The real-world outcomes of vedolizumab in patients with ulcerative colitis in Korea: a multicenter retrospective study

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Abstract

Aim: This study examined the real-world effectiveness and safety outcomes of vedolizumab in ulcerative colitis (UC) patients who had failed anti-tumor necrosis factor (anti-TNF) therapy in Korea.

Methods: A retrospective chart review study was conducted in adults with moderate to severely active UC who had failed anti-TNF agents and subsequently received vedolizumab. Clinical response and clinical remission at week 6 and 14 after vedolizumab initiation was evaluated. Safety outcomes were also reported. Outcome rates were compared with a matched sub-cohort derived from the open-label sub-cohort of the GEMINI 1 trial using the optimal matching method.

Results: A total of 105 patients (mean age, 45.3 years; 63.8% male) were included. At week 6, 55.8% (n = 43/77) achieved a clinical response and 18.2% (n = 14/77) achieved clinical remission. At week 14, 73.2% (n = 52/71) achieved a clinical response and 39.4% (n = 28/71) achieved clinical remission. When non-response imputation was used, the clinical response rate at week 6 and week 14 were 40.1% (n = 43/105) and 49.5% (n = 52/105) respectively. Of the 105 patients, 16 (15.2%) experienced at least one adverse event. The matched analysis showed that the clinical response rate at week 6 was higher in the matched sub-cohort of this study (24/47, 51.1%) *versus* the matched sub-cohort from the GEMINI 1 open-label cohort (12/47, 34.3%, p = 0.019). The clinical remission rates at week 6 were similar (7/47, 14.9% *versus* 9/47, 19.1%, p = 0.785).

Conclusions: In the real-world setting, vedolizumab is effective and well tolerated within the first 14 weeks of use in Korea. The proportion of patients experiencing clinical response and clinical remission at 6 and 14 weeks appeared to be largely consistent with that observed in real-world studies from other regions and populations.

Keywords: Korea, remission, response, ulcerative colitis, vedolizumab

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Introduction

Anti-tumor necrosis factor (anti-TNF) agents, including infliximab, adalimumab, and golimumab, have transformed the therapeutic landscape of ulcerative colitis (UC), after their favorable efficacy data have been demonstrated in randomized controlled trials.[1–3] However, up to one-third of the patients with UC have failed to respond to anti-TNF therapy.[1,4,5] Following the failure to anti-TNF therapy, there is currently no clear guidelines on whether the next step should be to try other anti-TNF agents or to switch to

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drugs with different mechanism of action (e.g. vedolizumab).[6]

Vedolizumab was recently made available for the treatment of patients with UC in Korea, and, since January 2020, is indicated for use in biologically naïve patients. Vedolizumab is a humanized monoclonal antibody that selectively antagonizes α4β7 integrin receptors, thereby inhibiting the migration of lymphocytes into the gastrointestinal tract.[7] Such migration is impaired without causing systemic immunosuppression, as opposed to other treatment options for UC such as anti-TNF agents and janus kinase (JAK) inhibitors.[8] As the mode of action of vedolizumab is different from that of anti-TNF, vedolizumab may represent an effective treatment option for patients with (or at higher risk of) either primary or secondary anti-TNF failure.

The landmark GEMINI 1 trial, which included 895 patients with UC across 34 countries, reported favorable results of vedolizumab induction and maintenance therapy.[9] The clinical trial found that clinical response rate at week 6 was almost double the placebo arm. At week 52, the proportion of patients who had experienced clinical remission was twice as high in the vedolizumab group (Q8W) *versus* the placebo group. Vedolizumab was also shown to be well tolerated with a favorable safety profile.[9]

Following the GEMINI 1 trial, multiple real-world studies have since been conducted, albeit largely focused on Western populations.[10–12] A recent systematic review and meta-analysis of these available real-world evidences suggested that the effectiveness and safety of vedolizumab were highly consistent with that reported by the pivotal GEMINI 1 study.[13] A recent controlled trial in Japan[14] has provided some evidence on a similar and favorable efficacy of vedolizumab for Japanese UC patients. Unfortunately, observation data on how much vedolizumab is effective and safe under the real-world clinical setting in Asia remain scarce. As a result, we conducted this study to evaluate the real-world effectiveness and safety of vedolizumab in patients with UC who failed anti-TNF therapy in Korea. We also sought to compare our data against a matched subset of the GEMINI 1 cohort.

