ORIGINAL ARTICLE - GASTROENTEROLOGY (CLINICAL)

Potential benefits of immunomodulator use with vedolizumab for maintenance of remission in ulcerative colitis

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Abstract

Background and Aim: This study aimed to determine the efficacy and safety of vedolizumab treatment with or without concomitant immunomodulator use in Japanese patients with moderate-to-severe ulcerative colitis.

Methods: Among enrolled patients in a phase 3 study conducted in Japan (clinicaltrials. gov, NCT02039505), data from patients allocated to 300-mg intravenous vedolizumab for induction and maintenance phases were used for this exploratory analysis. Efficacy endpoints were clinical response, clinical remission, and mucosal healing at week 10 and clinical remission and mucosal healing at week 60, and disease worsening and treatment failure during the maintenance phase.

Results: At week 10, the differences in clinical response, clinical remission, and mucosal healing rates between the subgroups (those with concomitant immunomodulator use minus those without) were 0.7 (95% confidence interval: −14.3, 15.7), 3.3 (95% confidence interval: −8.5, 15.2), and 1.8 (95% confidence interval: −13.0, 16.5), respectively. At week 60, the differences in clinical remission and mucosal healing between the subgroups with and without concomitant immunomodulator use were 26.1 (95% confidence interval: −3.5, 55.6) and 29.9 (95% confidence interval: 1.4, 58.4), respectively. The proportions of patients without treatment failure at day 330 of the maintenance phase were 90.7% with concomitant immunomodulator use and 73.7% without. No marked differences in incidence of infections were observed between subgroups.

Conclusions: This study suggested the possibility that concomitant immunomodulator use may be beneficial to maintain the clinical efficacy of vedolizumab.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) with an unpredictable clinical course, characterized by intermittent periods of relapse and remission.[1] The prevalence of UC is lower in Asian countries than in Western countries.[2] However, whereas the prevalence of UC has plateaued in Western countries, it has been increasing steadily in Japan.[2] The precise etiology of IBD remains unclear, but altered immune intestinal cell trafficking has been implicated in its pathogenesis, resulting in inflammation in the digestive tract.[1,3–6]

Current UC medications are not curative[7]; pharmacological interventions aim to treat acute and active disease and prevent relapse during remission.[1] Over time, the treatment paradigm for UC has moved towards corticosteroid-free remission and mucosal healing.[1] Available treatments include 5-aminosalicylic acid (5-ASA), oral corticosteroids (OCSs), immunomodulators (IMs), and biological therapies.[8]

Vedolizumab is a humanized monoclonal immunoglobulin G1 antibody that specifically binds to α4β7 integrin and blocks lymphocyte infiltration into the gut, reducing local inflammation without inducing systemic immunosuppression.[9–11] Vedolizumab is approved in over 60 countries (including the USA, Europe, and Japan) and is indicated for the induction and maintenance treatment of patients with moderate-to-severe UC and Crohn's disease (CD) who have had an inadequate response, lost response, or were intolerant to conventional therapy (e.g. IMs and OCS) or anti-tumor necrosis factor-α (TNF-α) therapy.[12–14] The approval of vedolizumab for the indication of UC in Japan was based on results from a Japanese phase 3 study and the global GEMINI 1 study.[5–7,15–17] The Japanese phase 3 study reported a higher clinical response rate with vedolizumab *versus* placebo during induction therapy (39.6% *vs* 32.9%; $P = 0.27$) and a statistically significantly higher rate of clinical remission during maintenance therapy (56.1% *vs* 31.0%; $P = 0.02$). Notably, clinical response rate during induction therapy in the anti-TNF-α-naïve subgroup was higher in patients who received vedolizumab (53.2%) than in those who received placebo (36.6%).[16] In GEMINI 1, vedolizumab demonstrated a significant improvement compared with placebo in both the induction and maintenance of clinical remission.[15]

The outcomes of concomitant biologics and IMs, such as azathioprine (AZA) and 6-mercaptopurine (6-MP), are of interest for IBD treatment.[18–21] A recent post-hoc analysis suggested that the benefit of concomitant IM and anti-TNF-α therapy may be due to reduced antidrug antibody formation and higher serum concentrations of anti-TNF-α drug.[22]

