The Journal of Clinical Pharmacology
2021, 61(9) 1174–1181

DOI: 10.1002/jcph.1877

Vedolizumab Immunogenicity With Long-Term or Interrupted Treatment of Patients With Inflammatory Bowel Disease

Timothy Wyant, PhD[1], Lili Yang, MS[2], Richard A. Lirio, MD[1], and Maria Rosario, PhD[1]

Abstract

Patients in the GEMINI 1 or 2 study (NCT00790933; Eudra CT2008-002784-14) with ulcerative colitis or Crohn disease had low immunogenicity rates after vedolizumab treatment for up to 52 weeks. We report immunogenicity rates from the GEMINI long-term safety (LTS) study using a new drug-tolerant electrochemiluminescence assay, including analyses in patients who received continuous vedolizumab induction and maintenance in GEMINI 1 or 2 and long term safety, or vedolizumab induction and placebo maintenance in GEMINI 1 or 2 followed by re-treatment in long term safety (treatment interruption). Patients were enrolled in GEMINI long term safety from GEMINI 1, 2, or 3, or as de novo vedolizumab-treated patients; all received vedolizumab 300 mg intravenously every 4 weeks. Vedolizumab antidrug antibody (ADA) status was determined by electrochemiluminescence assay; ADA-positive samples were characterized by neutralizing activity. Vedolizumab ADA data were available for 1753 patients: 1513 continuously treated with vedolizumab before/during GEMINI long term safety, 240 re-treated after treatment interruption. Among continuously treated patients, 36 (2.4%) were ADA positive (15 persistently, 20 neutralizing ADA positive). Among re-treated patients, 53 (22.1%) were ADA positive (42 persistently, 40 neutralizing ADA positive). Longitudinal immunogenicity rates increased during placebo maintenance (19.4% at week 52), then decreased in GEMINI long term safety to rates (0 at the final visit) similar to continuously treated patients. ADA positivity was 1.1% vs 2.5% (continuous treatment) and 23.1% vs 22.0% (re-treatment) among patients with and without infusion-related reactions, respectively. Long-term vedolizumab treatment was associated with generally low immunogenicity rates; vedolizumab–re-treated patients had higher rates during placebo maintenance, which decreased during re-treatment. No relationship was observed between immunogenicity and infusion-related reactions.

Keywords

Crohn disease, GEMINI LTS, immunogenicity, long-term safety, ulcerative colitis, vedolizumab

Ulcerative colitis (UC) and Crohn disease (CD) are serious, chronic inflammatory bowel diseases that generally require long-term maintenance therapy. Treatment guidelines from the American College of Gastroenterology and the European Crohn's and Colitis Organisation recommend consideration of biologic therapies that target tumor necrosis factor, integrins, or interleukins for patients with moderate to severe disease who do not respond to, or are intolerant of, conventional therapy.[1–4] However, biologic therapies harbor an intrinsic risk for the development of antidrug antibodies (ADAs), which can be associated with a reduction in primary therapeutic efficacy, loss of response after an initial response, and potential for increased adverse events.[5] Given the clinical implications of safe and effective treatment, additional evaluation of immunogenicity associated with more recently approved biologics is warranted.

Vedolizumab is a gut-selective, $\alpha_4\beta_7$ integrin–binding, humanized monoclonal antibody that is approved to treat moderately to severely active ulcerative colitis and Crohn Disease.[6,7] Previous phase 3, double-blind, randomized, placebo-controlled studies demonstrated that vedolizumab was effective and well tolerated in patients with ulcerative colitis (GEMINI 1) or Crohn Disease (GEMINI 2 and 3).[8–10] Furthermore, vedolizumab therapy induced low immunogenicity rates in patients with ulcerative colitis (GEMINI 1) or Crohn Disease (GEMINI 2).[8,9,11] In the GEMINI long-term safety (LTS) study, long-term vedolizumab therapy was well tolerated and provided both clinical and health-related quality-of-life benefits.[12–15]

Immunogenicity was initially assessed using a drug-sensitive enzyme-linked immunosorbent assay (ELISA)

[1]Takeda Development Center Americas Inc., Cambridge, Massachusetts, USA
[2]Takeda Pharmaceuticals International Inc., Cambridge, Massachusetts, USA

Submitted for publication 15 February 2021; accepted 16 April 2021.