Methods

A multicenter retrospective chart review of the electronic medical records was conducted across 13 centers in Korea, where data were collected using web-based case report forms. Adult patients with UC (≥ 19 years of age) and the following characteristics were included: (i) diagnosed with definite UC, (ii) had failed anti-TNF therapy (primary or secondary) or discontinued due to other reasons such as patient preference and adverse event, and (iii) had received at least one dose of intravenous (IV) vedolizumab between August 2017 and December 2018. Vedolizumab were administered to the eligible patients *via* IV infusion at weeks 0, 2, and 6, then every 8 weeks thereafter.

The primary outcome was clinical response at week 6 after two infusions of vedolizumab (weeks 0 and 2). Clinical response was defined as a reduction in the partial Mayo score of at least 3 points and a decrease of at least 30% from the baseline score, with a decrease of at least 1 point on the rectal bleeding subscore, or an absolute rectal bleeding subscore of 0 or 1.[15] The secondary outcomes were (1) clinical responses at week 14, (2) clinical remission at week 6, (3) clinical remission at week 14, (4) endoscopic response at week 6, (5) endoscopic response at week 14, (6) endoscopic remission at week 6, (7) endoscopic remission at week 14, and (8) safety outcomes. Clinical remission was defined as a partial Mayo score of at most 2, without any subscore being greater than 1.[16] Endoscopic response was defined as a decrease of at least 50% from a baseline Mayo endoscopic subscore. Endoscopic remission was defined as a Mayo endoscopic subscore of 0–1; complete endoscopic remission was defined as a Mayo endoscopic subscore of 0.

The safety outcomes included adverse events of special interest (AESIs), serious adverse event (SAEs), and pregnancy-related outcomes documented during the treatment period. AEs that had occurred on or after the start of IV vedolizumab therapy were abstracted from the medical charts and coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. AESIs included serious infections, opportunistic infections, hepatitis viral infection, gastrointestinal infections, respiratory infections, other clinically significant infections, malignancies, infusion-related reactions, and hepatic injury. SAEs included UC exacerbation (e.g., new signs and symptoms of UC), cytomegalovirus infection, adenoiditis, mouth ulceration, and skin ulcers). SAE is referred to as any untoward

medical occurrence that, at any dose, has resulted in death (or an immediate risk of death), persistent or significant disability or incapacity, and hospitalization (or prolongation of existing hospitalization). Safety analyses were performed for those who have received at least one dose of vedolizumab (i.e., full eligible study cohort).

Other covariates extracted included age, sex, body mass index (BMI), smoking history, family history of inflammatory bowel diseases, comorbidities, duration of UC, extent of UC, extraintestinal manifestations, and medication history (within 5 years prior to vedolizumab initiation) and concomitant medications use.

Statistical analysis

Continuous variables were expressed as the median and interquartile range (IQR) and categorical variables as number and percentage (%). Differences in continuous variables between subgroups were compared using the Mann–Whitney U test. Comparisons between categorical variables were analyzed using the Fisher's exact test or Chi–squared test. Analysis of all study outcomes were performed on non-missing cases only (complete case analysis) as the primary analysis. Given the risk for attrition bias with real-world observational data and potential effect of right censoring, we also performed a non-response imputation (NRI) analysis for the clinical response at week 6 (the primary outcome) and at week 14. In the NRI, all cases with missing data at weeks 6 and 14 were imputed as non-responders, irrespective of their response status prior to these time points. Subgroup analyses were performed for the following factors: (1) duration of UC (<1 year, 1–<3 years, 3–<7 years, and ≥7 years), disease extent (proctosigmoiditis, left-sided colitis, extensive colitis, pancolitis, and unknown), number of prior anti-TNF agents (one, two, and three), the type of failure (inadequate response, loss of response, intolerance, or others), and the type of concomitant medication exposure (corticosteroids, immunosuppressants, corticosteroids and immunosuppressants, and no corticosteroids or immunosuppressants).

In addition, outcome data were compared with a matched cohort (of vedolizumab-treated patients) derived from the open-label cohort of the GEMINI 1 pivotal trial. Only anti-TNF experienced subjects were included for matching. The two cohorts were matched by the following covariates: age,

sex, BMI, smoking status, duration of UC, extent of UC, baseline Mayo score, number of prior hospitalization (12 months), and concomitant steroid use (yes/no). Matching was performed using the optimal matching method *via* the MatchIt package of the R statistical environment.[17] Optimal matching allows for the efficient finding of a matched comparator group that has the smallest average absolute distance by Mahalanobis measure across all the potential matched pairs within the two comparing cohorts.[18] Covariate balance was assessed using the *t*-test (for numerical variables) and the Chi–squared or the Fisher's exact test (for categorical variables) after matching. All analyses were performed using the R version 3.3.1 and evaluated at a two-sided significance level of $p < 0.05$.

