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Effect of vedolizumab treatment on extraintestinal articular manifestations in patients with inflammatory bowel disease: meta-analysis

1. Included studies

12 studies including 7,296 IBD patients treated with vedolizumab.

2. Incidence of articular events

De novo or worsening joint EIMs: 8.7%.
Worsening of pre-existing EIMs: 31.9%.

3. Clinical response

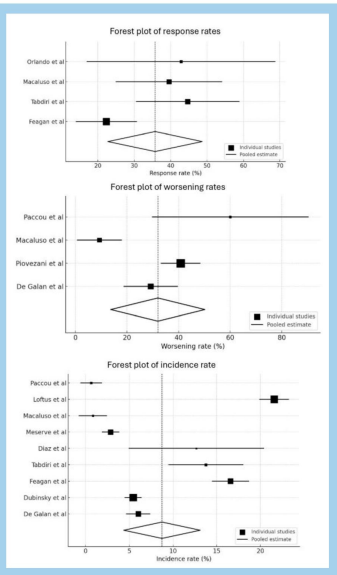
Overall joint response: 35%.
(Peripheral 32%, Axial 23%)

4. Differences by IBD subtype

Higher joint event rates in Crohn's disease vs ulcerative colitis (13.8% vs 10.1%)

5. Clinical interpretation

Vedolizumab shows a low risk of inducing articular EIMs but limited effectiveness in improving them.



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Effect of vedolizumab treatment on extraintestinal articular manifestations in patients with inflammatory bowel disease: meta-analysis

Short title: Vedolizumab on articular EIMs in IBD: Meta-analysis

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Author Contributions: DCD: study design, data collection, data analysis, data interpretation, writing the original draft. CYC, and CCC: data collection, data interpretation, Writing - Review & Editing SGL: study design, data interpretation, Writing - Review & Editing

Abbreviations:

The following abbreviations are used in this manuscript:

- IBD: Inflammatory Bowel disease
- CD: Crohn's disease
- UC: Ulcerative Colitis
- EIM: Extraintestinal Manifestation
- VDZ: Vedolizumab

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Lay summary

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, can affect not only the digestive system but also other parts of the body. One of the most common extra-intestinal problems involves the joints, causing pain, swelling or stiffness. Vedolizumab is a medication widely used to treat inflammation in the gut, but its impact on joint symptoms has been unclear.

We carried out a meta-analysis, pooling data from 12 studies that included 7,296 patients with IBD who were treated with vedolizumab. We looked at two main questions:

1. How often do new joint problems appear, or existing ones worsen, during treatment?
2. How often do joint symptoms improve with vedolizumab?

Our results showed that new or worsening joint symptoms occurred in about 9% of patients, and worsening of pre-existing joint problems in about 32%. These rates were similar between Crohn's disease and ulcerative colitis. Overall, about one in three patients experienced an improvement in joint symptoms while on vedolizumab. Improvement was more common in peripheral joints (arms and legs) and less common in axial involvement (spine and sacroiliac joints).

In summary, vedolizumab appears to carry a low risk of causing new joint issues, but its ability to improve existing joint symptoms is limited, especially in axial disease. These findings can help guide treatment decisions for people with IBD who also suffer from joint problems and highlight the importance of personalised therapy based on each patient's pattern of disease.

Abstract:

Introduction: Joint extraintestinal manifestations (EIMs) are a frequent complication in patients with inflammatory bowel disease (IBD). The effectiveness of vedolizumab in this context remains uncertain, with conflicting results reported. Some studies have even suggested a potential worsening of joint manifestations during treatment.

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Methods: We conducted a meta-analysis of observational studies reporting joint EIM outcomes in patients with Crohn's disease or ulcerative colitis treated with vedolizumab. New-onset and worsening of existing joint manifestations were analysed separately from improvement or clinical response. A systematic search was performed in EMBASE, PubMed, and MEDLINE in June 2023, with the final search conducted on 15 June 2023. Grey literature, including preprints and conference abstracts, was excluded. The primary outcomes were the pooled incidence of joint EIMs and the rate of clinical response.

Results: Twelve studies including a total of 7,296 patients met the inclusion criteria. The pooled was 8.7% (95% CI, 4.3-13%) for incidence of joint EIMs was and 31.9% for worsening. The pooled clinical response rate was 35% (95% CI, 22-48%), with a response rate of 32% for arthritis/arthralgia and 23% for spondyloarthritis. All analyses demonstrated high heterogeneity.

Conclusions: Vedolizumab treatment appears to be associated with a relatively low incidence of new or worsening joint EIMs. However, its effectiveness in improving joint manifestations is limited.

Keywords: Inflammatory bowel disease. Vedolizumab. Extraintestinal manifestation.