Corresponding Author:
Lili Yang, MS, Clinical Biomarker Innovation & Development, Takeda Pharmaceuticals International Inc., 35 Landsdowne Street, Cambridge, MA 02139
Email: LiLi.Yang@Takeda.com

Timothy Wyant, Richard A. Lirio, and Maria Rosario were employees of Takeda at the time of this research.

in prior studies and in GEMINI long term safety. To address the limitation of drug-sensitive assays, a new drug-tolerant acid dissociation electrochemiluminescence (ECL) assay was developed and used on samples collected from July 15, 2015, onward, and on a small subset of samples collected before that date. Here, we report long-term vedolizumab immunogenicity rates using the ECL assay in patients with ulcerative colitis or Crohn Disease who participated in the GEMINI program (GEMINI 1, 2, and 3 and GEMINI long term safety), including those who received vedolizumab continuously and those who received vedolizumab induction therapy and were then randomized to placebo maintenance treatment in GEMINI 1 or 2 before being re-treated with vedolizumab in GEMINI long term safety (treatment interruption).

Methods

Study Population and Design

The GEMINI long term safety study was conducted in accordance with the Declaration of Helsinki and in compliance with the institutional review board regulations of the US Code of Federal Regulations, Good Clinical Practice regulations and guidelines, and all applicable local regulations. All patients gave written informed consent.

GEMINI long term safety was a multicenter, open-label study that enrolled patients from a long-term phase 2 study (ClinicalTrials.gov Identifier: NCT00619489), GEMINI 1,[8] GEMINI 2,[9] GEMINI 3,[10] and vedolizumab-naive (de novo) patients. The GEMINI 1, 2, and 3 trial eligibility criteria have been previously reported.[8–10] Patients in the GEMINI long term safety de novo cohort were adults aged 18 to 80 years with moderately to severely active ulcerative colitis (based on a partial Mayo score) or Crohn Disease (based on the Harvey-Bradshaw Index), diagnosed within 3 months from enrollment. Patients were excluded if they had an abdominal abscess, extensive colonic resection, short bowel syndrome or a history of >3 small-bowel resections, symptomatic intestinal stenosis or a stoma, malignancy, chronic hepatitis B or C infection, active or latent tuberculosis, or immunodeficiency. Patients with unstable or uncontrolled medical conditions, surgery requiring general anesthesia within 30 days from enrollment, plans to undergo major surgery during the study period, clinically relevant laboratory abnormalities, current or recent drug or alcohol dependence, or active psychiatric disease were also excluded. Intake of cyclosporine or thalidomide within 30 days of enrollment; infliximab or certolizumab pegol within 60 days of enrollment; or natalizumab, efalizumab, or rituximab at any time were not permitted. Further details on the GEMINI long term safety study can be found in the published report.[15]

Patients from GEMINI 1 and 2 received either placebo or vedolizumab 300 mg intravenous (IV) induction. At week 6, patients with a clinical response to vedolizumab were randomly assigned to maintenance treatment with placebo, vedolizumab every 8 weeks (Q8W), or vedolizumab every 4 weeks (Q4W). All patients from GEMINI 3 received vedolizumab 300 mg IV induction only, before enrolling in GEMINI long term safety, in which all patients were treated with vedolizumab 300 mg IV Q4W. As a result, patients in GEMINI long term safety could have been treated with vedolizumab continuously or could have had initial vedolizumab induction treatment followed by placebo maintenance and then vedolizumab re-treatment in GEMINI long term safety (Figure 1).

Study Assessments

Blood samples for evaluating vedolizumab immunogenicity (the presence of vedolizumab ADAs in serum) were collected during GEMINI 1, 2, and 3 at weeks 0 and 6, and then every 12 weeks until week 52; these have been reported elsewhere.[8–10] In GEMINI long term safety, blood samples were collected before vedolizumab infusion at week 4; at 16-week intervals from week 20 to week 196; at weeks 220, 248, 272, 300, 324, and 352; and at the final safety visit 16 weeks after the last vedolizumab infusion. Immunogenicity was initially assessed using a validated, drug-sensitive, biotinylated, bridging ELISA.[16] To address the possible underestimation of on-drug immunogenicity that may occur with a drug-sensitive assay, a new drug-tolerant assay was later developed using acid dissociation ECL. This new assay has a drug tolerance of at least 50 μg/mL of vedolizumab with 500 ng/mL of positive control (affinity purified rabbit anti-vedolizumab antibodies), $\leq$25 μg/mL of vedolizumab with 100 ng/mL of positive control, and $\leq$5 μg/mL of vedolizumab with 10 ng/mL of positive control. The ECL assay was used on samples collected from July 15, 2015, onward and also on a small subset collected before that date. We report the results of ADA assessment using the ECL assay.