Ethical considerations

This study was approved by all the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) of each participating center according to the local requirements (including Asan Medical Center IRB approval # 2018-0869). Reporting of this study is in accordance with the Strengthening the Reporting of Observational studies in Epidemiology guideline.[19]

Results

A total of 124 patients were identified and screened from the medical records, where 105 patients met the inclusion criteria. All 105 patients had adequate data for safety outcomes analysis (adverse events and pregnancy-related outcomes). Varying degree of patient attrition from baseline to weeks 6 and 14 were seen, resulting in the differing availability of outcome data for the various observation points. A flow chart is shown in Figure 1, which demonstrate the derivation and availability of data on the various outcome analyses (i.e., clinical and endoscopic response/remission at week 6 and 14).

Of the 105 patients, the median age was 47.0 (IQR = 23.0) years and 63.8% were males. The median full Mayo score at baseline was 9.0 (IQR = 2.0) where 46.7% had pancolitis. The majority of the patients had been previously treated with one or more aminosalicylates (93/105, 88.6%), corticosteroids (71/105, 67.6%), and immunosuppressants (56/105, 53.3%) prior to vedolizumab initiation. About
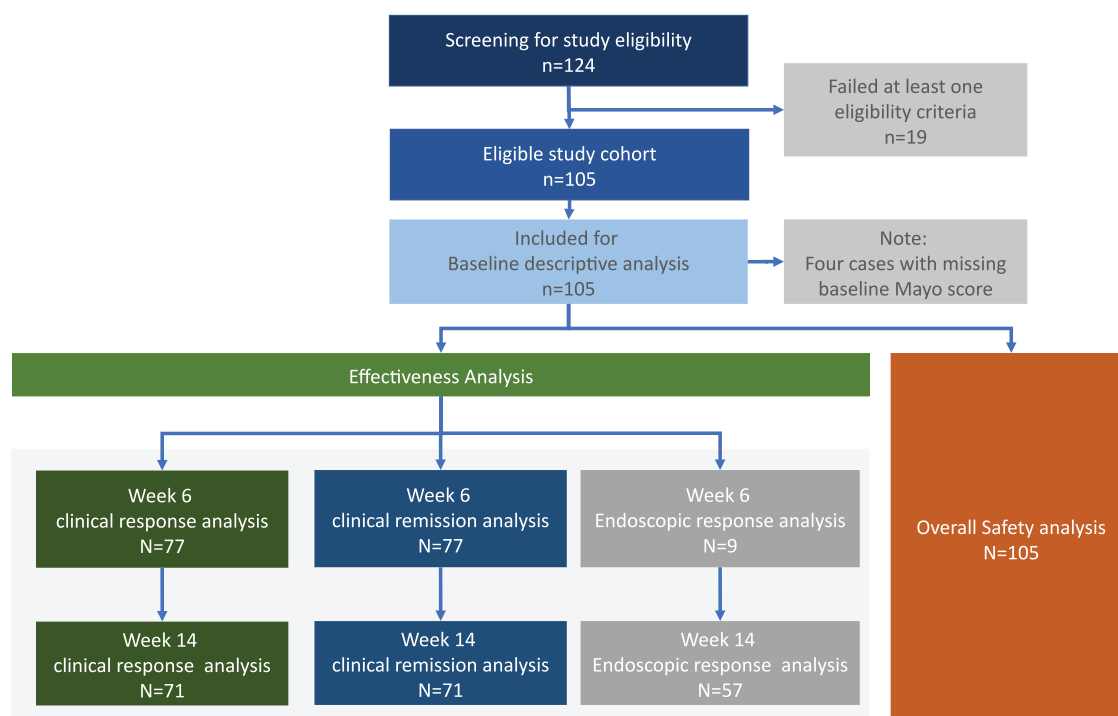
Figure 1. Flow diagram demonstrating the derivation of the analysis cohorts.

31.4% (33/105) of the study cohort had more than one prior anti-TNF therapy. The median duration of these prior anti-TNF therapy was 8.4 months (IQR = 16.7). The full demographic and clinical characteristics of the study cohort is shown in Table 1.

