

The impact of vedolizumab and ustekinumab on articular extra-intestinal manifestations in inflammatory bowel disease patients: a real-life multicentric cohort study

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TL is the guarantor of this article. TL, JG, MT and CDG designed the research study, TL, MT and CDG coordinated the retrospective data collection, MT, JG, HP, FMG, AE, PT, LV, AJA, RFI, TH, YZ, LPR, TL helped with the retrospective collection of the personal data of the included patients, CDG, MT and GBG performed the statistical analyses, all authors have written and/or critically revised the manuscript and all authors approved the final version of the article. CDG and MT should be considered shared first authors.

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Non-standard abbreviations:

IBD: inflammatory bowel diseases; EIM: extraintestinal manifestations; CD: Crohn's disease; UC: ulcerative colitis; EN: erythema nodosum; PG: pyoderma gangrenosum; PSC: primary sclerosing cholangitis; AIH: autoimmune hepatitis; NSAID: Non-steroidal anti-inflammatory drugs; TNF α : tumour necrosis factor alpha; VDZ: vedolizumab; UST: ustekinumab; MAdCAM-1: Mucosal addressin cell adhesion molecule-1; PsA: psoriatic arthritis; SpA: spondyloarthritis; SD: standard deviation; IQR: interquartile range; aOR: adjusted Odds ratio; NA: not applicable; 95% CI: 95% confidence interval

ABSTRACT

Background and aims

Extra-intestinal manifestations are frequently reported in inflammatory bowel diseases. However, data comparing the effect of vedolizumab and ustekinumab on articular extra-intestinal manifestations are limited. The aim was to evaluate differences in new onset and evolution of pre-existing joint extra-intestinal manifestations during both treatments.

Methods

An international multicentric retrospective study was performed on inflammatory bowel disease patients who started vedolizumab or ustekinumab between May 2010 and December 2020. Extra-intestinal manifestations were assessed at baseline and joint extraintestinal manifestations were evaluated throughout the 2-year follow-up. Arthropathy was defined by joint inflammation (arthritis/sacroiliitis), diagnosed by a rheumatologist, and arthralgia as articular pain without confirmed inflammation. Additionally, skin, ocular and hepatic extra-intestinal manifestations were assessed at baseline. Uni- and multivariate analyses were performed.

Results

In total 911 patients (vedolizumab:584; ustekinumab:327) were included. Deterioration of pre-existing arthropathy and rate of new onset arthropathy were not significantly associated with vedolizumab over ustekinumab. Arthropathy was reason to stop treatment in 6 vedolizumab and 2 ustekinumab patients. The odds of developing new arthralgia within 6 months was higher in patients who took vedolizumab compared to ustekinumab (aOR: 2.28 [1.01-5.15], $p=0.047$). However, this effect was not sustained during the 2-year follow-up (aOR: 1.35 [0.80-2.29], $p=0.259$). Deterioration of pre-existing arthralgia was comparable

between ustekinumab and vedolizumab treated patients. In 2 vedolizumab-treated patients arthralgia was reason to stop treatment.

Conclusions

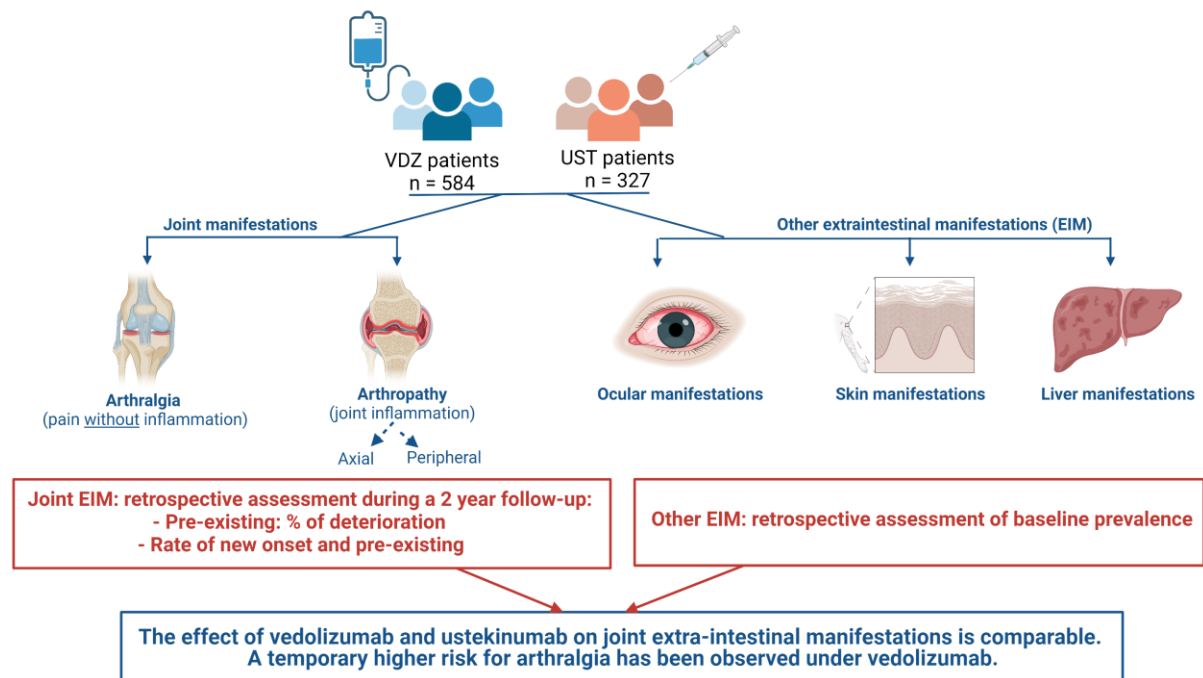
Vedolizumab and ustekinumab can be used safely in patients with articular extra-intestinal manifestations. Only a temporary increased risk for developing arthralgia has been observed under vedolizumab.