Given that vedolizumab is a humanized monoclonal antibody with a low immunogenic profile,[15,16] any benefit of vedolizumab with a concomitant IM would be unlikely to be attributed to antidrug antibody formation. In GEMINI 1, 3.7% of patients who received vedolizumab with available blood samples were positive for anti-vedolizumab antibodies (AVAs) at any time, and 1.0% had samples that were persistently positive (i.e. ≥ 2 consecutive positive samples) through week 52.[15] Clinical and real-world studies have assessed concomitant IM with vedolizumab, albeit with limited patient numbers and treatment duration.[15,23–25]

Here, we conducted an exploratory analysis of a phase 3 study to determine the efficacy, safety, and immunogenicity of vedolizumab with concomitant IM in Japanese patients with moderate-to-severe UC.

Methods

Study design and patients. Data were obtained from a randomized, double-blinded, placebo-controlled study that investigated the efficacy, safety, and pharmacokinetics of vedolizumab as induction and maintenance therapy in Japanese patients with moderate-to-severe UC (clinicaltrials.gov identifier: NCT02039505). This exploratory analysis investigated the efficacy and safety of vedolizumab by concomitant IM. The study was conducted in accordance with standards for Good Clinical Practice and all applicable regulations, and the ethical principles of the Declaration of Helsinki. Local and regional regulatory requirements were adhered to at each study center. Institutional review board approval was obtained from all study centers prior to study initiation. The study was registered on clinicaltrials.gov before the first patient was enrolled. All patients provided written informed consent prior to enrolment.

The primary study design has been reported in detail elsewhere (Fig. S1).[16] Briefly, eligible patients were aged 15–80 years, with total or left-sided UC diagnosis ≥ 6 months before enrollment, and had a baseline full Mayo score of 6–12 with an endoscopic subscore ≥ 2. Another eligibility criterion was patients had to have experienced treatment failure with an IM, corticosteroid, or anti-TNF-α, within 5 years before informed consent. IM failure included refractoriness (patients whose response was inadequate despite treatment for ≥ 12 weeks) or intolerance (patients who were unable to receive continuous treatment owing to adverse reactions), and corticosteroid failure included resistance (patients whose response was inadequate despite treatment of ≥ 40-mg/day prednisolone equivalent [oral or intravenous] for ≥ 1 week or 30–40 mg/day for ≥ 2 weeks), dependence (patients who had failed to reduce the dosage to < 10 mg/day owing to recurrence during gradual dose reduction), or intolerance (patients who were unable to receive continuous treatment owing to adverse reactions).

For the induction phase, patients were enrolled into cohort 1 (2:1 randomization to vedolizumab 300 mg or placebo). Patients received study drug (vedolizumab or placebo) by intravenous infusion at weeks 0, 2, and 6. After completion of patients' enrollment

into cohort 1, patients were enrolled into cohort 2 and received vedolizumab 300 mg at weeks 0, 2, and 6 to secure the sample size in the maintenance phase. Patients of cohorts 1 and 2 showing clinical response to vedolizumab at week 10 entered the maintenance phase at week 14 and were randomized (1:1) to receive vedolizumab 300 mg or placebo at weeks 14, 22, 30, 38, 46, and 54.

Concomitant use of an IM (AZA or 6-MP) with the study drug was allowed when initiated at least 83 days before the first study drug dose and was continued at the same dose from 27 days before the first study drug dose. Dose reduction or discontinuation was allowed only because of adverse reactions. Concomitant use of OCS ($\leq$ 30 mg/day) with study drug was allowed when initiated at least 14 days before the first study drug dose and continued at the same dose from 13 days before the first study drug dose. Dose modification was not allowed until 10 weeks after the first study drug dose. When clinical response was achieved at week 10 or later, dose reduction of OCS was initiated preferably per the prespecified schedule from the visit when clinical response was observed (when > 10 mg/day had been dosed, the dosage was to be gradually reduced by 5–10 mg per 2 weeks to reach 10 mg/day; when $\leq$ 10 mg/day had been dosed or achieved by gradual reduction, the dosage was to be gradually reduced by 2.5–5 mg per 2 weeks to achieve corticosteroid-free status). Concomitant use of 5-ASA was allowed when initiated at least 14 days before the first study drug dose and continued at the same dose from 13 days before the first study drug dose. Dose reduction or discontinuation was allowed only because of adverse events (AEs). Concomitant use of corticosteroid enemas or suppositories was prohibited.