Introduction

Inflammatory Bowel Disease (IBD) comprises a group of chronic inflammatory disorders, primarily Crohn's disease (CD) and ulcerative colitis (UC), characterised by alternating periods of flare-ups and remission. Beyond the intestinal inflammation, IBD frequently presents with extraintestinal manifestations (EIMs), affecting various organ systems. Epidemiological data suggest that up to 50% of patients experience at least one EIM[1]. These manifestations are diverse, with musculoskeletal, dermatological, and ophthalmological involvement being the most common[2].

The management of EIMs in IBD necessitates a multidisciplinary approach. Among the available treatments, anti-tumour necrosis factor (anti-TNF) agents have shown the strongest evidence of efficacy in this context[3-5]. However, their use is not always

effective or feasible in all patients. According to the most recent ECCO guidelines on the management of EIMs in IBD[6], anti-TNFs are recommended for articular involvement, with methotrexate also considered a valid option. In contrast, non-steroidal anti-inflammatory drugs (NSAIDs) should be used cautiously due to their potential to exacerbate intestinal inflammation[7].

Vedolizumab (VDZ) is a monoclonal antibody that selectively targets the α4β7 integrin, thereby inhibiting lymphocyte migration to the gut. It is approved for the treatment of both CD and UC in adults and has demonstrated an excellent safety profile, making it an appealing option for frail patients[8,9]. Nevertheless, while VDZ is effective in controlling luminal disease, its impact on joint EIMs remains uncertain. The available data are heterogeneous and derived mainly from observational studies[10-13] and post hoc analyses of clinical trials[14]. Some authors have even suggested that vedolizumab may induce or worsen joint EIMs[15,16].

Given the conflicting and limited evidence, we conducted a meta-analysis of published studies to evaluate the effect of vedolizumab on joint EIMs in patients with IBD. This work aims to provide more robust data on a clinically relevant issue that affects the daily management of a significant proportion of patients.

Materials and Methods

Data Sources and Study Selection

A systematic literature search was conducted in the MEDLINE, PubMed, and EMBASE databases, without language restrictions, to identify observational studies evaluating the impact of vedolizumab (VDZ) in two clinical scenarios: (i) the incidence of de novo or worsening joint extraintestinal manifestations (EIMs) in patients with inflammatory bowel disease (IBD) treated with VDZ; and (ii) the response or remission of pre-existing joint EIMs in such patients. The search covered all studies published up to June 2023.

The following terms were used in the bibliographic search strategy: *'vedolizumab' [Supplementary Concept]* AND *'Inflammatory Bowel Diseases' [MeSH]* AND (*'Spondyloarthritis' [MeSH]* OR *'Axial Spondyloarthritis' [MeSH]* OR *'Non-Radiographic Axial Spondyloarthritis' [MeSH]* OR *'Arthritis' [MeSH]* OR *'extraintestinal manifestations'*).

Titles and abstracts of potentially relevant studies were screened for eligibility. Full-text articles were retrieved and reviewed to confirm inclusion. In addition, congress communications and references from relevant articles, reviews, or meta-analyses were examined to identify any additional eligible studies.

Eligibility Criteria

Studies were selected according to the following predefined criteria: i) they reported results on at least one of the following outcomes: occurrence of de novo joint extraintestinal manifestations (EIMs), worsening of pre-existing joint EIMs, and/or improvement or clinical response of joint EIMs; ii) they were observational studies or post hoc analyses of clinical trials; iii) they involved vedolizumab (VDZ) treatment in adult patients with inflammatory bowel disease (IBD); and iv) they reported a minimum follow-up duration of four months.

Case series were excluded, as were studies in which VDZ was administered in combination with another biological agent or small molecule. Only peer-reviewed studies published in indexed scientific journals were considered eligible. Grey literature—including conference abstracts, dissertations, and unpublished reports—was excluded. This decision was based on several methodological considerations:

(1) to ensure a minimum standard of quality and peer review; (2) to avoid the inclusion of studies with incomplete data reporting or limited transparency; and (3) to enhance the reproducibility and reliability of the results.

This meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Evaluation of Results and Data Extraction

All articles were independently reviewed by two authors based on the predefined inclusion criteria. Discrepancies were resolved by consensus with the involvement of a third author. For each study, proportions (ranging from 0 to 1) of patients experiencing clinical response to vedolizumab (VDZ) or the incidence/worsening of joint extraintestinal manifestations (EIMs) were extracted from the reported outcomes.

The following parameters were recorded: incidence of new onset articular EIMs and worsening of previously existing EIMs; response/remission of previously existing EIMs. Patients with CD and UC were analyzed separately when this information was available. EIMs were collectively and separately analyzed between spondyloarthritis (SpA) and arthritis/arthralgia when possible. The rate of use of concomitant immunomodulators, date of publication, study design, follow-up time, and the way data were recorded were also collected.

In most observational studies, clinical response was based on the treating investigator's subjective assessment, whereas post hoc analyses of clinical trials employed standardised questionnaires. Two studies used validated diagnostic criteria to identify new EIMs, although none applied standardised definitions to assess worsening. Only two studies reported assessment by a rheumatologist.