Keywords: spondyloarthropathy, biologicals, inflammatory bowel disease

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Graphical abstract

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INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic relapsing inflammatory disorders of the gastrointestinal tract, with extraintestinal manifestations (EIMs) occurring in up to 55% of Crohn's disease (CD) and 35% of ulcerative colitis (UC) patients. The pathophysiology of EIMs in IBD remains poorly understood. One of the proposed hypotheses is that bacterial translocation across the leaky intestinal barrier might trigger an adaptive immune response to epitopes expressed not only by the intestinal bacteria but also at specific extraintestinal sites¹. Usually, the activity of these EIMs runs in parallel with the underlying intestinal IBD activity, though their activity can also be dissociated¹⁻⁶. The most frequently occurring EIMs affect the joints (peripheral or axial arthritis), the skin (erythema nodosum (EN), pyoderma gangrenosum (PG), Sweet's syndrome), the hepatobiliary tract (primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH)) and the eyes (episcleritis, scleritis and uveitis). Less frequently it involves the lungs, heart, pancreas or the vascular system^{1,7,8}.

Optimal treatment of EIMs is one of the essential aspects of IBD care, given their impact on the quality of life of patients with IBD. Therapeutic strategies for EIMs include non-steroidal anti-inflammatory drugs (NSAID) and corticosteroids, however, caution is needed when prescribing NSAID and steroids in patients with IBD, since they are not suitable as long-term maintenance treatment because of their potential risk of severe adverse events. Amongst the biologicals used for IBD the largest experience exists with tumour necrosis factor alpha (TNF α) inhibitors that have shown a beneficial effect on several types of EIMs^{6,9-13}. Since over one-third of the patients with IBD fails to respond or loses their response to these agents, in recent years new biologicals entered the IBD armamentarium⁵. These newer treatment options include vedolizumab (VDZ) and ustekinumab (UST), which are increasingly used, both in first or secondary lines of maintenance treatment¹⁴.

Vedolizumab is a humanized monoclonal antibody targeting integrin heterodimer $\alpha 4\beta 7$ on circulatory T cells and inhibits the binding to mucosal addressin cell adhesion molecule-1

(MAdCAM-1), which is specifically found on the high endothelial venules of the gut and therefore stops gut-homing^{14,15}. Theoretically, the gut-selectivity of VDZ implies little effect on EIMs, nonetheless, the available data are contradictory since both detrimental as well as beneficial effects of VDZ on EIMs have been observed in real life practice¹⁶⁻²².

Ustekinumab is an antibody to the p40 subunit of IL-12 and IL-23 and, in contrast to VDZ, has a systemic mechanism of action with an already proven clinical efficacy in psoriasis, psoriatic arthritis (PsA) and IBD, but not in (axial) spondyloarthritis (SpA)²³⁻²⁶. However, some studies do report new onset arthralgia or PsA after initiation of UST²⁵⁻²⁸.

This large retrospective, international, multicentric study aimed at assessing the real-life effect of both VDZ and UST on joint EIMs associated with IBD. Since the clinical consequences and treatment for both arthropathies and arthralgia are fundamentally different, a clear distinction was made between peripheral arthritis or sacroiliitis and arthralgia when assessing joint EIMs.

MATERIALS AND METHODS

Patient inclusion and study design

An international multicentric retrospective study was performed in 10 collaborative centres in Belgium and Spain (Supplementary table 1). Inflammatory bowel disease patients, who initiated VDZ or UST treatment between May 2010 and December 2020 at one of the participating centres, were identified through hospitals' medical records. All patients were at least 18 years of age at treatment initiation and were previously diagnosed with CD or UC (IBD-undifferentiated cases were excluded). A minimal follow-up duration of 8-14 weeks was required, unless treatment was stopped earlier due to the development of complications or clear non-responsiveness to treatment. No other exclusion criteria were implemented.