Efficacy endpoints. Rates of clinical response (reduction of $\geq$ 3 points and $\geq$ 30% from baseline in the full Mayo score and $\geq$ 1 point decrease on the rectal bleeding subscore or an absolute rectal bleeding subscore $\leq$ 1), clinical remission (full Mayo score $\leq$ 2 and no subscore > 1), mucosal healing (endoscopic subscore $\leq$ 1) at week 10, and clinical remission and mucosal healing at week 60 were analyzed in subgroups by concomitant IM use at week 0. During the maintenance phase, disease worsening (increase of partial Mayo score by $\geq$ 3 points compared with week 10 for two successive visits and partial Mayo score of $\geq$ 5; partial Mayo score of 9 in two successive visits for patients with partial Mayo score > 6 at week 10) and treatment failure (disease worsening, use of rescue medication, or study discontinuation due to drug-related AEs) were assessed in subgroups defined by concomitant IM use at week 0.

Safety. The incidence of AEs and infections (per System Organ Class and Preferred Term of MedDRA ver. 19.0) was summarized by concomitant IM use at week 0.

Immunogenicity. Blood sampling for immunogenicity tests was conducted at weeks 0, 10, 30, and 60, and 16 weeks after the last dose, and presence of neutralizing AVA was determined using electrochemiluminescence assay.[26]

Pharmacokinetics. Blood sampling for pharmacokinetic analysis was conducted at weeks 2, 6, 10, 14, 22, 30, and 60. Serum vedolizumab concentrations were determined using enzyme-linked immunosorbent assay.[26]

Statistical analysis. Among patients enrolled in this study, the data of patients allocated to the vedolizumab group in the induction or maintenance phases were used for this exploratory analysis. Subgroup analysis with or without concomitant IM use at week 0 was conducted for efficacy endpoints at weeks 10 and 60. Point estimation and 95% confidence intervals (CIs) were calculated for differences in the rates of efficacy endpoints achieved between the subgroup with concomitant IM and without concomitant IM at week 0. Time to disease worsening and time to treatment failure from first dose in the maintenance phase were determined using the Kaplan–Meier method. Patients who were judged not to have disease worsening were defined as censored cases, and time to final assessment of partial Mayo score was used for analysis of time to disease worsening. Patients who were judged not to have treatment failure were defined as censored cases, and time to final visit in the maintenance phase was used for analysis of time to treatment failure. Statistical tests were not conducted for subgroups in the present analysis because of limited patient numbers. Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patients and baseline characteristics. In the induction phase, the number of patients enrolled into cohort 1 in the subgroup with concomitant IM use and without concomitant IM use was 80 and 84, respectively. Baseline patient characteristics in the induction phase are summarized in Table 1. The proportion of patients who experienced IM-refractory failure before enrollment into this study was higher in patients with concomitant IM (72.5% [58/80]) than without (9.5% [8/84]).

In the maintenance phase, the number of patients in the subgroup with concomitant IM use and without concomitant IM use was 22 and 19, respectively. Baseline patient characteristics in the maintenance phase are also summarized in Table 1. Prior IM-refractory failure was 68.2% (15/22) in the subgroup with concomitant IM use and none (0%) in the subgroup without concomitant IM. A lower proportion of patients experienced prior OCS failure in the subgroup with concomitant IM use (63.6% [14/22]) than in that without (84.2% [16/19]). A lower proportion of patients received concomitant OCS at week 0 in the subgroup with concomitant IM use (18.2% [4/22]) than in that without (47.4% [9/19]).