Data Synthesis and Statistical Methods

Pooled estimates for the incidence/worsening of joint EIMs and the clinical response to VDZ were calculated using a random-effects model, appropriate for accounting for between-study variability and assuming that included studies represent a random sample of the wider evidence base.

Heterogeneity across studies was evaluated using the I^2 statistic, with values <50% interpreted as low, 50–75% as moderate, and >75% as high heterogeneity. The τ^2 statistic (Tau-squared) and 95% prediction intervals were also computed to further characterise between-study variability.

Potential publication bias was assessed using funnel plots, where the logarithm of the effect size was plotted against the standard error. Egger's regression test was applied, with a p-value <0.05 indicating possible publication bias.

The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies. Two reviewers independently rated each study, with discrepancies resolved by consultation with a third reviewer (CYC). Based on NOS scores, studies were categorised as poor quality (0–2), moderate/acceptable quality (3–5), or high quality (6–9).

To assess the impact of study characteristics on the incidence outcomes, a subgroup analysis was conducted to explore potential influencing factors, including the following parameters: study design, type of arthropathy (axial or peripheral), method of arthropathy assessment, data collection method, and the specialist responsible for the evaluation.

Since the number of studies available for the outcome of interest was fewer than 10, it was not possible to perform a meta-regression. Additionally, the number of studies evaluating the other outcomes analysed (worsening rate and response rate) was insufficient to conduct sensitivity analyses.

Results

From the initially identified 820 studies through bibliographic database searches and other sources, after removing duplicate results, two reviewers independently assessed titles and abstracts, eliminating 785 studies clearly irrelevant for this meta-analysis. Consequently, 31 studies were selected for full-text evaluation. Of these, 12 studies(1-12) meeting inclusion and exclusion criteria were ultimately chosen, encompassing a total of 7,296 patients meeting inclusion criteria (Figure 1).