Persistently ADA-positive patients were defined as those with at least 2 consecutive confirmed positive results in GEMINI 1, 2, or 3 or GEMINI long term safety. Confirmed ADA-positive samples were further assessed for the ability of ADA to neutralize vedolizumab binding to recombinant human integrin $\alpha_4\beta_7$, using a drug-tolerant acid dissociation ECL assay. This new neutralization assay has a drug tolerance of at least 50 μg/mL of vedolizumab with 250 ng/mL of positive control (affinity purified rabbit anti-vedolizumab antibodies), up to 5 μg/mL of vedolizumab with 80 ng/mL of positive control, and no

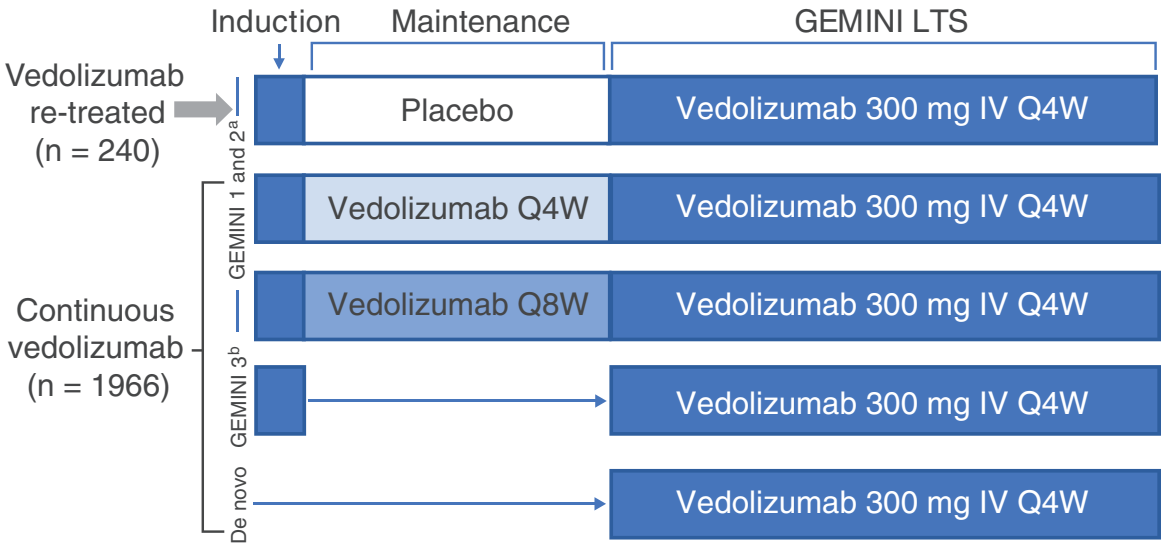

Figure 1. Continuous use and vedolizumab–re-treated cohorts in GEMINI long term safety. IV, intravenous; long term safety, long-term safety; Q4W, every 4 weeks; Q8W, every 8 weeks. [a]Non–intent-to-treat patients in GEMINI 1 and 2 received vedolizumab Q4W during maintenance and were also eligible for enrollment in GEMINI long term safety. This included patients treated with placebo during induction and week 6 nonresponders. [b]GEMINI 3 included patients treated with placebo during induction who were also eligible to enroll in GEMINI long term safety.

drug tolerance at 36 ng/mL of positive control. Incidence of investigator-defined infusion-related reactions was also analyzed.

Statistical Analyses

Data on patient baseline demographics and disease characteristics included all patients with ADA results. Data on the ADA status overall and by study visit, concomitant immunomodulator use, and occurrence of infusion-related reactions included patients with ADA results obtained using the ECL assay. Descriptive statistics were used to summarize all data.

Results

Immunogenicity was originally assessed using an ELISA in all 2206 patients from GEMINI long term safety: 1966 had been treated with vedolizumab continuously and 240 were re-treated with vedolizumab following a break in previous vedolizumab therapy. Patients treated continuously with vedolizumab (n = 1966) included 752 (38.3%) patients with ulcerative colitis and 1214 (61.7%) patients with Crohn Disease. Patients treated with placebo maintenance in GEMINI 1 or 2 and then re-treated with vedolizumab in GEMINI long term safety (n = 240) included 113 (47.1%) with ulcerative colitis and 127 (52.9%) with Crohn Disease. Patient characteristics, disease characteristics, and rates of concomitant immunomodulator or corticosteroid use were similar between the 2 groups at time of enrollment in GEMINI long term safety (Table 1). Vedolizumab ADA data collected in GEMINI 1 and 2 before the first vedolizumab dose showed <1% of vedolizumab-treated patients were ADA-positive using both ECL (9/1427) and ELISA (13/1434) assays.

