remission at Week 14 was achieved in 48.3% of the patients, and 41.4% remained in remission at Week 52. Three [10.3%] patients required surgery. There were no infusion reactions. Four patients [13.8%] experienced adverse reactions, including pneumonia and *Clostridium difficile* infection. VDZ was discontinued in three patients.[23] These results are comparable to the general RWE data.

Table 2. Pooled prevalence of main adverse events in real-world studies with vedolizumab in inflammatory bowel disease [IBD]

Author	Adverse events, total *n*		Myalgia/arthralgia		Nasopharyngitis/upper respiratory tract infection		Infections		Skin eruptions	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Shelton[28]	18/172 [10%]	10.0%	4/172	2.0%			1/172	1.0%	4/172	2.0%
Amior[26]		32.0%	1/294	0.3%	24/294	8.0%	7/294	2.0%	13/294	4.0%
Baumgart[27]	85/212	40.0%	34/212	16.0%	7/212	3.0%	6/212	3.0%	26/212	12.0%
Dulai[30]	33/212	15.0%	5/212	2.0%	9/212	4.0%	14/212	7.0%	5/212	2.0%
Kopylov[25]	29/204	14.0%	2/204	1.0%	5/204	2.0%	6/204	3.0%	4/204	2.0%
Stallmach[31]	115/127	91.0%	47/127	37.0%			5/127	4.0%		
Vivio[29]	17/51	33.0%					4/51	8.0%	2/51	4.0%
Total	**390/1272**	**30% [95% CI 18%–53%]**	**93/1241**	**4% [95% CI 1–13%]**	**45/922**	**4% [95% CI 2–8%]**	**43.1272**	**3.4% [95% CI 2–6%]**	**53/1145**	**4% [95% CI 2–8%]**

CI, confidence interval.

6.6. Vedolizumab in patients after liver transplantation

A recent case series published in letter form addressed the use of VDZ in IBD patients after liver transplantation.[25] Ten patients were included; the median duration of follow-up was 13.1 months. The rates of response were 70% and 60% after 6 and 12 months, respectively. All patients were on corticosteroids at treatment onset. During the exposure to VDZ, five patients experienced a total of 11 infections [four cholangitis, four *Clostridium difficile* colitis, two empyema, and one pneumonia], probably reflecting a higher degree of immunosuppression in these patients. An additional case series described the results of treatment in five IBD patients following liver transplation for primary sclerosing cholangitis.[46] Clinical response was achieved in 3/5 patients [60%], two of whom were in clinical remission with mucosal healing after 14 weeks of treatment. Two patients were referred for colectomy. VDZ was well tolerated. During the period of follow-up, median 6.8 months [range 6.0–6.9], there were no reported opportunistic infections and liver synthetic function was stable.[46]

6.7. Therapeutic drug monitoring with vedolizumab

Although higher levels of infliximab and adalimumab were associated with clinical remission and mucosal healing in both UC and CD,[47–49] data regarding the pharmacokinetics of VDZ are still scarce. The GEMINI trials have demonstrated that VDZ drug levels were positively associated with clinical response at Week 6, especially among UC patients. Trough levels have been also shown to associate with endoscopic score among UC patients. However, drug levels have not been evaluated in relation to clinical or endoscopic outcomes at further time points. In a recent French publication, VDZ serum concentrations were not significantly different between responders and non-responders, although lower Week 6 trough levels [below 19.0 μg/mL] were associated with the need for interval shortening during the course of therapy.[29] Recent data from two unrelated 'real-world' cohorts, presented in abstract form, demonstrated a correlation between VDZ levels and biomarker response [CRP].[50,51]

Anti-VDZ antibodies [AVA] have been described, with varying formation rates. In GEMINI, AVA were reported in 4% of the patients; 0.5–1% AVA were persistent [two or more consecutive samples]. A sub-analysis of the VDZ phase 2 study included 37 UC patients and demonstrated a higher rate of 11% AVA, 5.5% persistent.[52,53] An additional study of 39 healthy volunteers who received a single VDZ infusion demonstrated a 54% rate of AVAs, 28% of them persistent.[54] Clinical relevance of AVA has not been established.

To conclude, preliminary data, which consist mostly of the GEMINI trials and sub-analyses, demonstrate a modest association between trough VDZ levels and clinical and biomarker response, more so in UC patients. AVA have been described with varying incidence rates, although data of their effect on clinical outcome are limited. Further large-scale studies are required in order to establish whether therapeutic drug monitoring [TDM] of VDZ therapy would improve patient care.