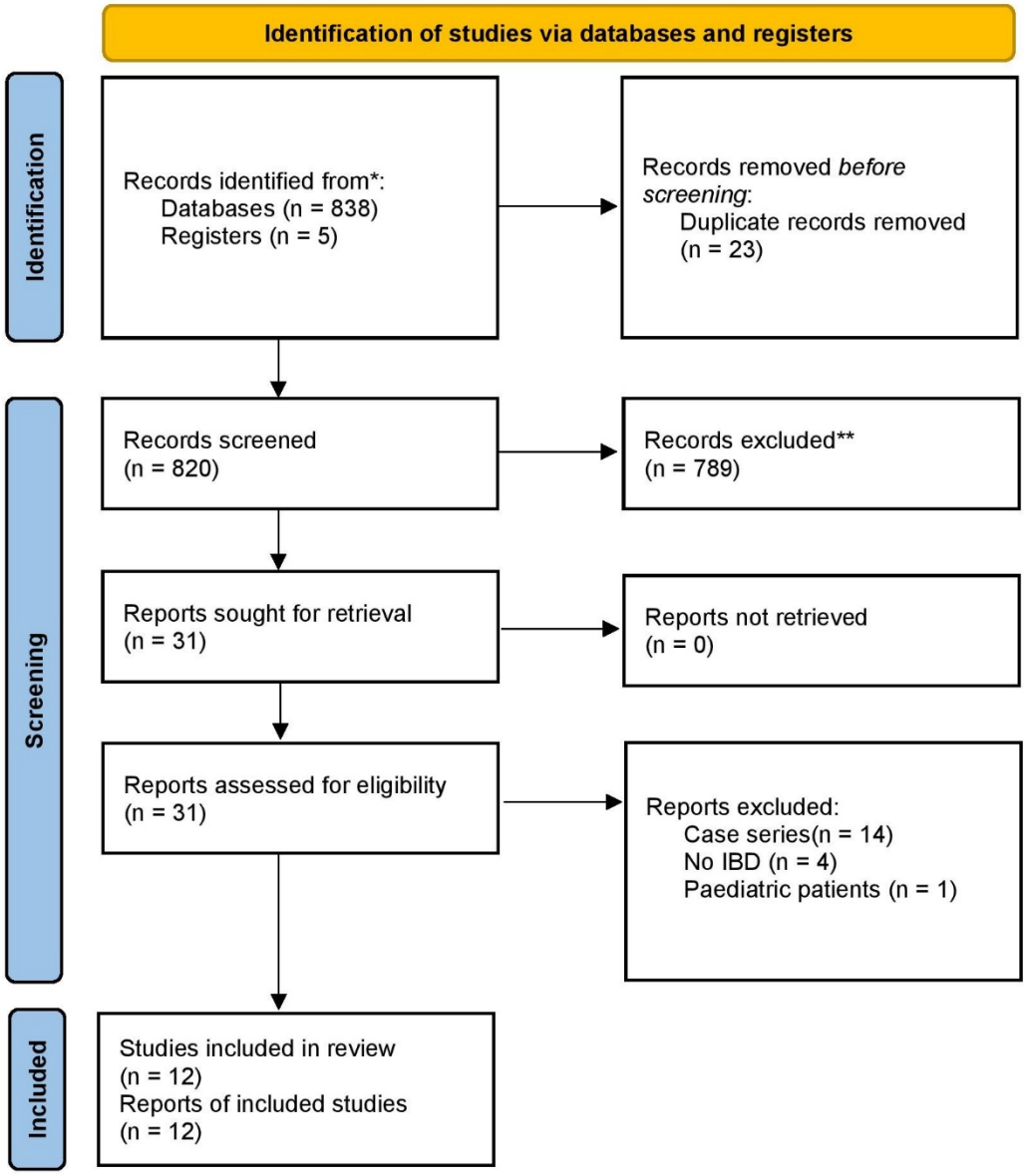

Fig. 1.

Characteristics and Quality of Included Studies

Of the 12 studies included, two were prospective cohorts, two were post-hoc analyses of clinical trials, and eight were retrospective cohort studies. Only five differentiated between Crohn's disease and ulcerative colitis. Among the retrospective studies, six obtained data from medical record reviews and two from databases. Only four studies used a validated questionnaire to assess joint symptoms, and in only two studies was the assessment performed by rheumatology specialist. The main study characteristics

are summarized in Table 1.

Regarding study quality, according to the NOS scale, 10 studies were classified as high quality, and two were considered acceptable.

Incidence or worsening of Joint EIMs

Nine of the included studies provided data on the incidence of events after the initiation of vedolizumab treatment. The pooled incidence rate was 8.74% (95% CI: 4.37%–13.11%, I^2 = 98.63%). *Figure 2A.*

Six studies separately reported data on the incidence of peripheral arthropathy, with an estimated rate of 12.09% (95% CI: 1.72%–20.04%, I^2 = 98.88%). *Figure 2B.* Valid data on the incidence of axial arthropathy were available from only one study, making pooled analysis unfeasible.

For the analysis based on the type of inflammatory bowel disease, it was not possible to distinguish between de novo incidence and worsening, nor between types of arthropathy.

The pooled event rate for Crohn's disease was 13.86% (95% CI: 8.82%–18.91%, I^2 = 76.21%), while for ulcerative colitis it was 10.15% (95% CI: 4.78%–15.52%, I^2 = 94.43%) Figures 2C and 2D.

On the other hand, four studies provided data to evaluate the worsening rate of pre-existing extraintestinal manifestations. The pooled worsening rate for both types of arthropathy combined was 31.93% (95% CI: 13.72%–50.14%, I^2 = 90.83%). Figure 3A. For axial arthropathy specifically, the estimated rate was 32.48% (95% CI: –17.02% to 81.98%, I^2 = 89.9%). Figure 3B. There were insufficient data to perform a separate analysis for the peripheral arthropathy subgroup.

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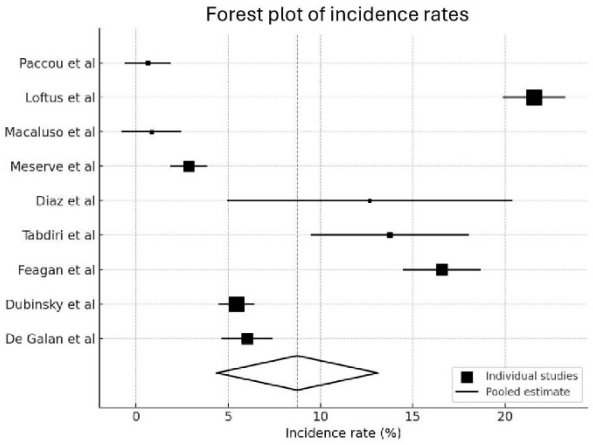
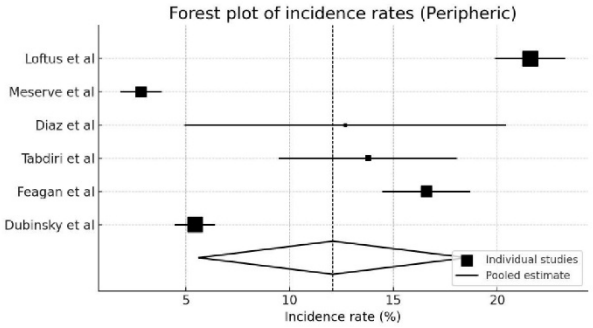


