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Review Article

Review Article

Vedolizumab Treatment in Extra-Intestinal Manifestations in Inflammatory Bowel Disease: A Systematic Review

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Abstract

Background and Aims: We aimed to summarize existing data on the effectiveness of vedolizumab in extra-intestinal manifestations [EIMs] in inflammatory bowel disease [IBD].
Methods: We conducted a systematic literature search in PubMed and the Cochrane Library, up to October 2018. Interventional and non-interventional studies as well as case-series studying vedolizumab and EIMs in adult patients with IBD were considered eligible.
Results: Three interventional studies [one randomized trial, n = 1032; and two open-label trials, n = 347], five non-interventional studies [n = 1496] and three case-series [n = 17] were included. Vedolizumab did not show any effectiveness in primary sclerosing cholangitis [PSC]. While no effect was seen in pre-existing manifestations regarding arthralgia and arthritis, the occurrence of new rheumatic symptoms was lower among vedolizumab users compared to placebo; occurrence was higher, however, with vedolizumab than with tumour necrosis factor inhibitors. Finally, vedolizumab appears not to be efficacious for the treatment of cutaneous manifestations.
Conclusions: There is no strong evidence to suggest that vedolizumab may be efficacious for the treatment of pre-existing EIMs [especially PSC, rheumatic and cutaneous manifestations], although it may reduce the occurrence of new EIMs.

Key Words: Anti-integrin therapy; extra-intestinal manifestations; inflammatory bowel disease

1. Introduction

Crohn's disease [CD] and ulcerative colitis [UC], together known as inflammatory bowel disease [IBD], are chronic conditions of the gastrointestinal tract.[1] Extra-intestinal manifestations [EIMs] occur in up to 55% of patients with CD and 35% of patients with UC.[2–4] Main EIMs are arthralgia and arthritis; however, they can target multiple organs, including the skin [pyoderma gangrenosum, erythema

nodosum and psoriasis], the liver (hepatitis, primary sclerosing cholangitis [PSC]) and the eye [iritis, and uveitis].[3–5] These manifestations can seriously affect the patient's quality of life,[6,7] and represent a substantial cost on the healthcare system;[8] therefore, they should be considered with regard to treatment decisions.[9]

The physiopathology of EIMs is only partially known. The parallel evolution of some EIMs [e.g. arthritis, erythema nodosum, pyoderma gangrenosum, iritis and uveitis] with intestinal disease activity, and the efficiency of tumour necrosis factor [TNF] inhibitors, suggest a TNF pathway.[10,11] However, TNF alone is not a sufficient answer to the mechanisms of EIMs. Some theory suggests a migration of pro-inflammatory leukocytes from the gut to target organs, through upregulation of the adhesion molecule MAdCAM-1 [mucosal vascular addressin cell adhesion molecule 1].[12]

Vedolizumab is a humanized IgG-1 monoclonal antibody, specifically targeting the a4b7 integrin of migrating lymphocytes, and is an approved induction and maintenance treatment in both UC and CD. The efficacy of vedolizumab for clinical response and remission, mucosal healing, and corticosteroid-free remission has been demonstrated in phase 3 randomized, double-blind multicentre placebo-controlled trials.[13–15] No controlled trials have specifically assessed the effectiveness of vedolizumab in EIMs in IBD patients. With this aim, we performed a systematic review to identify and summarize the available evidence regarding the effectiveness of vedolizumab in EIMs.

2. Methods

2.1. Search strategy

To identify studies examining the role of vedolizumab in EIMs in IBD, we performed a systematic literature search in PubMed and the Cochrane Library, up to October 2018. We also searched major international conference proceedings [European Crohn's and Colitis Organization, Digestive Disease Week and United European Gastroenterology Week; 2015–2018]. Finally, the bibliographies of included publications were checked for any additional relevant citations.

2.2. Selection criteria

Our search strategy included common search strings for disease-related and drug-related terms [Supplementary Table 1]. Interventional and non-interventional studies, as well as case-series studying vedolizumab and EIMs in IBD, were considered eligible for inclusion, irrespective of publication type [i.e. short reports and abstracts were also considered eligible]. The following inclusion criteria were imposed: [1] adult patients [>18 years] diagnosed with IBD; [2] use of vedolizumab; [3] assessment of treatment effectiveness on EIMs [i.e. musculoskeletal, metabolic bone disease, cutaneous, ocular, hepatobiliary, vascular and haematological]; [4] assessment of occurrence of new EIMs; and [5] publication in English. Studies were excluded if they did not report [or reported insufficient data for] the outcomes of interest.

