Gastroenterol Hepatol. 2019;42(10):650–656

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

SPECIAL ARTICLE

Questions and answers about the management of Crohn's disease and ulcerative colitis with vedolizumab☆

Joaquín Hinojosa del Val[a,*], **Manuel Barreiro-de Acosta**[b]

[a] *Unidad de EII, Hospital de Manises, Universidad Católica de Valencia, Valencia, Spain*
[b] *Unidad de EII, Servicio de Aparato Digestivo, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain*

Received 12 July 2019; accepted 21 August 2019
Available online 22 November 2019

KEYWORDS
Vedolizumab;
Crohn's disease;
Ulcerative colitis;
Management;
Clinical practice

Abstract Vedolizumab is an anti-integrin monoclonal antibody indicated for the treatment of patients with moderately to severely active Crohn's disease and ulcerative colitis who have failed conventional or anti-TNF therapies. The objective of this article is to answer a series of very practical questions regarding the management of both diseases with vedolizumab, based on data from published literature, as well as on the experience acquired by the authors in clinical practice in recent years.

PALABRAS CLAVE
Vedolizumab;
Enfermedad de Crohn;
Colitis ulcerosa;
Manejo;
Práctica clínica

Preguntas y respuestas sobre el manejo de la enfermedad de Crohn y la colitis ulcerosa con vedolizumab

Resumen Vedolizumab es un anticuerpo monoclonal anti-integrina indicado para el tratamiento de pacientes con enfermedad de Crohn y colitis ulcerosa moderada a grave, tras fracaso a terapia convencional o a anti-TNFs. El objetivo del presente artículo es dar respuesta a una serie de preguntas eminentemente prácticas respecto al manejo de ambas enfermedades con vedolizumab, tanto a través de evidencia clínica publicada, como de la experiencia adquirida por los autores en la práctica clínica a lo largo de los últimos años.

☆ Please cite this article as: Hinojosa del Val J, Barreiro-de Acosta M. Preguntas y respuestas sobre el manejo de la enfermedad de Crohn y la colitis ulcerosa con vedolizumab. Gastroenterol Hepatol. 2019;42:650–656.
* Corresponding author.
E-mail address: jhinojosad@gmail.com (J. Hinojosa del Val).

2444-3824/

Introduction

Vedolizumab (VDZ) is a humanised monoclonal antibody that specifically binds to lymphocyte integrin $\alpha4\beta7$ and thus inhibits their transendothelial migration to the bowel.[1] It is indicated for the treatment of adult patients with moderate to severe Crohn's disease (CD) and ulcerative colitis (UC) who have exhibited an insufficient response, loss of response or safety problems on conventional treatment (corticosteroids or immunomodulators) or TNF inhibitors. The recommended dose is 300 mg IV in weeks 0, 2 and 6 (induction) and every eight weeks thereafter (maintenance).[1] Its efficacy and safety for the treatment of CD and UC was demonstrated in the GEMINI studies.[2] In recent years, various studies conducted under real-life conditions have been published, as have systematic reviews and meta-analyses of these studies; these have offered results consistent with those seen in clinical trials.[3,4]

The objective of this study was to answer a number of questions regarding the management of CD and UC with VDZ, both through the published scientific evidence and through the experience acquired by the authors in clinical practice.

Should corticosteroids be administered during induction therapy with vedolizumab?

The GEMINI 1 study showed that, in UC, administration of corticosteroids during induction with VDZ did not substantially affect VDZ efficacy (response in week 6: 29.8 % placebo + corticosteroids vs 49.2 % VDZ + corticosteroids, $p = 0.004$; 20.0 placebo vs 44.4 % VDZ, $p < 0.001$).[5]

However, in CD, a *post-hoc* analysis of the GEMINI 2 and 3 studies showed that concomitant use of corticosteroids increased the efficacy of VDZ (GEMINI 2: clinical remission in week 6, 19.0 % VDZ + corticosteroids vs 10.9 % VDZ, difference: 8.1; 95 % CI: 1.1–15.0; GEMINI 3: clinical remission in week 10, 34.2 % VDZ + corticosteroids vs 22.7 % VDZ, difference: 11.6; 95 % CI: 2.9–20.2).[6]