Data collection

Patient demographic and clinical characteristics were retrospectively collected from the electronic patients' records and included age, gender, age at diagnosis, height, weight, baseline EIMs, disease location, surgical treatment for IBD, previous use of biologicals,

concomitant drug use, smoking behaviour and reason to stop (previous) treatments during the studied therapies. Retrospectively, the evolution of pre-existing and the development of new joint EIMs was assessed at different timepoints: after induction (week 8-14), 6 months, 1 year and 2 years of treatment.

Assessment of extra-intestinal manifestations

Before data collection and processing, the definition of the different EIMs was agreed upon by all participating researchers including rheumatologists. In the scope of this study, EIMs were defined as new onset when they were not reported before start of treatment.

Attending gastroenterologists identified potential new onset EIMs and assessed the evolution of pre-existing EIMs in patients' records. In the presence of inflammatory symptoms patients were referred to rheumatologist for diagnosis of new onset peripheral and/or axial arthropathy. Patients, that were diagnosed with both axial and peripheral arthropathy, were classified as axial arthropathy, since peripheral manifestations are often seen in patients with axial SpA²⁹.

A worsening of all investigated joint EIMs was defined as an increase in frequency or intensity of a joint EIM already reported at start of VDZ or UST. Within this study, a clear distinction was made between arthropathy and arthralgia⁵. All other joint symptoms, without confirmed inflammation, were classified as arthralgia. The following EIMs were only assessed at baseline: skin EIMs (EN, PG and Sweet's syndrome), ocular EIM (scleritis, episcleritis and uveitis) and hepatic EIMs (PSC, AIH or an overlap syndrome of both).

Statistical analysis.

All analyses were performed in SPSS statistics version 27 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0, Armonk, NY, USA). GraphPad Prism® (GraphPad Software Inc., San Diego, CA, USA) was used for graphical representations of data. Descriptive statistics were presented as means \pm standard deviations (SD) for

continuous variables with a normal distribution, medians with interquartile ranges (IQR) for data with a non-normal distribution and percentages for categorical variables. Chi-square or Fisher's exact test were performed to compare categorical variables between the different treatments, continuous variables were analysed with the independent sample t-test (or Mann-Whitney U test in case of non-normal distribution). A two-tailed $p < 0.05$ was considered statistically significant. Next, univariate and multivariate binomial logistic regression analyses were performed to identify risk factors associated with the development and worsening of arthropathies and arthralgias at the different timepoints. The multivariate logistic regression model included risk factors for EIM development previously identified in other studies, such as recent anti-TNF α use³⁰, luminal disease activity^{31,32}, disease duration¹ and was corrected for possible country associated bias (Belgium or Spain). Corticosteroid free remission was defined as intestinal clinical remission (physician's assessment) in patients without steroid use at the timepoint of assessment. A small percentage of patients were included twice in the dataset, since they were sequentially treated with both studied biologicals. To assure that the double inclusion of patients, both in the UST and VDZ cohort, did not influence the results, a sensitivity analysis was performed (see Supplementary Figure 1).

Ethical statement

The study protocol was reviewed and approved by the Ethical committee of the University Hospital of Ghent (EC2019-0978) as coordinating centre and obtained approval per requirements for each of the participating centres, following the Declaration of Helsinki.

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Characteristics of the study population

In total 911 patients with IBD were included, of whom 584 were treated with VDZ and 327 with UST. Baseline characteristics such as age, sex, body mass index, IBD type, disease location/behaviour and concomitant immunomodulator use were similar between VDZ and UST treated patients (Table 1). In patients with CD, an equal distribution among both treatments was seen whereas in UC most patients were treated with VDZ and only a minority with UST (88.8% vs 11.2%, $p<0.001$). In general, the UST cohort consisted of patients with more refractory disease, as reflected by the significantly higher percentage of previous anti-TNF α use ($p<0.001$) and perianal disease ($p<0.001$). Moreover, UST treated patients had a higher frequency of previous intestinal surgery and a longer disease duration compared to VDZ treated patients ($p<0.001$ and $p<0.001$, respectively). Inflammatory bowel disease patients, who initiated VDZ, also concomitantly used more systemic steroids compared to patients, who initiated UST treatment ($p<0.001$) (Table 1). No differences in disease activity at baseline could be identified between UST and VDZ treatment (Table 2).

Baseline EIMS

At baseline, the prevalence of EIMS was assessed (Table 3). No differences in cutaneous, ocular nor hepatic EIMS could be identified between both treatment groups. On the other hand, UST treated patients had a higher baseline prevalence of arthropathy and arthralgia compared to VDZ treated patients ($p=0.004$ and $p=0.044$; respectively).

