The Early Experience With Vedolizumab in the United States

Bharati Kochar, MD, MSCR,[*,†] *Yue Jiang, BS,*[‡] *Aaron Winn, PhD,*[§] *Edward L. Barnes, MD, MPH,*[*,†] *Christopher F. Martin, MSPH,*[†] *Millie D. Long, MD, MPH,*[*,†] *and Michael D. Kappelman, MD, MPH*[*,†]

Background: Post-marketing studies of new inflammatory bowel disease (IBD) therapies are needed to establish clinical effectiveness and safety in clinical practice. We aimed to describe the U.S. experience with vedolizumab in a commercially insured population.

Methods: We conducted a retrospective cohort study in Quintiles-IMS Legacy PharMetrics Adjudicated Claims Database from May 2014 to June 2016. We included new vedolizumab users with Crohn disease (CD) and ulcerative colitis (UC) between 18 and 64 years with ≥12 months of continuous enrollment prior to initiating vedolizumab. Outcomes included treatment persistence >14 weeks, late steroid use, IBD-related surgery and infections associated with hospitalization. We built multivariable regression models to identify predictors of treatment persistence and late steroid use.

Results: We identified 269 CD and 187 UC vedolizumab initiators. Only 60% of CD patients and 56% of UC patients remained on vedolizumab after 14 weeks without IBD-related hospitalization, surgery, and corticosteroid use. There were no significant predictors of treatment persistence. Steroid use in the first 2 months of vedolizumab initiation was a significant predictor of late steroid use in CD (odds ratio: 23.34; 95% confidence interval: 5.10–153.89). In the 6 months after vedolizumab initiation, 1.9% of CD and 5.9% of UC patients had an IBD-related surgery. Serious infections were <4%.

Conclusions: These data reflect the early U.S. experience with vedolizumab. The population-level response to vedolizumab therapy is just >50%. Steroids at the time of vedolizumab initiation is the strongest predictor of late steroid use in CD. Rates of surgery and serious infections are low. Vedolizumab, a newer biologic agent for inflammatory bowel disease, has shown good results in real life use. Over half of patients remain on it and do well after initiation. It is comparable in safety as the other newer treatments we have.

Key Words: Crohn disease, vedolizumab, ulcerative colitis

INTRODUCTION

The mainstay of maintenance therapy for moderate to severe inflammatory bowel disease (IBD) has traditionally been antitumor necrosis factor (TNF) alpha agents.[1, 2] However, given the systemic nature of these biological agents, they carry increased risks of infections and malignancies.[3–5] Furthermore, some patients who require immunosuppression do not respond to anti-TNF agents.[6–8] Therefore, other mechanisms of immunosuppression are needed for the treatment of IBD.

Vedolizumab is a humanized monoclonal antibody against the gut-specific $\alpha_4\beta_7$ integrin. It blocks leukocyte adhesion and migration into the gut. Its predecessor, natalizumab, was found to be efficacious in the treatment of Crohn disease (CD); however, its use was limited by a risk of developing progressive multifocal leukoencephalopathy among individuals previously exposed to JC virus. As vedolizumab targets a gut-specific molecule, theoretically, the risk of infections and malignancies due to systemic immunosuppression should be lower than natalizumab and other forms of systemic

immunosuppression.[9, 10] Vedolizumab was approved for use in IBD in 2014 and marketed under the brand name Entyvio. In clinical trials, vedolizumab was shown to beneficial for the induction and maintenance of remission in CD and ulcerative colitis (UC).[11, 12] However, it is well established that subjects in IBD clinical trials do not represent the IBD patient population in clinical practice.[13] Hence, real-world evidence to describe the clinical effectiveness and safety of vedolizumab in routine clinical practice are needed to better inform treatment decisions.