7. Discussion

The current pooled analysis of the RWE data suggests that the real-world efficacy and safety of VDZ are comparable to what was reported by GEMINI studies.

The effect of VDZ appears to be cumulative, with a longer duration of treatment being associated with higher rates of response.

The optimal timing for definition of primary response/non-response is currently unclear, as the effect of VDZ may be somewhat delayed in some patients; it appears diligent to wait for at least 14 weeks and sometimes even longer before discontinuation of treatment, attempting interval shortening to q4 weeks in non-responders or partial responders.

One of the most striking differences between the RCT and the RWE populations is the percentage of anti-TNF naive patients. In the RWE series, the number of anti-TNF naive patients is very low [8.5%], with a vast majority of the included patients previously failing at least one, and frequently two or more, previous biologics. GEMINI 1 included 48.1% anti-TNF naive UC patients, and GEMINI II 38.2% anti-TNF naive patients.[4,6] In fact, the CD population in the RWE series is much closer to that of GEMINI III, which included only anti-TNF experienced patients.[7] Very limited data published in abstract form suggest that the response in anti-TNF naive patients may be substantially better; however, further data are required.[13] Importantly, the response to anti-TNFs appears to be significantly better in biologic-naive patients as well.[55,56]

Real-life series demonstrate the utility of VDZ in additional patient populations that were excluded or under-represented in RCTs. VDZ appears to be efficacious in paediatric and elderly patients; very preliminary data suggest efficacy in patients after liver transplantation and patients with ostomy/ileo-anal pouches.

The safety of VDZ in pregnancy requires thorough evaluation. Currently available data include pregnancies during participation in the GEMINI trials, preliminary results from the PIANO registry, and scarce case reports. Additional data are expected from the PIANO registry and additional retrospective series.

To date, there is no evidence pointing to a potential association of VDZ treatment with malignancy. However, significantly longer duration of follow-up is required in order to draw any meaningful conclusion on this matter.

The benefit of combination therapy with immunomodulators is still unclear. For infliximab, the superior clinical efficacy of combination therapy is well established[57,58]; for adalimumab, the results are still inconclusive.[48,59,60] The clinical benefit of combination therapy is most likely a result of diminished immunogenicity and suppression of anti-drug antibodies.[47,49,51,61–64] In GEMINI studies, combination therapy was not associated with improved outcomes.[4–7] Importantly, the correlation between vedolizumab trough levels and clinical response appears to be less robust than for anti-TF biologics, although the data are still very limited; moreover, the prevalence of anti-vedolizumab antibodies appears to be quite low and their neutralising capacity and impact on trough levels and clinical outcomes are unclear. Currently, a single study suggested a benefit for combination therapy with vedolizumab[31]; additional studies are required to determine whether this strategy should be recommended.

There are multiple limitations to retrospective real-life studies. Primarily, there was a significant heterogeneity in study design, including the definitions of response and remission. Most of the studies used clinical scores, but Dulai *et al.*[18] reported PGA-based outcomes; and Kopylov *et al.*[13] used a combination of clinical scores, and PGA when clinical scores were unavailable. Dulai *et al.*[18] reported the data retrospectively, whereas other studies used a prospective approach. Moreover, all the included series, with the exception of Vivio *et al.*, included multicentre patient cohorts; such an approach may result in significant differences in clinical approaches and decision-making, when multiple physicians were involved in the care of the patients. Such heterogeneity limits the interpretation of both the original studies and the pooled analysis.

Importantly, endoscopic data were available from two studies only.[17,18] This is one of the main drawbacks of RWE data in comparison with RCT data, as endoscopies were not routinely scheduled and performed in these series and the data were only available for a small subgroup biased by selection of these patients for endoscopy. Moreover, the endoscopy results were reported retrospectively in the larger series of the two.[36]

Results pertaining to treatment of EIMs are very limited for all therapeutic agents, including anti-TNFs, immunomodulators, and ustekinumab; aside of a single prospective study with adalimumab,[65] all other reports are retrospective and very limited by absence of a verified quantitative method for assessment of response.[66–68]

In summary, VDZ appears to be effective in UC and CD in real-world studies in multiple populations, including those traditionally outside the scope of RCTs. Additional postmarketing data are required for a multitude of efficacy and safety issues such as extra-intestinal manifestations, healing of perianal fistulas, safety in pregnancy and lactation, perioperative complications, and more.