In actual clinical practice, the ENEIDA registry study did not show better outcomes in patients with inflammatory bowel disease (IBD) who received concomitant corticosteroids, although no analysis that made a distinction between diseases (UC/CD) was performed.[7] Similarly, in the clinical practice studies conducted by the VICTORY consortium, concomitant treatment with corticosteroids was not associated with significant differences in efficacy.[8,9]

However, given that in all studies corticosteroids were already being administered on initiation of treatment with VDZ, it is difficult to set out a recommendation with regard to whether they should be introduced when treatment is started with VDZ where corticosteroids were not being administered. Therefore, in our clinical practice, both in UC and in CD, if the patient is on corticosteroids when treatment is started with VDZ, we keep him or her on the same dose, and, if the patient is not on corticosteroids, we generally introduce them (1 mg/kg, oral route), according to a regular decreasing regimen.

Can immunomodulators be suspended in patients treated with vedolizumab?

Although the results of a *post-hoc* analysis of the GEMINI studies suggest that immunomodulators do not appear to substantially affect the efficacy of VDZ, no clear conclusions may be drawn due to methodological limitations.[10]

However, a recent review of the use of immunomodulators in patients with IBD treated with VDZ concluded, based on the data available from both clinical trials and clinical practice, that adding immunomodulators to VDZ in patients with UC does not translate to an increased therapeutic effect. In CD, the evidence presented was less conclusive because, although in the majority of studies reported an additive effect was not observed with combination therapy, one study did identify concomitant treatment with immunomodulators as a variable predictive of a better clinical response.[11]

In clinical practice, it could be suggested that immunomodulators not be administered to patients with UC treated with VDZ but that its course be observed, whereas in CD, we would suggest that patients be kept on immunomodulators in combination with VDZ, in particular if they are receiving them when they start VDZ, provided that they present no related contraindications and the risk of adverse effects is assessed, with the option to suspend them in patients who have had repeated infections.

The fact that combined therapy does not seem to significantly influence the efficacy of VDZ, in particular in UC, has led us to recommend its use in monotherapy, especially in the most fragile patients, to enhance safety. VDZ in monotherapy would also be an option in populations of patients in whom the combination of TNF inhibitors and immunomodulators in the long term has been associated with a risk of lymphoma, such as young males and older patients.[11]

When should response to induction therapy be evaluated?

In the GEMINI 1 study, two induction doses were administered (weeks 0 and 2) to patients with UC, and in week 6 significant differences were found versus placebo in the percentage of patients in clinical remission (5.4 % placebo vs 16.9 % VDZ, $p = 0.001$).[5]

In the GEMINI 2 study, patients with CD received the same induction therapy and, similarly, significant differences were seen in week 6 versus placebo in the percentage of patients in clinical remission (6.8 % placebo vs 14.5 % VDZ; $p = 0.02$).[12]

Strikingly, the GEMINI studies evaluated the efficacy of induction in week 6, instead of doing so following administration of all induction doses (weeks 0, 2 and 6), as had been done previously with infliximab and adalimumab, since it would be predictable that, following week 6 and up to week 8, a larger number of patients could improve.

In the GEMINI 3 study, conducted in CD, the difference between VDZ and placebo in the proportion of patients in clinical remission was significant in week 10, following three induction doses (weeks 0, 2 and 6) (13.0 % placebo vs 28.7 % VDZ; $p < 0.0001$).[13] It is interesting to note that in this

study the population enrolled was more refractory than in the GEMINI 2 study, as 76 % of patients had previously experienced failure to respond to TNF inhibitors, whereas in the GEMINI 2 study this percentage was 58 %. Therefore, it seems that, in CD, clinical remission induced by VDZ would be later in more refractory patients. This fact is corroborated by the observation that, in the subgroup of patients naive to TNF inhibitors enrolled in the GEMINI 3 study, the difference in percentages of patients who achieved clinical remission between the group treated with placebo and the group treated with VDZ was significant in week 6, following two induction doses (12.0 % placebo vs 31.4 % VDZ; p = 0.012), whereas in patients with prior failure to respond to TNF inhibitors, this difference was significant in week 10, following three induction doses (12.1 % placebo vs 26.6 % VDZ; p = 0.001).[13]

