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Impact of vedolizumab therapy on extra-intestinal manifestations in patients with inflammatory bowel disease: a multicentre cohort study nested in the OBSERV-IBD cohort

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Summary

Background: The effectiveness of vedolizumab as a treatment for extraintestinal manifestations (EIM) is questionable due to its gut-specificity.

Aim: To assess effectiveness of vedolizumab for EIM in patients with inflammatory bowel disease (IBD) in a large real-life experience cohort.

Methods: Between June and December 2014, 173 patients with Crohn's disease and 121 with ulcerative colitis were treated with vedolizumab. Patients were followed until week 54. EIM activity was assessed at weeks 0, 6, 14, 22, 30 and 54 by using a 3-step scale: complete remission, partial response and no response.

Results: At baseline, 49 (16.7%) patients had EIMs of which 47 had inflammatory arthralgia/arthritis, four had cutaneous lesions and two had both rheumatologic and skin EIM. At week 54, 21 (44.7%) patients had complete remission for inflammatory arthralgia/arthritis and three (75%) for cutaneous EIM. In multivariate analysis, complete remission of inflammatory arthralgia/arthritis was associated with clinical remission of IBD (OR = 1.89, IC95% [1.05-3.41], P = .03) and recent onset of inflammatory arthralgia/arthritis (OR = 1.99, IC95% [1.12-3.52], P = .02). During the follow-up period, 34 (13.8%) patients without any EIM at baseline, developed incident cases of inflammatory arthralgia/arthritis consisting mostly of peripheral arthralgia without evidence of arthritis and 14 (4.8%) incident cases of paradoxical skin manifestation.

Conclusion: Vedolizumab therapy is commonly associated with improvement in EIM. This was associated with quiescent IBD and recent EIM. However, paradoxical skin manifestation and inflammatory arthralgia/arthritis may occur upon vedolizumab therapy.

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All the members of the OBSERV-IBD study group are listed in the Appendix.

1 | INTRODUCTION

Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are chronic, disabling and progressive diseases involving mainly the gastrointestinal tract.[1] Patients with inflammatory bowel disease (IBD) experience at least one extra-intestinal manifestation (EIM) in up to 50% of the cases.[2] EIM have a negative impact on the patient's quality of life and may interfere with treatment decision-making.[2-4] EIMs are more common in CD than UC and there is a broad range of manifestations. The most prevalent EIMs in IBD are arthralgia/arthritis and skin manifestations.[2,4] Most EIMs run in parallel with the intestinal disease activity but they may also have distinct course requiring multidisciplinary management.

Vedolizumab is a fully humanized monoclonal antibody that blocks specifically the migration of a subset of leucocytes arboring the $\alpha4\beta7$ integrin into inflamed intestinal tissue.[5] The efficacy and safety of vedolizumab have been demonstrated in three pivotal phase 3 clinical trials, in patients with moderate-to-severe UC and CD, as induction and maintenance therapy.[6-8] The Real-World Effectiveness and Safety of Vedolizumab has been confirmed in prospective and retrospective cohorts of patients in routine practice.[9-13] The gut-specificity of vedolizumab makes questionable its efficacy for EIMs.[14] Interestingly, the presence of an active homing axis between the gut and inflamed joint has been reported in patients with ankylosing spondylitis through the presence of cells expressing the $\alpha4\beta7$ integrin in the inflamed joints and the upregulation of MadCAM-1 in the endothelium.[15-18] The efficacy of vedolizumab for EIMs in IBD is unknown.

The French observatory on effectiveness and safety of vedolizumab in patients with inflammatory bowel disease (OBSERV-IBD) study has included all consecutive IBD patients who were treated with vedolizumab for active UC and CD between June and December 2014. Here, we evaluated for the first time the effectiveness of vedolizumab therapy on EIMs in patients with active UC and CD treated with vedolizumab in the OBSERV-IBD cohort and we looked at predictors of success.