Post-marketing studies published to date have evaluated cohorts from large tertiary care centers and may not be generalizable to the broader U.S. population.[14–17] The only nationwide studies are from Scandinavian nations; however, the treated population in these countries is probably different than in the United States due to international variation in the management of IBD and availability of biological agents.[18–20] Therefore, characterizing the early use of vedolizumab and outcomes with vedolizumab in a large, unselected U.S. population is urgently needed. We sought to 1) describe the population of patients initiated on vedolizumab in a large, commercially insured U.S. population, 2) use this real-world evidence to describe the effectiveness and safety of vedolizumab, and 3) identify predictors of persistence of vedolizumab therapy and need for steroids beyond vedolizumab initiation to characterize the population most likely to safely respond to this new treatment.

METHODS

We conducted a retrospective cohort study in the Quintiles-IMS Legacy PharMetrics Adjudicated Claims Database, a large health insurance claims database of commercially insured individuals across the United States including claims from May 2014 to June 2016.

Patient Population

Our study population included individuals between the ages of 18 and 64 years with at least 2 healthcare contacts, on different days, with an associated an International Classification of Disease (ICD)-9 or ICD-10 code for CD or UC. If there were claims for both diagnoses, disease assignment was made based on the majority of the last 9 claims. Previous studies using administrative claims data have defined an IBD disease cohort using similar combinations of diagnosis codes.[21–23]

We limited the cohort to subjects with IBD who had at least 1 code for vedolizumab. After October 2014 and January 2016, the Healthcare Common Procedure Coding System (HCPCS) code of C9026 and J code of J3380, respectively, were assigned for vedolizumab. To identify vedolizumab infusions prior to these dates, we used a previously published algorithm that incorporated unlisted J codes (J3490 and J3590) or the HCPCS code for unspecified chemotherapy (C9399) with a cost of infusion greater than $4,500. This algorithm was found to be specific for vedolizumab infusions in subjects with IBD.[24] The index date was the date of the first code for vedolizumab.

Notable exclusion criteria were use of ustekinumab, natalizumab, cyclosporine, and tacrolimus, as these medications tend to signal unusual or refractory disease that is not seen in routine clinical practice. We excluded UC patients who had a code for a colectomy in the year prior to vedolizumab initiation again to ensure routine use of biologic therapy. We also excluded patients with less than 12 months of continuous enrollment prior to the date of vedolizumab initiation.

Analysis

We first described the demographics of this population as well as reported comorbidities by the Charlson comorbidity index. We reported those who were on an anti-TNF agent in the 12 months prior to vedolizumab initiation. We also reported other IBD medications before vedolizumab initiation from the following classes of medications: corticosteroids (defined as a prescription for at least a 14-day course), 5-aminosalicylate agents, and immunomodulators (methotrexate and thiopurines).

For the effectiveness outcomes, we only included a sample that had at least 6 months of continuous enrollment after vedolizumab initiation. The effectiveness outcomes of interest were 1) treatment persistence, defined as ≥1 dose of vedolizumab after 14 weeks of initiation, 2) late steroid use, defined as a prescription for oral corticosteroids 4–6 months after vedolizumab initiation, and 3) IBD-related colorectal surgery in the 6 months after vedolizumab initiation as specified by CPT codes (Supplementary Table 1). The safety outcome in this analysis was infections requiring hospitalizations, which is a definition previously used in the literature.[5, 25]

CD and UC were analyzed separately. Continuous variables are reported as means with SD and compared using the Student t-test. Categorical variables are reported as proportions with corresponding percentages and compared Fisher exact test.

Multivariable logistic regression models were constructed to determine predictors of treatment persistence and late steroid use. Relevant clinical predictors of interest were determined a priori based on clinical judgment. Clinical predictors included age 40 or older, male sex, Charlson comorbidity index greater than 0, receipt of anti-TNFs in the year prior to initiation, corticosteroid use in the 1–3 months prior to vedolizumab initiation, IBD-related hospitalization in prior year, methotrexate use in the first 90 days after vedolizumab initiation (in the CD models only), concomitant thiopurines use, defined as a prescription from the date of vedolizumab initiation to 3 months after and early corticosteroid use, defined as a prescription for corticosteroids from the date of vedolizumab initiation to 2 months after initiation. Although abdominal surgery for CD prior to vedolizumab initiation was determined to be clinically relevant, it was not included due to model fit concerns given the low numbers of people affected.