Regarding studies in actual clinical practice, it is interesting to point out that they evaluate the efficacy of induction at the time of administration of the first maintenance dose, i.e. in week 14.[3]

In clinical practice, it is inappropriate to draw conclusions on efficacy in week 6 since only two doses have been administered, whereas the summary of product characteristics states that induction must be done with three doses, both in UC and in CD (weeks 0, 2 and 6). Therefore, unless worsening occurs, it would be necessary to evaluate response in week 10, following administration of the three induction doses, and not to consider the possibility of a primary failure to respond to VDZ before week 14; this approach applies to both CD and UC. In our clinical practice, patients with primary failure to respond to TNF inhibitors are almost always administered the week 10 dose and have their response evaluated in week 14. In all other patients (naive patients, patients with secondary failures and patients with intolerance to TNF inhibitors), administration or non-administration of the week 10 dose is determinant of the clinical response observed.

In patients who receive the week 10 dose, we usually prescribe VDZ every four weeks until clinical remission is achieved, then return to a regimen of VDZ every eight weeks.

Despite the fact that the summary of product characteristics only recommends the week 10 dose in CD, in our clinical practice it has been seen that this may be useful in some patients with UC who respond late, especially in primary failures to TNF inhibitors.

How to proceed in case of observing loss of response to vedolizumab?

In the GEMINI studies, in case of loss of response dose intensification was not considered. However, these patients were allowed to enter an open-label extension study and receive VDZ every four weeks. Among patients who started this strategy, 28 % of those with UC and 32 % of those with CD were found to be in clinical remission in week 52.[14,15] Therefore, the summary of product characteristics indicates that administration every four weeks may benefit patients who have experienced a decrease in response.[1]

In the VICTORY consortium clinical practice study conducted in CD, in which 91 % of patients had been previously treated with TNF inhibitors, 7.0 % (6/86) of patients who achieved a response to induction required intensification due to loss of response, following a median follow-up period of 39 weeks.[8]

In the ENEIDA registry study, in which practically all patients had previously received TNF inhibitors, after a median follow-up period of 12 months, the rate of loss of clinical response was 28.8 per 100 patients per year. Among these patients, 60 % had their dose intensified, 28.6 % presented clinical remission and 30.6 % presented clinical response.[7] This means that 59.2 % of intensified patients recovered clinical response at a minimum.

In a population of 459 patients with IBD, the majority of whom had failed to respond to TNF inhibitors (80 %), Shmidt et al.[16] found a rate of loss of response with VDZ at 12 months of 35 %. Intensification by means of shortening of the interval between doses (from 8 to 4 or 6 weeks) allowed clinical remission to be achieved in 18 % (6/33) of patients and clinical response to be recovered in 49 % of patients (16/33).[16] In other words, at least response could be recovered in 67 % of patients.

Peyrin-Biroulet et al.,[17] in a systematic review and meta-analysis of clinical trials and clinical practice studies, in which the vast majority of patients had been previously treated with TNF inhibitors, reported incidences of loss of response of 39.8 and 47.9 per 100 patients per year of follow-up in UC and CD, respectively. However, the main limitation of this analysis is the fact that the majority of the studies included have follow-up periods of less than one year, and that rates of response after a year were projected based on them. In any case, the increased frequency of infusions allowed response to be recovered in 53.8 % of the patients who had experienced loss of response.