2 | PATIENTS AND METHODS

2.1 | Study population

Between June and December 2014, 294 patients with active IBD including 173 patients with active CD (Harvey-Bradshaw Index (HBI) $\geq$ 6) and 121 with active UC (partial Mayo score > 4) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or at least one anti-TNF agent and who were treated with vedolizumab were included in a French national multicentre cohort study (OBSERV-IBD).[13,19] Patients were followed from the first infusion at week 0 through week 54. Each patient received written information concerning the product. Physicians were committed by the French regulatory authorities to collect efficacy and safety information on a prospective basis independently from any commercial entity. Exclusion criteria included unclassified colitis, EIM without significant IBD activity as the initial indication for vedolizumab, prevention of CD postoperative recurrence, an ostomy and pregnancy or lactation. The protocol was approved by ethics committee (CCTIRS N° 15.403).

Vedolizumab was administered intravenously at a dose of 300 mg at weeks 0, 2 and 6 as induction therapy and then at a dose of 300 mg every 8 weeks as maintenance therapy.[6-8] The concomitant use of steroids and/or immunomodulators was allowed according to investigator's decision and was recorded at every visit. Optimization of vedolizumab therapy at a dose of 300 mg every four weeks was also allowed in case of insufficient response to vedolizumab therapy according to investigator's decision.

2.2 | Data collection

Information was collected on a prospective basis by physicians from week 0 to week 52. Patient demographic and clinical characteristics included age at diagnosis, gender, smoking habits, CD location and behaviour according to the Montreal classification, UC extent according to the Montreal classification, history of medical and surgical treatment of IBD and familial history of IBD and concomitant treatment with corticosteroids or immunosuppressants.[13,19]

2.3 | Outcome measures

All patients were submitted to a standardized follow-up protocol with physical examination, EIM assessment and calculation of HBI or partial Mayo clinic score for CD and UC patients, respectively, as well as C-reactive protein (CRP, mg/L), haemoglobin (g/dL), leucocyte ($/10^9$/L) and platelet ($/10^9$/L) counts determination and adverse events collection.[20,21] The evaluations were performed at weeks 0, 6, 14, 22, 30 and 54.

EIM was defined according to the 2016 European Crohn's and Colitis Organization guidelines.[2] Inflammatory arthritis was defined as a documented episode of arthritis, confirmed by the gastroenterologist who included the patient, without any other cause. Inflammatory arthralgia was defined as persistent or recurrent joint pain, associated with night pain, improvement with exercise, and morning stiffness lasting at least 30 minutes.[22-25] Inflammatory arthritis/arthritis was categorized as inflammatory axial pain and/or peripheral inflammatory arthralgia/arthritis. Paradoxical manifestation was defined as the appearance of new-onset manifestations under vedolizumab therapy, confirmed by a dermatologist and/or a rheumatologist as a paradoxical manifestation and including cutaneous paradoxical manifestation (psoriasiforma and eczematiform), rheumatological paradoxical manifestation and lupus-like manifestation.[26-28] Efficacy on EIM was calculated retrospectively using a simple 3-step scale used in previous studies.[29,30] Briefly, patients were categorized as having the following: (1) no response, meaning no improvement or worsening of symptoms; (2) partial response, meaning improvement of symptoms or reduction in the steroid dose without worsening of symptoms; or (3) complete remission, meaning absence or almost absence of all clinical symptoms without increasing the steroid dose.

IBD activity was evaluated according to HBI or partial Mayo Clinic score in CD and UC patients, respectively. Clinical remission was defined as a HBI score of 4 or less for CD patients and a partial Mayo Clinic score of less than 3 with a combined stool frequency and rectal bleeding subscore of 1 or less.[31] Clinical response was defined as a reduction in the HBI score of at least 3 points for CD patients and as a reduction in the partial Mayo Clinic score of at least 3 points and a decrease of at least 30%, with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1 from the baseline score for UC patients.

