SYSTEMATIC REVIEW AND META-ANALYSIS

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Association Between Vedolizumab Treatment and Arthritis/ Arthralgia in Patients with Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Background & Aims: Vedolizumab is a humanized gut selective drug that targets α4β7 integrin and has been used successfully in the treatment of inflammatory bowel disease (IBD). Pivotal studies have already demonstrated the drug's safety, but some real-life cohorts have shown an increase in arthralgia and arthritis in patients using vedolizumab. These findings raised the question of whether these joint symptoms are extraintestinal manifestations of IBD (since the drug acts only in the gut) or if they are associated with the use of vedolizumab. This systematic review and meta-analysis aimed to assess the incidence of arthralgia/ arthritis in patients receiving vedolizumab and to investigate whether these events are indeed drug related.
Methods: Pubmed, Cochrane, and Scopus were searched for randomized clinical trials reporting the incidence of joint manifestations in patients with Crohn's disease (CD) or ulcerative colitis (UC) who were treated with vedolizumab. The considered outcomes were arthritis and arthralgia. We used RevMan to calculate the pooled incidence of the reported outcomes and their corresponding 95% confidence intervals (95% CI).
Results: The search strategy yielded 4,206 articles. After removal of duplicates and screening of results, 6 randomized studies met the inclusion criteria. A total of 3,134 patients with moderately to severe IBD were included. Of those, 2,119 were randomized to receive vedolizumab and 1,015 to placebo. In the intervention group, 210 patients developed arthritis or arthralgia of any kind while 84 patients developed those symptoms in the placebo group (RR=1.09; 95%CI: 0.86-1.38; p=0.49, I2=0%), showing no significant association. Results also showed no significant association between exposure and the studied outcome after comparing CD (RR=1.02; 95%CI: 0.76-1.37, p=0.89, I2=0%) and UC (RR=1.24; 95%CI: 0.81-1.89, p=0.32, I2=43%) separately.
Conclusions: The meta-analysis showed no association of these symptoms to the treatment with vedolizumab. Therefore, the new onset of worsening arthritis and arthralgia may be associated with the course of the disease itself, with the body's response to the drugs or with the exclusion of corticosteroids or anti-TNF from concomitant treatment with vedolizumab. Further studies with larger sample sizes are required, especially randomized clinical trials comparing anti-TNF, corticosteroid and immunomodulators to evaluate the incidence of joint manifestations in patients with IBD and even other rheumatological manifestations that may be associated as well.

Key words: inflammatory bowel disease – ulcerative colitis – Crohn's disease – vedolizumab – extraintestinal manifestations.

Abbreviations: ADA: adalimumab; CD: Crohn's disease; EIM: extraintestinal manifestation; IBD: inflammatory bowel disease; IFN: infliximab; IL: interleukin; JAK: Janus kinase; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; RZB: risankizumab; TNF: tumor necrosis factor; TOFA: tofacitinib; UC: ulcerative colitis; UST: ustekinumab; VDZ: vedolizumab.

INTRODUCTION

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), are inflammatory immune-mediated conditions of the gastrointestinal tract, which present with chronic and relapsing symptoms. Half of patients with IBD will experience at least one extraintestinal manifestation (EIM), of which joint manifestations are the most prevalent [1]. Arthritis/arthralgia affects 25-30% of IBD patients, often running in parallel with intestinal disease activity, leading to psychological distress and substantially impacting their quality of life [2].

Vedolizumab is an effective drug for inducing remission in moderate to severe UC and CD [3, 4]. This drug is a monoclonal antibody that blocks cellular adhesion molecules by targeting α4β7 integrin, thus inhibiting the migration of leukocytes into inflamed intestinal tissue [5, 6]. Vedolizumab's selective inhibition of the α4β7 integrin maintains systemic immune responses, offering an effective IBD treatment that minimizes the risk of compromising overall immune function [7].

Reported vedolizumab-induced EIMs are described more commonly as musculoskeletal and dermatologic symptoms, such as arthropathy, aphthous stomatitis, perianal fistulas, and pyoderma gangrenosum [8, 9, 10]. Crohn's disease patients had overall more EIMs than patients with UC [11]. In this context, despite compelling data suggesting the safety profile of vedolizumab, new onset or worsening arthritis and arthralgia are commonly reported as the main side effects of this medication even though those symptoms sources have been poorly investigated [12,13]. There are studies that suggest those EIMs in patients with IBD may just be a manifestation of the disease's pathophysiology, while others report that EIMs are resolved during vedolizumab's treatment.