All statistical analyses were performed using SAS (version 9.3) statistical software (SAS Institute, Cary, NC).

RESULTS

Study Population

We identified 269 CD patients and 187 UC patients who initiated vedolizumab between May 2014 and June 2016. In the CD cohort, 60% were female and in the UC cohort, 48% were female. The median age in the CD cohort was 43 years and in the UC cohort, it was 44 years. Median follow-up after vedolizumab initiation in the CD cohort was 33 weeks and it was 28 weeks in the UC cohort. In the CD cohort, 37% had a comorbidity index of 1 or more and in the UC cohort, it was 27%. In the year prior to vedolizumab initiation, 56% of CD patients and 60% of UC patients were prescribed an anti-TNF agent; 42% of CD patients and 58% of UC patients were prescribed systemic corticosteroids. In the year prior to vedolizumab initiation, 44% of CD patients had at least 1 emergency room (ER) visit, 27% of CD patients had at least one hospitalization, and 0.7% had luminal surgery. In the year prior to vedolizumab initiation, 39% of UC patients had at least 1 ER visit and 18% of UC patients had at least one hospitalization. Further characteristics of the study population are reported in Table 1.

We assessed corticosteroid use concomitant with vedolizumab initiation. Of those who initiated vedolizumab, 16.4% of CD patients and 25.1% of UC patients were prescribed steroids from the date of vedolizumab initiation to 60 days after initiation. We also assessed concomitant immunomodulator use, defined as a prescription from initiation of vedolizumab to 90 days after initiation. In the CD cohort, 19.7% received a prescription for concomitant thiopurines and 10.8% received a prescription for concomitant MTX. In the UC cohort, 23.0% received a prescription for concomitant thiopurines. In the 6 months after vedolizumab initiation, 3.1% of CD patients and 3.0% of UC patients received a prescription for an anti-TNF agent.

Effectiveness

In the CD cohort, 64.6% of those who initiated vedolizumab had a claim for vedolizumab after 14 weeks of therapy, a marker of persistence of therapy. In the UC cohort, 66.9% of those who initiated vedolizumab had a claim for vedolizumab after 14 weeks of therapy. Of those who initiated vedolizumab, 11.3% of CD patients and 16.8% of UC patients received a prescription for steroids 4–6 months after initiation. These results are depicted in Figures 1 and 2. Of those who initiated vedolizumab, 1.9% of CD patients and 5.9% of UC patients had a luminal surgery in the 6 months after vedolizumab initiation. Hospitalization rates were also low: 13.8% of CD patients and 11.9% of UC patients had an IBD-related hospitalization in the 6 months after vedolizumab initiation. In total, 60% of CD patients and 56% of UC patients remained on vedolizumab after 14 weeks without hospitalizations, surgery, and corticosteroid use.

TABLE 1. Characteristics of Vedolizumab Initiators in the Quintiles-IMS Legacy PharMetrics Adjudicated Claims Database Between May 2014 and June 2016

	Crohn Disease	Ulcerative Colitis
n	269	187
Median age, y (IQR)	43 (34–55)	44 (35–56)
% Female	59.9	48.1
Median Follow-up, wk (IQR)	33 (21–62)	28 (18–52)
Region		
% East	18.6	23.0
% Midwest	40.1	32.1
% South	17.8	20.3
% West	23.4	24.6
CCI		
%0	63.2	73.3
%1	21.2	16.0
%2+	15.6	10.7
Medication use[a]		
% Steroid[b]	41.6	57.8
% 5-ASAs[c]	16.0	52.4
% Thiopurine	32.0	39.0
% Methotrexate	15.6	8.0
% Anti-TNF	56.1	59.9
Healthcare use[a]		
% ER visit	43.5	38.5
% hospitalized	28.6	17.6
% luminal surgery	0.7	0.0
% with CT scan	39.8	25.1
% with MRI	24.5	8.0
% with endoscopy	63.6	77.0

CT, computed tomography; MRI, magnetic resonance imaging; IQR, interquartile range; CCI, Charlson comorbidity index.
[a]In the year prior to vedolizumab initiation.
[b]Steroids defined as a more than 2-wk course of any oral systemic formulation.
[c]5-Aminosalicylates: oral formulations only.

