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Vedolizumab-Related Arthralgias in Patients with Inflammatory Bowel Disease: A Systematic Review

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1. Abstract

1.1 Background: Multiple papers have reported the development of new-onset arthralgias with vedolizumab (VDZ) for the treatment of Inflammatory Bowel Disease (IBD). Other studies have shown that VDZ may help in preexisting enteropathic spondyloarthropathy. We sought to probe this issue by conducting a systematic review.

1.2. Methods: Embase, Medline, Cochrane Central, and Web of Science were searched up to June 29, 2020 for randomized controlled trials evaluating vedolizumab treatment in patients with IBD in which development of arthralgias was noted. Risk of bias and quality were assessed using Cochrane's collaboration tool and the GRADE system, respectively. PROSPERO registration number: CRD42020197101.

1.3. Results: Four hundred sixty-one discrete articles were retrieved. Five studies (n=2,899) met inclusion criteria. Comparing the risk of arthralgia in patients treated with VDZ and placebo yielded odds ratio's which ranged between 1.01 (95% confidence interval (CI) 0.61-1.65) and 10.20 (95% CI: 0.53-195.78). While each study noted an increased incidence of arthralgias in patients receiving VDZ, none proved statistically significant. Studies were heterogeneous in disease populations, VDZ dosage, time-points for evaluation, and data points collected. Post-hoc analyses suggested an increased risk of arthralgias in patients with prior TNF inhibitor use.

1.4. Conclusion: The included studies showed a trend toward increased arthralgias in patients with IBD who received VDZ. However, our study lacked any statistically significant findings to identify a clear link. More research is needed to substratify which patients develop arthralgias when treated with VDZ in order to better understand whether heightened risk can be predicted prior to treatment initiation.

2. Introduction

Vedolizumab (VDZ) is a humanized IgG1 monoclonal antibody selectively targeting the integrin α4β7 and blocking its interaction with MAdCAM-1, a ligand of lymphocytic homing receptors, impeding

the trafficking of lymphocytes to the gut mucosa [1]. Its use for the treatment of Crohn's Disease (CD) and Ulcerative Colitis (UC) has continued to grow since approval by the United States Food and Drug Administration and the European Union in 2014 [2]. Large trials have illustrated its efficacy in both inducing and maintaining clinical responsiveness in patients with moderate to severe CD and UC [3,4].

As a result of the increasing utilization of VDZ, researchers have attempted to evaluate whether its mechanism of action results in an improvement or clinical worsening of extraintestinal manifestations (EIM). On the one hand, active EIMs are thought to correspond with mucosal inflammation of the gut, in part as a result of a shared epitope among different organ systems [5]. Therefore, VDZ should offer a therapeutic benefit for those features outside of the Gastrointestinal Tract (GIT). At the same time, the EIMs may actually stem from systemic inflammation and not from the GIT, and accordingly, may not respond to VDZ. In fact, many have theorized that trafficking of leukocytes away from the gut has resulted in their increased circulation and homing to other extraintestinal sites such as the joints [6].

Many retrospective observational studies have found that patients with inflammatory bowel disease (IBD) develop new-onset or worsening of arthralgias when treated with VDZ, often listed as one of the most common Adverse Events (AE) [7-12]. Similarly, multiple prospective observational studies have reported on the development of joint pains associated with VDZ treatment, even in patients who achieve clinical remission within the gut [13-16]. There have also been numerous open label trials describing both the worsening of and the development of new arthralgias [17-19]. In addition, a number of case series have depicted a total of 20 patients with joint complaints associated with VDZ use, most commonly triggered during the first four months of treatment, generally with axial involvement, only one fifth of whom had a background history of musculoskeletal complaints, and which developed despite effective control of gut inflammation in 80% of cases [20-22].

On the other hand, multiple papers have found that the development of arthralgias is rare in IBD patients treated with VDZ [23, 24]. Some have even shown an improvement or altogether resolution of joint pains in conjunction with VDZ treatment and control of gut inflammation [25-27]. Still, others have shown that both may occur- resolution of baseline arthritis/arthralgias and incident new cases of arthropathy- when patients treated show clinical response to VDZ along the GIT [28].

While the correlation between VDZ and arthropathies have been previously explored, studies may have been confounded by several factors: the inherent association between IBD and spondyloarthropathy, the possible tapering of other immunosuppressive medications prior to VDZ initiation, and the often poor reporting of musculoskeletal complaints among non-rheumatologic clinicians. Accordingly, no clear conclusions have been drawn about the nature of this relationship. We sought to perform a systematic review to evaluate the randomized controlled trials (RCT) assessing VDZ for the treatment of IBD in which arthralgias emerged.