New onset and evolution of pre-existing EIMs during VDZ and UST treatment

Arthropathy

Evolution of pre-existing arthropathy

In patients with pre-existing arthropathy, 14/39 (35.9%) of VDZ and 9/40 (22.5%) of UST patients had a worsening of the arthropathy during the 2-year follow-up ($p=0.190$, Figure 1A). In a multivariate regression model, the worsening of pre-existing arthropathy was not associated with the current treatment (adjusted odds ratio (aOR) VDZ: 1.95 [95% confidence interval: 0.61-6.21]; $p=0.258$) nor previous anti-TNF α use (aOR: 1.30 [0.43-3.90]; $p=0.646$) nor corticosteroid use during treatment (aOR: 1.29 [0.42-3.96]; $p=0.652$) nor the country of data assessment (aOR Spain: 1.88 [0.59-6.00]; $p=0.286$) nor disease duration (aOR 0.99 [0.94-1.05]; $p=0.830$) nor smoking (aOR 1.63 [0.49-5.39]; $p=0.426$). Next, the evolution of pre-existing arthropathy was assessed at the different timepoints; and was again comparable between VDZ and UST (Figure 1B). None of the included variables were associated with worsening of pre-existing arthropathy at the different timepoints (Table 4). Next, within the pre-existing arthropathies, peripheral and axial disease were assessed separately. No risk factors could be identified for a worsening of peripheral or axial arthropathy, neither during the complete 2-year follow-up nor at the specific timepoints (see Supplementary Figure 2 and Supplementary Table 2).

New onset arthropathy

New onset arthropathy was diagnosed in 11 (2%) and 7 patients (2.4%) after VDZ and UST initiation, respectively ($p=0.692$, Figure 1C). In a multivariate regression model, assessing new onset arthropathy during the 2-year follow-up, neither VDZ (aOR: 0.82 [0.30-2.29]; $p=0.708$) nor previous anti-TNF α use (aOR: 0.57 [0.20-1.62]; $p=0.290$) nor corticosteroid use (aOR: 0.43 [0.14-1.32]; $p=0.141$) nor smoking (aOR: 2.06 [0.73-5.85]; $p=0.175$) nor the country of data assessment (aOR Spain: 1.44 [0.51-4.10]; $p=0.493$) nor disease duration (aOR: 1.00 [0.95-1.05], $p=0.979$) were identified as risk factors.

In a next step, the different timepoints were assessed separately. At 6 months, the proportion of patients developing arthropathy was comparable between both treatments: 4 (0.8%) VDZ patients and 1 (0.4%) UST patient ($p=0.663$, Figure 1D). After 1 year of follow-up, this increased to 5 (1.2%) in the VDZ cohort and 5 (2.5%) in the UST cohort ($p=0.312$) and the same trend remained after 2 years of treatment (8 (2.5%) and 3 (2.1%), respectively – $p=1.000$). After 1 year of VDZ treatment, all 5 cases of new onset arthropathy concerned axial disease. In 3 out of 5 new arthropathy cases under UST treatment, peripheral arthritis was diagnosed. Next, multivariate regression models were performed to assess risk factors for new onset arthropathy at the separate timepoints, 6 months and 1 year (Table 5). Arthropathy was the reason to stop treatment in 6 VDZ (1.03%) and 2 UST (0.61%) treated patients ($p=0.483$).

Arthralgia

Evolution of pre-existing arthralgia

The rates of worsening pre-existing arthralgia were comparable between UST and VDZ both during the complete 2-year follow-up (Figure 2A) as at the specific timepoints. Pre-existing arthralgia worsened after 6 months of treatment in 5 out of 30 (16.7%) VDZ patients. In contrary, worsening was not seen in UST-treated patients (Figure 2B). After 1 year of treatment, rates of worsening were almost negligible: 1/27 VDZ-treated patients (3.7%) and 2/16 UST-treated patients (12.5%) ($p=0.545$). After 2 years of treatment, deterioration was only seen in 1 out of 21 (4.8%) VDZ-treated patients with pre-existing arthralgia and not in UST-treated patients. When assessing risk factors for a worsening of pre-existing arthralgia over the complete 2-year period, neither VDZ use (aOR 1.25 [0.27-5.72]; $p=0.774$) nor previous anti-TNF α use (aOR 4.63 [0.91-23.57]; $p=0.065$) nor corticosteroid use during treatment (aOR: 3.35 [0.59-18.85]; $p=0.171$) nor the country of data assessment (aOR Spain: 3.66 [0.65-20.63]; $p=0.142$) nor disease duration (aOR 1.02 [0.91-1.15]; $p=0.719$) nor smoking (aOR 0.16 [0.02-1.50]; $p=0.109$) were associated with arthralgia worsening. Due to

the low numbers of deterioration of pre-existing arthralgia, no multivariate analysis could be performed to assess risk factors at the separate timepoints.