In patients with IBD naive to TNF inhibitors, Kopylov et al.[18] reported, as anticipated, rates of loss of response significantly lower than in studies in which the majority of patients had experienced prior failure to respond to TNF inhibitors. After follow-up periods of 44 weeks in CD and 42.5 weeks in UC, respectively, the rate of loss of response was 0 % (0/27) in CD and 10 % (9/90) in UC. The EVOLVE clinical practice study, also conducted in patients naive to TNF inhibitors, showed rates of intensification in UC of 16.3 % at 12 months and 24.7 % at 24 months, and in CD of 16.6 % at 12 months and 23.2 % at 24 months, respectively.[19,20]

In our practice, similarly to that reported in the studies published, we see greater losses of response in patients who have received prior treatments with TNF inhibitors. In case of loss of response to VDZ, our approach consists of intensification, shortening of the interval of administration to four weeks, and, sometimes, more anecdotally, re-induction.

Better understanding how levels of VDZ and anti-VDZ antibodies influence loss of response will probably aid in optimising treatments in the future.

What is the efficacy of vedolizumab in patients naive to TNF inhibitors?

Various *post-hoc* analyses of the GEMINI studies have examined the effect of VDZ in patients naive to TNF inhibitors, i.e. as a first-line biologic therapy. Feagan et al.[21] reported that patients with UC naive to TNF inhibitors enrolled in

the GEMINI 1 study showed higher rates of response, clinical remission and mucosal healing in week 6 than those with previous failure to respond to a TNF inhibitor (clinical response: 53.1 % vs 39.0 %; clinical remission: 23.1 % vs 9.8 %; mucosal healing: 49.2 % vs 30.5 %). Similarly, in week 52 patients naive to TNF inhibitors showed higher rates of efficacy than those who had previously failed to respond to TNF inhibitors (lasting clinical response: 60.7 % vs 44.6 %; clinical remission: 46.9 % vs 36.1 %; mucosal healing: 60.0 % vs 44.6 %).

Also in CD, patients naive to TNF inhibitors who participated in the GEMINI 2 and 3 clinical trials presented higher percentages of clinical response and clinical remission in week 6 than those observed in patients with previous failures to TNF inhibitors (clinical response: 40.3 % vs 33.1 %; clinical remission: 22.7 % vs 13.3 %).[22]

The results of the VARSITY clinical trial were recently reported; this was conducted in primarily bio-naive patients with UC (the protocol limited the proportion of patients with prior exposure to TNF inhibitors to a maximum of 25 %). In this study, rates of clinical remission with VDZ after a year were significantly higher than those achieved with adalimumab (31.3 % VDZ vs 22.5 % adalimumab, p = 0.0061).[23]

In UC, Narula et al.,[9] using VICTORY consortium data, showed that in patients naive to TNF inhibitors, percentages of clinical remission were 51 % at six months and 61 % at 12 months, whereas in patients with a prior failure to a TNF inhibitor they were 31 % and 48 %, respectively, and in patients with two or more prior failures to TNF inhibitors they were 28 % and 44 %, respectively.

Data from this same registry have shown that, in CD, patients with prior exposure to TNF inhibitors, compared to patients who were naive to TNF inhibitors, showed significantly lower rates of clinical response (p = 0.022), clinical remission (p = 0.007), mucosal healing (p = 0.001) and remission without corticosteroids (p = 0.024); it was observed that the decrease in efficacy was proportionate to the number of TNF inhibitors used previously.[8]

Kopylov et al.,[18] in their clinical practice study in patients with CD and UC naive to TNF inhibitors, showed efficacy results superior to those published in cohorts of patients in which the majority had experienced prior failures to TNF inhibitors. In week 14, 82.0 % of patients with CD and 79.1 % of patients with UC showed a response to treatment; 64.0 % and 39.5 %, respectively, were in clinical remission, and 52.0 % and 36.6 %, respectively, were in remission without corticosteroids. In the last visit (following a median follow-up period of 44.0 weeks in CD and 42.5 weeks in UC), rates of clinical response were 77.1 % in patients with CD and 76.7 % in patients with UC; rates of clinical remission were 68.6 % and 67.0 %, respectively; and rates of remission without corticosteroids were 60.0 % and 59.2 %, respectively.