In a multivariable regression model adjusting for all covariates, there were no significant predictors of persistence of vedolizumab therapy in CD and UC cohorts (Tables 2 and 3). In a second multivariable regression model, concomitant steroid prescription was a significant predictor of late steroid use in CD (odds ratio: 23.34, 95% confidence interval: 5.10–153.89). In CD, patients treated with steroids in the 3 months prior to vedolizumab initiation had a greater odds of being prescribed steroids after induction, although this association is not statistically significant (odds ratio: 2.64, 95% confidence interval: 0.59–11.65). Associations between concomitant thiopurine use, defined as a prescription for a thiopurine in the 90 days after vedolizumab initiation, and late steroid use were inconsistent for CD and UC and not statistically significant.

Safety

Overall rates of hospitalized infections after vedolizumab initiation were low. The most common infection after vedolizumab initiation was septicemia; 3.3% in the CD cohort and 1.6% in the UC cohort had a hospitalization with a diagnosis of septicemia in the 6 months after vedolizumab initiation. Clostridium difficile (C.diff) was the second most common infection with 2.6% in the CD cohort and 1.6% in the UC cohort having a hospitalization with a diagnosis of C.diff in the 6 months after vedolizumab initiation. However, 4.1% of the CD cohort and 2.1% of the UC cohort had a hospitalization

with a diagnosis of C.diff in the 12 months prior to vedolizumab initiation. With the exception of 1 patient in the CD cohort who had a hospitalization associated with a diagnosis of histoplasmosis in the 6 months after vedolizumab initiation, there were no other codes for serious fungal or mycobacterial infections after vedolizumab initiation.

DISCUSSION

This is one of the earliest reports of the broad clinical experience with vedolizumab in the United States. In this study of short-term clinical effectiveness and safety of vedolizumab, we found that only 65% of CD patients and 67% of UC patients continued vedolizumab therapy for more than 14 weeks after initiation. Furthermore, only 60% of CD patients and 56% of UC patients remained on vedolizumab past 14 weeks without an IBD-related hospitalization, IBD-related surgery and corticosteroid use. Taken together, these results suggest that slightly more than half of vedolizumab-treated IBD patients achieve a desirable short-term outcome. Overall, vedolizumab appears to be well tolerated. These real-world clinical effectiveness and safety data can be used to inform clinical decision making and appropriately counsel patients initiating vedolizumab to establish realistic patient and clinician expectations.