A total of seventy-seven subjects provided sufficient data for the assessment of clinical response and clinical remission at week 6; 71 subjects did so for the same assessment at week 14 (Figure 1). Based on these cases, more than half of the available cases (43/77, 55.8%) achieved clinical responses at week 6, while 18.2% (14/77) achieved clinical remission. At week 14, almost three quarters of the cases with sufficient data (52/71, 73.2%) achieved clinical response and 39.4% (28/71) achieved clinical remission (Table 2). Changes of the partial Mayo score and subscores at week 6 and week 14 from baseline are presented in Table 3. Using NRI for the analysis of the primary outcome, the proportion achieving a clinical response at week 6 was 40.1% ($n = 43/105$). At week 14, NRI analysis indicated a clinical response rate of 49.5% ($n = 52/105$).

Only nine patients had a valid Mayo endoscopic subscore assessment done at week 6. Of those, two patients (2/9, 22.2%) achieved an endoscopic response at week 6. At week 14, 57 patients had a valid Mayo endoscopic subscore, where close to half (28/57, 49.1%) achieved both an endoscopic response and an endoscopic remission. Endoscopic outcomes at week 6 and week 14 are presented in Table 4.

Overall, 15.2% (16/105) of the patients experienced at least one AE. The most common AEs were UC exacerbation (6/105, 5.7%), upper respiratory tract infections (5/105, 4.8%), and arthralgia (2/105, 1.9%). Five patients (4.8%) had at least one SAE, which included: UC exacerbation (3/105, 2.9%), cytomegalovirus infection (1/105, 1.0%), adenoiditis, and mouth/skin ulceration (1/105, 1.0%).

Data from 47 patients in this study were successfully matched (1:1) to 47 anti-TNF experienced subjects from the open-label cohort of the GEMINI 1 study. Table 5 shows the covariate balance for the two sub-cohorts before and after optimal matching. Compared with the matched (open label) sub-cohort of the GEMINI 1 trial, the week 6 clinical response rate was higher in the matched sub-cohort of this study (24/47, 51.1% *versus* 12/47, 25.5%, $p = 0.019$). No statistically

Table 1. Demographic and clinical characteristics of the UC cohort at baseline.

Demographics and clinical characteristics	Overall cohort
Age (year)	
Median (IQR)	47.0 (23.0)
Sex, *n* (%)	
Male	67 (63.8)
Female	38 (36.2)
BMI (kg/m^2)	
Median (IQR)	21.4 (4.3)
Smoking status – *n* (%)	
Current smoker	4 (3.8)
Former smoker	31 (29.5)
Never smoked	62 (59.0)
Unknown	8 (7.6)
Family history, *n* (%)	
Ulcerative colitis	3 (2.9)
Sibling(s)	2 (1.9)
Parent(s)	1 (1.0)
Comorbidities, *n* (%)	
Hypertension	5 (4.8)
Diabetes mellitus	2 (1.9)
Autoimmune hepatitis	1 (1.0)
Rheumatoid arthritis	1 (1.0)
Categorical duration of UC, *n* (%)	
<1 year	3 (2.9)
≥1–<3 years	22 (21.0)
≥3–<7 years	30 (28.6)
≥7 years	13 (12.4)
Unknown	37 (35.2)
Disease extent, *n* (%) (up to a week before or at baseline)	
Proctosigmoiditis	24 (22.9)
Left-sided colitis	22 (21.0)

(continued)

Table 1. (Continued)

Demographics and clinical characteristics	Overall cohort
Extensive colitis	2 (1.9)
Pancolitis	49 (46.7)
Unknown	8 (7.62)
Partial Mayo score at baseline	
Median (IQR)	6.0 (2.0)
Unknown (%)	4 (3.8)
Full Mayo score at baseline	
Median (IQR)	9.0 (2.0)
Unknown (%)	10 (9.5)
Extraintestinal manifestations, *n* (%) (up to 12 months before or at baseline)	
Yes	6 (5.7)
No	99 (94.3)
Prior medications *n* (%)	
Anti-TNFs	105 (100.0)
Infliximab	71 (67.6)¥
Adalimumab	55 (52.4)¥
Golimumab	20 (19.0)¥
Aminosalicylates	93 (88.6)
Corticosteroids	71 (67.6)
Immunosuppressants*	56 (53.3)
Antibiotics	21 (20.0)
Probiotics	3 (2.9)
Opioids	1 (1.0)
Duration of prior anti-TNF therapy (months)	
Median (IQR)	8.4 (16.7)
Number of prior anti-TNF therapy, *n* (%)	
One (1) prior anti-TNF	72 (68.6)
Two (2) prior anti-TNFs	25 (23.8)
Three (3) prior anti-TNFs	8 (7.6)
Type of prior anti-TNF failure+, *n* (%)	
Inadequate response	53 (50.5)
Loss of response	32 (30.5)
Intolerance	10 (9.5)

(continued)

Table 1. (Continued)