Vedolizumab ADA data from a new ECL assay were available for 1753 of 2206 patients enrolled in GEMINI long term safety: 1513 had received continuous treatment, and 240 had been re-treated with vedolizumab. Among patients continuously treated with vedolizumab, 36 of 1513 (2.4%) were ADA positive at ≥1 assessments during GEMINI 1, 2, 3, or long term safety, of which 15 were persistently positive and 20 developed neutralizing antibodies. Among the patients who were re-treated with vedolizumab during GEMINI long term safety, 53 of 240 (22.1%) were ADA positive at any time, 42 were persistently positive, and 40 developed neutralizing antibodies (Table 2).

Longitudinal assessment of ADAs in patients from the start of GEMINI 1 or 2 through GEMINI long term safety showed lower cumulative vedolizumab immunogenicity rates for the Q8W and Q4W cohorts who received vedolizumab maintenance (4.3% [10/234] and 3.0% [7/234], respectively) than for patients who received placebo maintenance after vedolizumab induction (22.1% [53/240]). In the placebo maintenance cohort, rates of ADA positivity were 1.3% (3/234) at the end of induction and increased after a break in treatment during maintenance therapy (8.7% [18/206], 20.2% [24/119], and 19.4% [21/108] at weeks 14, 38, and 52, respectively). ADA positivity rates after vedolizumab re-treatment in GEMINI long term safety were 7.7% (1/13) at week 4, 0 at weeks 20 and 36, and remained at or near 0 through 404 weeks of treatment (Table 3).

Table 1. Baseline Patient and Disease Characteristics at Enrollment in GEMINI long term safety[a]

Characteristic	Continuous Vedolizumab (N = 1966)	Vedolizumab Re-treated[b] (N = 240)
Patients with UC, n (%)	752 (38.3)	113 (47.1)
Patients with CD, n (%)	1214 (61.7)	127 (52.9)
Age, y, mean (SD)	38.5 (13.2)	38.7 (12.9)
Sex, n (%)		
Male	991 (50.4)	120 (50.0)
Female	975 (49.6)	120 (50.0)
Current smoker, n (%)	360 (18.3)	46 (19.2)
Prior anti-TNF exposure, n (%)	1129 (57.4)	99 (41.3)
Concomitant medications, n (%)		
Immunomodulators	619 (31.5)	88 (36.7)
Corticosteroids	1063 (54.1)	136 (56.7)
Immunomodulators + corticosteroids	327 (16.6)	45 (18.8)
No immunomodulators or corticosteroids	611 (31.1)	61 (25.4)
Disease duration at enrollment, y, mean (SD)	8.8 (7.9)	8.9 (8.1)
Partial Mayo score, median (range)	6.0 (1-9)	6.0 (3-9)
Harvey-Bradshaw Index, median (range)	10.0 (2-27)	11.0 (5-27)
Vedolizumab exposure, mo, mean (SD)	37.7 (28.4)	39.8 (30.4)

CD, Crohn disease; LTS, long-term safety; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.
Percentages are calculated using the number of patients with nonmissing results.
[a] Includes the GEMINI long term safety safety population, defined as all patients.
[b] Patients randomized to vedolizumab at induction and to placebo at maintenance.

Table 2. Summary of Overall Vedolizumab ADA Status of Patients During GEMINI 1, 2, or 3 and GEMINI long term safety

Overall ADA Status	Continuous Vedolizumab (N = 1513)	Vedolizumab Re-treated[a] (N = 240)
ADA negative, n (%)[b]	1477 (97.6)	187 (77.9)
ADA positive, n (%)[c]	36 (2.4)	53 (22.1)
Transiently positive, n	21	11
Persistently positive, n	15	42
Any neutralizing ADA positive, n[d]	20	40

ADA, antidrug antibody; LTS, long-term safety.
Percentages are calculated using the number of patients with nonmissing results.
[a] Patients randomized to vedolizumab at induction and to placebo at maintenance in GEMINI 1 or 2, and re-treated with vedolizumab in GEMINI long term safety.
[b] Patients with no positive ADA results at any time during GEMINI 1, 2, 3, or long term safety.
[c] Patients with positive ADA results at any time during GEMINI 1, 2, 3, or long term safety.
[d] A neutralizing vedolizumab ADA with no reportable titer was considered missing (ie, no detectable positive neutralizing ADA was present in the sample).