Not unexpectedly, the population in this real-world cohort is different than the population in the registration trials and tertiary care cohorts. Median age was higher in this cohort than the VICTORY consortium, but similar to the GEMINI trials.[11, 12, 26] Unlike the GEMINI 1 trial in which 41% of UC patients were anti-TNF experienced, 60% of UC patients in this real-world cohort were TNF-experienced. Unlike the VICTORY consortium, where 91% of CD patients were anti-TNF experienced, 56% of CD patients in this cohort were TNF-experienced. Concomitant corticosteroid use was lower
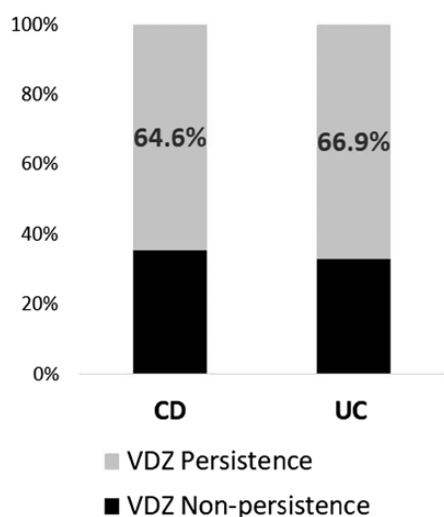
FIGURE 1. Vedolizumab persistence, defined as a dose of vedolizumab 14 wk after initiation, in the Quintiles-IMS Legacy PharMetrics Adjudicated Claims Database between May 2014 and June 2016
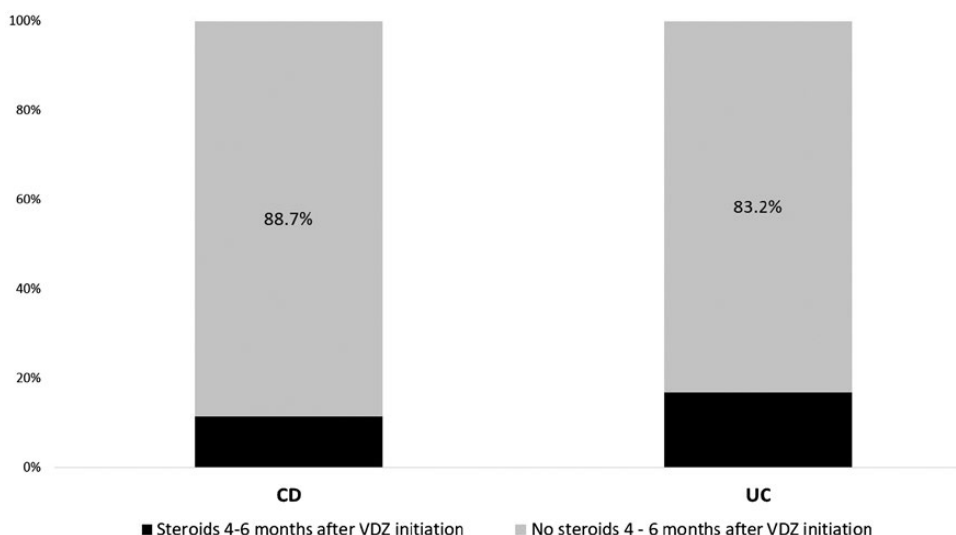
FIGURE 2. Corticosteroid prescription 4–6 mo after vedolizumab initiation in the Quintiles-IMS Legacy PharMetrics Adjudicated Claims Database between May 2014 and June 2016.

TABLE 2. Regression Models for Persistence of Vedolizumab (VDZ) Therapy and Late Corticosteroid Use in Crohn Disease Patients

	VDZ Persistence		Late Steroid Use[a]	
	aOR	95% CI	aOR	95% CI
Age > 40 y	1.11	0.63–1.96	2.83	0.66–15.69
Male sex	1.03	0.59–1.82	2.31	0.48–13.10
Charlson comorbidity index > 0	0.65	0.36–1.17	0.98	0.19–4.75
IBD-related hospitalization in 1 y prior	0.91	0.49–1.72	0.42	0.05–2.36
Anti-TNF use in 1 y prior	1.24	0.71–2.16	1.50	0.30–8.77
Prior steroid use[b]	0.63	0.30–1.35	2.64	0.59–11.65
Concomitant thiopurine use[c]	1.26	0.63–2.59	0.22	0.01–1.76
Concomitant methotrexate use[c]	1.70	0.72–4.40	1.35	0.18–8.29
Early steroid use[d]	1.01	0.49–1.72	23.34	5.10–153.89

VDZ persistence is defined as having a claim for VDZ at least 14 wk after initiation. Steroid use is defined as having a prescription for corticosteroids at least 4 mo after VDZ initiation. aOR, adjusted odds ratio; CI, confidence interval.
[a]Defined as a prescription 4–6 mo after vedolizumab initiation.
[b]Defined as a prescription 90–30 d prior to vedolizumab initiation.
[c]Defined as a prescription from the index date to 90 d after vedolizumab initiation.
[d]Defined as a prescription from the index date to 60 d after vedolizumab initiation.