2.3. Data extraction

After removal of duplicates, studies were excluded if the title and/or abstract showed that the study did not meet the selection criteria. Then, a careful full-text review of selected studies was performed to examine the presence of information on the topic of interest. We extracted data regarding the study characteristics [i.e. study objectives and design, inclusion and exclusion criteria, study duration, patient demographics] and baseline IBD characteristics [including frequency of EIMs], treatment for IBD and for EIMs, measures of treatment effectiveness for EIMs and digestive symptoms, and occurrence of new EIMs.

3. Results

A flow diagram depicting the findings of the searches, and the selection process, is provided in Figure 1. Eleven studies met the eligibility criteria and were included: three interventional studies [one randomized trial, n = 1032; and two open-label trials, n = 347], five non-interventional studies [n = 1496] and three case-series [n = 17]. The main characteristics and results of these clinical studies are presented in Table 1.

3.1. Interventional and non-interventional studies

3.1.1. Primary sclerosing cholangitis

Three clinical studies examined vedolizumab efficacy for PSC. Caron *et al.*[16] led a retrospective observational multicentre study of 54 patients, 33 with UC and 21 with CD, all with a diagnosis of PSC. Mean follow-up was 19.4 months and all patients received 300 mg of vedolizumab at weeks 0, 2 and 6 and then at a dose of 300 mg every 4 or 8 weeks [according to the investigator's decision] up to week 54. There was no significant difference in decrease of serum alkaline phosphatase [ALP] concentration of at least 50% from baseline [primary end point], nor for aspartate aminotransferase [AST], γ-glutamyl transferase [γ-GT] and total bilirubin changes [Supplementary Table 2].

In another retrospective single-centre study, Tse *et al.*[17] analysed data from 27 patients [UC: 16, CD: 10, indeterminate colitis: 1]. There was no significant difference in ALP, AST, ALT and bilirubin levels between evaluation at baseline and at 6–8 months or 12–14 months. There was also no significant change in radiographic imaging of biliary tree dilatation and strictures. Three patients had an elastography score before and after vedolizumab, again with no significant change [Supplementary Table 3].

Christensen *et al.*[18] published a retrospective multicentre study with 34 patients, [UC: 18, CD: 16], with a median follow-up of 9 months. Again, there was no significant difference for all liver tests between baseline and weeks 14 and 30 [Supplementary Table 4].

3.1.2. Arthralgia/arthritis

Feagan *et al.*[19] conducted a post-hoc analysis of GEMINI trials. GEMINI were randomized controlled trials examining vedolizumab as induction and maintenance therapy for UC patients, CD patients and CD patients who had previously failed TNF inhibitors [GEMINI 1, 2 and 3, respectively]. Overall, 1032 patients [UC: 273, CD: 759] were randomized, with a 52-week follow-up for GEMINI 1 and 2, and 10-week follow-up for GEMINI 3. A total of 85 EIM events was recorded in GEMINI 1, 554 in GEMINI 2 and 70 in GEMINI 3.

In GEMINI 1, only adverse event report forms were available for analysis; it was not possible to distinguish between new or worsening of baseline EIMs, and there was no significant difference in the relative likelihood of events, for all patients. In GEMINI 3, 9% of patients [19 of 209] in the vedolizumab group and 11% of patients [23 of 207] in the placebo group experienced new or worsening arthritis/arthralgia, but statistical analyses were not performed.

In patients with CD, vedolizumab was significantly less likely than placebo to be associated with new/worsening arthritis/arthralgia (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.44–0.89). Similar incidences of sustained resolution of arthritis/