2.4 | Statistical analysis

All included patients were evaluated from the inclusion at week 0 visit through week 54. All analyses were performed on an intent-to-treat manner. The data are expressed as a number (%) for qualitative data and as a mean ± the standard deviation (SD) or median [interquartile range] for quantitative data. The proportions of patients with no improvement, partial response and complete remission of EIMs, were compared at every time point using Chi-square test, without correction for multiple testing. The proportions of patients who met the criteria for the latter end points during the follow-up period were computed relatively to the whole population included at week 0. To identify predictors of complete remission of EIM, univariate analysis using the chi-square test and then multivariate analysis using binary logistic regression models were then applied and adjusted to the above-mentioned variables with an ascending stepwise procedure using Wald test. The EIM-free survival was calculated using the Kaplan–Meier method in patients without EIM at the time of inclusion. The survival distributions were compared using the log-rank test. To identify the independent factors, a Cox proportional hazard model was adjusted with an ascending stepwise procedure. Variables with $P < .10$ in univariate analysis were considered to be potential adjustment variables for the multivariate analysis. Quantitative values were converted to qualitative values by dichotomy from median value in two distinct groups of equal sizes. Variables with $P < .10$ in univariate analysis were considered to be potential adjustment variables for the multivariate analysis. All analyses were two-tailed, and p values less than 0.05 were considered significant. All statistical evaluations were performed using SPSS statistical software (SPSS Inc., v17, Chicago, IL, USA). All authors had access to the study data and had reviewed and approved the final manuscript.

3 | RESULTS

3.1 | Study population

A total of 294 patients with IBD were enrolled in the OBSERV-IBD cohort study and were treated with vedolizumab therapy (Figure S1). The demographic and clinical characteristics and medication history at week 0 of the 294 patients who were enrolled in the OBSERV-IBD cohort study are listed in Table S1. Two hundred seventy-two patients completed the whole induction period and were evaluated at week 14 whereas 22 discontinued vedolizumab between Week 0 and week 14 for primary nonresponse in 18 cases, infusion-related in two and infectious adverse events in two. Thirty-five patients discontinued vedolizumab immediately after the week 14 visit while 237 were enrolled in the maintenance period. At week 54, 166 patients (94 patients in the CD group and 72 in the UC group) were still treated with vedolizumab maintenance therapy while 71 patients discontinued vedolizumab between week 14 and week 54 for lack of response in 67 cases, pregnancy in three and loss of follow-up in one. The outcome measures of efficacy of vedolizumab therapy at every time point from week 6 to week 54 are listed in Table S2.

3.2 | Impact of vedolizumab therapy on extra-intestinal manifestations present at baseline

At baseline, 68 (23.1%) patients had EIMs of whom 41 had inflammatory arthralgia/arthritis alone, three had inflammatory arthralgia/arthritis and cutaneous EIMs, three had inflammatory arthralgia/arthritis and aphthous stomatitis, two had cutaneous EIMs alone, and 19 had aphthous stomatitis.

Inflammatory arthralgia/arthritis (n = 47) consisted of peripheral inflammatory arthralgia/arthritis in 35 patients, inflammatory axial pain in six, and both in six. Median delay between the onset of inflammatory arthralgia/arthritis and vedolizumab introduction was 3.5 (2.0-13.0) months. The demographic and clinical characteristics and medication history at week 0 of the whole study cohort according to the presence of inflammatory arthralgia/arthritis are listed in Table 1. The presence of inflammatory arthralgia/arthritis at baseline was significantly associated with female gender, uncomplicated Crohn's disease and a past history of paradoxical manifestations upon previous anti-TNF therapy.

Cutaneous EIMs included erythema nodosum in two cases, pyoderma gangrenosum in one, and necrotizing vasculitis in one patient.

Impact of vedolizumab on inflammatory arthralgia/arthritis present at baseline from week 6 to week 54 is presented in Figure 1. At week 54, among the 47 patients with inflammatory arthralgia/arthritis present at baseline, 21 (44.7%) had complete remission while ten (21.3%) were still symptomatic with inflammatory arthralgia/arthritis and 16 (34.0%) had discontinued vedolizumab for lack of response (one at week 6, four at week 22, nine at week 30 and two between week 30 and week 54). Complete remission of inflammatory arthralgia/arthritis was observed in 56.3% of patients who continued vedolizumab therapy for 54 weeks as compared 40.0% of those who discontinued the drug ($P = .36$). After vedolizumab discontinuation, five patients were switched to ustekinumab, three were treated with steroids, three underwent surgery, two to anti-TNF agent, one patient was treated with chemotherapy for rectal carcinoma and one patient received no treatment due to ongoing pregnancy. In multivariate analysis, complete remission of inflammatory arthralgia/arthritis present at baseline was significantly associated with clinical remission of IBD as defined by HBI or partial Mayo Clinic score (OR = 1.89, IC 95% [1.05-3.41], $P = .03$) and a delay between the onset of inflammatory arthralgia/arthritis and