Sixty-four patients received AZA at week 0 at the following daily doses: 25–30 mg in 9 patients (14.1%); 50–75 mg in 42 patients (65.6%); and 100–150 mg in 13 patients (20.3%). Sixteen patients received 6-MP at week 0 at the following daily doses: 4–25 mg in 6 patients (37.5%); 30–50 mg in 7 patients (43.8%); and 60–80 mg in 3 patients (18.8%). Mean duration of concomitant use of IM was 83 days in the induction phase and 288 days in the maintenance phase.

Table 1 Baseline characteristics of patients by concomitant IM at week 0[†]

	Induction phase		Maintenance phase	
	Concomitant IM at week 0		Concomitant IM at week 0	
	With (n = 80)	Without (n = 84)	With (n = 22)	Without (n = 19)
Mean age, years (SD)	42.3 (14.2)	42.4 (14.7)	44.1 (15.7)	41.8 (12.8)
Age group, n (%)				
≥ 35 years	54 (67.5)	54 (64.3)	15 (68.2)	14 (73.7)
Male, n (%)	52 (65.0)	47 (56.0)	13 (59.1)	8 (42.1)
Mean duration of UC, years (SD)	6.5 (5.6)	7.9 (6.8)	9.5 (8.4)	7.6 (7.3)
Duration of UC, n (%)				
< 1 year	4 (5.0)	3 (3.6)	0 (0.0)	2 (10.5)
1 to < 3 years	21 (26.3)	21 (25.0)	4 (18.2)	6 (31.6)
3 to < 7 years	28 (35.0)	23 (27.4)	9 (40.9)	4 (21.1)
≥ 7 years	27 (33.8)	37 (44.0)	9 (40.9)	7 (36.8)
Full Mayo score, mean (SD)	8.1 (1.5)	8.5 (1.6)	8.3 (1.6)	7.9 (1.7)
Mayo score, n (%)				
6–8	48 (60.0)	40 (47.6)	11 (50.0)	13 (68.4)
9–12	32 (40.0)	44 (52.4)	11 (50.0)	6 (31.6)
Disease localization, n (%)				
Pancolitis	46 (57.5)	55 (65.5)	14 (63.6)	14 (73.7)
Left-sided colitis	34 (42.5)	29 (34.5)	8 (36.4)	5 (26.3)
Prior anti-TNF-α, n (%)				
Yes (anti-TNF-α-exposed)	43 (53.8)	42 (50.0)	12 (54.5)	5 (26.3)
No (anti-TNF-α-naïve)	37 (46.3)	42 (50.0)	10 (45.5)	14 (73.7)
Prior IM failure, n (%)	63 (78.8)	36 (42.9)	15 (68.2)	7 (36.8)
Refractory	58 (72.5)	8 (9.5)	15 (68.2)	0
Intolerance	5 (6.3)	28 (33.3)	0	7 (36.8)
Prior corticosteroids failure, n (%)	52 (65.0)	57 (67.9)	14 (63.6)	16 (84.2)
Resistance	14 (17.5)	10 (11.9)	3 (13.6)	4 (21.1)
Dependence	37 (46.3)	44 (52.4)	11 (50.0)	10 (52.6)
Intolerance	1 (1.3)	3 (3.6)	0	2 (10.5)
Concomitant OCS at week 0, n (%)				
Yes	21 (26.3)	31 (36.9)	4 (18.2)	9 (47.4)
No	59 (73.8)	53 (63.1)	18 (81.8)	10 (52.6)
Concomitant 5-ASA at week 0, n (%)				
Yes	69 (86.3)	76 (90.5)	20 (90.9)	19 (100.0)
No	11 (13.8)	8 (9.5)	2 (9.1)	0