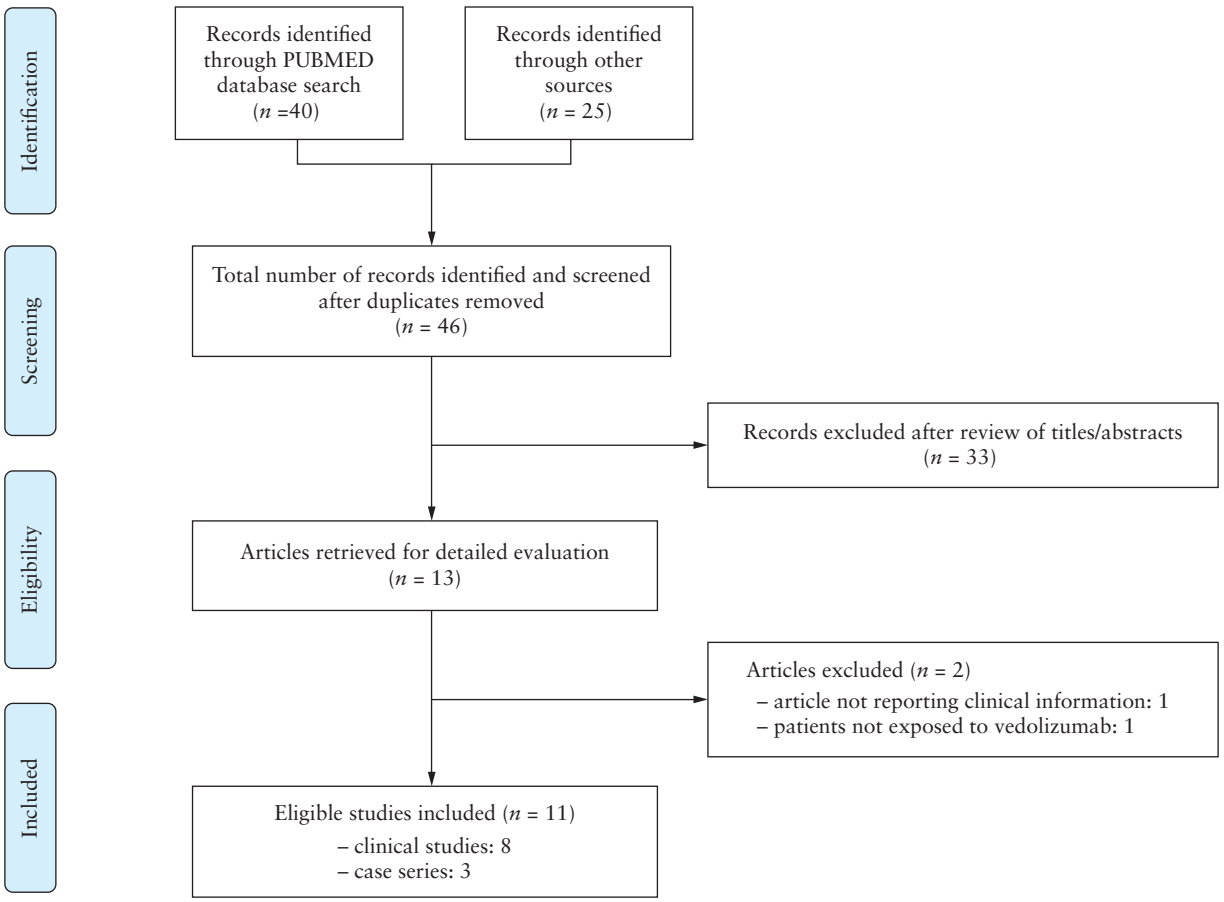

Figure 1. Flowchart of study selection and inclusion. Articles were only counted in one of the exclusion groups, even though articles could be excluded for more than one reason

arthralgia occurred with vedolizumab and placebo. In CD patients on corticosteroids at baseline, a decrease in corticosteroid dose increased the risk of new/worsening arthritis/arthralgia (odds ratio [OR], 7.49; 95% CI, 3.50–15.97) regardless of treatment; and in those achieving corticosteroid-free status, arthritis/arthralgia was less likely with vedolizumab than with placebo [HR, 0.14; 95% CI, 0.05–0.35].

By contrast, in patients with UC, vedolizumab and placebo showed similar incidence of new/worsening of arthritis/arthralgia. In UC patients on corticosteroids at baseline, arthritis/arthralgia was more likely in those achieving corticosteroid-free status than in those continuing corticosteroids [HR, 2.63; 95% CI 1.13–6.11]; and in those achieving corticosteroid-free status, the incidence of arthritis/arthralgia was similar with vedolizumab and placebo. Patients with prior anti-TNF exposure were more likely to experience new or worsening arthritis/arthralgia than patients who were anti-TNF-naïve.