In the cohort of patients naive to TNF inhibitors in the EVOLVE study, rates of clinical remission were 57.3 % after 12 months and 79.0 % after 24 months in UC, and 52.3 % after 12 months and 69.7 % after 24 months in CD. Rates of persistence were 82.5 % at 12 months and 75.1 % at 24 months in UC, and 85.6 % at 12 months and 71.4 % at 24 months in CD.[19,20]

Administration of VDZ in patients naive to TNF inhibitors is supported not only by the evidence available from clinical trials and actual clinical practice, but also by the ECCO guidelines which, both in UC (statement 12I) and in CD (statements 5C, 5D, 5E and sections 5.3.2 and 5.4.3), indicate that VDZ may be used as a first-line biologic in different clinical scenarios.[24,25]

Could vedolizumab be an option as a first-line biologic therapy in scenarios of cortico-dependence, refractoriness to oral corticosteroids or failure to respond to immunomodulators?

The GEMINI 1 clinical trial demonstrated VDZ's capacity for causing remission without corticosteroids in patients with UC in week 52 (13.9 % placebo vs 31.4 % VDZ every eight weeks [p = 0.01] / 45.2 % VDZ every four weeks [p < 0.001])[5]; this effect was greater in patients naive to TNF inhibitors (44.6 %) than in patients with prior failure to TNF inhibitors (26.7 %).[21]

Similarly, the GEMINI 2 clinical trial reported a higher percentage of patients with CD who presented remission without corticosteroids in week 52 with VDZ (15.9 % placebo vs 31.7 % VDZ every eight weeks [p = 0.02] / 28.8 % VDZ every four weeks [p < 0.04])[12]; again, capacity for inducing remission without corticosteroids was greater in patients naive to TNF inhibitors (41.9 %) than in patients with prior failures to these drugs (20.2 %).[22]

In a systematic review and aggregate analysis by Engel et al.,[3] in a population in which more than 90 % of all patients had received prior treatment with TNF inhibitors, the proportion of patients in remission without corticosteroids in week 14 was 29 % in CD and 25 % in UC. A meta-analysis by Schreiber et al.[4] reported similar results in week 14, 25 % in CD and 26 % in UC, but also showed that, at 12 months, 31 % of patients with CD and 42 % of patients with UC were in remission without corticosteroids.

In a study by the VICTORY consortium conducted in actual clinical practice in patients with UC,[9] rates of remission without corticosteroids at six and 12 months were 21 % and 37 %, respectively, and in a study this same consortium conducted in patients with CD,[8] rates of remission without corticosteroids at 6 and 12 months were 18 % and 34 %, respectively.

However, in a European clinical practice study by Kopylov et al.,[18] conducted in a population with IBD naive to TNF inhibitors, the percentages of patients in remission without corticosteroids were significantly higher, both following induction (week 14), 52.0 % in CD and 36.6 % in UC, and in the long term (last follow-up; median 44 weeks in CD and 42.5 weeks in UC), 60.0 % in CD and 59.2 % in UC.

In the GEMINI 1 study, patients with UC with prior failure to immunomodulators experienced rates of clinical remission with VDZ in week 52 that were significantly higher than those treated placebo (18.0 % placebo vs 44.6 VDZ every six weeks; [p = 0.001] / 50.0 % VDZ every four weeks; [p < 0.001]).[5]

The ECCO UC guidelines state that VDZ is an option to be considered as a first-line biologic therapy in patients with cortico-dependence, refractoriness to oral corticosteroids or failure to respond to thiopurines (statements 11I, 11J and 11K).[24] The ECCO guidelines for the treatment of CD specify

that VDZ is a suitable alternative in cases of moderate to severe diseases with ileocaecal or colonic involvement that are refractory to steroids (statements 5 C, 5 D and 5 E); it may also be administered following failure to respond to immunosuppressants (section 5.3.1).[25]

Ultimately, based on the data available, in clinical practice the use of VDZ should be considered as an early treatment in scenarios of cortico-dependence, refractoriness to oral corticosteroids or failure to respond to immunomodulators.