Conflict of Interest

SB-H received consulting and advisory board fees and/or research support from AbbVie, MSD, Janssen, Takeda, and Celltrion. UK received speaker fees from Abbvie, Jannsen, and Takeda, research support from Takeda and Jannsen, and consulting fees from Takeda and CTS.

Author Contributions

TE: data extraction and drafting of the manuscript; BU drafted the manuscript; DY: statistical analysis, drafted the manuscript; SB-H and RE revised the manuscript for scientific content; UK conceived of the study and drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

References

1. Yanai H, Hanauer SB. Assessing response and loss of response to biological therapies in IBD. *Am J Gastroenterol* 2011;**106**:685–98.
2. Ben-Horin S. Loss of response to anti-tumor necrosis factors: what is the next step? *Dig Dis* 2014;**32**:384–8.
3. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol* 2016;**7**:e135.
4. Feagan BG, Rutgeerts P, Sands BE, *et al.*; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;**369**:699–710.
5. Lam MC, Bressler B. Vedolizumab for ulcerative colitis and Crohn's disease: - results and implications of GEMINI studies. *Immunotherapy* 2014;**6**:963–71.
6. Sandborn WJ, Feagan BG, Rutgeerts P, *et al.*; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;**369**: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**:618–27.e3.
8. 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**:229–39.e5.
9. Loftus EV Jr, Colombel JF, Feagan BG, *et al.* Long-term efficacy of vedolizumab for ulcerative colitis. *J Crohns Colitis* 2017;**11**:400–11.
10. Mosli MH, MacDonald JK, Bickston SJ, *et al.* Vedolizumab for induction and maintenance of remission in ulcerative colitis: a Cochrane systematic review and meta-analysis. *Inflamm Bowel Dis* 2015;**21**:1151–9.
11. Feagan BG. Current issues in the design of clinical trials in IBD. *Nestle Nutr Inst Workshop Ser* 2014;**79**:19–28.