When looking at gut response, in GEMINI 2, both clinical response and clinical remission at weeks 6 and 52 were significantly associated with better sustained resolution of baseline arthritis/arthralgia [$p < 0.05$], but in all three GEMINI studies in both CD and UC patients, no association was observed between clinical response or remission status and new/worsening EIMs.

Tadbiri *et al.*[20] published a nested multicentre cohort study of 294 patients [UC: 121, CD: 173] treated with vedolizumab [54 weeks of follow-up]. At baseline, 47 patients [16%] had arthritis or arthralgia, three with cutaneous EIMs and three with aphthous stomatitis; 35 had peripheral arthralgia/arthritis, six axial and six both. At week 54, 56.3% of the patients who had continued vedolizumab were in remission vs 40% of those who had discontinued earlier [$p = 0.36$]. Patients in IBD remission were more likely to achieve rheumatological remission, as were patients treated for less than 3.5 months after appearance of EIMs.

Among patients free of EIMs at baseline, 34 [13.8%] developed arthralgia/arthritis, significantly associated with CD and prior diagnosis of ankylosing spondylitis. Arthralgia/arthritis consisted of peripheral inflammatory arthralgia/arthritis in 25 patients, inflammatory axial pain in two and both in seven. The frequency of developing inflammatory arthralgia/arthritis during vedolizumab therapy was 2.4, 5.2, 8.9, 13.9 and 17.5% at weeks 6, 14, 22, 30 and 54, respectively.

Orlando *et al.*[21] are currently conducting a prospective single-centre study. Preliminary results from 53 patients [UC: 19, CD: 34] indicate that eight patients had a history of IBD-associated spondyloarthritis but were inactive at the time of initiation of vedolizumab, whereas 14 patients had active spondyloarthritis when vedolizumab was started, all with peripheral arthropathy, and two with peripheral and axial arthropathy. There was no case of induction or flare of arthritis and/or sacroiliitis reported in the entire cohort. Six of the 14 patients with active spondyloarthritis [46.2%] experienced a sharp clinical benefit on arthralgias. One of them was in gut remission at week 6, three were in gut remission at week 12 and one was in treatment failure at week 14.

Table 1. Summary of characteristics of clinical studies

Study	EIM	IBD patients included [*N*]	Study design	Follow-up	Concomitant treatments	Efficacy of treatment on EIMs
Caron *et al.*, 2018[16]	PSC [ALP AST ALT bilirubin]	All = 54 UC = 33 CD = 21	Retrospective observational multicentre study	19.4 months [mean] [14.0–29.9]	CS = 38 [51%] IS = 23 [31%] Ursodeoxycholic acid = 65 [87%]	[mean change, *p* value] ALP W30 –0.4 U/L; *p* = 0.41 W54 –0.4 U/L; *p* = 0.70 AST W30 + 0.4 U/L; *p* = 0.42 W54 –0.2 U/L; *p* = 0.78 ALT W30 –0.1 U/L; *p* = 0.89 W54 –0.7 U/L; *p* = 0.28 Total bilirubin W30 –0.8 U/L; *p* = 0.24 W54 –0.7 U/L; *p* = 0.39
Tse *et al.*, 2018[17]	PSC [ALP AST ALT bilirubin]	All = 27 UC = 16 CD = 10 IC = 1	Retrospective single-centre study	6–8 months [23] 12–14 months [19]	CS = 7 [26%] IS = 6 [23%] Ursodeoxycholic acid = 7 [26%]	[mean change, *p* value] ALP M6 + 50 U/L; *p* = 0.11 M12 + 58 U/L; *p* = 0.24 AST M6 –2 U/L; *p* = 0.90 M12 –1 U/L; *p* = 0.98 ALT M6 –8 U/L; *p* = 0.78 M12 + 0 U/L; *p* = 0.99 Total bilirubin M6 –0.5 µmol/L; *p* = 0.46 M12 + 0.4 µmol/L; *p* = 0.70
Christensen *et al.*, 2018[18]	PSC [ALP AST ALT bilirubin]	All = 34 UC = 18 CD = 16	Retrospective multicentre study	9 months [median]	Tacrolimus = 9 [26%] IS = 13 [38%] CS = 12 [35%] Ursodeoxycholic acid = 7 [21%]	[mean change, *p* value] ALP W14 –3 U/L; *p* = 0.35 W30 –32 U/L; *p* = 0.99 AST W14 –17 U/L; *p* = 0.22 W30 –8 U/L; *p* = 0.69 ALT W14 –13 U/L; *p* = 0.46 W30 –5 U/L; *p* = 0.81 Bilirubin W14 + 0.1 U/L; *p* = 0.62 W30 + 0.1 U/L; *p* = 0.96
Feagan *et al.*, 2018[19]	Arthralgia/arthritis	All = 1032 UC = 273 CD = 759	RCT [post-hoc analysis]	Gemini 1 & 2 = 52 weeks Gemini 3 = 10 weeks	CS = 364 [35%] IS = 157 [15%] Both = 159 [15%]	Sustained remission: Gemini 2 VDZ vs PLA: HR, 1.56; 95% CI, 0.93–2.59 Gemini 3 VDZ vs PLA: HR, 1.40; 95% CI, 0.73–2.67 New arthritis/arthralgia: Gemini 2 VDZ vs PLA: HR, 0.55; 95% CI 0.36–0.84 Gemini 3 VDZ vs PLA: HR, 0.75; 95% CI, 0.37–1.53 New and worsening arthritis/arthralgia: Gemini 1 VDZ vs PLA: HR, 0.99; 95% CI, 0.52–1.90 Gemini 2 VDZ vs PLA: HR, 0.63; 95% CI, 0.44–0.89