3. Methods

3.1. Search strategy

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement (Supplementary Figure S1) [29]. The protocol for this study was registered on the website of PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/), registration number CRD42020197101. Embase, Medline, Cochrane Central, and Web of Science were searched from 1946 to June 29, 2020. The search was conducted utilizing the PICOS format (Patients, Interventions, Comparators, Outcomes and Studies) as follows: P: adult participants (age ≥ 18 years) with IBD; I: received VDZ treatment; C: control group given placebo; O: arthralgias; S: RCTs.

Manual searches of reference citations in the reviewed literature sources was subsequently performed. A detailed description of the search strategy is provided in supplementary figure S2. Two authors (from among: JBS, MT, EI, HK) independently reviewed each of the titles and abstracts for eligible studies. All disagreements were resolved by consensus among the authors.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5

METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-May
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-Jun
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

Section/topic	#	Checklist item	Reportedon page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-Sep
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Supplementary Figure S1: PRISMA 2009 checklist.

3.2. Eligibility criteria

- Eligibility was limited to:
- Studies involving humans;
- With ≥18 year-old participants enrolled;
- Which were RCTs comparing treatment with VDZ versus placebo;
- With atleast one case of new-onset arthralgia reported within the listed AEs.

Studies were excluded if:

- They were abstracts, case-reports, editorials, comments, letters, reviews, meta-analyses, observational studies, or open-label trials;
- Duplicate; or
- Written in languages other than English or without English translated versions available.

3.3. Study Selection

Two researchers (from among: JBS, MT, EI, HK) independently performed the initial screening of each paper by title and abstract. Full texts were retrieved for all articles which were deemed potentially eligible, and were screened accordingly. Any disagreements were resolved by consensus among the researchers.

3.4. Data Extraction and Synthesis

The selected studies were reviewed with the data extracted independently by two researchers (JBS, MT). Conflicting data was resolved by consensus between the researchers. Information related to author, publication year, country/region, study type, sample size, age, and outcomes were put into a bibliographic database using Microsoft® Office Excel® version 14.0 software (Microsoft, Redmond, WA, USA). Corresponding authors were contacted by email to provide additional data where needed. Among papers describing the same cohort of patients, the most up-to-date study was considered for inclusion.

3.5. Assessment of Risk Bias and Quality

The risk of bias of the RCTs was evaluated using the Cochrane Collaboration's tool, evaluating sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias [30]. The included studies were stratified according to risk of bias. The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach was used to rate overall quality of the evidence [31]. Two reviewers (from among: JBS, YGP, MT) independently assessed the risk of bias and evaluated the quality of each of the included papers. Disagreements were resolved by consensus among the researchers.

3.6. Data Collection

A narrative synthesis of the included studies was performed around the sample size, disease population, participant demographics, baseline disease activity, length of disease, prior immunosuppressive treatments, presence of arthralgias, other side effects to treatment, Odds Ratio (OR), and 95% confidence interval (CI) measurements.

3.7. Ethical Considerations

Due to the nature of this study, a systematic literature review, there was no need for institutional review board approval.

4. Results

4.1. Study Selection

Four hundred sixty-one titles and abstracts were screened, 159 were retrieved as full text articles. A total of 5 studies (published in 7 articles) met eligibility criteria and were included in the review [3, 4, 32-36]. The PRISMA flowchart, depicting the process of study selection, is shown in (Figure 1).

4.2. Risk of Bias and Quality of Evidence

Each of the domains for the five included studies were deemed low risk of bias. The detailed assessments or risk of bias and the ratings for quality of evidence are displayed in (Supplementary Figures S3 and S4) and (Supplementary Table S1).

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to June 29, 2020>
Search Strategy:

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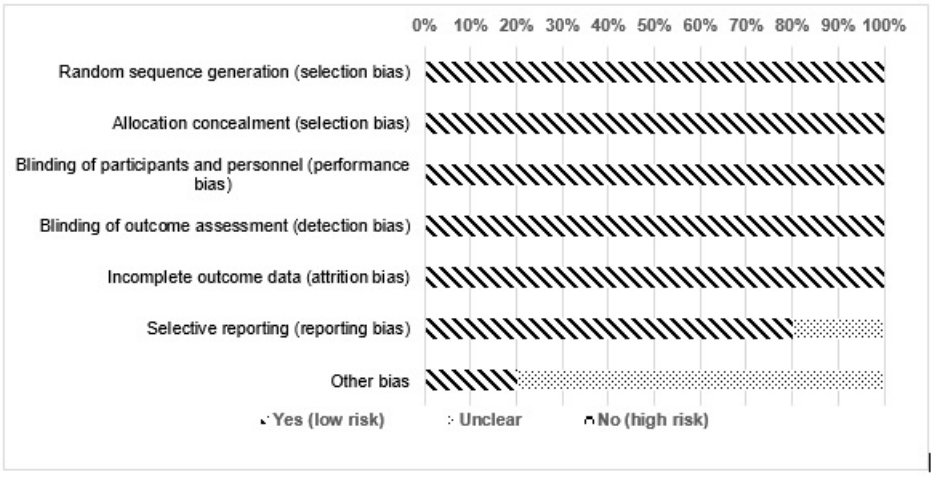
1 ('inflammatory bowel disease*' or 'crohn disease*' or 'ulcerative colitis').mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (101380)
2 (vedolizumab or mln02 or entyvio).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (975)
3 (arthralgia* or 'joint pain*' or monoarthralgia* or polyarthralgia* or arthritis or monarthritis or sacroiliitis or polyarthritis or spondylitis or spondylarthritis or 'joint swelling*').mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (256725)
4 |1 and 2 and 3 (42)