New onset arthralgia

When assessing the total follow-up duration, the rates of new onset arthralgia were comparable between VDZ (9.8%) and UST (7.3%) ($p=0.218$, Figure 2C). The risk factors during the 2-year follow-up were assessed and VDZ was not associated with an increased risk of arthralgia (aOR 1.35 [0.80-2.29]; $p=0.259$), neither was previous anti-TNF α use (aOR 0.85 [0.53-1.38]; $p=0.513$) nor corticosteroid use (aOR 1.38 [0.83-2.29]; $p=0.210$) nor disease duration (aOR 1.01 [0.98-1.03]; $p=0.699$) nor smoking (aOR 1.19 [0.67-2.11]; $p=0.564$). Remarkably, a lower reporting of arthralgia was noted in the Spanish centres compared to the Belgian centres (aOR 0.51 [0.29-0.90]; $p=0.021$). Nevertheless, in VDZ-treated patients, a higher frequency of new onset arthralgia was seen within 6 months of treatment in comparison to UST-treated patients (VDZ: 36/508 (7.1%), UST: 9/286 (3.1%); $p=0.021$, Figure 2D). This same trend continued after 1 year of treatment (VDZ: 44/438 (10%), UST: 13/229 (5.7%); $p=0.055$); however, this was not the case after 2 years of treatment (VDZ: 39/337 (11.6%), UST: 14/165 (8.5%); $p=0.290$). From the patients with a new onset arthralgia at 1 year, the majority had peripheral arthralgia: 33/44 (75%) VDZ patients and 12/13 (92.3%) UST patients.

In multivariate regression analyses, the use of VDZ was significantly associated with an increased risk of developing new onset arthralgia at 6 months (aOR: 2.28 [1.01–5.15], $p=0.047$) but not after 1 year (aOR: 1.61 [0.80–3.23], $p=0.178$). Previous anti-TNF α use, sex, smoking, and corticosteroid free remission did not influence the risk of new onset arthralgia; again, less arthralgia was seen in Spain compared to Belgium (Table 6). In 2 patients, treated with VDZ, arthralgia was the reason to stop treatment ($p=1.000$).

DISCUSSION

Since the IBD armamentarium is still growing and EIMs are an essential aspect of IBD care, there is a need for more data regarding the effect of the newer treatment options, such as VDZ and UST, on EIMs⁶. The current study is – to the best of our knowledge – the largest real-life, retrospective, multicentric study to assess the impact of VDZ and UST on EIMs in patients with IBD.

Similar demographic characteristics for both treatments were identified in this cohort. The proportion of patients with UC and CD was comparable in VDZ-treated patients, in contrary to the UST cohort where a CD preponderance was seen. This can be attributed to the fact that UST was initially approved for the treatment of moderate-to-severe CD and only later for the treatment of moderate-to-severe UC^{33,34}. In addition, the UST group had a longer median disease duration and patients appeared to have more refractory disease based on the higher percentage of previous anti-TNF α use, previous intestinal surgery and perianal disease³⁵.

Patients within the VDZ treatment group also received more systemic steroids at initiation, this can possibly be explained by the slower mode of action of VDZ treatment³⁶.

The prevalence of cutaneous, ocular and liver EIMs before treatment initiation was similar between both cohorts and comparable to previous reports^{5,8}. Nevertheless, in UST-treated patients there was a higher baseline prevalence of arthropathy and arthralgia. This could indicate a physician's preference to initiate UST over VDZ in these cases due to previous reports of arthritis occurrence and flare-up under VDZ^{18,37}. It could also be linked to longer disease duration in UST-treated patients¹.

Even though previous studies investigated arthralgia and arthropathy without clear differentiation by a rheumatologist^{4,16}, it is known that arthralgia is more common than confirmed arthritis in IBD and requires a different treatment strategy⁴². Therefore, the two pathologies were clearly distinguished.

A worsening of pre-existing arthropathy was seen in 35.9% of VDZ patients and 22.5% of UST patients, this difference was not statistically significant at $p < 0.05$. Multiple studies have previously described a worsening of pre-existing inflammatory joint disease under VDZ treatment^{18,37,44,45}. On the other hand, 44.7% out of the 47 patients with baseline inflammatory arthralgia/arthritis achieved complete remission after 54 weeks of VDZ treatment in the OBSERV-IBD cohort⁴⁰. Moreover, new onset or worsening of arthritis/arthralgia was not associated with VDZ in the post-hoc analyses of the GEMINI study compared to placebo¹⁶. Importantly, in both studies, no clear distinction was made between arthralgia and arthritis and the latter compared VDZ to placebo^{16,40}.