TABLE 1 Demographic and baseline disease characteristics and medication histories of 294 patients with inflammatory bowel disease included in the OBSERV-IBD cohort study according to the presence of inflammatory arthralgia/arthritis at baseline

Characteristic	Inflammatory arthralgia/ arthritis (n = 47)	Absence of inflammatory arthralgia/ arthritis (n = 247)	*P*
Age, yr	38.0 ± 13.8	39.8 ± 14.0	.43
Female gender, no (%)	34 (72.3%)	129 (52.2%)	.02
BMI, kg/m²	21.6 ± 5.6	21.9 ± 4.1	.81
Smoking habits, no (%)			
Past smoker	21 (48.8%)	101 (43.3%)	.51
Active smoker	7 (16.3%)	42 (18.1%)	1.00
Duration of disease, yr	11.8 ± 8.9	10.6 ± 7.3	.37
Prior diagnosis of ankylosing spondylitis	6 (12.8%)	17 (7.0%)	.23
Age at diagnosis			
A1: ≤16 yr	9 (19.1%)	41 (16.6%)	.67
A2: 17-40 yr	33 (70.2%)	159 (64.4%)	.51
A3: > 40 yr	5 (10.6%)	47 (19.0%)	.21
Crohn's disease, no (%)	34 (72.3%)	139 (56.3%)	.05
Disease location, no (%)			
Ileal	8 (23.5%)	25 (18.0%)	.47
Colonic	6 (17.6%)	34 (24.5%)	.50
Ileocolonic	20 (58.8%)	80 (57.6%)	1.00
Upper GI tract	1 (2.9%)	9 (6.5%)	.69
Disease phenotype, no (%)			
Nonstructuring – Nonpenetrating	21 (61.8%)	56 (40.3%)	.03
Stricturing	9 (26.5%)	55 (39.6%)	.17
Penetrating	4 (11.8%)	28 (20.1%)	.33
Perianal disease, no (%)			
Harvey-Bradshaw Index	11.0 ± 3.2	10.0 ± 4.4	.17
Ulcerative colitis	13 (27.7%)	108 (43.7%)	.05
Proctitis	1 (7.7%)	8 (7.4%)	1.00
Left-sided colitis	3 (23.1%)	26 (24.1%)	1.00
Pancolitis	9 (69.2%)	74 (68.5%)	1.00
Mayo clinic score	8.6 ± 1.4	8.3 ± 2.5	.45
Past history of paradoxical reaction	9 (19.1%)	23 (9.3%)	.07
Cutaneous paradoxical manifestation	2 (4.3%)	6 (2.4%)	.38
Rheumatological paradoxical manifestation	8 (17.0%)	23 (9.3%)	.12
Prior medications			
Immunosuppressant			
Purine analogues	43 (91.5%)	239 (96.8%)	.11
Methotrexate	19 (40.4%)	107 (43.3%)	.75
anti-TNF therapy, no. (%)			
One anti-TNF agent	47 (100%)	243 (98.4%)	1.00
≥1 anti-TNF agents	41 (87.2%)	199 (80.6%)	.41
Concomitant medications			
Glucocorticoids only	12 (25.5%)	88 (35.6%)	.24
Immunosuppressants only[a]	7 (14.9%)	33 (13.4%)	.82
Glucocorticoids and immunosuppressants	4 (8.5%)	26 (10.5%)	.80
No glucocorticoids or immunosuppressants	24 (51.1%)	101 (40.9%)	.20
Biologic variables			
Haemoglobin level, g/L	12.2 ± 2.6	12.1 ± 2.8	.30
Leucocytes count, 10^9/L	9170 ± 4019	8482 ± 4193	.84
Platelets count, 10^9/L	365 ± 141	3347 ± 121	.46
hsCRP level, mg/L	27.8 ± 33.4	23.8 ± 25.6	.45

Variables are presented as n (%), mean ± standard deviation.
P values for all categorical variables are based on a two-sided chi-square test. *P* values for continuous variables are based on Mann-Whithney test.

vedolizumab introduction less than 3.5 months (OR = 1.99, IC95% [1.12-3.52], *P* = .02) (Table S3).