Therefore, we aimed to perform a systematic review of the literature and meta-analysis of randomized controlled trials (RCTs) comparing vedolizumab use for IBD with placebo in order to assess the incidence of articular events in those patients. The main objective of this article is to investigate the safety of vedolizumab, and the drug's role in the reported joint manifestations and symptoms responsible for causing a major deterioration in the quality of life.

METHODS

The systematic review and meta-analysis were performed according to Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines [14]. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42022380262§ [15].

Study Eligibility

Studies that met the eligibility criteria were included: (1) randomized controlled trials (RCTs); (2) comparing vedolizumab with placebo; (3) in patients with inflammatory bowel disease; and (4) reporting at least one of the clinical outcomes of interest. We excluded studies with (1) overlapping patient populations; (2) without a placebo control group; and (3) not reporting any outcomes of interest.

Search Strategy and Data Extraction

MEDLINE, Scopus, and Cochrane Library databases were systematically searched from inception until September 2022. A combination of keywords was used in the search strategy: „inflammatory bowel disease", "IBD", „Crohn's disease", „ulcerative colitis", „irritable bowel syndrome", "vedolizumab", and "entyvio". No filter or geographic location restriction was applied. Moreover, the references of included articles were analyzed to identify additional eligible studies. Three authors (G.A., C. G., and J. M.) independently performed the screening and studies' selection. Disagreements were resolved through discussion among authors including a fourth reviewer (D.B.).

Two authors (G.A. and B.F.) independently extracted data on baseline demographic characteristics and desired outcomes from published papers and their respective supplementary materials when necessary. Collected data was recorded on a predefined spreadsheet. Any discrepancies were reconciled by a third author (C.G.).

Endpoints and Subgroup Analysis

Our systematic review and meta-analysis focused on vedolizumab's effects on the joints. The main outcome was the incidence of arthralgia/arthritis, with data extracted from included studies. Importantly, we sought to evaluate the side effects of vedolizumab on the joints compared to placebo.

Although being included in the spectrum of inflammatory bowel disease, CD and UC have different nuances regarding their etiologies, clinical features, complications, and management. Therefore, a subgroup analysis was performed to assess any differences in the incidence of arthralgia between the two patient cohorts being treated with vedolizumab.

Five out of the six included RCTs had both induction and maintenance phases. Aiming to analyze the long-term effects of vedolizumab in IBD patients, we focused on data from the maintenance phases for all applicable studies. Although GEMINI 3 was a trial consisting of an induction phase only, we included it in our overall analysis to capture a broader range of possible occurrences of arthralgia. To eliminate potential confounding factors related to different therapy phases, we performed a sensitivity analysis with only the data from the maintenance phase, removing GEMINI 3.

Quality Assessment

The included studies were assessed using the Cochrane Collaboration's tool for assessing the risk of bias in RCTs [16]. Five domains are evaluated using the revised tool to assess the risk of bias in RCTs (RoB 2) [17]: (1) randomization process; (2) deviations from the intended interventions; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported result. Each domain is scored as "low risk", "some concerns", or "high risk" of bias. Three authors independently performed the risk of bias assessment (G.A., C.G. and B.F.). Disagreements were resolved by consensus with a fourth reviewer (D.B.). The publication bias was assessed using funnel plots of study weights versus point estimates.

Statistical Analysis

Data analysis was performed using Review Manager (RevMan; version 5.4.1; Cochrane Collaboration, 2020, London, United Kingdom) [18]. Binary endpoints were collected as the number of events and number of individuals at risk to produce summary effects of both screening strategies in terms of relative risks (RRs) with 95% confidence intervals (CIs).

Heterogeneity was measured using the Cochrane Q test and I-squared (Higgins I2) test. Values considered significant for heterogeneity included p-value inferior to 0.10 and I2>25%. A fixed-effect model was used for endpoints with I2 < 25% (low heterogeneity). A DerSimonian and Laird random-effects model was used for pooled outcomes with high heterogeneity.

RESULTS

Study Selection and Baseline Characteristics

Initially, the search across three databases yielded a total of 4,206 studies. After removing 593 duplicates and 4,167 unrelated studies, 39 were reviewed. Ultimately, 6 randomized controlled trials were included [19-24] (Fig. 1). A total of 3,134 patients with moderate to severe inflammatory bowel disease were included, of whom 2,119 received vedolizumab and 1,015 received placebo. Three studies focused on CD [19, 20, 21], and three on UC [22, 23, 24]. Among the patients, 48.3% were female and 57.1% had prior exposure to anti-TNF drugs. Furthermore, 36.3% of the patients received concomitant corticosteroid treatment at the beginning of the studies. The weighted mean age of patients across all studies was 38.2 years. Population characteristics are summarized in Table I. Supplementary materials from three studies were used [19, 22, 23]. Two studies [20, 24] were used for both the baseline demographics table and the outcomes table, while one study [23] was used only for the baseline demographics table.