In contrast to a possible deleterious effect of VDZ on the evolution of pre-existing arthropathies, UST has an already proven effectiveness in peripheral PsA⁴⁶ and recently a favourable effect was also identified on axial PsA manifestations⁴⁷. The IL-23/Th17 pathway has also been implicated in the pathogenesis of axial SpA, however, trials on this subject showed no effectiveness of UST for this indication²⁶. Literature regarding the influence of UST on arthritis in IBD patients is limited, but several reports have been published and showed promising results for the treatment of rheumatological EIMs associated with IBD⁴⁸⁻⁵⁰. However, future prospective data is expected from the TENOR trial⁵¹. In addition, UST had a beneficial effect on the articular symptoms in CD patients with SpA, predominantly peripheral SpA^{52,53}.

In contrast to the OBSERV-IBD study, where 13.8% of patients developed inflammatory arthralgia/arthritis during VDZ treatment, the rate of new onset arthropathy in the current study was low and comparable between VDZ (2%) and UST (2.4%)⁴⁰. In the UST cohort, new onset arthropathy was in 3 out of 5 cases peripheral disease, despite the fact that UST has the most evidence for a beneficial effect on peripheral arthritis and less in axial disease^{46,49,54}. This paradoxical occurrence of (peripheral) arthropathy under UST has also been reported in other studies⁴⁸. In this study, only a minority of patients stopped treatment due to arthropathy.

In general, IBD and inflammatory joint diseases share several features, such as certain predisposing factors, a relapsing-remitting pattern and an over-active immune response; however, they can be maintained by different immunological pathways⁵⁵. Hence, the fact that no significant difference could be identified between UST and VDZ in the development of new onset arthropathies, might be due to both treatments not interfering with the involved inflammatory pathway and cytokine interactions between both the gut and the joints.

When focussing on pre-existing arthralgia, the evolution over a 2-year follow-up period was comparable between VDZ and UST, and a worsening was only rarely seen, in line with available literature^{28,41}. These findings suggest that both VDZ and UST can be safely used in patients with pre-existing arthralgia. However, it should be taken into account that the rate of pre-existing arthralgia was quite low, and the lack of differentiation between both treatments might be a consequence of insufficient statistical power.

The risk of new onset arthralgia at 6 months of follow-up was associated with VDZ treatment, which confirms the findings of Engel *et al.*²⁰ and Mader *et al.*⁵¹ who reported arthralgia (and myalgia) as the most common adverse event under VDZ treatment. The prevalence of new onset arthralgia in the current cohort was comparable to the study of Dupré and colleagues⁴³. Despite this association at 6 months, VDZ was not identified as a risk factor for arthralgia development over the complete 2-year follow-up period and arthralgia was rarely the reason to stop VDZ (n=2). These results are comparable to the data of the US VICTORY consortium¹⁷ and the study of Meserve and colleagues³⁹ where only 2.4% and 0.4% of patients, respectively, required VDZ discontinuation due to arthralgia. Conversely, arthralgia was identified as a potential adverse event of UST^{56,57} and new onset arthralgia has been reported in other studies examining UST, with a prevalence up to 16.7%^{28,58}. These were often transient, comparable to this study where arthralgia was never the reason to stop UST treatment²⁸.

In general, recent anti-TNF α withdrawal is seen as a risk factor for new or worsening of EIMs³⁰. Surprisingly, in this study, the use of TNF α inhibitors within 4 months before VDZ or

UST initiation had no significant impact on the evolution of pre-existing or appearance of new-onset joint EIMs. The reason for this effect is still to be elucidated. Another risk factor for worsening of EIMs is active intestinal disease which has been associated with the activity of certain EIMs such as EN, episcleritis and pauciarticular peripheral arthritis^{30,62}. Nevertheless, in this cohort, no significant association could be identified between luminal disease activity, as defined by corticosteroid free remission, and new-onset or worsening of axial and/or peripheral articular EIMs³⁰⁻³². Importantly, only a small number remained when separating peripheral and axial arthritis. Therefore, it was not possible to fully examine the effect of intestinal disease on these separate arthritis phenotypes.

Due to the retrospective study design, there was a risk of potential bias in the number of EIMs and the evolution assessment. However, since both VDZ and UST were assessed retrospectively, the design is unlikely to have caused a bias in favour of one of both treatments. Next, there was an uneven distribution between UC and CD in UST patients, due to the later reimbursement of UST for UC, which might have an impact on the number of diagnosed EIMs. Due to the low rates of skin, ocular and hepatic EIMs no conclusions could be drawn regarding to the effect of UST and VDZ on these EIMs. Corticosteroid free remission was defined as remission in patients without corticosteroid use at the specific timepoint of assessment, but because of the retrospective design, no information is available on how long these patients were in sustained corticosteroid free remission. Biochemical and endoscopic intestinal remission could not be included in the regression model due to insufficient data. Despite this is a large international study, no data was available regarding the ethnicity. This could possibly limit the generalizability, since Basu and colleagues⁶³ already reported that joint involvement is higher among Caucasians UC patients compared to Hispanics. Additionally, the retrospective design of this study implied that the occurrence of EIMs was only recorded during pre-planned physician visits, and the exact date of EIM occurrence in between these visits was not recorded. Hence, an exact time-to-event analysis