Considering cutaneous EIMs, one patients experienced complete remission at week 54. The patient with pyoderma gangrenosum did not experience any improvement of the skin lesion and discontinued vedolizumab after the week 22 visit.

Considering aphthous stomatitis, one patient experienced complete remission from week 14 to week 54. The only patient with refractory aphthous stomatitis also had refractory Crohn's disease with primary nonresponse to vedolizumab therapy. She discontinued vedolizumab therapy at week 6 and was treated with ustekinumab.

3.3 | Incident cases of extra-intestinal manifestation during vedolizumab therapy

After excluding the 47 patients with inflammatory arthralgia/arthritis at baseline, inflammatory arthralgia/arthritis was observed in 34 patients (13.8%) of whom 17 (50%) were in clinical remission of IBD as defined by HBI or partial Mayo Clinic score. Nine patients had a prior diagnosis of ankylosing spondylitis and one had a prior diagnosis of thaumatological paradoxical manifestation.[23] Two patients had cutaneous paradoxical manifestations simultaneously to inflammatory arthralgia/arthritis. The latter patient had discontinued certolizumab pegol as third-line anti-TNF therapy after developing peripheral inflammatory arthralgia associated with an elevated titre of

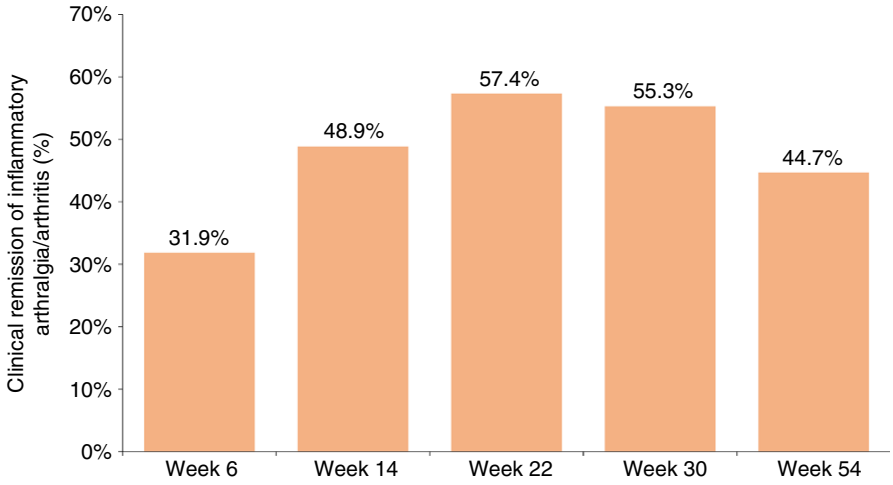

FIGURE 1 Clinical remission rates of inflammatory arthralgia/arthritis present at baseline upon vedolizumab therapy from week 6 to week 54 in patients with inflammatory bowel disease.
Panel represents the proportion of patients who experienced complete remission of inflammatory arthralgia/arthritis present at baseline, on an intent-to-treat manner and relatively to the whole population included at week 0

antinuclear antibodies and native double-stranded DNA antibodies. Inflammatory arthralgia/arthritis consisted of peripheral inflammatory arthralgia/arthritis in 25 patients, inflammatory axial pain in two, and both in seven. Twelve patients (35.3%) had evidence of arthritis and 22 (64.7%) inflammatory arthralgia without evidence of arthritis. In patients with incidental inflammatory arthralgia/arthritis, vedolizumab was discontinued for lack of response on IBD and inflammatory arthralgia/arthritis in seven patients and despite clinical remission of IBD in two patients. Vedolizumab was continued in 25 patients with analgesic therapy for inflammatory arthralgia/arthritis including four with introduction of concomitant methotrexate therapy. The probability of developing inflammatory arthralgia/arthritis during vedolizumab therapy was 2.4%, 5.2%, 8.9%, 13.9% and 17.5% at week 6, week 14, week 22, week 30 and week 54, respectively (Figure 2). In multivariate analysis, incident cases of inflammatory arthralgia/arthritis were significantly associated with Crohn's disease (OR = 2.50 IC95% [1.04-5.88], p= 0.04) and prior diagnosis of ankylosing spondylitis (OR = 3.70, IC 95% [1.49-9.10], p = 0.005). Cumulative incidence of inflammatory arthralgia/arthritis from baseline to week 54, including patients with inflammatory arthralgia/arthrtitis at baseline and incidental cases during the follow-up period, is presented in Figure S2.