[†]Percentages may not add up to 100% due to rounding.
5-ASA, 5-aminosalicylic acid; IM, immunomodulator; OCS, oral corticosteroid; SD, standard deviation; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis.
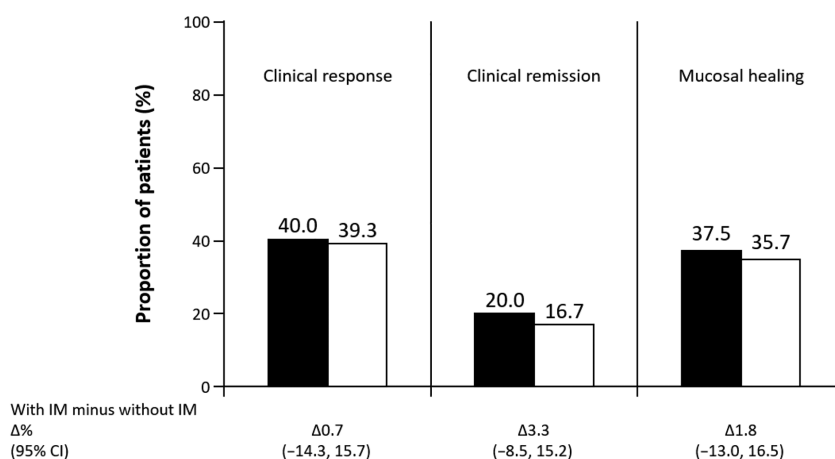

Figure 1 Efficacy endpoints at week 10. CI, confidence interval; IM, immunomodulator. ▪▪▪, with IM (n = 80); ▫▫▫, without IM (n = 84).

Efficacy outcomes in induction phase. Figure 1 shows efficacy outcomes at week 10 by concomitant IM at week 0. The differences in clinical response, clinical remission, and mucosal healing rates between the subgroups (those with concomitant IM minus without) were 0.7 (95% CI: −14.3, 15.7), 3.3 (95% CI: −8.5, 15.2), and 1.8 (95% CI: −13.0, 16.5), respectively.

Efficacy outcomes in the maintenance phase. Efficacy outcomes at week 60 by IM status are shown in Figure 2. The differences in clinical remission and mucosal healing between the subgroups (those with concomitant IM minus without) were 26.1 (95% CI: −3.5, 55.6) and 29.9 (95% CI: 1.4, 58.4), respectively.
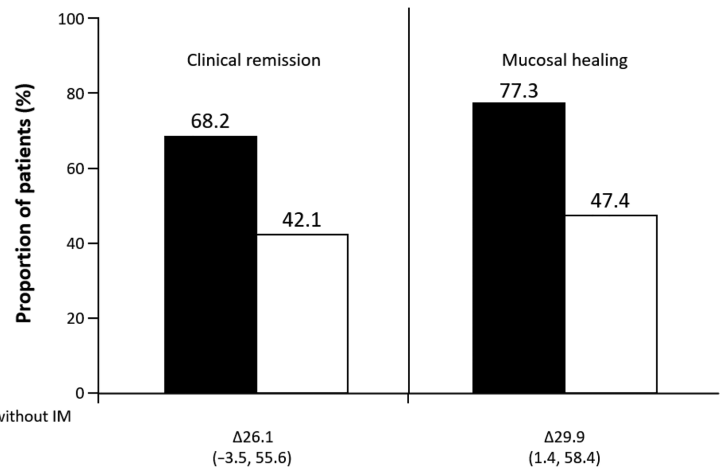

Figure 2 Efficacy endpoints at week 60. CI, confidence interval; IM, immunomodulator. ▪▪▪, with IM (*n* = 22); ▪▪▪, without IM (*n* = 19).