Table 1. Continued

Study	EIM	IBD patients included [*N*]	Study design	Follow-up	Concomitant treatments	Efficacy of treatment on EIMs
Tadbiri *et al.*, 2018[20]	Several	All = 294 UC = 121 CD = 173	Prospective multicentre study	54 weeks	CS = 100 [34%] IS = 40 [14%] Both = 30 [10%]	EIM at baseline: Remission of pre-existing arthralgia: 44.7%, if continued VDZ 56.3% vs 40% if discontinued [$p = 0.36$] Remission of arthralgia and IBD: OR = 1.89, CI 95% [1.05–3.41], $p = 0.03$ Remission of arthralgia and introduction of VDZ < 3.5 months: OR = 1.99, CI 95% [1.12–3.52], $p = 0.02$ Cutaneous remission: 1/5 [20%] Aphthous stomatitis remission: 1/19 [5.2%] New EIM: Arthralgia/arthritis: 34 [13.8%] New arthralgia/arthritis and CD: OR = 2.50, CI 95% [1.04–5.88], $p = 0.04$ New arthralgia/arthritis and prior diagnosis of ankylosing spondylitis: OR = 3.70, CI 95% [1.49–9.10], $p = 0.005$ Cutaneous manifestation: 14 [4.8%] 1 episcleritis.
Orlando *et al.*, 2018[21]	Spondyloarthritis	All = 53 UC = 21 CD = 32	Prospective single-centre study	2.6 ± 1.6 months [mean]	CS = 51 [96.2 %]	No induction or flare Improvement [active SpA, all peripheral arthropathy] = 6 [46.2%]
Dubinsky *et al.*, 2018[22]	Several	All = 1310 UC = 554 CD = 756	Retrospective study using de-identified insurance claims data	Mean duration 33 weeks	VDZ vs anti-TNF [infliximab, certolizumab, adalimumab, golimumab]	CD: Any new EIM: IRR: 1.49; 95% CI, 1.18–1.88; erythema nodosum: IRR, 4.29; 95% CI, 1.73–10.64; aphthous stomatitis: IRR, 3.73; 95% CI, 1.51–9.23; episcleritis/scleritis: IRR, 2.51; 95% CI, 1.02–6.14; arthropathy: IRR, 1.45; 95% CI, 1.15–1.84; PSC: IRR, 7.79; 95% CI, 3.32–18.27; uveitis/iritis: IRR, 2.89; 95% CI, 1.35–6.18 UC: Any new EIM: IRR, 1.20; 95% CI, 0.91–1.59; aphthous stomatitis: IRR, 3.67; 95% CI, 1.30–10.34; pyoderma gangrenosum: IRR, 4.42; 95% CI, 1.00–19.45; PSC: IRR, 3.44; 95% CI, 1.23–9.68
Kim *et al.*, 2018[23]	Several	All = 71 UC = 40 CD = 35	Retrospective single-centre study	Unknown	Unknown	New EIM: 26.8% [19/71] 8 arthralgias, 7 perianal fistulas, 2 pyoderma gangrenosum, 1 erythema nodosum, 1 spondylitis, 1 uveitis