Supplementary Figure S2: Search strategy.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Feagan et al. 2005	✓	✓	✓	✓	✓	✓	?
Feagan et al. 2013	✓	✓	✓	✓	✓	✓	✓
Sandborn et al. 2013	✓	✓	✓	✓	✓	?	✓
Sands et al. 2014	✓	✓	✓	✓	✓	✓	?
Motoya et al. 2019	✓	✓	✓	✓	✓	✓	?

Supplementary Figure S3: Risk of bias of each article according to Cochrane Collaboration's tool.



Supplementary Figure S4: Risk of bias graph according to Cochrane Collaboration's tool presented as percentages across all included studies.

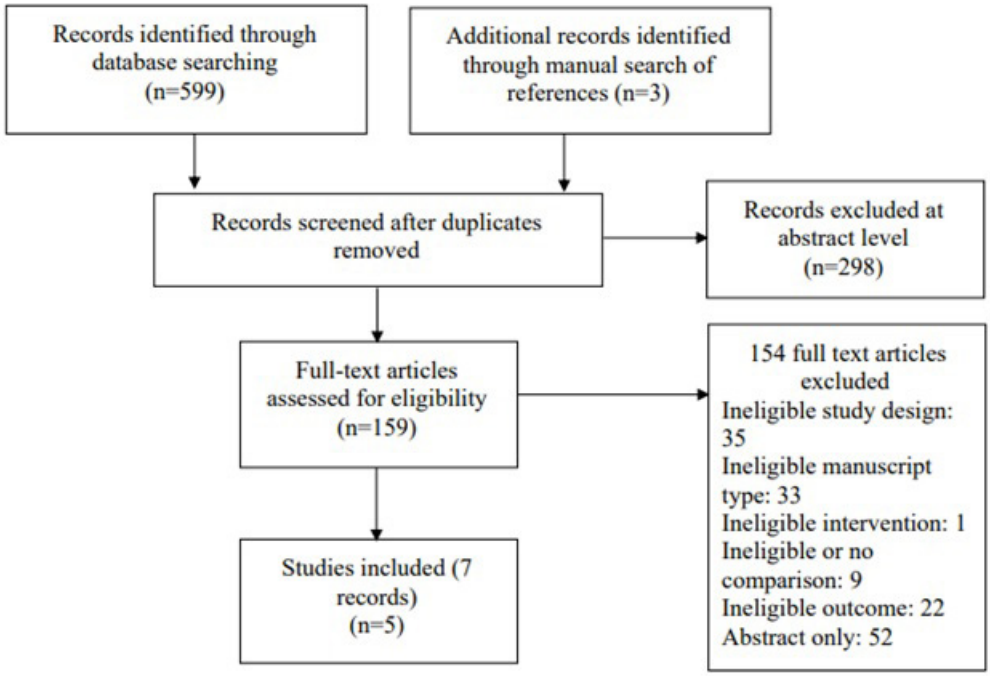


Figure 1: PRISMA flowchart illustrating selection process

Supplementary Table SI: Evaluation of the quality of evidence according to GRADE system.

First author, year	Design	No. of patients	Risk of publication bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality	Importance
Feagan et al. 2005	Multicenter, double-blind, placebo-controlled trial	181	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	high	moderate
Feagan et al. 2013	Randomized, double-blind, placebo-controlled	895	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	limited analysis of AEs[1]	high	high
Sandborn et al. 2013	Randomized, parallel-group, doubleblind, placebo-controlled. 285 medical centers in 39 countries	1115	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	limited analyses of AEs[1] and of subgroups[2]	high	moderate
Sands et al. 2014	Randomized, placebo-controlled, double-blind, multinational, multicenter trial	416	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	high	moderate
Motoya et al. 2019	Randomized, double-blind, placebo-controlled	292	no serious risk of bias	no serious inconsistency	no serious inconsistency	no serious imprecision	limited subgroup analysis[2]	moderate	moderate

[1]AEs tabulated according to maintenance treatment with patients who may have received placebo or vedolizumab in induction phase.
[2]Study not powered to detect differences between treatment subgroups.