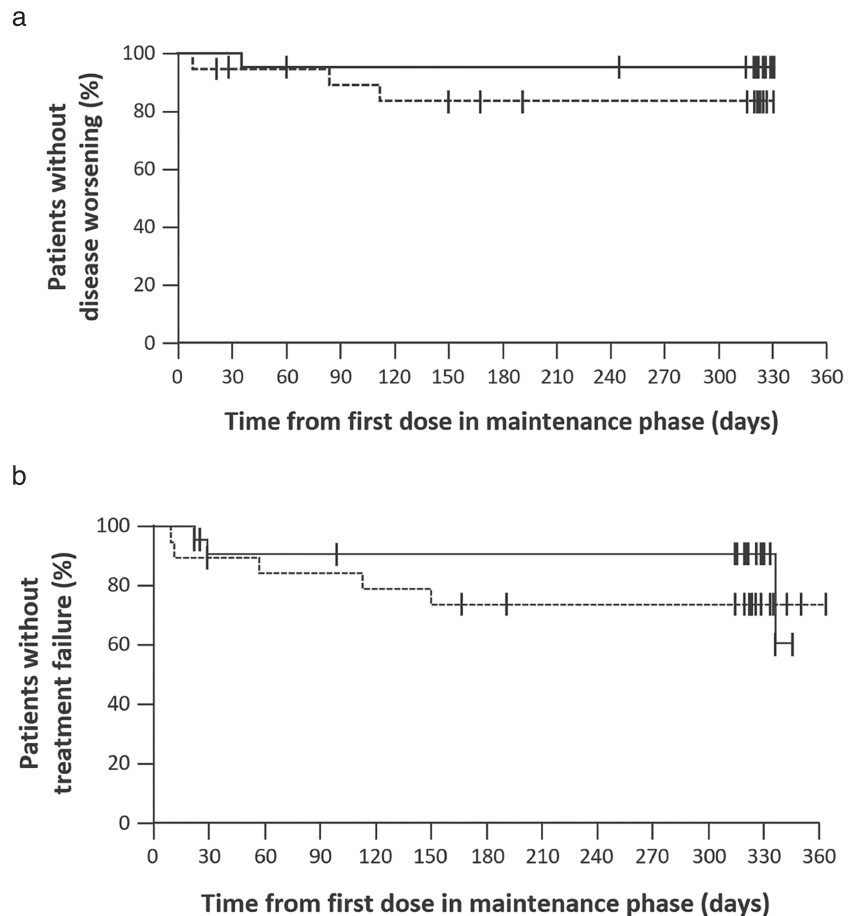**Figure 3** (a) Time to disease worsening and (b) time to treatment failure during maintenance phase by concomitant immunomodulator (IM) at week 0. ▪▪▪, with IM (*n* = 22 at day 0); ▪▪▪, without IM (*n* = 19 at day 0).

The time to disease worsening and time to treatment failure by concomitant IM use at week 0 in the maintenance phase are shown in Figure 3. The proportions of patients without disease worsening until day 330 of the maintenance phase were as follows: vedolizumab with IM, 95.2% (95% CI: 70.7, 99.3), and vedolizumab without IM, 83.6% (95% CI: 57.3, 94.4) (Fig. 3a). The proportions of patients without treatment failure until day 330 of the maintenance phase were as follows: vedolizumab with IM, 90.7% (95% CI: 67.6, 97.6), and vedolizumab without IM, 73.7% (95% CI: 47.9, 88.1) (Fig. 3b).

Table 2 Incidence of adverse events according to concomitant IM at week 0 in the induction phase (up to week 10)

	Concomitant IM at week 0	
	With ($n = 80$)	Without ($n = 84$)
Overall, n (%)	39 (48.8)	43 (51.2)
Infections and infestations, n (%)	17 (21.3)	17 (20.2)
Nasopharyngitis	13 (16.3)	10 (11.9)
Cytomegalovirus infection	—	1 (1.2)
Pneumonia	1 (1.3)	1 (1.2)
Angular cheilitis	—	1 (1.2)
Bronchitis	—	1 (1.2)
Folliculitis	1 (1.3)	1 (1.2)
Pharyngitis	—	1 (1.2)
Sinusitis	1 (1.3)	—
Device-related infection	1 (1.3)	—
Genital herpes	—	1 (1.2)
Laryngitis	—	1 (1.2)
Oral candidiasis	—	1 (1.2)
Otitis media	—	1 (1.2)
Pericoronitis	—	1 (1.2)
Periodontitis	—	1 (1.2)

IM, immunomodulator.