ADA positivity rates were lower among patients continuously treated with vedolizumab with or without immunomodulator coadministration: 3 of 385 (0.8%) versus 28 of 980 (2.9%), respectively. In the vedolizumab–re-treated group, 40 of 151 (26.5%) patients without concomitant immunomodulator use were ADA-positive compared with 7 of 65 (10.8%) patients with concomitant immunomodulator use (Table 4).

Overall, 100 of 1753 (5.7%) patients reported an infusion reaction: 87 of 1513 (5.8%) in the continuous vedolizumab group and 13 of 240 (5.4%) in the vedolizumab–re-treated group. Rates of ADAs were similar between patients with infusion reactions and those without in the continuously treated cohort (1.1% [1/87] vs 2.5% [35/1426]) or the re-treated cohort (23.1% [3/13] vs 22.0% [50/227]). None of the 87 patients receiving continuous vedolizumab who had an infusion reaction were persistently ADA positive, whereas 2 of 13 (15.4%) patients re-treated with vedolizumab who had an infusion reaction were persistently ADA positive (Table 5). Infusion reaction rates were low overall and occurred at a similar frequency in patients who were ADA positive vs ADA-negative in the continuously treated cohort (2.8% [1/36] vs 5.8% [86/1477], respectively) and in the re-treated cohort (5.7% [3/53] vs 5.3% [10/187], respectively).

Discussion

In this study, a total of 36 of 1513 (2.4%) patients continuously treated with vedolizumab had at least 1 confirmed ADA-positive serum sample measured with a validated ECL assay; 15 patients were persistently positive, and 20 had neutralizing antibodies. These results are in line with previously published immunogenicity rates using an ELISA in GEMINI 1 and

Table 3. Vedolizumab ADA Status by Study Visit for Patients in GEMINI 1 and 2, and GEMINI long term safety

	Maintenance ITT		
Study Visit, n/N (%)	Vedolizumab Re-treatment[a] (N = 240)	Vedolizumab Q8W (N = 234)	Vedolizumab Q4W (N = 234)
Any ADA positive[b]	53/240 (22.1)	10/234 (4.3)	7/234 (3.0)
GEMINI 1 or 2 induction			
Week 0 (predose)	2/234 (0.9)	1/229 (0.4)	2/227 (0.9)
Week 6	3/234 (1.3)	3/231 (1.3)	2/228 (0.9)
GEMINI 1 or 2 maintenance			
Week 14	18/206 (8.7)	8/211 (3.8)	2/209 (1.0)
Week 26	36/150 (24.0)	2/156 (1.3)	1/176 (0.6)
Week 38	24/119 (20.2)	2/144 (1.4)	1/159 (0.6)
Week 52	21/108 (19.4)	1/131 (0.8)	0/151 (0)
GEMINI 1 or 2 early termination	21/122 (17.2)	2/86 (2.3)	0/72 (0)
GEMINI long term safety[c]			
Week 4	1/13 (7.7)	0/13 (0)	0/18 (0)
Week 20	0/13 (0)	0/13 (0)	0/18 (0)
Week 36	0/12 (0)	0/14 (0)	0/18 (0)
Week 52	0/13 (0)	0/13 (0)	0/18 (0)
Week 68	0/11 (0)	0/10 (0)	0/17 (0)
Week 84	0/11 (0)	0/11 (0)	0/18 (0)
Week 100	0/13 (0)	0/13 (0)	0/19 (0)
Week 116	0/14 (0)	0/12 (0)	0/19 (0)
Week 132	0/15 (0)	0/12 (0)	0/18 (0)
Week 148	0/13 (0)	0/12 (0)	0/17 (0)
Week 164	0/14 (0)	0/12 (0)	0/17 (0)
Week 180	1/18 (5.6)	0/15 (0)	0/18 (0)
Week 196	1/29 (3.4)	0/34 (0)	0/31 (0)
Week 220	1/50 (2.0)	0/57 (0)	0/51 (0)
Week 248	1/71 (1.4)	0/79 (0)	0/55 (0)
Week 272	0/67 (0)	0/55 (0)	0/52 (0)
Week 300	0/41 (0)	0/32 (0)	0/34 (0)
Week 324	0/21 (0)	0/6 (0)	0/12 (0)
Week 352	0/10 (0)	0/4 (0)	0/5 (0)
Week 376	0/4 (0)	0/0 (0)	0/2 (0)
Week 404	0/3 (0)	0/0 (0)	0/0 (0)
Final safety visit	0/58 (0)	0/73 (0)	1/62 (1.6)

ADA, antidrug antibody; ITT, intent to treat; LTS, long-term safety; Q4W, every 4 weeks; Q8W, every 8 weeks.