4.3. Study Characteristics

Five double-blinded RCTs evaluating 2,899 patients with IBD initiating treatment with VDZ were included in this review [3, 4, 32-34]. In one study, VDZ was administered as essentially first line treatment [32] whereas in the remaining studies, VDZ was given as atleast second line treatment [3, 4, 33-34]. Follow-up time ranged from 6 to 76 weeks with a median follow-up time of 52 weeks. All of the studies were multicenter RCTs; one study took place in Japan alone, one in the USA and Canada, one across 5 continents, and in more than 30 countries in the remaining two studies. Four out of the 5 included studies were funded by pharmaceutical companies [3, 4, 33-34]. (Table 1) summarizes the characteristics of the included studies.

4.4. Study Participants

The number of randomized patients in the included studies ranged from 181 to 1115 [3, 4, 32-34]. In 4 of the listed studies, mean age ranged from 36 to 43 years [3, 4, 32-34]. In the fifth study, a median age of 36 was provided [33]. In 3 of the studies, the majority of participants were male [3, 32, 34], while in the remaining, the majority were female [4, 33]. (Table 2) provides a more detailed summary of the baseline characteristics of the participants in the included studies.

4.5. Data from RCTs

In 2005, Feagan et al [32] published an RCT to evaluate the efficacy of VDZ and to assess optimal dosing in patients with UC. One hundred eighty-one patients were included, in which patients were evenly split into three arms- placebo and two different doses of VDZ. Included patients had evidence of active disease as measured by both clinical and endoscopic parameters and were required to be naïve to anti-tumor necrosis factor (TNF) therapies, and had only previously received glucocorticoids or mesalamine. The study met its primary endpoint, demonstrating that after 6 weeks, patients receiving VDZ (33% in the 0.5mg/kg dose group and 32% in the 2mg/kg dosage) experienced clinical remission significantly more than those who were receiving placebo with an overall p value of 0.03.

Table 1: Characteristics of the included studies.

Author, publication year, trial name	Study period	Study design; phase; funding	No. of centers, countries	Follow Up	N total randomized	Key inclusion criteria	Primary outcomes	Intervention, N randomized	VDZ dose (mg)
Feagan et al, 2005, none	Dec 2000-Feb 2003	randomized, double-blind, PBO-controlled study; n/a; none	20, 2 (USA, Canada)	6 wks	181	UCCS of 5-9 pts, with a score of atleast 1 on stool frequency or rectal bleeding, and MBS of at least 2 on sigmoidoscopy, with disease a minimum of 25cm from anal verge; no prior therapy or 5-ASA if given for ≥4 wks with stable dose for ≥2 wks	At wk 6: UCCS of 0 or 1 and MBS of 0 or 1 without evidence of rectal bleeding	Participants (n=181) were randomized 1:1:1 to receive low dose (n=58), high dose (n=60), or PBO (n=63)	low dose: 0.5 mg/kg or high dose: 2 mg/kg
Feagan et al, 2013, GEMINI I	2008-2012	Randomized, double-blind, PBO-controlled; phase 3; Millennium Pharmaceuticals, Inc.	211, 34	52 wks	895	Moderately to severely active UC; demonstrated in the past 5 yrs inadequate response, loss of response, or intolerance to immunomodulators and/or TNFi and/or CS	At wk 6: reduction in complete Mayo score of ≥ 3 pts and ≥30% from baseline with decrease in rectal bleeding subscore of ≥1 pt or absolute rectal bleeding subscore of ≤1 pt. At 52 wks: complete Mayo score of ≤2 pts and no individual subscore >1 pt	Induction Phase (wk 0-6): Cohort 1 (n=374) randomized and treated with double-blind VDZ (at wks 0,2), cohort 2 (n=521) treated with open-label VDZ (at wks 0,2). Maintenance phase (wk 6-52): VDZ-treated subjects cohort 1 and 2 who demonstrated CR (n=373) were randomized in a 1:1:1 ratio to double-blind Rx with VDZ q4w (n=125), VDZ administered q8w (n=122) or PBO (n=126); VDZ who did not respond at 6 wks continued open-label VDZ q4w (n=330)	300

Sandborn et al, 2013, GEMINI II	Dec 2008-May 2012	Randomized, double-blind, PBO-controlled; phase 3; Millennium Pharmaceuticals, Inc.	285 centers, 39 countries	52 wks	Moderately to severely active CD; involvement of the ileum and/or colon; demonstrated in the past 5 yrs inadequate response, loss of response, or intolerance to immunomodulators and/or TNFi and/or CS	At wk 6: % of subjects achieving CDAI ≤150 at wk 6; % of subjects with CDAI 100 pts below baseline. At wk 52: % of subjects with CDAI ≤150 at 52 wks	Induction Phase (wk 0-6): Cohort 1 (n=368) randomized and treated with double-blind VDZ (at wks 0,2), cohort 2 (n=747) treated with open-label VDZ (at wks 0,2). Maintenance phase (wks 6-52): VDZ-treated subjects cohort 1 and 2 who demonstrated CR (n=461) were randomized in a 1:1:1 ratio to double-blind RX with VDZ q4w (n=154), VDZ administered q8w (n=154) or PBO (n=153); VDZ who did not respond at wk 6 continued open-label VDZ q4w (n=412)	300
Sands et al, 2014, GEMINI III	Nov 2010-Apr 2012	Randomized, double-blind, PBO-controlled; phase 3; Takeda Pharmaceuticals International, Inc.	107, ? (listed continents: North America, Europe, Asia, Africa, and Australia)	16 wks	Moderately to severely active CD; involvement of the ileum and/or colon; demonstrated in the past 5 yrs inadequate response, loss of response, or intolerance to imunosuppressives and/or TNFi and/or CS	At wk 6: % of subjects within TNFi failure population with CDAI ≤150	Participants (n=416) were randomized 1:1 to receive VDZ (n=209) or PBO (n=207) at wks 0,2,6	300