Table 3 Incidence of adverse events according to concomitant IM at week 0 in the maintenance phase (from week 14)

	Concomitant IM at week 0	
	With ($n = 22$)	Without ($n = 19$)
Overall, n (%)	17 (77.3)	19 (100.0)
Infections and infestations,[†] n (%)	11 (50.0)	11 (57.9)
Nasopharyngitis	9 (40.9)	9 (47.4)
Gastroenteritis	—	2 (10.5)
Pharyngitis	—	1 (5.3)
Enteritis infectious	1 (4.5)	—
Folliculitis	—	1 (5.3)
Otitis media	1 (4.5)	—
Sinusitis	—	1 (5.3)
Appendicitis	1 (4.5)	—
Conjunctivitis	—	1 (5.3)
Cystitis	1 (4.5)	—
Pneumonia	—	1 (5.3)

[†]Incidence of infections and infestations were summarized based on System Organ Class and Preferred Term of MedDRA ver. 19.0.
IM, immunomodulator.

Safety. The incidences of AEs by concomitant IM use in the induction and maintenance phases are shown in Tables 2 and 3, respectively. No marked differences were observed in the incidence of overall AEs between patients with and without IM use. In the induction phase, infections were reported in the vedolizumab group as follows: with concomitant IM use, 21.3% (17/80), and without concomitant IM use, 20.2% (17/84). In the maintenance phase, infections were reported in the vedolizumab group as follows: with concomitant IM use, 50.0% (11/22), and without concomitant IM use, 57.9% (11/19). Most infections were nasopharyngitis.

Immunogenicity. Blood samples were available for analysis in 116 patients (70.7%) during the induction phase and 33 patients (80.5%) during the maintenance phase. Of the patients with available blood samples, 1.8% (1/55) of those without concomitant IM use and none with concomitant IM use ($n = 61$) were neutralizing AVA-positive at week 10 of the induction phase. No patients were neutralizing AVA-positive during the maintenance phase (without concomitant IM, $n = 17$; with concomitant IM, $n = 16$).

Pharmacokinetics. Blood samples were available for analysis in 110 patients (67.1%) at week 10 and 25 patients (61.0%) at week 60. The mean (standard deviation) vedolizumab serum concentrations at week 10 were 27.5 (12.6) µg/mL for patients with concomitant IM use ($n = 60$) and 36.1 (15.3) µg/mL for patients without concomitant IM use ($n = 50$). Those at week 60 were 19.2 (9.2) µg/mL for patients with concomitant IM use ($n = 13$) and 23.3 (8.5) µg/mL for patients without concomitant IM use ($n = 12$).

Discussion

The results of this exploratory analysis in Japanese patients with UC who were treated with vedolizumab showed a significantly higher mucosal healing rate at week 60 in the subgroup with concomitant IM use than that without. Moreover, the proportion of patients without disease worsening and treatment failure at day 330 of the maintenance phase tended to be higher in the subgroup with concomitant IM than that without concomitant IM. However, this benefit cannot be explained by the immunogenicity and pharmacokinetics of IM. No marked differences were observed in the proportion of neutralizing AVA-positive patients and vedolizumab serum concentrations at week 60 between the subgroups with concomitant IM and those without concomitant IM. Importantly, we confirmed a low immunogenicity of vedolizumab in this Japanese population because no patients were neutralizing AVA-positive during the maintenance phase regardless of the use of IM.

In the present study, most patients received a daily dose of AZA < 75 mg at baseline (the most commonly used doses were 50 mg/day of AZA or 30 mg/day of 6-MP), which is lower than that received by patients in North America and Europe. In Caucasian patients, the recommended doses for IMs are 1.5–2.5 mg/kg/day for AZA and 0.75–1.5 mg/kg/day for 6-MP; however, Japanese patients are more likely to develop AEs owing to their lower metabolic capacity.[27] Despite the relatively low daily dose of thiopurine in the present study, concomitant use of

thiopurine may help with inducing and maintaining remission in patients with UC.[28]