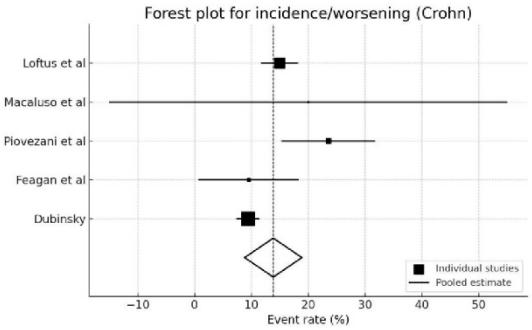
Vedolizumab vs baseline

Pooled rate: 8,74% (CI95% 4,37%-13,11%)
Heterogeneity: Tau^2= 0,00424 I^2= 98,63
Predictal Interval= -4,75% a 22,23%



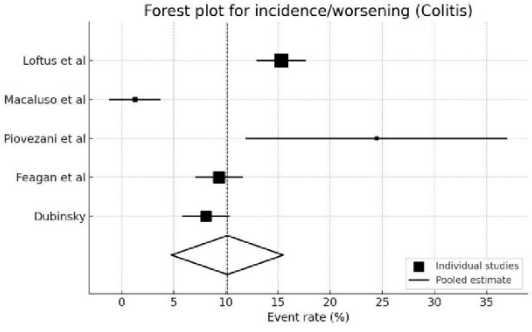
Vedolizumab vs baseline

Pooled rate: 12,09% (CI 95% 1,72%-20,04%)
Heterogeneity: Tau^2= 0,00614 I^2= 98,88
Predictal Interval= -4,57 a 28,74



Vedolizumab vs baseline

Pooled rate: 13,86% (CI95% 8.82% to 18.91%)
Heterogeneity: Tau^2= 0.00190 I^2= 76.21%
Predictal Interval= 3.93% to 23.79%



Vedolizumab vs baseline

Pooled rate: 10,15% (CI95% 4.78% to 15.52%)
Heterogeneity: Tau^2= 0,00320 I^2= 94,43%
Predictal Interval= −2.17% to 22.48%

Figure 2. Pooled rate of incidence of de novo MEIs and incidence/worsening of previous extraintestinal articular manifestations accordint to type of IBD. a) Overall de novo incidence b) De novo incidence for peripheral arthropathy only c) Incidence or worsening in Crohn's disease d) Incidence or worsening in ulcerative colitis.

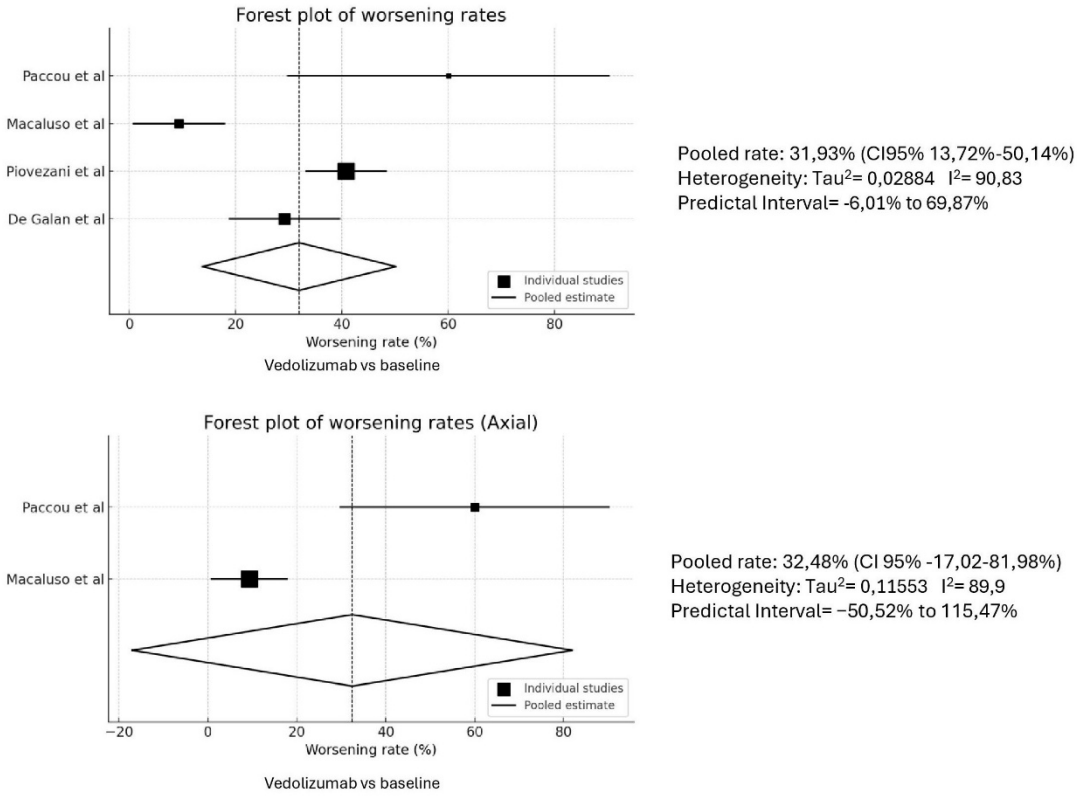


Figure 3. Pooled rate of worsening of pre-existent MEIs. a) Overall worsening of pre-existing artropathy b) Pooled rate of worsening of axail artropathy MEIs.