Pooled Analysis of all Studies

Pooled data on arthritis or arthralgia of any kind showed no significant difference between the patients treated with vedolizumab (210/2,119; 9.9%) and patients who received placebo (84/1,015; 8.3%) (RR=1.09; 95%CI: 0.86-1.38; p=0.49; Fig. 2).

Subgroup Analysis

We aimed to explore the main outcome in subgroups according to the different forms of IBD, namely CD and UC, as detailed in the Supplementary file. The analysis showed no statistically significant difference in the incidence of arthritis or arthralgia comparing the vedolizumab and the placebo groups both in the CD subgroup (RR=1.02; 95%CI: 0.76-1.37, p=0.89; Fig. 3) and in the UC subgroup (RR=1.24; 95%CI: 0.81-1.89, p=0.32; Fig. 3).

Sensitivity Analysis

A sensitivity analysis was performed with only studies that had a maintenance phase. Only one study of the six included had only the induction phase, and therefore was excluded from this analysis. There was still no significant difference between the patients treated with vedolizumab and patients who received placebo (RR=1.09; 95%CI: 0.85-1.40; p=0.51; Fig. 4).

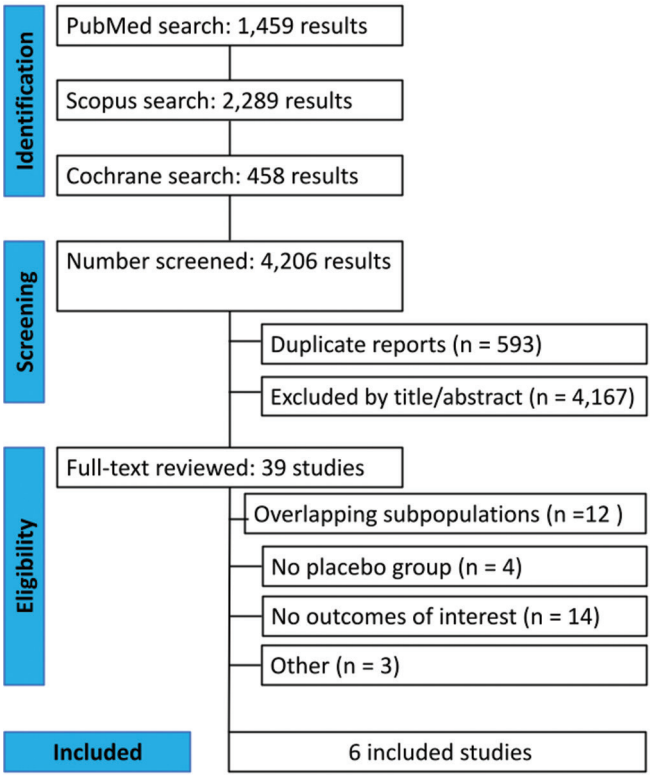

Fig. 1. PRISMA flow diagram of study screening and selection. The search strategy in PubMed, Scopus and Cochrane yielded 4,206 studies, of which 39 were fully reviewed for inclusion and exclusion criteria. A total of 6 studies were included in the meta-analysis.

Quality assessment

RoB-2 tool was utilized to assess the quality of included studies. Two studies demonstrated high quality and low risk across performance, selective reporting, and other analyzed biases [20, 21]. One study raised some concerns [19] and three were found to have a high risk of bias [22, 23, 24]. The main outcome showed minimal variability among the studies, and overall heterogeneity was zero. A summary of the quality assessment for each individual RCT can be found in the Supplementary file.