In GEMINI 1, the efficacy of vedolizumab was similar among patients with concomitant IM use at baseline and those without in both the induction and maintenance phases, albeit with small patient numbers.[15] Furthermore, no consistent benefit of vedolizumab with concomitant IM in the induction phase has been observed in patients with IBD in real-world studies.[24,25] As reported, the baseline characteristics of this study differ slightly from GEMINI 1 and similar population studies.[15,23–25] Notably, the overall severity or disease activity, treatment history, and treatment pattern may explain the differences observed in the benefits of the concomitant treatments.[16] In addition, the difference in metabolism and effectiveness of thiopurine in Japanese patients may reflect the result of concomitant use.[11,28] The limited clinical benefit of vedolizumab and concomitant IM use was reported in a retrospective study that evaluated the efficacy of vedolizumab in 96 patients with CD and 40 with UC.[23] The results of this retrospective analysis showed that the addition of IM after vedolizumab induction was a significant predictor of clinical response or remission at week 54 in patients with CD, although not in those with UC.[23] The latter finding may be due to the lower number of patients with UC. The characteristics of the UC patients between the aforementioned retrospective study and ours are very similar, except for a higher rate of pancolitis, at 50% and 62%, respectively.[16,23] The rates of patients benefiting from a concomitant IM were similar between the two studies, as well as the clinical benefit trends.[23]

The concomitant use of an IM did not affect the safety of vedolizumab in the induction or maintenance phases. No marked differences in the incidence of infections were observed among the subgroups. The immunogenicity of vedolizumab is known to be low, and it was not expected to be improved by the concomitant use of IM.[15] Only one patient was reported to be neutralizing AVA-positive (induction phase, without concomitant IM) in our study with no impact on efficacy.[16] This is in contrast to a previous study in which the addition of AZA to infliximab appeared to reduce immunogenicity and increase trough drug concentrations, potentially contributing to the greater efficacy of the combined therapy.[18] The results of the present analysis suggest that the clinical benefit maintained by vedolizumab in combination with an IM was unrelated to immunogenicity. Based on the currently available data, including results from this study, there is no evidence for an effect of the concomitant use of IMs on the pharmacokinetics of vedolizumab.[16,29–31]

The full mechanisms underpinning our observations here are unclear. UC is an immune-mediated (lymphocytic) inflammatory disease. One possibility may relate to differences in the mode of action of vedolizumab and IMs. Suppression of the local migration of lymphocytes (led by vedolizumab), which have become less susceptible to immune responses (led by IM), may enhance treatment. Given the differences in mode of action among the available agents and the activation of alternative signaling circuits after blockade of a single cytokine, exploring multi-cytokine blocker combinations, including vedolizumab, maybe be also of benefit for the IBD patients.[32]

Immunomodulators may be beneficial to maintain the clinical efficacy of vedolizumab. However, our exploratory analysis has various limitations. First, we retrospectively conducted an exploratory analysis in subgroup of a phase 3 study. Second, baseline characteristics between subgroups were not balanced; for example, of the patients enrolled in the induction phase, the proportion that experienced prior IM-refractory failure was approximately 70% in the subgroup with concomitant IM use compared with approximately 10% in the subgroup without concomitant IM use. These observations may skew the results. Third, blood samples for analysis of immunogenicity and pharmacokinetics were not available for all patients. Fourth, the number of patients at week 60 was too small to draw any definitive conclusions. Moreover, multiplicity of statistical analysis should be considered. Finally, we did not measure thiopurine metabolite 6-thioguanine or NUDT15 genotype in the current study. Therefore, our data should be interpreted with caution. However, this is the first exploratory analysis of this kind in a Japanese UC population treated with vedolizumab; further clinical and real-word studies with a larger number of patients are required to fully evaluate the therapeutic value of concomitant use of IMs with vedolizumab.

Acknowledgments

Data availability statement. Takeda makes patient-level, de-identified datasets and associated documents available after applicable marketing approvals and commercial availability have been received, an opportunity for the primary publication of the research has been allowed, and other criteria have been met as set forth in Takeda's Data Sharing Policy (see https://www.takedaclinicaltrials.com/ for details). To obtain access, researchers must submit a legitimate academic research proposal for adjudication by an independent review panel, who will review the scientific merit of the research and the requestor's qualifications and conflict of interest that can result in potential bias. Once approved, qualified researchers who sign a data-sharing agreement are provided access to these data in a secure research environment.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supporting Information