Egger's regression tests for publication bias were significant for the overall analysis of all studies (p=0.036) and for the SpA development subgroup (p<0.001). However, both analyses of peripheral arthropathies/arthralgias (p=1.91) and both analyses based on IBD type (p=0.262 for CD and p=0.176 for UC) were non-significant.

Treatment Response

Lastly, the rate of clinical response to VDZ treatment in previously active joint EIMs was analyzed. In this scenario, the pooled response rate was 35.72% (95% CI 22,78% -48,66%, I^2 69.18%, Figure 4A). When analyzed separately by the type of joint EIM, patients with axial artropathy had a pooled response rate of 23.24% (95% CI NA, Figure 4 B) and patients with peripheric artropathy had a pooled response rate of 32.75% (95% CI 10.9-54.59%, $I^2$85.76%, Figure 4C).

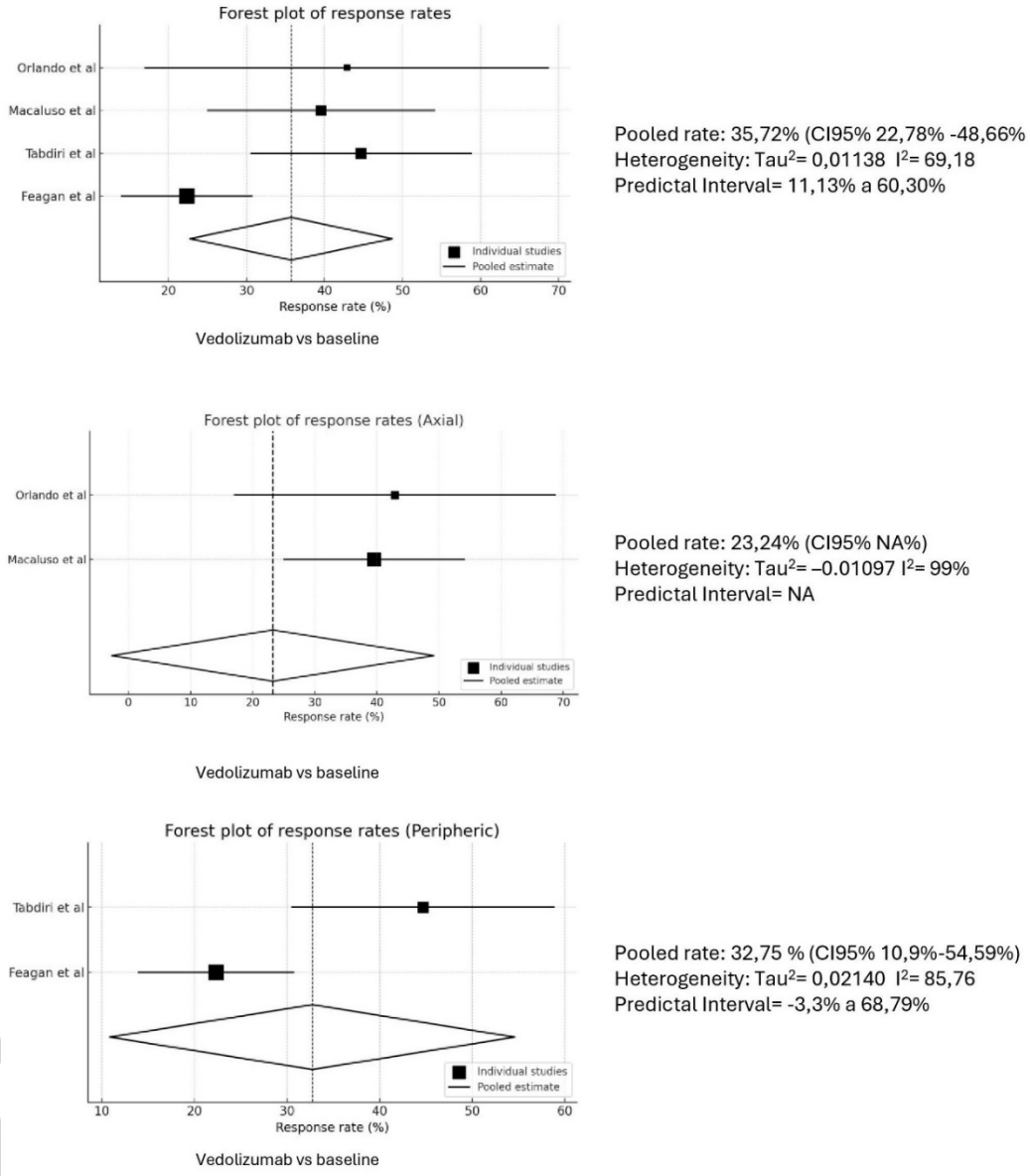


Figure 4. Pooled rate of clinical improvement of extraintestinal articular manifestations. A) Any manifestation B) Peripheric artropathy C) Axial artropathy.