Motoya et al, 2019, none	Feb 2014-Jun 2018	Takeda Pharmaceutical Company Limited	100, 1 (Japan)	76 wks	Total or L sided UC atleast 6m prior to study; moderately or severely active UC; meet failure criteria to atleast 1 of the following in prior 5y: CS, AZA or 6-MP, TNFi	At wk 10: reduction in complete Mayo score of ≥3 pts and ≥30% from baseline with decrease in rectal bleeding subscore of ≥1 pt or absolute rectal bleeding subscore of ≤1 pt; at wk 60: complete Mayo score of ≤2 pts and no individual subscore >1 pt	Induction phase (wks 0-10): Cohort 1 (n=246) was randomized 2:1 to receive VDZ (n=164) or PBO (n=82), cohort 2 (n=46) received VDZ only at wks 0,2,6; subjects showing CR to VDZ at wk 10 (n=83) were randomized 1:1 to receive VDZ (n=41) or PBO (n=42) at wk 14 then q8w up to 54 wks	300

Apr: April; AZA: azathioprine; CD: Crohn's disease; CDAI: clinical disease activity index; CR: clinical response; CS: corticosteroids; Dec: December; Feb: February; Jun: June; L: left; MBS: Mayo bleeding score; Nov: November; PBO= placebo; pt: point; q4w: every 4 weeks; q8w: every 9 weeks; Rx: treatment; TNFi: tumor necrosis factor inhibitor; UC: ulcerative colitis; UCCS: ulcerative colitis clinical score; wks: weeks; yr: year; VDZ: vedolizumab; 5-ASA: mesalamine; 6-MP: mercaptopurine

Table 2: Baseline characteristics of the included participants.

First author, year	No. of participants (n)	No. of males (%)	Age	Primary disease	Mean length of disease (years)	Current smoker	Current treatment	Prior TNFi (n)
Feagan, 2005	181	98 (54.1)	Mean: 41.4	UC	6.6	8	151 on 5-ASA	none
Feagan, 2013	895	525 (58.7)	Mean: 40.3±13.1	UC	6.9 ± 6.4	55 (6.1)	332 (37.1) on CS only; 159 (17.8) on IS (AZA on 5-MP); 149 (16.6) on CS + IS	Prior TNFi: 431 (48.2)
Sands, 2014	416	180 (43.2)	Median: 35.9	CD	8.2	u/a	CS: 228; IS: 140; 5-ASA: 129	Prior TNFi: 115
Sandborn, 2013	1115	520 (46.6)	Mean: 36.1 ± 12.1	CD	9.0±7.8	298 (26.7)	CS: 381 (34.2); IS: 181 (16.2); CS+ IS: 189 (17.0)	Prior TNFi: 689/1115 (61.8)
Motoya, 2019	292	180 (61.1)	Mean: 42.8	UC	7.9	u/a	5-ASA: 259; CS: 55, IS: 105; IS + CS: 41	Prior TNFi: 150

AZA: azathioprine, CD: Crohn's disease; CS: corticosteroids; IS: immunosuppressives (unspecified); No.: number; TNFi: tumor necrosis factor inhibitor; u/a: unavailable; UC: ulcerative colitis; 5-ASA; mesalamine; 6-MP: mercaptopurine

AEs did not differ significantly among the groups (p=0.50). Arthralgias were experienced by 4 (7%) in the low dose group, 7 (12%) in the high dose group, and 5 (8%) in the placebo group without a detectable statistically significant difference among all those treated with VDZ compared with placebo, as calculated by the authors using Fisher's test (p= 0.75). Further analysis yielded an OR of 1.19 with a 95% CI of 0.40-3.60 [32].