Demographics and clinical characteristics	Overall cohort
Unknown	10 (9.5)
Concomitant medications for UC, *n* (%)	
Corticosteroids only	14 (13.3)
Immunosuppressants only	6 (5.7)
Corticosteroids and immunosuppressants	5 (4.8)
No corticosteroids or immunosuppressants	80 (76.2)

¥Sum to more than 100% due to more than one use.
*Immunosuppressants considered are azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, mycophenolate mofetil, tacrolimus, and thalidomide.
+Data captured as free-text initially and subsequently coded manually into the four categories. Entries such as 'dampened responsiveness', 'primary non-response', 'no response', and 'no effect' were coded as inadequate responses. Entries such as 'secondary loss of response', 'recurrence of symptoms', and 'loss of response' were coded as a loss of response. Entries such as 'cytomegalovirus infection', 'hypotension', and 'intolerance' were coded as intolerance. Other free-text entries such as 'principal investigator's judgement' and 'drug change' etc. were considered as unknowns.
BMI, body mass index; IQR, interquartile range; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.

significant difference was observed in terms of clinical remission rate [7/47, 14.9% (this study) *versus* 9/47, 19.1% (GEMINI 1 open label matched sub-cohort), $p = 0.785$] (Table 6).

The overall AEs rate in this study was 15.2% (16/105). In the full anti-TNF experienced, vedolizumab-treated sub-cohort of GEMINI 1 trial [i.e., inclusive of both randomized cohort (a.k.a. cohort 1) and open-label cohort (a.k.a. cohort 2)], it was 53.9% (164/304) over the induction therapy period (up to 6 weeks). The SAE rates were similar for both studies (Table 7).

Subgroup analyses found no significant difference between clinical responses across a range of subgroup factors at week 6 (Table 8). At week 14, the distribution of patients by the number of prior anti-TNF agents was different between the clinical responders and non-responders were more likely to have a lower number of prior anti-TNF therapy compared with non-responders ($p < 0.001$, unadjusted). Of the 47 patients previously exposed to one anti-TNF agent, 40 patients (85.1%) showed a clinical response, while none of the five patients previously exposed to three anti-TNF agents showed a clinical response at week 14 (Table 8).

Discussion

Limited Asian specific real-world studies concerning UC patients using vedolizumab have been reported or presented previously.[20–23] This study adds to this body of evidence, showing favorable effectiveness at week 6 after administration of

Table 2. Clinical response and remission rate at week 6 and week 14 post vedolizumab administration (complete case analysis and analysis with non-response imputation).

Outcomes at week 6	Complete case analysis (*n* = 77) (%)	Analysis with NRI* (*n* = 105) (%)
Clinical response rate, *n* (%)	43 (55.8)	43 (40.1)
Clinical remission rate, *n* (%)	14 (18.2)	–
Outcomes at week 14	**Complete case analysis (n = 71) (%)**	**Analysis with NRI* (n = 105) (%)**
Clinical response rate, *n* (%)	52 (73.2)	52 (49.5)
Clinical remission rate, *n* (%)	28 (39.4)	–

*Clinical response rate at week 6 and week 14 where patients with missing partial Mayo score were assumed to be a non-responder to vedolizumab. "–" means analysis not performed.
NRI, non-response imputation.

vedolizumab. More than half of the observed patients achieved a clinical response and close to 20% of them achieved clinical remission. At week 14, the effectiveness improved further; almost three quarters of the patients achieved a clinical response and close to 40% of them achieved clinical remission. Vedolizumab also showed a favorable safety profile, with a small number of reported AEs.

The results of the real-world effectiveness of vedolizumab shown in this study are comparable, and largely consistent with the open-label sub-cohort from GEMINI 1 study that was matched one-to-one to those in this study. In addition, the crude week 6 clinical response rate was close to the higher end of the 95% CI of the average reported in a systematic review of real-world evidence on vedolizumab (55.8% in this study *versus* 49% in the review), while the week 6 crude clinical remission rate (18.2%) was within the 95% CI range of the review (13–41%). In terms of safety outcomes, our data shows a lower AE rate, despite the longer observation period. Due to the different study design (i.e., retrospective observation *via* chart review *versus* prospective clinical trial) and the unmatched and unadjusted nature of the comparison, it is important that interpreting these two sets of AE rates crudely should be done with caution (further discussed on study limitation). However, based on other real-world studies reported so far, it is suggestive that the safety profiles of vedolizumab approximate the understanding generated from the key clinical trials data, particularly the GEMINI studies.[9,13,15,22,24]

When compared with several real-world studies that focus specifically on those who had failed

Table 3. Changes of the partial Mayo score and subscore at week 6 and week 14 post vedolizumab administration from baseline.