[a] Placebo-treated patients were randomized to vedolizumab at induction and to placebo at maintenance.

[b] Total number of patients with positive ADA results at any time during GEMINI 1, 2, or long term safety.

[c] Intravenous vedolizumab was administered Q4W to all patients in each cohort.

2, wherein 56 of 1434 (3.9%) patients treated with vedolizumab for up to 52 weeks were ADA positive; 9 patients were persistently positive, and 33 developed neutralizing antibodies.[8,9,12] Unlike previous analyses, the present study specifically investigated vedolizumab immunogenicity in a subset of patients in GEMINI long term safety who received vedolizumab induction treatment followed by placebo maintenance treatment, then received vedolizumab retreatment during GEMINI long term safety. More patients in this interrupted cohort were ADA positive than patients in the continuous vedolizumab cohort at any time (22.1% vs 2.4%, respectively). More patients re-treated with vedolizumab than treated with continuous vedolizumab were persistently ADA positive and developed neutralizing antibodies. The reason for this observation is currently unknown. However, similar to previous observations in the GEMINI long term safety study, the rate of ADA development did not seem to be dependent on the duration of treatment interruption.[14] Additionally, longitudinal immunogenicity rates in re-treated patients increased during placebo maintenance and then decreased in GEMINI long term safety to levels similar to patients treated with continuous vedolizumab.

Immunogenicity rates were not compared statistically between Q4W and Q8W vedolizumab dosing; however, the differences are expected because vedolizumab levels at Q4W are higher than at Q8W treatment.[17] This highlights a limitation of the ECL assay, in which higher (>25 μg/mL) vedolizumab trough concentrations may interfere with the detection of

Table 4. Overall Vedolizumab ADA Status of Patients During GEMINI 1, 2, or 3 and GEMINI long term safety With and Without Concomitant Immunomodulator Use

Concomitant Immunomodulators, n/N (%)	Continuous Vedolizumab (N = 1513)	Vedolizumab Re-treated[a] (N = 240)
Yes	385/1513 (25.4)	65/240 (27.1)
ADA positive[b]	3/385 (0.8)	7/65 (10.8)
Transiently positive	3/385 (0.8)	0/65 (0)
Persistently positive	0/385 (0)	7/65 (10.8)
Any neutralizing ADA positive[c]	0/385 (0)	4/65 (6.2)
No	980/1513 (64.8)	151/240 (62.9)
ADA positive[b]	28/980 (2.9)	40/151 (26.5)
Transiently positive	17/980 (1.7)	11/151 (7.3)
Persistently positive	11/980 (1.1)	29/151 (19.2)
Any neutralizing ADA positive[c]	18/980 (1.8)	31/151 (20.5)

ADA, antidrug antibody; LTS, long-term safety.
Percentages are calculated using the number of patients with nonmissing results.
[a] Patients randomized to vedolizumab at induction and to placebo at maintenance in GEMINI 1 or 2, and re-treated with vedolizumab in GEMINI long term safety.
[b] Patients with positive ADA results at any time during GEMINI 1, 2, 3, or long term safety.
[c] Neutralizing ADA with no reportable titer was considered missing (ie, no detectable positive neutralizing ADA was present in the sample).

Table 5. Overall Vedolizumab ADA Status During GEMINI 1, 2, or 3 and GEMINI long term safety for Patients With and Without an Infusion Reaction

Infusion Reactions, n/N (%)[a]	Continuous Vedolizumab (N = 1513)	Vedolizumab Re-treated[b] (N = 240)
Yes	87/1513 (5.8)	13/240 (5.4)
ADA positive[c]	1/87 (1.1)	3/13 (23.1)
Transiently positive	1/87 (1.1)	1/13 (7.7)
Persistently positive	0/87 (0)	2/13 (15.4)
Any neutralizing ADA positive[d]	1/87 (1.1)	2/13 (15.4)
No	1426/1513 (94.2)	227/240 (94.6)
ADA positive[c]	35/1426 (2.5)	50/227 (22.0)
Transiently positive	20/1426 (1.4)	10/227 (4.4)
Persistently positive	15/1426 (1.1)	40/227 (17.6)
Any neutralizing ADA positive[d]	19/1426 (1.3)	38/227 (16.7)