When is relief of symptoms seen with vedolizumab?

In a *post-hoc* analysis of GEMINI trials, which analysed symptoms reported by patients, Feagan et al.[26] showed improvement of symptoms in week 2, when the first post-baseline evaluation was made. The proportion of patients with UC who showed in week 2 the combined variable of Mayo subscale score for rectal bleeding = 0 with a score on the Mayo subscale for frequency of bowel movements $\leq$1 was significantly higher in patients treated with VDZ than in patients treated with placebo (10.1 placebo vs 19.1 VDZ; $p < 0.05$). In patients with CD, the decrease in the combined score for abdominal pain and frequency of bowel movements was significantly higher in patients treated with VDZ than in patients treated with placebo also in week 2, i.e. in the first assessment following the start of treatment (−7.2 placebo vs −14.2 VDZ; $p < 0.05$).[26]

In addition, the subgroup analysis showed that the patients who enjoyed earlier improvement of symptoms were, in particular, those who were naive to TNF inhibitors. In week 2, 22.3 % of patients with UC naive to TNF inhibitors versus 14.7 % of patients with prior exposure to TNF inhibitors presented a combined score for rectal bleeding = 0 and a frequency of bowel movements $\leq$1. Similarly, whereas patients with CD naive to TNF inhibitors achieved in week 2 a reduction in their combined score for abdominal pain and frequency of bowel movements of 19.1 %, in patients previously exposed to TNF inhibitors a corresponding reduction of 11.2 % was achieved.[26]

In clinical practice, we have observed that, effectively, response to VDZ may be later in multi-refractory patients, especially in CD. However, in selected groups of patients, both in CD and in UC, the speed of the therapeutic effect may be similar to that shown by other biologic drugs in these patients.

What effect does vedolizumab have on extraintestinal manifestations?

Immune-mediated extraintestinal manifestations have a variable relationship with inflammatory bowel activity. Type 1 peripheral joints and erythema nodosum have a strong relationship with bowel inflammation; type 2 peripheral joints, pyoderma gangrenosum and uveitis have an intermediate relationship, and axial joints (sacroiliitis and spondylitis) follow a course independent of IBD. VDZ, due to its specific mechanism of action in the gastrointestinal tract, should be evaluated essentially in the treatment of extraintestinal manifestations related to bowel activity.

In a *post-hoc* analysis of the GEMINI clinical trials, treatment with VDZ in CD was associated with a reduction in both likelihood of new cases of arthritis/arthralgia and likelihood of worsening thereof. In UC, no increase was observed in the incidence of these events during treatment with VDZ.[27]

In the OBSERV-IBD cohort study, VDZ was associated with improvement in extraintestinal manifestations. At the start of the study, 44.7 % (21/47) of patients with arthritis/arthralgia and 75.0 % (3/4) of patients with skin lesions were in clinical remission in week 54, although new extraintestinal manifestations were also reported during follow-up.[28]

A recent review of retrospective series and case reports of patients with peripheral spondyloarthropathies associated with IBD suggests that VDZ is effective in this scenario (39–45 %).[29]

The efficacy of VDZ in the treatment of non-joint extraintestinal manifestations is limited to short series of case reports in which erythema nodosum, pyoderma gangrenosum and uveitis are the manifestations that present a good initial response to VDZ.[30]

Ultimately, the evidence available on the treatment of IBD in patients with extraintestinal manifestations with VDZ is limited, but it suggests that it is a treatment option to be considered in patients with extraintestinal manifestations related to inflammatory bowel activity.

Conclusions

According to the studies available (clinical trials and observational studies), VDZ represents a safe and effective alternative in patients with moderate to severe UC and CD who have experienced failure to conventional therapy or TNF inhibitors. Patients naive to TNF inhibitors exhibit an increased therapeutic benefit in terms of efficacy/effectiveness and, consistently, greater persistence on treatment and lower rates of intensification. Thus, it can be considered as a first-line treatment option in scenarios of cortico-dependence, refractoriness to corticosteroids or failure to respond to conventional immunomodulators.