Cutaneous paradoxical manifestation was observed in 14 (4.8%) patients: 11 had psoriatic lesions, two had psoriasiform eczema skin lesions and one had eczema skin lesions. Eight patients out of 14 had experienced similar cutaneous manifestation when treated with anti-TNF agents including two who discontinued anti-TNF therapy preceding treatment of IBD. None had a previous history of psoriasis or eczema. Cutaneous paradoxical manifestation was distributed in single (n = 8) or multiple (n = 6) sites. The most frequently affected areas were the face (n = 8) including the scalp, retroauricular flexures and the areas around the nostrils, palms and soles (n = 5), abdomen (n = 5) and flexures (n = 4). All the patients were treated with topical treatments and with PUVA therapy in one case. Complete resolution was noticed in nine patients including two with recurrences during follow-up whereas five patients discontinued vedolizumab therapy because of insufficient control of the digestive disease activity.

With the exception of the occurrence of episcleritis in one patient, no other EIM was reported during the follow-up period.

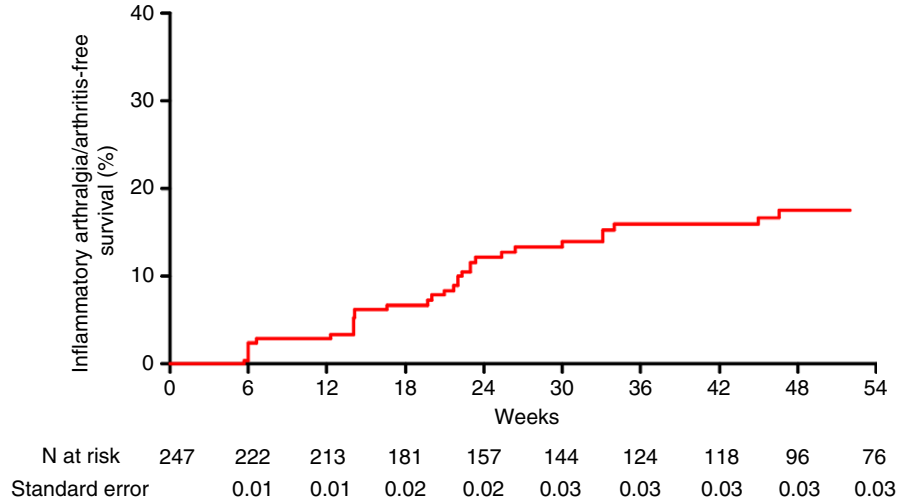

FIGURE 2 Kaplan–Meier curves of 247 patients with inflammatory bowel disease assessing the occurrence of incident cases of inflammatory arthralgia/arthritis upon vedolizumab therapy

4 | DISCUSSION

EIMs are frequent and can be disabling in IBD patients. Their management represents a challenge in clinical practice. This is the first large cohort study investigating the impact of vedolizumab on EIM of patients with IBD by using a post-hoc analysis nested in the OBSERV-IBD cohort. Among the 47 patients with inflammatory arthralgia/arthritis present at baseline, almost half of the cases achieved complete remission of their rheumatological symptoms. Conversely, incident cases of inflammatory arthralgia/arthritis occurred upon vedolizumab therapy in 34 patients (13.9%). Cutaneous paradoxical manifestation occurred upon vedolizumab therapy in 14 (4.8%) patients of whom eight had experienced similar cutaneous manifestation upon anti-TNF therapy.