In 2013, the GEMINI 1 study group [3] conducted 2 integrated RCTs to assess the effect of VDZ on induction and maintenance of active disease in patients with UC. Prior TNF exposure was permitted. In the trial of induction therapy, patients were either randomized to receive VDZ or placebo at weeks 0 and 2, with evaluation of disease activity at the sixth week. In the subsequent maintenance trial, participants in either cohort who were deemed to have responded to VDZ at week 6 were randomized to receive VDZ every 4 or 8 weeks or to receive placebo through week 52. The study met its primary endpoint defined by a reduction in the Mayo Clinic score of atleast 3 points and a decrease of atleast 30% from baseline, with either a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1. The study also met its designated primary outcome for the maintenance phase, clinical remission at week 52.

The authors evaluated AEs by comparing all patients who had received VDZ as maintenance therapy with the group that were given placebo during the maintenance phase, whether they had received placebo or VDZ during induction. They did not find significant differences in the category of any AE (p= 0.23) as well as among serious AEs (p= 0.06) in the induction trial. Similarly, there was no difference in any AEs in those receiving VDZ every 8 weeks and every 4 weeks compared with placebo (p=0.65 and 0.49, respectively) nor any difference in serious AEs (p=0.06 and 0.09, respectively) during the maintenance phase. While there was an increased rate of development of arthralgias in those receiving VDZ during the trial, this was not statistically significant (OR 1.01; 95% CI 0.61-1.65: p= 0.98) [3].

The GEMINI 2 study group [4] conducted a trial with an identical design to that of the GEMINI 1 group assessing VDZ response in patients with active CD instead. The study met part of its primary endpoint in the trial of induction therapy evaluating for clinical remission (CDAI ≤150) at week 6 (p= 0.02) though not for clinical response (decrease in CDAI-100 response ≥100) (p= 0.23). In the maintenance phase, the primary endpoint of clinical remission at week 52 was achieved in patients receiving VDZ every 8 weeks (p <0.001) and every 4 weeks (p= 0.004).

There were no significant differences in any reported AEs (p= 0.56) as well as serious AEs (p= 0.29) in the induction trial. Similarly, there was no difference in any AE in those receiving VDZ every 8 weeks and every 4 weeks compared with placebo (p=0.32 and 0.86, respectively) nor any difference in serious AEs (p=0.46 and 0.77, respectively) in the maintenance phase. Similarly, the authors evaluated arthralgias in all those who received VDZ in the maintenance phase compared with those who had received placebo as maintenance, regardless of what they had received during the induction, and did not find a statistically significant increased rate of arthralgias (OR 1.02; 95% CI 0.69-1.50: p= 0.92) [4].

The GEMINI 3 study group [33] conducted a phase 3 RCT to evaluate the efficacy of VDZ in patients with moderately to severely active CD with an objective toward assessing those who had previously failed anti-TNF therapy. In this trial, patients were randomized to receive VDZ or placebo (1:1) at weeks 0,2, and 6 and were assessed at week 6. This trial did not meet its primary outcome assessing clinical remission, as defined by CDAI≤ 150 at week 6, among those participants with prior anti-TNF failure (p= 0.433).

There were no significant differences in the AEs (p= 0.418) and in the drug-related AEs (p= 0.965) in patients who received VDZ compared with placebo. Similarly, no significantly increased risk of arthralgias was identified at week 6 in those who had received VDZ (OR 1.11; 95% CI 0.44-2.78: p= 0.831). This study also evaluated musculoskeletal pain apart from arthralgias and found that the while there was an increased risk of myalgias, this difference was not significant (OR 9.09; 95% CI 0.49-169.88: p= 0.140) [33].

Most recently, Motoya et al [34] performed a phrase 3 RCT in Japan looking at patients with active UC, who were permitted to have previously used anti-TNF agents. This study was split into a double-blinded cohort, who were randomized to receive VDZ or placebo, and an open label cohort who were assessed following completion of induction, at week 10. All patients who showed a clinical response to VDZ during induction were randomized 1:1 to receive VDZ or placebo every 8 weeks through week 54 with clinical evaluation at week 60. In addition, anyone could receive re-induction open label VDZ followed by treatment every 8 weeks up to 94 weeks if they had not had a clinical response to VDZ or placebo during the induction, experienced disease worsening, had received rescue treatment during the maintenance phase, or completed week 60 of maintenance, with an evaluation at 16 weeks following the last dosage received. This study did not reach its primary endpoint for the induction phase, a clinical response at week 10, as defined by a reduction in the full Mayo score of ≥3 and atleast 30% from baseline as well as ≥ 1 on the rectal bleeding subscore or an absolute rectal bleeding subscore ≤1 (p= 0.272). It did however meet its primary endpoint for the maintenance phase, designated as clinical remission (full Mayo score ≤2 and no subscore > 1) at week 60 (p= 0.021).

There was no significant difference in the development of AEs in the VDZ group compared with placebo in the induction phase (p= 0.720) nor in the maintenance phase (p= 0.2668). Similarly, there was no difference in the development of serious AEs in the induction (p= 0.409) and maintenance phases (p= 0.670). In addition, there was no significant difference in the development of arthralgias during the induction phase (OR 1.57; 95% CI 0.17-14.29: p= 0.688)

nor during the maintenance phase (OR 10.20; 95% CI 0.53-195.78: p= 0.123) [34].