Table I. Baseline characteristics of included studies

Studies	Population	Patients, n	Age, y*	Gender (female)(%)	Prior anti-TNF use, n	Full Mayo Score#	CDAI Score¶	Baseline corticosteroids, n&
		VDZ/PLA	VDZ/PLA	VDZ/PLA	VDZ/PLA	VDZ/PLA	VDZ/PLA	VDZ/PLA
Motoya 2019 [23]	UC	41 / 42	43 / 42.6	48.8 / 45.2	17 / 14	8.1 / 7.9	N/A	9 / 11
VISIBLE 1 [24]	UC	160 / 56	39.3 / 39.4	40 / 39.3	64 / 20	9 / 9	N/A	66 / 24
VISIBLE 2 [20]	CD	275 / 134	38.2 / 36.1	42.9 / 50.7	168 / 71	N/A	318 / 309	64 / 31
GEMINI 1 [22]	UC	620 / 275	40.1 / 40.8	41.3 / 41.4	311 / 120	8.5 / 8.5	N/A	226 / 106
GEMINI 2 [19]	CD	814 / 301	35.5 / 37.9	53.4 / 53.2	535 / 154	N/A	323 / 325	280 / 101
GEMINI 3 [21]	CD	209 / 207	37.9 / 38.6	43.9 / 50.8	158 / 157	N/A	313.9 / 301.3	110 / 108

UC: ulcerative colitis; CD: Crohn's disease; VDZ: Vedolizumab; PLA: Placebo; N/A: not available; n: number; y: years; %: percentage of patients relative to total number in each study group; *: Mean or median; # Full Mayo Score: clinical measure specific to ulcerative colitis; reported as mean or median when available; ¶: Crohn's Disease Activity Index; reported as mean or median when available; &: Number of patients receiving only corticosteroids at the beginning of the study.

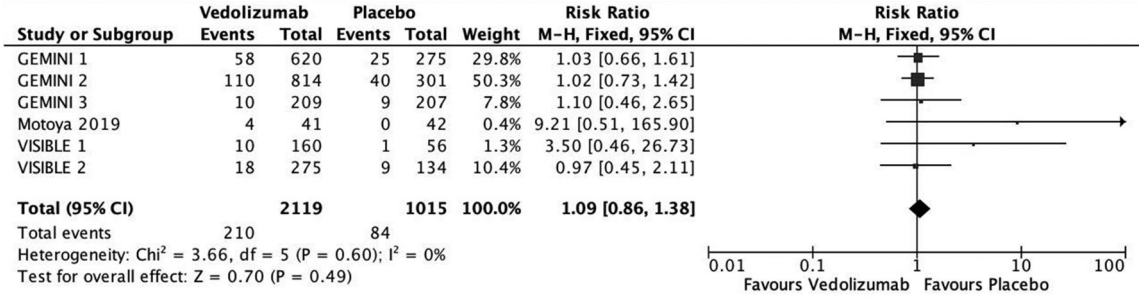

Fig. 2. There was no significant difference regarding the incidence of arthritis or arthralgia when comparing vedolizumab with placebo. CI: confidence interval; M-H: Mantel-Haenszel.

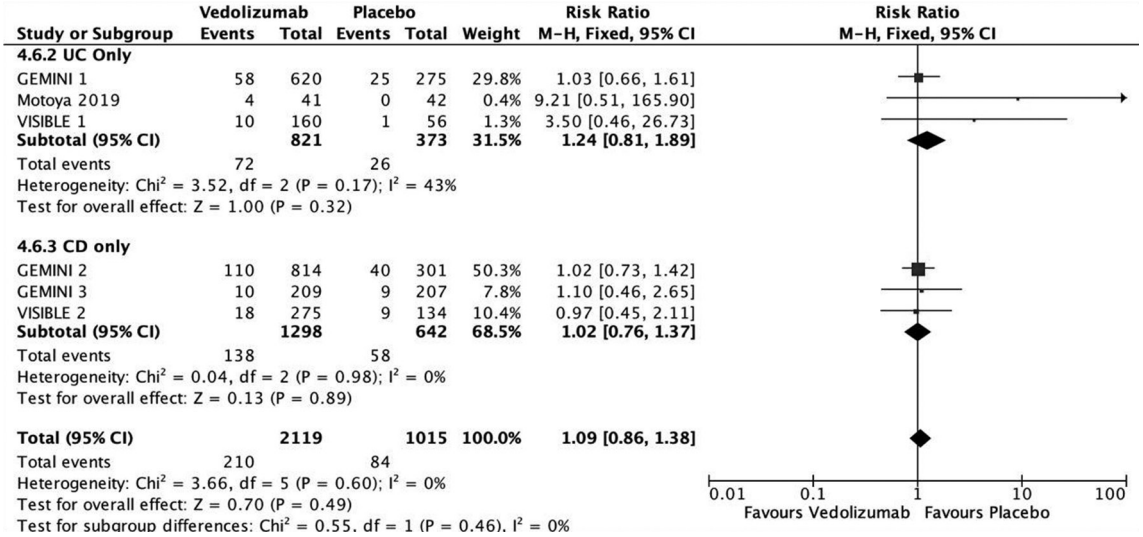

Fig. 3. In the subgroup analyses for both Crohn's Disease and Ulcerative Colitis, there was no significant difference between patients receiving vedolizumab and placebo. CI: confidence interval; M-H: Mantel-Haenszel.