ADA, antidrug antibody; LTS, long-term safety.
Percentages are calculated using the number of patients with nonmissing results.
[a] Defined by investigator.
[b] Patients randomized to vedolizumab at induction and to placebo at maintenance in GEMINI 1 or 2, and retreated with vedolizumab in GEMINI long term safety.
[c] Patients with positive ADA results at any time during GEMINI 1, 2, 3, or long term safety.
[d] Neutralizing ADA with no reportable titer was considered missing (ie, no detectable positive neutralizing ADA was present in the sample).

low-titer ADA (ie, 10 ng/mL rabbit anti-vedolizumab positive control used during validation).[18]

While some studies indicated vedolizumab immunogenicity was not impacted by concomitant immunomodulator use,[5,11,19] possibly because of relatively low overall vedolizumab immunogenicity rates. Other studies have indicated concomitant immunomodulators therapy was associated with decreased immunogenicity.[8,9,20] In the current analysis, immunogenicity was lower in the continuously vedolizumab-treated patients receiving concomitant immunomodulators compared with those who were not (0.8% vs 2.9%). However, importantly in context of treatment interruptions, fewer patients in the vedolizumab–re-treated group with than without concomitant immunomodulator use were observed to be ADA positive (10.8% vs 26.5%). The lower ADA rate observed with concomitant immunomodulators vs without immunomodulators is in line with other research on immunomodulators and biologic therapeutics.[21] The development of ADAs has been associated with an increased risk of infusion reactions, particularly with anti–tumor necrosis factor therapy.[22,23] In contrast, consistent with previous reports,[12,18] the current analysis does not indicate that ADA status affects the rate of infusion reactions for vedolizumab. Rates of infusion reactions were similar in ADA-positive vs ADA-negative patients in the continuously treated cohort (1/87 [1.1%] vs 35/1426 [2.5%]) and in the re-treated group (3/13 [23.1%] vs 50/227 [22.0%]). Altogether, these results suggest a low impact of immunogenicity on vedolizumab safety in inflammatory bowel disease.[12]

Although vedolizumab clinical efficacy was not explored in this post hoc analysis, real-world data support the conclusion that ADAs do not appear to play a major role in vedolizumab efficacy,[24] even in patients who discontinue and later restart vedolizumab treatment.[25,26] This is further supported by previously published results[27] and that low-titer ADA positive status (10-50 titer values) had minimal effect on the pharmacokinetics of vedolizumab,[18] whereas higher-titer ADAs (≥250 titer values) affect vedolizumab clearance.[28] Additionally, a recent report suggested that immunogenicity was not a primary driver of vedolizumab treatment failure.[24]

Conclusions

This post hoc analysis of ADA using a new drug-tolerant ECL assay in patients treated continuously with vedolizumab and patients retreated with vedolizumab provides additional evidence supporting low overall immunogenicity rates, even with long-term vedolizumab use. Treatment interruption induced an increase in ADA rates that decreased with vedolizumab retreatment. There was no substantial difference in infusion reactions between the 2 cohorts, suggesting

only minimal clinical impact from a transient increase in vedolizumab immunogenicity.

Acknowledgments

Medical writing support was provided by Merrylle Morales-Dizon, MD, of ProEd Communications, Inc., and was funded by Takeda. Editorial assistance was provided by Daniella Babu, PhD, of Excel Medical Affairs, Fairfield, CT, United States and was funded by Takeda.

Conflicts of Interest

Timothy Wyant and Richard A. Lirio are former employees of Takeda. Lili Yang is an employee of Takeda and holds stock or stock options. Maria Rosario was an employee of Takeda at the time that this research was conducted and is an inventor on granted patents and pending patent applications related to the clinical pharmacology of vedolizumab.

Funding

This study was sponsored by Takeda.

Author Contributions

All authors had access to the study data; contributed to data interpretation, manuscript drafting, critical review, and revision; and approved the final manuscript for submission.

Data-Sharing Statement

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Data are available upon request via application at https://search.vivli.org.