	Patients with valid partial Mayo score at	
	Week 6 (*n* = 77)	Week 14 (*n* = 71)
Reduction in partial Mayo score		
Median (IQR)	3.0 (3.0)	3.0 (3.0)
Reduction in stool frequency subscore		
Median (IQR)	0.0 (1.0)	1.0 (2.0)
Reduction in rectal bleeding subscore		
Median (IQR)	1.0 (1.0)	1.0 (2.0)
Reduction in physician's global assessment subscore		
Median (IQR)	1.0 (1.0)	1.0 (1.0)
IQR, interquartile range.		

anti-TNF therapy (similar to this study), the outcome rates appeared to be largely consistent.[15,25,26] In a French study[15] and a US study with a multicenter cohort,[26] the clinical response/remission at week 6 were 41%/32% and 45.0%/15.0%, respectively, which were not quite different with the results of this study (55.8%/18.2%). Data from another anti-TNF failures-focused study which enrolled 29 patients with UC from 37 Belgian centers[25] has also indicated a similar trend, that is, the reported week 10-response rate was 59% and the remission rate was 10%. Evidence suggests that early response to biologic treatment in UC may be predictive of favorable outcomes over the longer term.[27,28] As a result, our observation provides some support that patients treated with

Table 4. Endoscopic response and remission rates at week 6 and week 14 post vedolizumab administration.

	Post vedolizumab administration	
	Week 6	Week 14
Number of patients with a valid Mayo endoscopic subscore among those with a baseline Mayo endoscopic subscore ⩾ 2	9	57
Endoscopic response rate, *n* (%)	2 (22.2)	28 (49.1)
Endoscopic remission rate, *n* (%)	2 (22.2)	28 (49.1)
Complete endoscopic remission rate, *n* (%)	0 (0)	4 (7.0)

Endoscopic response was defined as a decrease of at least 50% from baseline Mayo endoscopic subscore. Endoscopic remission was defined as Mayo endoscopic subscore of 0–1. Complete endoscopic remission was defined as Mayo endoscopic subscore of 0.

Table 5. Comparison of covariates balance pre- and post-optimal matching.

	Pre-matching			Post-matching		
	Korea	*GEMINI 1*	*p*-value	*Korea*	*GEMINI 1*	*p*-value
	n = 105	*n* = 222		*n* = 47	*n* = 47	
Age, years						
Median (IQR)	47.0 (23.0)	39.7 (21.5)	<0.001	43.0 (24.5)	38.2 (24.9)	0.559
Male sex, *n* (%)	67 (63.8)	122 (55.0)	0.127	28 (59.6)	27 (57.4)	0.836
BMI, kg/m^2						
Median (IQR)	21.4 (4.3)	24.0 (6.1)	<0.001	21.3 (4.5)	22.0 (5.7)	0.407
Smoking status, *n* (%)						
Current smoker	4 (3.8)	15 (6.8)	0.019	4 (8.5)	1 (2.1)	1.000
Former smoker	31 (29.5)	76 (34.2)		13 (27.7)	19 (40.4)	
Never smoked	62 (59.0)	131 (59.0)		30 (63.8)	27 (57.4)	
Disease duration, years						
Median (IQR)	3.6 (4.0)	5.7 (8.3)	<0.001	4.1 (3.3)	3.9 (3.6)	0.959
Number of prior hospitalizations						
Median (IQR)	0 (0.0)	0 (1.0)	0.976	0 (1.0)	0 (1.0)	1.000
Concomitant steroid use, *n* (%)	19 (18.1)	114 (51.4)	<0.001	10 (21.3)	12 (25.5)	0.631
Disease extent, *n* (%)						
Proctosigmoiditis	24 (22.9)	23 (10.4)	0.044	13 (27.7)	4 (8.5)	0.550
Left-sided colitis	22 (21.0)	76 (34.2)		11 (23.4)	19 (40.4)	
Extensive colitis	2 (1.9)	24 (10.8)		1 (2.1)	5 (10.6)	
Pancolitis	49 (46.7)	99 (44.6)		22 (46.8)	19 (40.4)	
Baseline Mayo score						
Median (IQR)	9.0 (2.0)	8.0 (3.0)	0.022	9.0 (2.0)	9.0 (2.0)	0.947

BMI, body mass index; IQR, interquartile range.

vedolizumab will likely have better, longer-term benefit given the positive outcomes observed at the early treatment stage. This study filled an important knowledge gap by focusing on the real-world effectiveness of vedolizumab in the sub-group of UC patients who have failed anti-TNF therapy which appear to be lacking in our current literature base.[6,13] Our data provided the needed evidence on this aspect in a group of Eastern Asian who lack response to anti-TNF therapy.