via Cox regression could not be modelled on our data. Therefore, we opted for a multivariable regression analysis which is more statistically appropriate for this study design. The current study also has several strengths; this is to our knowledge the first real world study to compare the effect of VDZ vs UST on joint EIMs. Due to the multicentric international collaboration a large population could be assessed during a long follow-up of 2 years. Importantly, the distinction between arthropathy and arthralgia permitted a study of the evolution of true joint inflammation opposed to the subjective complaint of arthralgia, in contrary to many previous studies. Although we are aware that the optimal way of assessing these conditions would be with a prospective design, we also believe that the current data represent the real life experience in a large cohort of patients in a multicentre setting. A comprehensive approach was used taking into account different known confounders such as previous anti-TNF use and the relationship with luminal disease.

To confirm the findings of the current study more prospective trials on this subject are warranted, which would also make a time-to-event analysis possible. Studies in a multidisciplinary team would be of most value, since the advice of a rheumatologist is vital for the correct identification of potential inflammatory joint diseases. The finalization of such a study can reduce the excessive treatment burden by optimizing treatment options for both IBD and the articular EIMs, and therefore will imply that medication costs can be minimized to the utmost necessary.

In conclusion, the evolution of pre-existing and development of new articular EIMs were comparable between both UST and VDZ. The current study demonstrated some evidence for more new-onset arthralgia in VDZ treated patients compared to UST, however, this is rarely a true arthropathy and this is almost never a reason to stop treatment. Nonetheless, before initiating a biological a baseline multidisciplinary assessment is crucial to select the most optimal treatment for each individual patient.

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REFERENCES

1. Vavricka SR, Schoepfer A, Scharl M, *et al.* Extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2015;21:1982-1992.
2. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, Sandborn WJ. The natural history of adult crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;105:289-297.
3. Zippi M, Corrado C, Pica R, *et al.* Extraintestinal manifestations in a large series of italian inflammatory bowel disease patients. *World J Gastroenterol* 2014;20:17463-17467.
4. Dubinsky MC, Cross RK, Sandborn WJ, *et al.* Extraintestinal manifestations in vedolizumab and anti-tnf-treated patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2018;24:1876-1882.
5. Harbord M, Annese V, Vavricka SR, *et al.* The first european evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohn's Colitis* 2016;10:239-254.
6. Greuter T, Rieder F, Kucharzik T, *et al.* Emerging treatment options for extraintestinal manifestations in IBD. *Gut* 2021;70:796-802.
7. Greuter T, Vavricka SR. Extraintestinal manifestations in inflammatory bowel disease - epidemiology, genetics, and pathogenesis. *Expert Rev Gastroenterol Hepatol* 2019;13:307-317.
8. Garber A, Regueiro M. Extraintestinal manifestations of inflammatory bowel disease: Epidemiology, etiopathogenesis, and management. *Current Gastroenterol Reports* 2019;21:1-13.
9. Brooklyn TN, Dunnill MG, Shetty A, *et al.* Infliximab for the treatment of pyoderma gangrenosum: A randomised, double blind, placebo controlled trial. *Gut* 2006;55:505-509.

10. Kaufman I, Caspi D, Yeshurun D, *et al.* The effect of infliximab on extraintestinal manifestations of crohn's disease. *Rheumatol Int* 2005;25:406-410.
11. Rispo A, Scarpa R, Di Girolamo E, *et al.* Infliximab in the treatment of extra-intestinal manifestations of crohn's disease. *Scan J Rheumatol* 2005;5:387-391.
12. Herfarth H, Obermeier F, Andus T, *et al.* Improvement of arthritis and arthralgia after treatment with infliximab (remicade) in a german prospective, open-label, multicenter trial in refractory crohn's disease *Am J Gastroenterol* 2002;97:1-3.
13. Smolen J, Landewe RB, Mease P, *et al.* Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: The rapid 2 study. A randomised controlled trial. *Ann Rheym Dis* 2009;68:797-804.
14. Hindryckx P, Vande Castele N, Novak G, *et al.* The expanding therapeutic armamentarium for inflammatory bowel disease: How to choose the right drug[s] for our patients? *J Crohn's Colitis* 2018;12:105-119.
15. Lobaton T, Vermeire S, Van Assche G, Rutgeerts P. Review article: Anti-adhesion therapies for inflammatory bowel disease. *Aliment Pharmacol Ther* 2014;39:579-594.
16. Feagan BG, Sandborn WJ, Colombel JF, *et al.* Incidence of arthritis/arthralgia in inflammatory bowel disease with long-term vedolizumab treatment: Post hoc analyses of the gemini trials. *J Crohn's Colitis* 2019;13:50-57.
17. Dulai PS, Singh S, Jiang X, *et al.* The real-world effectiveness and safety of vedolizumab for moderate-severe crohn's disease: Results from the US victory consortium. *Am J Gastroenterol* 2016;111:1147-1155.
18. Varkas G, Thevissen K, De Brabanter G, *et al.* An induction or flare of arthritis and/or sacroiliitis by vedolizumab in inflammatory bowel disease: A case series. *Ann Rheumat Dis* 2017;76:878-881.
19. Baumgart D, Bokemeyer B, Drabik A, Stallmach A, Schreiber S. Vedolizumab germany consortium vedolizumab induction therapy for inflammatory bowel disease