12. Deepak P, Park SH, Ehman EC, *et al.* Crohn's disease diagnosis, treatment approach, and management paradigm: what the radiologist needs to know. *Abdom Radiol [NY]* 2017;**42**:1068–86.
13. 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;**23**:404–8.
14. Amiot A, Grimaud JC, Peyrin-Biroulet L, *et al.*; Observatory on Efficacy and of Vedolizumab in Patients With Inflammatory Bowel Disease Study Group; Groupe d'Etude Therapeutique des Affections Inflammatoires du tube Digestif. Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2016;**14**:1593–601.e2.
15. Baumgart DC, Bokemeyer B, Drabik A, Stallmach A, Schreiber S; Vedolizumab Germany Consortium. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice–a nationwide consecutive German cohort study. *Aliment Pharmacol Ther* 2016;**43**:1090–102.
16. 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**:2879–85.
17. Vivio EE, Kanuri N, Gilbertsen JJ, *et al.* Vedolizumab effectiveness and safety over the first year of use in an IBD clinical practice. *J Crohns Colitis* 2016;**10**:402–9.
18. Dulai PS, Singh S, Jiang X, *et al.* The real-world effectiveness and safety of vedolizumab for moderate-severe Crohn's disease: results from the US VICTORY Consortium. *Am J Gastroenterol* 2016;**111**:1147–55.
19. Stallmach A, Langbein C, Atreya R, *et al.* Vedolizumab provides clinical benefit over 1 year in patients with active inflammatory bowel disease - a prospective multicenter observational study. *Aliment Pharmacol Ther* 2016;**44**:1199212.
20. Conrad MA, Stein RE, Maxwell EC, *et al.* Vedolizumab therapy in severe pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2016;**22**:2425–31.
21. Julsgaard M, Kjeldsen J, Baumgart DC. Vedolizumab safety in pregnancy and newborn outcomes. *Gut* 2017;**66**:1866–7.
22. Meszaros M, Pageaux GP, Altwegg R. Management of ulcerative colitis using vedolizumab after liver transplantation for primary sclerosing cholangitis. *J Crohns Colitis* 2016;**10**:236.
23. Navaneethan U, Edminister T, Zhu X, Kommaraju K, Glover S. Vedolizumab is safe and effective in elderly patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2017;**23**:E17.
24. Sheridan J, Cullen G, Doherty G. Vedolizumab in pregnancy. *J Crohns Colitis* 2016;**11**:1025–6.
25. Wright AP, Fontana RJ, Stidham RW. Vedolizumab is safe and effective in moderate to severe inflammatory bowel disease following liver transplantation. *Liver Transpl* 2017;**23**:968–71.
26. Eriksson C, Marsal J, Bergemalm D, *et al.* Long-term effectiveness of vedolizumab in inflammatory bowel disease: A national study based on the Swedish national quality registry for inflammatory bowel disease [SWIBREG]. *Scand J Gastroenterol* 2017;**52**:722–9.
27. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–58.
28. Schwarzer G. Meta: An R package for meta-analysis. *R News* 2007;**7**:40–5.
29. Williet N, Boschetti G, Fovet M, *et al.* Association between low trough levels of vedolizumab during induction therapy for inflammatory bowel diseases and need for additional doses within 6 months. *Clin Gastroenterol Hepatol* 2017;**15**:1750–57.e3.
30. Singh N, Rabizadeh S, Jossen J, *et al.* Multi-center experience of vedolizumab effectiveness in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2016;**22**:2121–6.
31. Allegretti JR, Barnes EL, Stevens B, *et al.* Predictors of clinical response and remission at 1 year among a multicenter cohort of patients with inflammatory bowel disease treated with vedolizumab. *Dig Dis Sci* 2017;**62**:1590–6.
32. Eriksson C, Marsal J, Bergemalm D, *et al.*; SWIBREG Vedolizumab Study Group. Long-term effectiveness of vedolizumab in inflammatory bowel disease: a national study based on the Swedish National Quality Registry for Inflammatory Bowel Disease [SWIBREG]. *Scand J Gastroenterol* 2017;**52**:722–9.
33. Daperno M, D'Haens G, Van Assche G, *et al.* Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004;**60**:505–12.
34. Stallmach A, Schmidt C, Teich N. Vedolizumab for the treatment of ulcerative colitis. *Expert Rev Gastroenterol Hepatol* 2016;**10**:165–75.
35. Tadbiri S, Grimaud JC, Peyrin-Biroulet L, *et al.* Efficacy of vedolizumab in extra-intestinal manifestations in patients with inflammatory bowel disease: A post-hoc analysis of the observ-ibd cohort from the getaid [conference abstract: DOP025]. ECCO 2017; Barcelona, Spain.
36. Boland BS, Dulai PS, Chang M, Sandborn WJ, Levesque BG. Pseudomonas Meningitis During Vedolizumab Therapy for Crohn's Disease. *Am J Gastroenterol* 2015;**110**:1631–2.
37. Bye WA, Jairath V, Travis SPL. Systematic review: The safety of vedolizumab for the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;**46**:3–15.
38. 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**:185–90.
39. Lightner AL, McKenna NP, Moncrief S, *et al.* Surgical outcomes in vedolizumab-treated patients with ulcerative colitis. *Inflamm Bowel Dis* 2017, Aug 29. doi: 10.1097/MIB.0000000000001248. [Epub ahead of print.]
40. 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**:1423–9.
41. Ferrante M, de Buck van Overstraeten A, Schils N, *et al.* Perioperative use of vedolizumab is not associated with postoperative infectious complications in patients with ulcerative colitis undergoing colectomy. *J Crohns Colitis* 2017 2017, Jul 12. doi: 10.1093/ecco-jcc/jjx095. [Epub ahead of print.]
42. Mahadevan U, Vermeire S, Lasch K, *et al.* Vedolizumab exposure in pregnancy: outcomes from clinical studies in inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;**45**:941–50.
43. Mahadevan U, Martin C, Kane SV, *et al.* 437 do infant serum levels of biologic agents at birth correlate with risk of adverse outcomes? Results from the piano registry [conference abstract: DDW]. May 2016; San Diego, CA.
44. Mahadevan U, Vermeire S, Lasch K, *et al.* Editorial: vedolizumab in pregnancy - is gut selectivity as good for baby as it is for mum? Authors' reply. *Aliment Pharmacol Ther* 2017;**45**:1284.
45. Entyvio M. Food and Drug Administration. 2013. http://CFDEaRAa,www.accessdata.fda.gov/drugsatfda_docs/nda/2014/,. Accessed July 1, 2017.
46. Hartery K, O'Reilly S, Houlihan D, *et al.* Letter: vedolizumab for the management of inflammatory bowel disease in patients after liver transplantation for primary sclerosing cholangitis. *Aliment Pharmacol Ther* 2017;**45**:376–8.
47. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev* 2014;**13**:24–30.
48. Kopylov U, Ben-Horin S, Seidman E. Therapeutic drug monitoring in inflammatory bowel disease. *Ann Gastroenterol* 2014;**27**:304–12.
49. Ungar B, Chowers Y, Yavzori M, *et al.*; ABIRISK consortium. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. *Gut* 2014;**63**:1258–64.
50. Vermeire S, Gils A, Dreesen E, *et al.* Vedolizumab exposure correlates with clinical, biological and endoscopic outcomes in patients with inflammatory bowel disease [conference abstract: UEGW]. October 2016; Vienna, Austria.
51. Ungar B, Levy I, Yavne Y, *et al.* Optimizing anti-TNF-α therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2016;**14**:550–7.e2.
52. Parikh A, Leach T, Wyant T, *et al.* Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. *Inflamm Bowel Dis* 2012;**18**:1470–9.
53. Ungar B, Kopylov U, Waterman M, *et al.* Early vedolizumab drug levels and induction success in patients with inflammatory bowel disease [conference abstract: UEGW 2016]. October 2016; Vienna, Austria.
54. Rosario M, Dirks NL, Milch C, *et al.* A Review of the Clinical Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Vedolizumab. *Clin Pharmacokinet* 2017;**56**:1287–301.