The whole of this review has sought, using the evidence available both in controlled studies and in clinical practice, to answer questions about the use of VDZ in the treatment of patients with CD and UC, and to conclude each one with the suggested approach that the authors take in real-world clinical practice.

Conflicts of interest

Joaquín Hinojosa del Val has acted as a speaker, consultant and advisory member for MSD, AbbVie, Ferring, Faes Farma, Shire Pharmaceuticals, Chiesi, Otsuka Pharmaceutical, Pfizer-Hospira, Kern Pharma, UCB Pharma, Vifor Pharma, Janssen, Sandoz, Takeda and Dr. Falk Pharma.

Manuel Barreiro-de Acosta has received payments in connection to advisory boards and conferences for the following companies: MSD, AbbVie, Hospira, Takeda, Janssen, Kern, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk

Pharma, Chiesi, Gebro Pharma, Otsuka Pharmaceuticals and Tillotts Pharma.

The authors Joaquín Hinojosa del Val and Manuel Barreiro-de Acosta did not receive any payment for the preparation of this publication.

Acknowledgements

McCann assisted the authors with medical drafting (funded by Takeda).

References

1. European Medicines Agency. Entyvio (vedolizumab). Ficha técnica o resumen de las características del producto [accessed 05 Nov 2018]. Available from: https://www.ema.europa.eu/documents/product-information/entyvio-epar-product-information_es.pdf.
2. Lam MC, Bressler B. Vedolizumab for ulcerative colitis and Crohn's disease: results and implications of GEMINI studies. Immunotherapy. 2014;6:963–71.
3. Engel T, Ungar B, Yung DE, Ben-Horin S, Eliakim R, Kopylov U. Vedolizumab in IBD-lessons from real-world experience; a systematic review and pooled analysis. J Crohns Colitis. 2018;12:245–57.
4. Schreiber S, Dignass A, Peyrin-Biroulet L, Hather G, Demuth D, Mosli M, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. J Gastroenterol. 2018;53:1048–64.
5. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699–710.
6. Sands BE, Van Assche G, Tudor D, Tan T, et al. Vedolizumab in combination with corticosteroids for induction therapy in Crohn's disease: A post-hoc analysis of GEMINI 2 and 3. Inflamm Bowel Dis. 2019;25:1375–82.
7. Chaparro M, Garre A, Ricart E, Iborra M, Mesonero F, Vera I, et al. Short and long-term effectiveness and safety of vedolizumab in inflammatory bowel disease: results from the ENEIDA registry. Aliment Pharmacol Ther. 2018;48:839–51.
8. Dulai PS, Singh S, Jiang X, Peerani F, Narula N, Chaudrey K, et al. The real-world effectiveness and safety of vedolizumab for moderate-severe Crohn's disease: Results from the US VICTORY consortium. Am J Gastroenterol. 2016;111:1147–55.
9. Narula N, Peerani F, Meserve J, Kochhar G, Chaudrey K, Hartke J, et al. Vedolizumab for ulcerative colitis: Treatment outcomes from the VICTORY Consortium. Am J Gastroenterol. 2018;113:1345–54.
10. Feagan B, Siegel C, Melmed G, Isaacs K, Lasch K, Rosario M, et al. Efficacy of vedolizumab with and without continued immunosuppressant use in Gemini 1 and Gemini 2. Gut. 2016;65:A244–5.
11. Hedin C, Halfvarson J. Should we use vedolizumab as mono or combo therapy in ulcerative colitis? Best Pract Res Clin Gastroenterol. 2018;32-33:27–34.
12. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369:711–21.
13. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147:618–27.
14. Loftus EV Jr, Colombel JF, Feagan BG, Vermeire S, Sandborn WJ, Sands BE, et al. Long-term efficacy of vedolizumab for ulcerative colitis. J Crohns Colitis. 2017;11:400–11.