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, Crohn's disease; CI, confidence interval; CS, corticosteroid; EIM, extra-intestinal manifestation; HR, hazard ratio; IBD, inflammatory bowel disease; IC, indeterminate colitis; IS, immunosuppressant; IRR, incidence rate ratio; OR, odds ratio; PLA, placebo; PSC, primary sclerosing cholangitis; RCT, randomized controlled trial; TNF, tumour necrosis factor; UC, ulcerative colitis; VDZ, vedolizumab.

Table 2. Summary of the nine cases of arthritis/arthralgia occurrence

	Sex	Age [years]	HLA-B27	Concomitant medication	IBD	Gut response	Prior diagnosis of SpA	Vedolizumab exposure [weeks]	Rheumatological involvement	Rheumatological therapy	Overtime evolution
Wendling *et al.* study[24]											
1	F	41	Pos	AZA	CD	Good	Yes	12	Axial and peripheral	SZP	Partial improvement
2	F	21	Neg	MTX	CD	Moderate	No	16	Axial and peripheral	MTX	No improvement
3	F	49	NA	SZP	CD	Low	No	4	Axial and peripheral	MTX	No improvement
4	F	31	NA	AZA	CD	Good	No	8	Peripheral	MTX	No improvement
Varkas *et al.* study[25]											
1	F	50	Neg	Mesalazine	CD	Good HBI 0 at W14	No	8.5	Axial	IA, NSAID	Remission
2	F	28	Neg	AZA	UC	Good Mayo 0 at W10	No	8.3	Peripheral	IA	Remission
3	M	30	Neg	AZA	CD	Good HBI 0 at W28	Yes	2	Axial	NSAID	No improvement
4	F	47	Neg	Mesalazine	CD	Good HBI 1 at W32	No	16.3	Axial	IA	Remission
5	F	26	Neg	None	UC	Poor Mayo 3 at W10	No	10.5	Peripheral	CS	Remission

Abbreviations: AZA, azathioprine; CD, Crohn's disease; CS, corticosteroid; HLA, Human Leukocyte Antigen; IA, intra-articular infiltration; IBD, inflammatory bowel disease; MTX, methotrexate; NSAID, non-steroidal antiinflammatory drug; SpA, spondyloarthritis; SZP, salazopyrine; UC, ulcerative colitis.

3.1.3. Other extra-intestinal manifestations

In their study, Tadbiri *et al.*[20] also gathered data on other EIMs. At baseline, 23 patients [7.8%] had non-rheumatological EIMs, with two erythema nodosum, one pyoderma gangrenosum, one necrotizing vasculitis and 19 aphthous stomatitis. At week 54, only one patient with cutaneous EIMs and one with aphthous stomatitis experienced complete remission. During follow-up, 14 patients [4.8%] developed cutaneous EIMs, with 11 psoriasis, two psoriasiform skin lesions and one case of eczema skin lesions. Eight of 14 patients had experienced similar cutaneous manifestations when treated with anti-TNF agents, and none had a previous history of psoriasis or eczema. Nine patients reached complete resolution with symptomatic treatment. Only one patient had an ophthalmic EIM [episcleritis].

3.1.4. Incidence of EIMs during vedolizumab therapy

Apart from the studies mentioned, two studies specifically examined EIM occurrence under vedolizumab. Dubinsky *et al.*[22] published a retrospective study, using de-identified insurance claims data, comparing EIMs during treatment with vedolizumab and anti-TNF agents. A total of 731 and 17 324 unique CD patients on vedolizumab and anti-TNF agents were identified, respectively. Among these patients, 239 first-course and 517 second-course vedolizumab patients were identified, whereas there were 17 310 first-course and 2274 second-course anti-TNF patients. A total of 554 and 7896 unique UC patients on vedolizumab and anti-TNF agents, respectively, were identified, of whom 155 first-course and 399 second-course vedolizumab and 7885 first-course and 689 second-course anti-TNF patients were identified, respectively. Patients were required not to have been exposed to biologics before the first course of treatment. Mean duration of treatment was 33 weeks.