4.6. Post-Hoc Analyses

A post-hoc analysis of the GEMINI 2 trial [35], conducted by some of the members of the original study group, divided patients into those that were anti-TNF naïve and those who had previously failed anti-TNF therapy. By stratifying the participants, the authors found that, the risk of developing arthralgias when treated with VDZ compared with placebo during the induction was not greater among those who had formerly received anti-TNF agents (TNF-naïve: OR 1.26; 95% CI 0.26-6.00: p= 0.774 and TNF-failure: OR 1.24; 95% CI 0.64-2.41: p= 0.523). During the maintenance phase, on the other hand, there was an increased risk of developing arthralgias in those who had previously used anti-TNF treatments, though that difference was not statistically significant (TNF-naïve: OR 0.83; 95% CI 0.37-1.84: p= 0.648 and TNF-failure: OR 1.24; 95% CI 0.59-2.60: p= 0.566).

A second post-hoc analysis [36], also co-authored by several members of the GEMINI study group and published 2 years later, evaluated data from the 3 GEMINI trials. Prevalence of baseline arthritis/arthralgias, which was the most common EIM at baseline in both patients with CD and UC, was similar in all of the study arms assessed in GEMINI 2 and 3. As part of further analysis, the co-authors re-divided the patients into three groups based on whether they received: VDZ throughout, VDZ in the induction phase followed by placebo for maintenance, and placebo alone. They evaluated the probability of sustained resolution of arthritis/arthralgias with prevalences of 11.9%, 15.3%, and 11.2% according to the respective groupings. They found no significant difference among the groups (VDZ vs placebo: hazard ratio (HR), 0.99; 95% CI, 0.52–1.90; VDZ followed by placebo vs placebo alone: HR, 1.57; 95% CI, 0.70–3.28).

Further scrutiny revealed that in the GEMINI 2 trial, the probability of sustained resolution of arthritis/arthralgia was 51.2% in those who received VDZ during both phases, 41.4% in those who had received VDZ during induction followed by placebo in the maintenance phase, and 35.5% in those had had been given placebo throughout. Differences among groups were not statistically significant (VDZ alone vs. placebo alone: HR, 1.56; 95% CI, 0.93–2.59; VDZ followed by placebo vs placebo alone: HR, 1.40; 95% CI, 0.75–2.64). Their analysis also revealed that clinical response and clinical remission at weeks 6 and 52 significantly correlated with sustained resolution of baseline arthritis/arthralgia ($p < 0.05$). Evaluation of GEMINI 3 revealed sustained resolution of baseline arthritis/arthralgia at week 10 in 22% of the VDZ group and in 16% of the placebo group with no significant difference detected between the 2 arms (HR, 1.40; 95% CI, 0.73–2.67) [36].

A Cox analysis of GEMINI 2 found that when separating the participants into those who received VDZ alone, placebo alone, and VDZ followed by placebo, there was a significant increase in the incidence of arthritis/arthralgias in those who received VDZ during both trial phases and in the group who received VDZ during induction followed by placebo compared with those who remained on placebo throughout (VDZ alone vs. placebo alone: HR, 0.55; 95% CI 0.36–0.84); and (VDZ followed by placebo vs. placebo alone: HR, 0.45; 95% CI, 0.26–0.81). Moreover, patients with prior anti-TNF use were significantly more likely to develop new joint complaints compared with those who were anti-TNF naïve (HR, 2.20; 95% CI, 1.56–3.11) [36].

On the other hand, a Cox analysis of GEMINI 2 evaluating both new or worsening arthritis/arthralgias revealed that such findings were less likely in those who received VDZ and VDZ followed by placebo compared to those who received placebo alone (VDZ alone vs. placebo alone: HR, 0.63; 95% CI, 0.44–0.89; and VDZ followed by placebo vs. placebo alone: HR, 0.54; 95% CI, 0.34–0.87). Additionally, patients with prior anti-TNF failure were generally more likely to experience new and or worsening arthritis/arthralgia than naïve patients (HR, 1.81; 95% CI, 1.37–2.38) [36].

5. Discussion

We performed a systematic review of all of the randomized clinical trials evaluating use of VDZ as treatment for IBD which mentioned the development of joint-related complaints. Our review encompassed large trials in which close to 3,000 patients with both UC and CD with evidence of active disease were assessed. While previous reports have suggested that VDZ may induce new or worsening arthralgias [7-22], our analysis did not identify concrete evidence of an association between use of VDZ in IBD and the development of arthralgias.