More recently, vedolizumab use for anti-TNF-naïve patients with UC has been approved in Korea. Real-world evidence from the West has suggested that early initiation of vedolizumab may offer additional outcomes benefits.[29,30] Unfortunately, local data in Asia for this category of patients remain limited. Further effort should be invested to examine the potential benefits of vedolizumab among anti-TNF-naïve patients in Korea and Asia.

Table 6. Clinical response and clinical remission* at week 6-comparison between the one-to-one matched cohorts from this study and the open-label sub-cohort of GEMINI 1 study.

Outcomes	Comparative cohorts		Odds ratio (95% CI) and *p*-value
	Korean study; matched subjects (*n* = 47)	GEMINI 1 study; matched subjects from the open-label, anti-TNF failure cohort (*n* = 47)	
Week 6 clinical response rate – *n* (%)	24 (51.1)	12 (25.5)	3.01 (1.18–8.02); *p* = 0.019
Week 6 clinical remission rate – *n* (%)	7 (14.9)	9 (19.1)	0.74 (0.21–2.49); *p* = 0.785

*Please see the Supplemental Table for a summary of definitions for clinical response and remission used in the GEMINI 1 study *versus* this observational study.
CI, confidence interval; TNF, tumor necrosis factor.

Table 7. Adverse event rates between the full cohort of this study (up to week 14) and the full TNF-failure cohort from the GEMINI 1 study (induction phase only, up to week 6).

	Korean study; full cohort	GEMINI 1 study; full TNF-failure cohort
	n = 105	*n* = 304
Safety outcomes		
Any AE, *n* (%)	16 (15.2)	164 (53.9)
Any SAE, *n* (%)	5 (4.8)	12 (3.9)
Top 3 AEs in the current study		
UC exacerbation (%)	6 (5.7)	11 (3.6)
Upper respiratory tract infection (%)	5 (4.8)	6 (2.0)
Arthralgia (%)	2 (1.9)	11 (3.6)

AE, adverse event; SAE, serious adverse event; TNF, tumor necrosis factor; UC, ulcerative colitis.

Despite the value of the data, there are some limitations to consider. Firstly, the potential effect of selection bias. Without a randomization mechanism to assigning treatment, clinicians are likely to initiate the interested treatment to those patients who feature a certain (set of) characteristics.[31] It is challenging to anticipate the exact direction of this source of bias. However, it is highly reasonable to believe that patients who are more likely to benefit by the treatment will have a higher probability of receiving it. As a result, the observed outcomes are more likely to be in favor to them in the real-world *versus* the clinical trial. Secondly, in reviewing the medical chart, investigators are more likely to 'look' for recorded information in the medical chart to fulfil their 'expectation'. If the investigator expects that patients receiving vedolizumab should have a more favorable outcome, it is likely that they will 'look harder' for this information in order to 'confirm' their belief (hence confirmation bias). As a result, the data may be concluded that there is a higher effectiveness observed from those who received the treatment. In addition, due to the different study design [i.e., a prospective clinical trial (of GEMINI 1) *versus* a retrospective chart review], the way AEs captured and reported were

Table 8. Subgroup analyses of clinical response at week 6 and week 14.