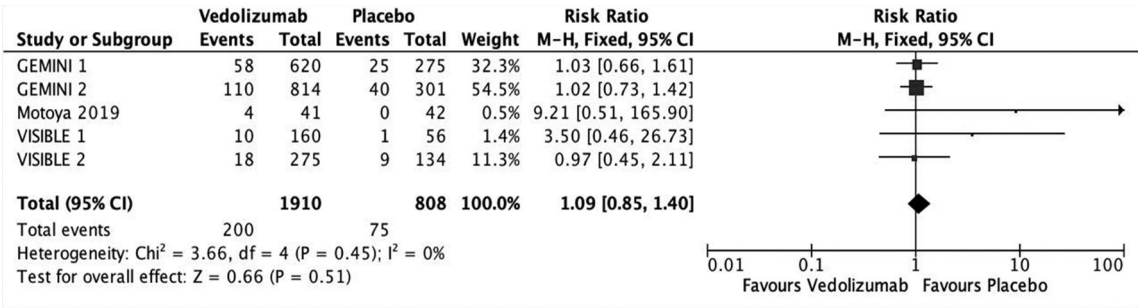

Fig. 4. Sensitivity analysis with all of the maintenance phase studies.

To better understand the potential of publication bias, a funnel plot was performed (Fig. 5). It displays a symmetrical clustering of four studies at the top, suggesting no publication bias among the most robust studies. Two studies positioned on the right side of the middle plot may indicate a potential publication bias among smaller studies. However, given the greater number of robust studies and their higher representation, any potential bias among smaller studies is unlikely to significantly impact the reliability of the results.

DISCUSSION

This systematic review and meta-analysis included 6 randomized studies with 2,119 IBD patients and revealed no significant difference between vedolizumab and placebo in the pooled analyses in terms of the development of arthritis or arthralgia.

Extraintestinal manifestations are frequently observed in patients with IBD, especially involving the musculoskeletal

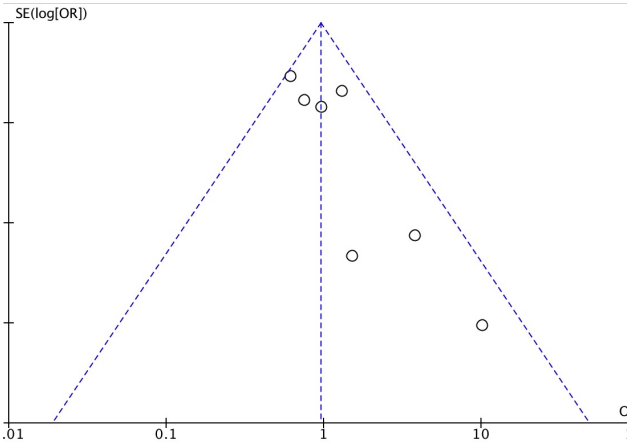

Fig. 5. Funnel plot showing a symmetrical clustering of four studies at the top, suggesting no publication bias among the most robust studies. Two studies positioned on the right side of the middle plot may indicate a potential publication bias among smaller studies.

system [25]. Vedolizumab is also known to have efficacy in inducing and maintaining remission in patients with moderate-to-severe IBD, however, previous studies have reported conflicting findings regarding its effect on EIMs. While some suggest an increased risk of skin and joint manifestations [26], others have indicated unknown efficacy [27] or lower occurrence of new EIMs during the treatment [28, 29].

The drug is assumed to act locally and is thus not expected to cause systemic immunosuppression. Some studies suggest that the lack of immunosuppression may have a negative effect on the EIMs of inflammatory bowel disease, since the immune system continues to function normally with a greater chance of forming immune complexes, for example [30]. On the other hand, there are studies that suggest EIMs in patients with IBD may just be a manifestation of the disease's pathophysiology. Individuals selected for the treatment with vedolizumab are generally patients with refractory and severe condition and, therefore, are more likely to develop peripheral arthralgia, ankylosing spondylitis, and other EIMs [31]. Other studies analyzed the treatment of EIMs in patients with IBD and vedolizumab was pointed as a possible effective medication for EIMs [32].