Compared with patients on anti-TNFs, CD patients treated with vedolizumab were more likely to develop EIMs. They also had a higher risk to specifically develop erythema nodosum, aphthous stomatitis, episcleritis/scleritis, arthropathy, PSC and uveitis/iritis compared with anti-TNF users. Kaplan–Meier analysis showed a higher probability of developing any EIM during a course of vedolizumab treatment [$p = 0.006$] compared with anti-TNF use; this was confirmed by multivariable modelling.

UC patients on vedolizumab did not show any significant increase in the incidence of any EIM compared with patients under anti-TNF agents; however, they were more likely to develop specific EIMs such as aphthous stomatitis, pyoderma gangrenosum and PSC. Kaplan–Meier analysis did not show any significant difference in the probability of developing any EIM based on treatment during the follow-up period in UC patients [$p = 0.412$]. Multivariable modelling also demonstrated no significant difference in the mean rate of any EIMs between vedolizumab- and anti-TNF-treated patients.

Kim *et al.*[23] conducted a retrospective single-centre study, with 71 patients [UC: 40, CD: 31]. A global risk of *de novo* EIMs [including fistulas] was found in 26.8% [19 of 71] patients started on vedolizumab, after a median of 3.75 months. Excluding fistulas, there were eight arthralgias, two pyoderma gangrenosum, one erythema nodosum, one spondylitis and one uveitis. Including fistulas, frequencies were similar in CD and UC.

3.2. Case-series

Three case-series of EIMs were included, mainly arthralgia/arthritis. Wendling *et al.*[24] reported four cases, all CD developing symptoms under vedolizumab, three with axial and peripheral arthralgia/arthritis, and one with isolated peripheral arthritis. The time between vedolizumab commencement and the onset of symptoms ranged

from 4 to 16 weeks. The first patient was the only one with a prior diagnosis of spondyloarthritis, had good gut response and partially improved with salazopyrine. The other three cases had low, moderate and good gut responses, and were treated with methotrexate, with no improvement of rheumatic symptoms [Table 2].

Varkas *et al.*[25] published a series of five cases of symptom occurrence under vedolizumab, two UC patients with peripheral arthralgia/arthritis and three CD patients with axial arthralgia/arthritis only, none with a prior diagnosis of spondyloarthritis. All but one had excellent gut responses. Rheumatological symptoms were treated by intra-articular infiltrations, non-steroidal anti-inflammatory drugs or corticosteroids, leading to remission except for one patient [Table 2].

Fleisher *et al.*[26] published a series of eight cases of EIM resolution under vedolizumab therapy [UC: 4, CD: 4]. The first four cases reported rheumatological symptoms, with three cases of axial and peripheral arthralgia/arthritis and one case of isolated peripheral arthralgia/arthritis. All symptoms resolved completely under vedolizumab, except for one patient [with a recurrence of back pain after 2 years], with no other specific treatment. Three cases were cutaneous EIMs: one erythema nodosum and two pyoderma gangrenosum [CD: 2, UC: 1]. The erythema nodosum and one pyoderma gangrenosum resolved after a third and sixth dose of vedolizumab, respectively, while the second pyoderma gangrenosum initially improved, but later recurred after 12 months of vedolizumab therapy. The last case was a patient with uveitis with steroid dependence. Vedolizumab allowed corticosteroids to be successfully stopped, and intestinal disease to go from mild activity to histological remission.

4. Discussion

As IBD is a systemic condition frequently associated with EIMs, there is growing interest in the efficacy of current therapies in these patients. The occurrence and management of EIMs with IBD pose an important challenge for clinicians. The efficacy of anti-TNF drugs has been well studied in these patients,[10] whereas the role of other biologics, such as vedolizumab, remains unclear. We included 11 studies, with three case-series and two prospective publications, for a total of 2892 patients. For most EIMs [apart from PSC and arthralgia], no analysis could be performed due to the limited number of events. Furthermore, outcome measures were different across studies, mainly clinical [except for PSC], with a risk of the investigator's interpretation. Clinical definition and characteristics of EIMs were also heterogeneous or variable across studies.