55. Taxonera C, Rodríguez C, Bertoletti F, *et al.*; Collaborators. Clinical outcomes of golimumab as first, second or third anti-TNF agent in patients with moderate-to-severe ulcerative colitis. *Inflamm Bowel Dis* 2017;**23**:1394–402.
56. Kestens C, van Oijen MG, Mulder CL, *et al.*; Dutch Initiative on Crohn and Colitis [ICC]. Adalimumab and infliximab are equally effective for Crohn's disease in patients not previously treated with anti-tumor necrosis factor-α agents. *Clin Gastroenterol Hepatol* 2013;**11**:826–31.
57. Colombel JF, Sandborn WJ, Reinisch W, *et al.*; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383–95.
58. Jones JL, Kaplan GG, Peyrin-Biroulet L, *et al.* Effects of concomitant immunomodulator therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease: a meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2015;**13**:2233–40.e1–2; quiz e177–8.
59. Kopylov U, Al-Taweel T, Yaghoobi M, *et al.* Adalimumab monotherapy versus combination therapy with immunomodulators in patients with Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis* 2014;**8**:1632–41.
60. Matsumoto T, Motoya S, Watanabe K, *et al.*; DIAMOND study group. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: a prospective, randomized trial. *J Crohns Colitis* 2016;**10**:1259–66.
61. Ben-Horin S, Chowers Y. Tailoring anti-TNF therapy in IBD: drug levels and disease activity. *Nat Rev Gastroenterol Hepatol* 2014;**11**:243–55.
62. Ungar B, Haj-Natour O, Kopylov U, *et al.* Ashkenazi Jewish origin protects against formation of antibodies to infliximab and therapy failure. *Medicine* 2015;**94**:e673.
63. Ungar B, Kopylov U, Engel T, *et al.* Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab. *Aliment Pharmacol Ther* 2017;**45**:276–82.
64. Yanai H, Lichtenstein L, Assa A, *et al.* Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clin Gastroenterol Hepatol* 2015;**13**:522–30.e2.
65. Löfberg R, Louis EV, Reinisch W, *et al.* Adalimumab produces clinical remission and reduces extra-intestinal manifestations in Crohn's disease: results from CARE. *Inflamm Bowel Dis* 2012;**18**:1–9.
66. Barreiro-de-Acosta M, Lorenzo A, Dominguez-Munoz JE. Efficacy of adalimumab for the treatment of extra-intestinal manifestations of crohn's disease. *Rev Esp Enferm Dig* 2012;**104**:468–72.
67. Peyrin-Biroulet L, Van Assche G, Gómez-Ulloa D, *et al.* Systematic review of tumor necrosis factor antagonists in extra-intestinal manifestations in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2017;**15**:25–36.e27.
68. Vavricka SR, Gubler M, Gantenbein C, *et al.*; Swiss IBD Cohort Study Group. Anti-TNF treatment for extra-intestinal manifestations of inflammatory bowel disease in the Swiss IBD cohort study. *Inflamm Bowel Dis* 2017;**23**:1174–81.