TABLE 3. Adjusted Odds of Persistence of Vedolizumab (VDZ) Therapy and Late Corticosteroid Use in Ulcerative Colitis Patients

	VDZ Persistence		Late Steroid Use[a]	
	aOR	95% CI	aOR	95% CI
Age > 40 y	1.45	0.73–2.91	0.47	0.11–1.71
Male sex	1.21	0.60–2.46	1.24	0.32–5.00
Charlson comorbidity index > 0	0.69	0.30–1.57	3.84	0.90–17.63
IBD-related hospitalization in 1 y prior	1.30	0.46–3.92	1.10	0.21–4.96
Anti-TNF use in 1 y prior	1.91	0.94–3.95	1.12	0.28–4.87
Prior steroid use[b]	0.67	0.28–1.55	1.67	0.41–6.63
Concomitant thiopurine use[c]	0.95	0.41–2.23	2.64	0.66–10.58
Early steroid use[d]	1.02	0.42–2.57	3.92	0.92–18.11

VDZ persistence is defined as having a claim for VDZ at least 14 wk after initiation. Steroid use is defined as having a prescription for corticosteroids at least 4 mo after VDZ initiation. aOR, adjusted odds ratio; CI, confidence interval; TNF, tumor necrosis factor.
[a]Defined as a prescription 4–6 mo after vedolizumab initiation.
[b]Defined as a prescription 90–30 d prior to vedolizumab initiation.
[c]Defined as a prescription from the index date to 90 d after vedolizumab initiation.
[d]Defined as a prescription from the index date to 60 d after vedolizumab initiation.

in this real-world cohort than the GEMINI trials, but in the same range as the VICTORY consortium.

The rates of success in vedolizumab initiators suggest that it is important to carefully select the population receiving vedolizumab and identify predictors of successful vedolizumab therapy. The existing literature: a combination of post hoc analyses of the clinical trials and multicentered tertiary care cohorts, are conflicting in identifying predictors of success with vedolizumab therapy. Although we observed a possible protective relationship of concomitant thiopurine use for late steroid use in CD, many other studies do not note concomitant immunomodulator use to be beneficial with vedolizumab therapy.[26–29] One other study from a tertiary center reported that concomitant immunomodulator use is predictive of clinical remission on vedolizumab at 54 weeks in CD patients.[16] Post hoc analyses of data from the GEMINI 1 and 2 trials demonstrated a lower rate of antidrug antibody development in those who were on immunomodulators during vedolizumab induction and placebo maintenance, but did not find this to be the case in those who were on vedolizumab for maintenance.[30] It is possible

that the immunomodulator is mediating the immunogenicity of vedolizumab, which is often under-estimated.[30] However, it may be more likely that the therapeutic effects of the thiopurine itself are conferring this protection against late steroid use. Interestingly, in our UC cohort, concomitant thiopurine use may be a predictor for late steroid use; this may suggest that those with disease severe enough to require combination therapy for UC may not respond adequately to vedolizumab. The role of concomitant immunomodulators with vedolizumab should be investigated in a prospective manner to better inform the clinician treating patients with vedolizumab.

We also identified steroid use at the time of vedolizumab induction as being a significant predictor of late steroid use. This has previously not been reported in other studies of vedolizumab. Our data suggest that steroid use concomitant with vedolizumab initiation may be a marker of more severe disease that may not respond as well to gut selective immunosuppression.

A few other studies assessed for predictors of response to vedolizumab therapy. Data from 8 UK hospitals did not reveal any predictors of clinical response, defined as a decrease in standardized disease scoring scales, to vedolizumab treatment.[31] A US multicenter cohort, also using disease activity indices to define response, reported that hospitalization after vedolizumab initiation for UC patients was a significant predictor of lack of response.[16] Using data from the registration trials, Dulai et al developed a scoring system to predict probability of response to vedolizumab in CD and validated this in a multicentered tertiary care cohort. The algorithm included no previous bowel surgery, anti-TNF exposure, or fistulizing disease, along with a high albumin and low C-reactive protein.[32] Interestingly, our study did not find prior anti-TNF use to be a significant predictor.