15. Vermeire S, Loftus EV Jr, Colombel JF, Feagan BG, Sandborn WJ, Sands BE, et al. Long-term efficacy of vedolizumab for Crohn's disease. J Crohns Colitis. 2017;11:412–24.
16. Shmidt E, Kochhar G, Hartke J, Chilukuri P, Meserve J, Chaudrey K, et al. Predictors and management of loss of response to vedolizumab in inflammatory bowel disease. Inflamm Bowel Dis. 2018;24:2461–7.
17. Peyrin-Biroulet L, Danese S, Argollo M, Pouillon L, Peppas S, Gonzalez-Lorenzo M, et al. Loss of response to vedolizumab and ability of dose intensification to restore response in patients with Crohn's disease or ulcerative colitis: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2019;17:838–4600.
18. Kopylov U, Verstockt B, Biedermann L, Sebastian S, Pugliese D, Sonnenberg E, et al. Effectiveness and safety of vedolizumab in anti-TNF-naïve patients with inflammatory bowel disease-A multicenter retrospective European study. Inflamm Bowel Dis. 2018;24:2442–51.
19. Yarur A, Mantzaris G, Silverberg M, Walshe M, Zezos P, Stein D, et al. Real-world effectiveness and safety of vedolizumab and anti-TNF in biologic-naive ulcerative colitis patients: Results from the EVOLVE study. J Crohn's Colitis. 2019;13 Supplement 1:S400–1.
20. Bressler B, Mantzaris G, Silverberg M, Zezos P, Stein D, Colby C, et al. Real-world effectiveness and safety of vedolizumab and anti-TNF in biologic-naive Crohn's disease patients: results from the EVOLVE study. J Crohn's Colitis. 2019;13 Supplement 1:S427–8.
21. Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B, Sankoh S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. Clin Gastroenterol Hepatol. 2017;15:229–39.
22. Sands BE, Sandborn WJ, Van Assche G, Lukas M, Xu J, James A, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease in patients naïve to or who have failed tumor necrosis factor antagonist therapy. Inflamm Bowel Dis. 2017;23:97–106.
23. Schreiber S, Peyrin-Biroulet L, Loftus EV, Danese S, Colombel JF, Abhyankar B, et al. VARSITY: A double-blind, double-dummy, randomised, controlled trial of vedolizumab versus adalimumab in patients with active ulcerative colitis. J Crohn's Colitis. 2019;13 Supplement 1:S612–3.
24. Harbord M, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. J Crohn's Colitis. 2017;11:769–84.
25. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, et al. Third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: diagnosis and medical management. J Crohns Colitis. 2017;11:3–25.
26. Feagan BG, Lasch K, Lissoos T, Cao C, Wojtowicz AM, Khalid JM, et al. Rapid response to vedolizumab therapy in biologic-naive patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2019;17:130–8.
27. Feagan BG, Sandborn WJ, Colombel JF, Byrne SO, Khalid JM, Kempf C, et al. Incidence of arthritis/arthralgia in inflammatory bowel disease with long-term vedolizumab treatment: post-hoc analyses of the GEMINI Trials. J Crohn's Colitis. 2019;13:50–7.
28. Tadbiri S, Grimaud JC, Peyrin-Biroulet L, Filippi J, Pariente B, Roblin X, et al. Efficacy of vedolizumab on extraintestinal manifestation in patients with inflammatory bowel disease: a post-hoc analysis of the OBSERV-IBD cohort from the GETAID. J Crohns Colitis. 2017;11:S42.

29. Felice C, Pugliese D, Papparella LG, Pizzolante F, Onori E, Gasbarrini A, et al. Clinical management of rheumatologic conditions co-occurring with inflammatory bowel diseases. Expert Rev Clin Immunol. 2018;14:751–9.

30. Fleisher M, Marsal J, Lee SD, Frado LE, Parian A, Korelitz BI, et al. Effects of vedolizumab therapy on extraintestinal manifestations in inflammatory bowel disease. Dig Dis Sci. 2018;63:825–33.