In the present study, vedolizumab was associated with complete remission of inflammatory arthralgia/arthritis present at baseline in 57.4% of patients at week 22 and even in 44.7% at week 54. Both peripheral and axial arthropathies responded similarly to vedolizumab therapy. Predictors of complete remission of inflammatory arthralgia/arthritis were the clinical remission of IBD according to specific clinical scoring and the recent occurrence of inflammatory arthralgia/arthritis before vedolizumab introduction ($<$ 3.5 months). Those results suggest an active recruitment of $\alpha4\beta7$ integrin-positive T-cells in inflamed joint as previously observed.[16-18,32] Similar findings have been observed with anti-TNF therapy in observational studies and in post-hoc analysis of randomized controlled studies with either infliximab or adalimumab.[33,34]

In the present study, half of patients did not achieve complete remission of inflammatory arthralgia/arthritis. Moreover, incident cases of inflammatory arthralgia/arthritis occurred upon vedolizumab therapy in 13.9%, especially in patients with Crohn's disease and prior diagnosis of ankylosing spondylitis. Indeed, the gut specificity of the $\alpha4\beta7$ integrin-MadCAM-1 trafficking pathway does not preclude effectiveness of vedolizumab on EIMs.[35] Arthritis occurrence or reactivation has been recently reported in case series of 9 patients with IBD treated with vedolizumab.[14,36] On the other hand, Orlando et al have also reported the short-term outcome of 53 patients with IBD treated with vedolizumab of whom 14 had active spondyloarthritis at the time of vedolizumab introduction. Rheumatological symptoms improved upon vedolizumab therapy in six of 14 patients with spondyloarthritis while no occurrence of new onset of spondyloarthritis was observed.[37] The fact that vedolizumab was associated with clinical remission of inflammatory arthralgia/arthritis in the present series suggest that vedolizumab may exert clinical benefit on inflammatory arthralgia/arthritis especially in patients when intestinal and arthritic inflammation occur synchronously. Nevertheless, it seems recommended not to use vedolizumab in patients with IBD and spondyloarthritis when other therapeutic options effective on both diseases are available.

Two decades after the introduction of anti-TNF agents, it is now widely accepted that paradoxical inflammation especially in the skin and the joints may appear upon anti-TNF therapy.[38-41] The cause of these manifestations is still intriguing as they may appear independently of the pharmacokinetic and immunogenicity of the drug. The high frequency of antinuclear and anti-double stranded DNA antibodies suggest that autoimmune mechanisms may be involved.[27,42] Paradoxical inflammation is considered as a drug-class effect of anti-TNF agents and is usually reversible upon drug cessation.[2] In the present study, cutaneous paradoxical manifestation was observed in 14 (4.8%) patients during the 54-week follow-up period and was in line with characteristics observed with anti-TNF agents.[38,39] Recently, paradoxical inflammation of the skin has also been reported in patients treated with ustekinumab, a drug frequently used to treat cutaneous paradoxical manifestations.[43-47] Although it is conceivable that such manifestation may be related to intestinal activity of IBD or cutaneous infection, paradoxical inflammation may be not restricted to the anti-TNF drug class and should be assessed with other biological agents.[48]

The OBSERV-IBD study is the largest to date and best-defined post-marketing cohort of patients with IBD treated with vedolizumab. Patients were recruited on a named-patient, compassionate-use basis set up by the French regulatory agencies before marketing authorization. This protocol ensures that every single patient treated in France during the study period has been included in this study and assessed for effectiveness and safety. Although the involvement of several centres could contribute to the heterogeneity of the clinician's assessment of the patient's response, it lends further support to the wider clinical relevance of the observations because they are derived from tertiary centres rather than any single centre with a particular policy. The use of a simple 3-step physician global assessment scale rather than validated clinical scores of disease activity could contribute to an estimation bias. However, the use of a physician's global assessment scale is widely used in many clinical studies in IBD and in other inflammatory chronic disease especially in rheumatology and dermatology.[29,49-52] Lastly study design limited interpretation of the nature of rheumatological EIM in particular the distinction between spondyloarthritis, IBD-related inflammatory arthralgia/arthritis and rheumatological paradoxical manifestation.

In conclusion, a potential benefit of vedolizumab therapy in the management of patients with IBD and associated inflammatory arthralgia/arthritis has been observed in the present study especially in patients that achieved complete remission of IBD. However, such benefit may be limited to patients with inflammatory arthralgia/arthritis that runs in parallel with intestinal activity. Paradoxical cutaneous manifestation may occur upon vedolizumab therapy suggesting that paradoxical inflammation is not restricted to the anti-TNF drug class. Further studies are warranted to better understand the position of vedolizumab therapy in patients with active and/or prior EIMs.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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