Infections rates were lower in this real-world cohort compared with multicentered cohorts in tertiary care centers, but consistent with a recently published systematic review of trials and cohort studies.[33] A recently published analysis of the clinical trials of vedolizumab reports that C.diff is the most commonly reported infection with the medication.[34] In our cohort, C.diff was the second most commonly reported serious infection (behind septicemia). We observed a lower rate of C.diff infections after initiation of vedolizumab than in the year prior vedolizumab initiation. This suggests that active colitis itself is a risk factor for C.diff.[35]

There are limitations of studying new IBD medications in claims databases, including not being able to assess disease activity or laboratory values as well as misclassification of IBD treatment history. However, understanding patterns of medication utilization and outcomes such as hospitalization, surgery, and infections across the country in various practice settings is helpful in determining treatment choices and counseling patients. By including a large number of patients from various practice and geographic settings across the United States, our study has broad external generalizability. Our effectiveness outcomes were limited by the smaller subset of patients who had at least 6 months of continuous enrollment after vedolizumab initiation. This limited the precision and power of our multivariate analyses. In addition, our study was not designed to assess longer-term outcomes, including malignancy. Future studies are needed to determine risks for, and rates of, malignancy with vedolizumab use to place it in context with anti-TNF agents.

CONCLUSIONS

Real-world users of vedolizumab have different baseline characteristics than those reported in the registration trials and in many tertiary care cohorts. In this real-world cohort, we found relatively low rates of treatment persistence with vedolizumab, suggesting that the population-level response is just over 50%. We also identified early steroid use to be associated with late steroid use with vedolizumab treatment in CD. Overall, vedolizumab appears to be safe without a high rate of serious infections.

SUPPLEMENTARY DATA

Supplementary data are available at *Crohn's & Colitis 360* online.

REFERENCES

1. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol.* 2018;113:481–517.
2. Peyrin-Biroulet L, Bouhnik Y, Roblin X, et al.; Gastroenterologist Nominal Group. French national consensus clinical guidelines for the management of ulcerative colitis. *Dig Liver Dis.* 2016;48:726–733.
3. Annese V, Duricova D, Gower-Rousseau C, et al. Impact of new treatments on hospitalisation, surgery, infection, and mortality in IBD: a focus paper by the Epidemiology Committee of ECCO. *J Crohns Colitis.* 2016;10:216–225.
4. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. *JAMA.* 2017;318:1679–1686.
5. Singh S, Heien HC, Sangaralingham LR, et al. Comparative effectiveness and safety of anti-tumor necrosis factor agents in biologic-naive patients with Crohn's disease. *Clin Gastroenterol Hepatol.* 2016;14:1120–1129.
6. de Silva PS, Nguyen DD, Sauk J, et al. Long-term outcome of a third anti-TNF monoclonal antibody after the failure of two prior anti-TNFs in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2012;36:459–466.
7. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. *Am J Gastroenterol.* 2011;106:674–684.
8. Gisbert JP, Panes J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. *Am J Gastroenterol.* 2009;104:760–767.
9. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut.* 2017;66:839–851.
10. Stallmach A, Schmidt C, Teich N. Vedolizumab for the treatment of ulcerative colitis. *Expert Rev Gastroenterol Hepatol.* 2016;10:165–175.
11. Sandborn WJ, Feagan BG, Rutgeerts P, et al.; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2013;369:711–721.
12. Feagan BGR, Sands BP, Hanauer BE, et al.; Gemini Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2013;369:699–710.
13. Ha C, Ullman TA, Siegel CA, Kornbluth A. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. *Clin Gastroenterol Hepatol.* 2012;10:1002–1007; quiz e78.
14. Meserve J, Aniwan S, Koliani-Pace JL, et al. Retrospective analysis of safety of vedolizumab in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2019;17:1533–1540.

15. Shmidt E, Kochhar G, Hartke J, et al. Predictors and management of loss of response to vedolizumab in inflammatory bowel disease. *Inflamm Bowel Dis.* 2018;24:2461–2467.