Egger's regression test for publication bias in this analysis was non-significant for both the overall analysis and patients with SpA (p=0.919 and p=0.123, respectively). However, publication bias was identified (p=0.008).

The proposed meta-regression analysis was not feasible due to the low number of studies potentially eligible for evaluation. Instead, a subgroup analysis was performed for those variables that were categorical. These results are presented in Table 2.

Discussion

is a well-established and safe treatment option for inflammatory bowel disease (IBD). Its mechanism of action—selective inhibition of the α4β7 integrin—prevents lymphocyte migration to the gastrointestinal tract while theoretically sparing other tissues(13).

This gut-selectivity underpins VDZ's excellent safety profile, including a lower risk of systemic infections, with the notable exception of *Clostridioides difficile(14)*. Consequently, VDZ is particularly useful in frail patients and those with a history of malignancy(15).

However, this same selectivity has raised concerns regarding its effectiveness in managing extraintestinal manifestations (EIMs), particularly joint involvement. This meta-analysis, to our knowledge, is the first to evaluate both the efficacy of VDZ in treating joint EIMs and the incidence of these manifestations during treatment.

We analysed twelve studies involving nearly 7,300 patients. The pooled incidence of de novo joint EIMs was 8.7%, while worsening of pre-existing joint manifestations occurred in 31.9% of patients. The overall response rate was estimated at 35.7%. However, substantial heterogeneity was observed in all analyses.

Several factors may explain this heterogeneity, including variation in study design, patient characteristics (e.g., disease subtype, corticosteroid use), and inconsistent definitions of joint EIMs. Many studies did not clearly differentiate between arthritis

and arthralgia—two distinct entities—and classification bias between inflammatory arthritis, non-inflammatory arthropathy, and non-specific musculoskeletal pain is likely. This issue is particularly pertinent given that most studies were retrospective and assessments were typically performed by gastroenterologists rather than rheumatologists. Prospective evaluations by rheumatologists would likely enhance diagnostic accuracy.

Only four studies used validated indices to measure treatment response, while most relied on the treating clinician's subjective assessment. The absence of standardised tools, especially rheumatologist-led assessments, introduces a notable risk of misclassification bias.

Previous reports have raised concerns regarding joint-related adverse events during VDZ therapy. Our analysis suggests that while these events are not negligible—with an incidence of 8.7%, and 12.1% for peripheral arthralgias—they are not as frequent as earlier anecdotal evidence implied.

Subgroup analyses revealed slightly higher incidence rates in patients with Crohn's disease (13.8%) than in those with ulcerative colitis (10%). These figures are comparable to the expected background prevalence of joint manifestations in IBD, generally estimated between 13% and 21%(16).

Regarding therapeutic response, our pooled estimates indicate modest efficacy: 35% overall, 32% in patients with peripheral arthralgias, and only 23% in those with axial manifestations. The particularly low response in axial disease is clinically relevant, as it likely reflects the distinct pathophysiology of this phenotype. Peripheral joint symptoms are more often linked to luminal inflammatory activity, which VDZ can effectively control, whereas axial disease appears to follow a more independent inflammatory course, making it inherently less responsive to gut-selective agents. This observation is consistent with previous evidence showing that even the most widely studied therapy for axial EIMs—anti-TNF agents—offers variable benefit, with data limited to four unblinded clinical trials involving around 100 patients (17-20). For ustekinumab, evidence remains inconclusive: while a systematic review suggested potential benefit (21), a post hoc analysis of the UNITI trials failed to confirm efficacy in Crohn's disease.

Similarly, for peripheral joint pathology, there are no high-quality randomized clinical trials. Response rates observed in this scenario for anti-TNF drugs vary from 12.5% to 73%(22-24). Regarding ustekinumab, available data for this scenario are contradictory. A systematic review in patients with arthralgia or psoriatic arthropathy showed that ustekinumab is effective in this scenario(21). However, the post-hoc analysis of the UNITI trials did not confirm it in patients with CD(25).

Taken together, our meta-analysis underscores that, across all phenotypes, the expected clinical response to VDZ remains limited—below 40% in every scenario—highlighting the need for cautious therapeutic decision-making, particularly when managing patients with axial disease. Although the overall risk of worsening pre-existing joint EIMs or developing de novo manifestations was relatively low (14%), our findings suggest that VDZ should be considered a second-line option in patients whose disease course is dominated by joint EIMs. In such cases, therapies with broader systemic activity, such as anti-TNF agents or JAK inhibitors, are generally preferred, although high-quality evidence for JAK inhibitors in this specific setting remains lacking. Importantly, these results do not support avoiding VDZ solely due to concerns about precipitating joint EIMs. Rather, its use should be guided by the overall balance between intestinal and extraintestinal disease activity, recognizing that while VDZ is a safe choice in this regard, its efficacy for controlling joint-predominant disease appears suboptimal.