Three of the trials included indeed showed an increased concentration of arthralgias in patients with CD receiving VDZ rather than placebo as part of the induction protocol [32, 33] and while receiving a maintenance dose [4]. Similarly, the other two studies showed that there were increased arthralgias in patients with UC treated with VDZ compared with placebo during the induction and maintenance phases [34, 3]. The OR's comparing these two groups ranged from just over 1 to more than 10, in the case of a UC cohort receiving VDZ maintenance treatment, highly suggestive of a trend toward a risk of arthralgias in those treated with VDZ. However, because none of our analyses reached statistical significance, these studies do not prove that there is a causal link between use of VDZ and the development of joint pains.

Post-hoc analyses of the GEMINI trials offer mixed conclusions. On the one hand, they found that when the participants of GEMINI 2 were stratified into 3 groups, dividing participants into those who received VDZ alone, placebo alone, and VDZ during induction followed by placebo maintenance, they did indeed find that there was an increased incidence in the development of arthritis/arthralgias in the 2 groups who received VDZ during the trial compared with those received placebo throughout [36]. On the other hand, they found that the composite endpoint of both new and worsening arthritis/

arthralgias was less likely to be met in those who received VDZ and VDZ followed by placebo compared with participants who received placebo alone.

Prior papers have suggested that the tapering of anti-TNF therapy in conjunction with initiation of VDZ may largely explain the joint complaints that develop in those receiving VDZ [37]. The post-hoc analysis stratifying the patients with CD included in the GEMINI 2 trial into those who had previously received anti-TNF treatment and those who were naïve found that during the maintenance phase alone, there was increased risk of developing arthralgias in those receiving VDZ compared with those given placebo among those who had previously been exposed to anti-TNF treatment [35]. These findings however, lacked statistical significance and therefore only hint at the presence of a link. The presence of many confounders with regard to disease activity, duration of disease, and use of corticosteroids in those who had previously been treated with anti-TNF agents, may explain the absence of a clearer correlation.

Previous research has demonstrated that use of VDZ alters the trafficking of gut-homing T lymphocytes, leaving them to continue circulating in the periphery [38]. While signaling alterations impact both effector and regulatory T-cell subsets, Th1 effector cells are most specifically targeted by VDZ, preventing their entrance into the GIT while the permitting the entry to other lymphocytic populations, ultimately leading to greater immunoregulation within the gastrointestinal mucosa [39]. At the same time, the resulting imbalance within the systemic circulation does strongly suggest an immunologic explanation for the subsets of patients who developed arthralgias with VDZ treatment as seen in the trials reviewed in our paper. Simultaneously, the development of arthralgias in smaller numbers in those who were treated with placebo may atleast in part be related to a parallel process taking place along the interwoven pathways of the psycho-neuro-endocrine-immune axes [40].

Our study has several limitations. Firstly, our search revealed a small number of RCTs which was heterogeneous in the included study populations, dosing regimens, and both time-and data-points analyzed. Another limitation is the lack of a statistical procedure for combining numerical data (such as a meta-analysis) from the different studies due to the limited number of studies and the differences in study characteristics, particularly in sample size, dose regimen, and co-medications. In addition, some of the studies also failed to distinguish the incidence of joint complaints induced by VDZ usage during induction and during maintenance and also did not reveal at which time point new-onset arthralgias first manifested. In addition, two of the studies, when enumerating the AEs, grouped together participants who received placebo during the maintenance phase regardless of what they had received for induction. Moreover, data was limited in terms of the characteristics of those who developed arthralgias including baseline disease, EIMs especially presence of an associated spondyloarthropathy, other immunosuppressive treatments, and clinical response which may have helped to stratify those at risk for developing arthralgias. Finally, in these papers and in the supplementary appendices provided, no information was provided regarding whether arthralgias led to drug discontinuation and whether resolution was achieved following VDZ cessation.

Despite these limitations, we were able to analyze 5 moderate to high quality randomized controlled trials involving a large number of patients with both CD and UC. We did not detect any statistically significantly increased risk of arthralgias in those treated with VDZ compared with placebo, indicating that there is no clear link. At the same time, our analysis yielded a trend toward increased arthralgias in those who received VDZ. These findings suggest that more studies are needed which evaluate the development of arthralgias in VDZ-treated IBD patients who are stratified according to baseline disease features and response to VDZ. Moreover, additional studies measuring the responses of different T-cell subsets together with evaluation of clinical and histological parameters of the gut and the assessment of EIM, will provide a clearer understanding of the relationship between the immunologic shifts induced by VDZ and the possible generation of arthralgias.

6. Conclusion

A systematic review of 5 RCTs evaluating the efficacy of VDZ in patients with active IBD did not identify a clear correlation between VDZ treatment and the development of arthralgias. At the same time, each study identified a trend toward increased arthralgias in those receiving VDZ compared with placebo. Clinicians should be aware of the presence of a possible link because of the significant morbidity associated with joint pains. Additional studies are needed stratifying patients into more homogenous subsets in order to evaluate whether those at risk of developing new or worsening arthralgias with VDZ treatment can be identified.

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