16. Allegretti JR, Barnes EL, Stevens B, et al. Predictors of clinical response and remission at 1 year among a multicenter cohort of patients with inflammatory bowel disease treated with vedolizumab. *Digest Dis Sci.* 2017;62:1590–1596.

17. De Vos M, Dhooghe B, Vermeire S, et al.; Belgian Inflammatory Bowel Disease Research and Development (BIRD). Efficacy of vedolizumab for induction of clinical response and remission in patients with moderate to severe inflammatory bowel disease who failed at least two TNF antagonists. *United Eur Gastroenterol J.* 2018;6:439–445.

18. Eriksson C, Marsal J, Bergemalm D, et al.; SWIBREG Vedolizumab Study Group. Long-term effectiveness of vedolizumab in inflammatory bowel disease: a national study based on the Swedish National Quality Registry for Inflammatory Bowel Disease (SWIBREG). *Scand J Gastroenterol.* 2017;52:722–729.

19. Ylisaukko-Oja T, Aaltonen J, Nuutinen H, et al. High treatment persistence rate and significant endoscopic healing among real-life patients treated with vedolizumab – a Finnish Nationwide Inflammatory Bowel Disease Cohort Study (FINVEDO). *Scand J Gastroenterol.* 2018;53:158–167.

20. Benchimol EIC, Erichsen SF, Long R, et al. International variation in medication prescription rates among elderly patients with inflammatory bowel disease. *J Crohns Colitis.* 2013;7:878–889.

21. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol.* 2007;5:1424–1429.

22. Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of pneumonia among patients with inflammatory bowel disease. *Am J Gastroenterol.* 2013;108:240–248.

23. Crockett SD, Hansen RA, Stürmer T, et al. Statins are associated with reduced use of steroids in inflammatory bowel disease: a retrospective cohort study. *Inflamm Bowel Dis.* 2012;18:1048–1056.

24. Dubinsky MC, Cross RK, Sandborn WJ, et al. Extraintestinal manifestations in vedolizumab and anti-TNF-treated patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2018. [Epub ahead of print].

25. Grijalva CG, Chen L, Delzell E, et al. Initiation of tumor necrosis factor-α antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA.* 2011;306:2331–2339.

26. Dulai PS, Singh S, Jiang X, et al. The real-world effectiveness and safety of vedolizumab for moderate-severe Crohn's disease: results from the US VICTORY consortium. *Am J Gastroenterol.* 2016;111:1147–1155.

27. Colombel JFL, Siegal EV, Lewis CA, Smyth JMD, Xu J, Abhyankar B. *Efficacy of Vedolizumab with Concomitant Corticoteroid or Immunomodulator Use in Patients with Crohn's Disease from GEMINI 2, In Digestive Disease Week*. Washington, DC: Gastroenterology; 2015.

28. Colombel JFL, Siegal EV, Lewis CA, et al. *Efficacy of Vedolizumab with Concomittant Corticosteroid or Immunomodulator Use in Patients with Ulcerative Colitis from GEMINI 1, In Digestive Disease Week*. Washington, DC, Gastroenterology; 2015.

29. 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;42:188–202.

30. Rosario M, Dirks NL, Milch C, et al. A review of the clinical pharmacokinetics, pharmacodynamics, and immunogenicity of vedolizumab. *Clin Pharmacokinet.* 2017;56:1287–1301.

31. Lenti MV, Levison S, Eliadou E, et al. A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: the Cross Pennine study. *Dig Liver Dis.* 2018;50:1299–1304.

32. Dulai PS, Boland BS, Singh S, et al. Development and validation of a scoring system to predict outcomes of vedolizumab treatment in patients with Crohn's disease. *Gastroenterology.* 2018;155:687–695.e10.

33. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther.* 2017;46:3–15.

34. Ng SC, Hilmi IN, Blake A, et al. Low frequency of opportunistic infections in patients receiving vedolizumab in clinical trials and post-marketing setting. *Inflamm Bowel Dis.* 2018;24:2431–2441.

35. Balram B, Battat R, Al-Khoury A, et al. Risk factors associated with clostridium difficile infection in inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis.* 2019;13:27–38.