Clinical response stratified by	Week post-initiation of vedolizumab					
	Week 6			Week 14		
	No (*n* = 34)	Yes (*n* = 43)	*p*-value	No (*n* = 19)	Yes (*n* = 52)	*p*-value
1. Duration of UC						
<1 year (%)	0 (0.0)	2 (7.7)	0.201	0 (0.0)	2 (5.4)	0.539
1–<3 years (%)	7 (26.9)	8 (30.8)		3 (23.1)	12 (32.4)	
3–<7 years (%)	11 (42.3)	13 (50.0)		6 (46.2)	18 (48.6)	
≥7 years (%)	8 (30.8)	3 (11.5)		4 (30.8)	5 (13.5)	
2. UC disease extent						
Proctosigmoiditis (%)	5 (14.7)	14 (32.6)	0.081	5 (26.3)	13 (25.0)	0.976
Left-sided colitis (%)	7 (20.6)	9 (20.9)		4 (21.1)	14 (26.9)	
Extensive colitis (%)	1 (2.9)	1 (2.3)		0 (0.0)	2 (3.8)	
Pancolitis (%)	17 (50.0)	19 (44.2)		10 (52.6)	22 (42.3)	
Unknown (%)	4 (11.8)	0 (0.0)		0 (0.0)	1 (1.9)	
3. Number of prior anti-TNF therapy						
One (1) prior anti-TNF (%)	19 (55.9)	30 (69.8)	0.478	7 (36.8)	40 (76.9)	<0.001
Two (2) prior anti-TNFs (%)	12 (35.3)	10 (23.3)		7 (36.8)	12 (23.1)	
Three (3) prior anti-TNFs (%)	3 (8.8)	3 (7.0)		5 (26.3)	0 (0.0)	
4. Type of prior anti-TNF failure+						
Inadequate response (%)	20 (58.8)	24 (55.8)	0.766	8 (42.1)	32 (61.5)	0.452
Loss of response (%)	9 (26.5)	10 (23.3)		7 (36.8)	13 (25.0)	
Intolerance (%)	1 (2.9)	4 (9.3)		2 (10.5)	3 (5.8)	
Unknown (%)	4 (11.8)	5 (11.6)		2 (10.5)	4 (7.7)	
5. Type of concomitant medication exposure						
Corticosteroids only (%)	3 (8.8)	8 (18.6)	0.640	2 (10.5)	8 (15.4)	0.691
Immunosuppressants only (%)	2 (5.9)	3 (7.0)		2 (10.5)	2 (3.8)	
Corticosteroids and immunosuppressants (%)	1 (2.9)	2 (4.7)		0 (0.0)	2 (3.8)	
No corticosteroids or immunosuppressants (%)	28 (82.4)	30 (69.8)		15 (78.9)	40 (76.9)	

+Data captured as free-text initially and subsequently coded manually into the four categories. Entries such as 'dampened responsiveness', 'primary non-response', 'no response', and 'no effect' were coded as inadequate responses. Entries such as 'secondary loss of response', 'recurrence of symptoms' and 'loss of response' were coded as a loss of response. Entries such as 'cytomegalovirus infection', 'hypotension', and 'intolerance' were coded as intolerance. Other free-text entries such as 'principal investigator's judgement' and 'drug change' etc. were considered as unknowns.
TNF, tumor necrosis factor; UC, ulcerative colitis.

accordingly different. In a prospective clinical trial, AE reporting is explicitly solicited from the trial participants by the investigator. In an observational study of retrospective nature (especially *via* chart review), AEs are typically noted/documented according to their significance to the patients and relevance to the clinicians. Patients were unlikely to report (and clinicians were unlikely to document) the mild and non-specific events. Events that result in significant morbidity and has a known specificity to their treatment are more likely to be escalated to the clinician (and hence being documented in the medical records). As a result, one would expect that AEs of greater significance reported in a real-world observational study will closer resemble those reported in the clinical trial. The mild and non-specific AEs will likely be under-reported. This expectation coincides well with our findings. We believe that the safety findings are meaningful to clinicians and researchers who would like to establish an understanding of the safety profile of vedolizumab under the real-world clinical setting and in the Korean population. The GEMINI safety data presented along will serve as the benchmark to facilitate their qualitative interpretation.

The issue of missing data is inherent in any real-world study, particularly in retrospective studies by chart review. For instance, there is a ~25% missing data on clinical response and remission at week 6 in this study. The reported outcome rates above were primarily performed based on a complete case approach, that is, cases with missing outcome data were excluded. In addition, we also considered a sensitivity analysis in which patients with missing a Mayo score at 6 weeks and 14 weeks were assumed to be non-responders to vedolizumab (a.k.a. NRI). The resultant clinical response rates based on this highly conservative assumption, remain highly consistent with the results observed from other real-world studies and randomized clinical trials, that is, clinical response rate of 43% (95% CI 38–49%) at week 6, and 56% (95% CI 50–62%) at week 14. This indicates that, even if we make the most conservative assumption on the pattern of (non-random) missing data in this analysis, the conclusion based on this real-world study will still be considered highly meaningful and significant.

Conclusion

In conclusion, this study has illustrated that, in the real-world setting, vedolizumab is effective and well tolerated within the first 14 weeks of use in patients with UC in Korea. The proportion of patients experiencing clinical response and clinical remission at weeks 6 and 14 appear to be largely consistent with that observed from real-world studies in other regions and populations.

Ethical approval

The Ethics Committee of all the participating centers approved the conduct of this study and waived the need to obtain consent for the collection, analysis and publication of this retrospectively

obtained and anonymized non-interventional study data. (Asan Medical Center IRB approval # 2018-0869)

Transparency
The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Supplemental material
Supplemental material for this article is available online.

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