References

1. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis*. 2017;11(7):769-784.
2. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
3. Feuerstein JD, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S. AGA Institute Clinical Guidelines Committee. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158(5):1450-1461.
4. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis*. 2020;14(1):4-22.
5. Vermeire S, Gils A, Accossato P, Lula S, Marren A. Immunogenicity of biologics in inflammatory bowel disease. *Therap Adv Gastroenterol*. 2018;11:1756283×17750355.
6. Vedolizumab [package insert]. Deerfield, IL: Takeda Pharmaceuticals America Inc; 2018.
7. Vedolizumab [summary of product characteristics]. Taastrup, Denmark: Takeda Pharma A/S; 2017.
8. 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(8):699-710.
9. 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(8):711-721.
10. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology*. 2014;147(3):618-627.e3.
11. Rosario M, Dirks NL, Milch C, et al. A review of the clinical pharmacokinetics, pharmacodynamics, and immunogenicity of vedolizumab. *Clin Pharmacokinet*. 2017;56(11):1287-1301.
12. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut*. 2017;66(5):839-851.
13. Loftus EV Jr, Colombel JF, Feagan BG, et al. Long-term efficacy of vedolizumab for ulcerative colitis. *J Crohns Colitis*. 2017;11(4):400-411.
14. Vermeire S, Loftus EV Jr, Colombel JF, et al. Long-term efficacy of vedolizumab for Crohn's disease. *J Crohns Colitis*. 2017;11(4):412-424.
15. Loftus EV Jr, Feagan BG, Panaccione R, et al. Long-term safety of vedolizumab for inflammatory bowel disease. *Aliment Pharmacol Ther*. 2020;52(8):1353-1365.
16. Rosario M, Dirks NL, Gastonguay MR, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther*. 2015;42(2):188-202.
17. Ltd TU. Entyvio 300 mg powder for concentrate for solution for infusion. *Datapharm Ltd*. https://www.medicines.org.uk/emc/product/5442/smpc#PRODUCTINFO. Accessed March 31, 2021.
18. Wyant T, Yang L, Rosario M. Comparison of the ELISA and ECL assay for vedolizumab anti-drug antibodies: assessing the impact on pharmacokinetics and safety outcomes of the phase 3 GEMINI trials. *AAPS J*. 2020;23(1):3.
19. Gouynou C, Peyrin-Biroulet C. Letter: addition of methotrexate neither restores clinical response nor improves the pharmacokinetic profile of vedolizumab-treated patients. *Aliment Pharmacol Ther*. 2017;46(10):1019-1020.
20. Rosario M, Polhamus D, Dirks N, et al. P529 Exposure-response relationship of vedolizumab subcutaneous treatment in patients with ulcerative colitis: VISIBLE 1. *J Crohns Colitis*. 2019;13(suppl 1):S377-S378.
21. Krieckaert CL, Bartelds GM, Lems WF, Wolbink GJ. The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review. *Arthritis Res Ther*. 2010;12(5):217.
22. Hindryckx P, Novak G, Vande Casteele N, et al. Incidence, prevention and management of anti-drug antibodies against therapeutic antibodies in inflammatory bowel disease: a practical overview. *Drugs*. 2017;77(4):363-377.
23. O'Meara S, Nanda KS, Moss AC. Antibodies to infliximab and risk of infusion reactions in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2014;20(1):1-6.

24. Van den Berghe N, Verstockt B, Tops S, Ferrante M, Vermeire S, Gils A. Immunogenicity is not the driving force of treatment failure in vedolizumab-treated inflammatory bowel disease patients. *J Gastroenterol Hepatol*. 2018;34(7):1175-1181.
25. Ungar B, Kopylov U, Yavzori M, et al. Association of vedolizumab level, anti-drug antibodies, and $\alpha 4\beta 7$ occupancy with response in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2018;16(5):697-705 e7.
26. Bian S, Dreesen E, Tang HT, et al. Antibodies toward vedolizumab appear from the first infusion onward and disappear over time. *Inflamm Bowel Dis*. 2017;23(12):2202-2208.
27. Rosario M, French JL, Dirks NL, et al. Exposure-efficacy Relationships for vedolizumab induction therapy in patients with ulcerative colitis or Crohn's disease. *J Crohns Colitis*. 2017;11(8):921-929.
28. Okamoto H, Dirks NL, Rosario M, Hori T, Hibi T. Population pharmacokinetics of vedolizumab in Asian and non-Asian patients with ulcerative colitis and Crohn's disease. *Intest Res*. 2021;19(1):95-105.