It is critical to consider various confounding factors that could influence the observed association between vedolizumab treatment and EIMs. Factors such as the severity and duration of the underlying inflammatory bowel disease could significantly impact the incidence of conditions like arthritis or arthralgia. Moreover, comorbidities may also predispose patients to develop these joint symptoms independently of the treatment. The interaction between vedolizumab and concurrent medications such as corticosteroids, immunosuppressants, and nonsteroidal anti-inflammatory drugs (NSAIDs), which are commonly used to manage IBD and its symptoms, may further complicate the clinical picture. Additionally, lifestyle factors including physical activity, diet, and smoking status, as well as the history of previous biologic therapy use, including anti-TNF agents, before switching to vedolizumab, might significantly affect the development of joint symptoms. Acknowledging and analyzing these factors are crucial for a comprehensive understanding of the treatment outcomes and the pathophysiological mechanisms involved in the development of EIMs in IBD patients treated with vedolizumab.

When compared to other drugs also used to treat moderate to severe IBD, studies have shown that VDZ shows higher rates of clinical remission and endoscopic improvement compared to adalimumab (ADA), a type of anti-TNF monoclonal antibodies, on UC treatment. ADA, however, had higher rates of corticosteroid-free clinical remission [33]. Tofacitinib (TOFA), an oral Janus kinase inhibitor, also showed higher rates of steroid-free clinical remission compared to VDZ in patients with prior history of anti-TNF use [34]. In CD patients, ADA and ustekinumab (UST) offer similar clinical and endoscopic remission in biologic-naive patients, but infliximab (IFX) ranks highest for inducing clinical remission [8]. After IFX failure, risankizumab (RZB), anti-IL-23 antibody, shows higher rates of steroid-free clinical remission compared to VDZ [9].

Regarding the safety of these drugs, anti-TNF therapies (e.g., ADA, IFX) are associated with increased risk of infections and possibly lymphoma and melanoma, especially in combination with thiopurines [10, 11]. JAK inhibitors are linked to dose-dependent increase in risk of infections and higher rates of major adverse cardiovascular events and thromboembolic events, especially in patients older than 50 years old, with increased risk or previous cardiovascular events or with a history of smoking. [35] VDZ offers a lower risk of serious adverse events compared to anti-TNF in both UC and CD [36, 37]. These findings corroborate our results, demonstrating the safety of the drug.

There are a few limitations to note in our systematic review and meta-analysis. First, despite including only high-quality study designs (RCTs), our risk of bias assessment indicated a high risk of bias in three studies and some concerns in one. Three of the studies [22-24] showed a high risk of bias due to a mix of open-label and double-blind phases. One of these [21] also had missing outcome data and a selection of reported results. To minimize potential biases, we preferred to use the maintenance phase of all studies and performed a sensitivity analysis by removing the only study without a maintenance phase. Second, even though a subgroup analysis was done, it is important to note that the subgroup analysis may have limited statistical power due to the limited number of studies providing data specifically on this outcome. Due to this fact, caution is necessary when interpreting and generalizing these findings, since a limited statistical power increases the chance of committing a Type II error. Third, variability in the definitions of arthritis and arthralgia among the included studies, coupled with the subjective nature of pain assessment, could skew the outcomes. Additionally, the use of medications such as oral corticosteroids or immunosuppressants by participants can introduce confounding factors, potentially masking or exaggerating vedolizumab's effects.

CONCLUSIONS

In patients with moderate to severe forms of IBD treated with vedolizumab, the drug does not seem to be responsible for the occurrence of arthritis and arthralgia. Therefore, these symptoms may be associated with the course of the disease

itself, the body's response to the drugs, or the exclusion of corticosteroids or anti-TNF from concomitant treatment with vedolizumab. Further studies with larger sample sizes are needed, especially RCTs comparing anti-TNF, corticosteroids, and immunomodulators to evaluate the incidence of joint manifestations in patients with IBD and other rheumatological manifestations that may be associated as well.

Conflicts of interest: None to declare.

Authors' contribution: G.A.H. conceived the study. G.A.H., C.G, and J.C.M. screened and selected the studies. G.A.H., B.T.Q.F., M.P.D. and J.C.M. extracted data. G.A.H., C.G., and B.T.Q.F. analyzed and interpreted data. All authors contributed to drafting the manuscript. G.A.H., C.G., and B.T.Q.F. critically revised the manuscript. D.B.O supervised the study. All authors read and approved the final version of the manuscript.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-5546

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