According to the findings of the primary studies, vedolizumab did not show any effectiveness in PSC,[16–18] with no changes in any biological assessment, imaging or elastography. However, the fact that biochemical tests were not improved during the limited period of treatment may not be an indication its ineffectiveness, because the absence of biochemical and elastographic deterioration may reflect an arrest of further PSC deterioration. Moreover, except in the study by Christensen *et al.*, disease duration and the severity of already established structural lesions in PSC patients who were included in these studies had not been assessed at the time of patient inclusion, and the concomitant use of ursodeoxycholic acid was heterogeneous across studies. Thus, prospective long-term dedicated trials are warranted to clarify the effect of vedolizumab on PSC.

Regarding arthralgia and arthritis, there was no significant resolution of pre-existing arthralgia under vedolizumab against placebo, except for patients with good digestive control. This result might be explained by the fact that some arthralgias [peripheral arthralgias of large joints] usually correlate with IBD activity, and not by a specific role of vedolizumab over arthralgias. Data were scarce for cutaneous EIMs and did not allow any analysis; they are not encouraging, however, with a low response rate in the largest series of patients.[20]

Regarding the occurrence of new EIMs, vedolizumab was significantly less likely than placebo to be associated with new or worsening arthritis/arthralgia in CD but not in UC patients. When comparing vedolizumab and anti-TNF therapy, CD patients had a higher risk of developing new EIMs under vedolizumab than under anti-TNF agents, while available data comparing those two classes of drugs in patients with UC did not find any significant difference, except for aphthous stomatitis, pyoderma gangrenosum and PSC. However, patients with EIMs treated with anti-TNF agents prior to receiving vedolizumab may have greatly benefited from anti-TNF therapy until they withdrew from this treatment for whatever reason. If these patients embarked on vedolizumab and early lost response to this agent, they may show a relapse of quiescent EIMs, especially those which follow the intestinal disease activity.

The potential mechanisms underlying the presence or absence of effects of vedolizumab on EIMs remain unknown. First, the assessment of new EIMs is probably biased by the presence of paradoxical manifestations. The physiopathology of those paradoxical EIMs is not well known, but they have also been described under anti-TNF therapy,[27–31] and ustekinumab.[32–35] Secondly, extra-intestinal expression of MAdCAM-1, which is normally restricted to the gut, may occur under some circumstances, and might induce extra-intestinal inflammation through aberrant homing of mucosal T cells.[12] Moreover, a recent study of four patients with extra-intestinal symptoms under vedolizumab therapy, and especially one with newly developed pulmonary CD, suggests that a shift in integrin-expression [a4b7 neutralization and simultaneous b1 upregulation] triggered by vedolizumab could cause an altered migrational behaviour of immune cells into organs other than the gut.[36,37] This might explain the excellent intestinal response to the drug accompanied by extra-intestinal manifestation of the disease at the same time.

Together, the findings of the primary studies included in our review suggest that vedolizumab may not be efficacious for pre-existing EIMs associated with IBD. By contrast, there were encouraging results showing a lower occurrence of new EIMs under vedolizumab treatment, especially for patients with CD, which may be due to the parallel course of some EIMs with IBD activity. These observations are consistent with the theory that control of inflammation in the digestive compartment is effective in reducing systemic inflammation. Nevertheless, these results mostly concern patients with CD, while available data regarding UC patients are lacking, and thus it seems difficult to extrapolate those findings to all IBD patients.

Last but not least, it is important to note that the quality of the existing evidence is modest, as the included studies are mostly based on a retrospective and observational design, and none of the three published interventional studies, one post-hoc analysis of randomized controlled trials and two open-label trials, had this effect of vedolizumab as a primary or secondary end point. Regarding case-series, they may report cases of vedolizumab-induced EIMs but they rarely report the overall population assessed for the presence of these *de novo* EIMs.

In conclusion, the use of vedolizumab may not be efficacious in IBD patients with pre-existing EIMs, but it might reduce the occurrence of new EIMs. However, large, prospective controlled studies dedicated to exploring the extra-intestinal impact of vedolizumab

are warranted to clarify the role of this agent in EIMs among IBD patients.

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Conflict of Interest

The authors declare that they have no competing interests relevant to this manuscript.

Author Contributions

T.C., S.B., N.M., S.D., L.P.B.: study concept and design. T.C., S.B., C.L.B.: acquisition of data, analysis and interpretation of data, drafting of the manuscript. N.M., S.D., L.P.B.: critical revision of the manuscript for important intellectual content. All the authors read and approved the final version of the manuscript.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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