Several limitations must be acknowledged. First, the meta-analysis is based primarily on retrospective observational data, which are inherently prone to bias. Second, musculoskeletal outcomes were frequently based on subjective clinician assessment, with limited involvement of rheumatologists. Third, the use of multicentre databases without patient-level identifiers raises the possibility of patient duplication, potentially inflating the sample size and biasing pooled estimates. Lastly, residual confounding—particularly related to concomitant corticosteroids or disease-modifying antirheumatic drugs (DMARDs)—cannot be excluded, despite efforts to account for known confounders.

This meta-analysis demonstrates that vedolizumab offers limited efficacy in the treatment of joint EIMs, with response rates below 40%. However, the risk of inducing

or worsening these manifestations appears low. These findings suggest that while vedolizumab may not be the preferred option for patients with significant joint involvement, it remains a valid therapeutic choice, particularly when concerns exist about systemic immunosuppression or safety.

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Data Availability Statement: The data presented in this study are available on request to the corresponding author with prior authorization of our Ethical Committee that can be obtained at https://www.iacs.es/investigacion/comite-de-etica-de-la-investigacion-de-aragon-ceica/ceica-evaluaciones-y-otras-presentaciones accessed on 05 May 2025.

Conflicts of Interest: Dr Casas-Deza has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Takeda, Janssen, Ferring and Faes Farma. Dr García-López has served as a speaker, advisory member for or has received research funding from AbbVie, Janssen, MSD, Pfizer, and Takeda.

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Table 1. Characteristics of included studies

Author	Year	Design	n	Difference between UC and CD	Evaluation of new EIM incidence	Evaluation of previous EIM worsening	Evaluation of EIM improvement	Type of EIM	Valoration method	Follow-up time (weeks)	Data collection method	Specialist assessing the response	Immunosupresor rate (%)
Paccou et al	2019	Retrospective cohorts	171	No	Yes	Yes	Yes	Axial	Validated indices	52	Direct	Gastroenterologist	
Loftus et al	2020	Clinical trial post hoc analysis	2243	Yes	Yes	No	No	Peripheral	Validated indices	108	Direct	Gastroenterologist	38
Orlando et al	2017	Prospective cohorts	53	No	Yes	Yes	Yes	Axial	Subjective	12	Direct	Gastroenterologist	
Macaluso et al	2018	Prospective cohorts	163	Yes	Yes	Yes	Yes	Axial	Validated indices	22	Direct	Gastroenterologist	8

Meserve et al	2019	Retrospective cohorts	1087	No	Yes	No	No	Peripheral	Subjective	42	Direct	Gastroenterologist	38
Diaz et al	2020	Retrospective cohorts	71	No	Yes	No	No	Peripheral	Subjective	108	Direct	Gastroenterologist	
Piovezani et al	2020	Retrospective cohorts	201	No	No	Yes	Yes	Peripheral	Subjective	68	Direct	Gastroenterologist	32
Tabdiri et al	2017	Prospective cohorts	294	Yes	Yes	No	Yes	Peripheral	Validated indices	108	Direct	Gastroenterologist	30
Feagan et al	2019	Clinical trial post hoc analysis	1032	Yes	Yes	No	Yes	Peripheral	Subjective	52	Direct	Gastroenterologist	15
Dupré et al	2020	Retrospective cohorts	112	No	No	No	No	Axial	Subjective	44	Database	Rheumatologist	49
Dubinsky et al	2018	Retrospective cohorts	1285	Yes	Yes	No	No	Peripheral	Subjective	48	Database	Diagnostic codes	50

De Galan et al	2022	Retrospective cohorts	584	No	Yes	Yes	No	Both	Subjective	108	Direct	Rheumatologist	22
UC: Ulcerative colitis; CD: Crohn Disease; EIM: Extra Intestinal Manifestation													

Table 2. Exploratory Subgroup Analysis for the Assessment of Heterogeneity						
Variable	**Subgrup**	**Pooled rate (%)**	**95% CI lower (%)**	**95% CI upper (%)**	**I^2 (%)**	**Studies**
Design	Retrospectiv	4,31	2,03	6,6	92,63	5
	Prospective	13,18	2,33	24,04	99,07	4
Type of EIM	Axial	0,01				2
	Periferical	12,09	5,64	18,53	98,88	6
Valoration method	Questionary	9,16	-1,72	20,04	99,32	4
	Subjetive	8,23	4,32	12,13	97,07	5
Data curacy	Direct	9,22	3,81	14,64	98,8	8
Specialist assessing the response	Gastroenterologist	9,73	3,22	16,24	98,97	7