- in clinical practice—a nationwide consecutive german cohort study. *Aliment Pharmacol Ther* 2016;43:1090-1102.
20. Mader O, Juillerat P, Biedermann L, *et al.* Factors influencing the outcome of vedolizumab treatment: Real-life data with objective outcome measurements. *United Eur Gastroenterol J* 2021;9:398-406.
 21. Cai T, Lin T-C, Bond A, *et al.* The association between arthralgia and vedolizumab using natural language processing. *Inflamm Bowel Dis* 2018;24:2242-2246.
 22. Orlando A, Orlando R, Ciccia F, *et al.* Clinical benefit of vedolizumab on articular manifestations in patients with active spondyloarthritis associated with inflammatory bowel disease. *Ann Rheum Dis* 2017;76:1-2.
 23. Armuzzi A, Ardizzone S, Biancone L, *et al.* Ustekinumab in the management of crohn's disease: Expert opinion. *Dig Liver Dis* 2018;50:653-660.
 24. Felice C, Pugliese D, Papparella LG, *et al.* Clinical management of rheumatologic conditions co-occurring with inflammatory bowel diseases. *Expert Rev Clin Immunol* 2018;14:751-759.
 25. Puig L. Paradoxical reactions: Anti-tumor necrosis factor alpha agents, ustekinumab, secukinumab, ixekizumab, and others. *Curr Probl Dermatol* 2018;53:49-63.
 26. Deodhar A, Gensler LS, Sieper J, *et al.* Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol* 2019;71:258-270.
 27. Felice C, Pugliese D, Papparella LG, *et al.* Clinical management of rheumatologic conditions co-occurring with inflammatory bowel diseases. *Expert Rev Clin Immunol* 2018;14:751-759.
 28. Biemans VB, van der Meulen-de Jong AE, Van Der Woude CJ, *et al.* Ustekinumab for crohn's disease: Results of the icc registry, a nationwide prospective observational cohort study. *J Crohn's Colitis* 2020;14:33-45.

29. de Winter JJ, Paramarta JE, de Jong HM, van de Sande MG, Baeten DL. Peripheral disease contributes significantly to the level of disease activity in axial spondyloarthritis. *RMD open* 2019;5:1-8.
30. Hanzel J, Ma C, Castele NV, *et al.* Vedolizumab and extraintestinal manifestations in inflammatory bowel disease. *Drugs* 2021;81:333-347.
31. Palm O, Moum B, Ongre A, Gran JT. Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: A population study (the ibsen study). *J Rheumatol* 2002;29:511-515.
32. Arvikar SL, Fisher MC. Inflammatory bowel disease associated arthropathy. *Curr Rev Musculoskelet Med* 2011;4:123-131.
33. Gutierrez A, Rodriguez-Lago I. How to optimize treatment with ustekinumab in inflammatory bowel disease: Lessons learned from clinical trials and real-world data. *Front Med* 2021;8:1-14.
34. Review EP. Ec approves expanded use of ustekinumab for ulcerative colitis. <https://www.europeanpharmaceuticalreview.com/news/99084/ec-approves-expanded-use-of-ustekinumab-for-ulcerative-colitis/> Accessed 12/08/2021, 2019.
35. Raine T, Verstockt B, Kopylov U, *et al.* Ecco topical review: Refractory ibd. *J Crohn's Colitis* 2021;1:1-49.
36. Kopylov U, Ron Y, Avni-Biron I, *et al.* Efficacy and safety of vedolizumab for induction of remission in inflammatory bowel disease—the israeli real-world experience. *Inflamm Bowel Dis* 2017;23:404-408.
37. Wendling D, Sondag M, Verhoeven F, *et al.* Arthritis occurrence or reactivation under vedolizumab treatment for inflammatory bowel disease. A four cases report. *Joint Bone Spine* 2018;85:255-256.
38. Levine JS, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease *Gastroenterol Hepatol* 2011;7:1-7.

39. Meserve J, Aniwani S, Kolianni-Pace JL, *et al.* Retrospective analysis of safety of vedolizumab in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2019;17:1533-1540.
40. Tadbiri S, Peyrin-Biroulet L, Serrero M, *et al.* Impact of vedolizumab therapy on extra-intestinal manifestations in patients with inflammatory bowel disease: A multicentre cohort study nested in the observ-ibd cohort. *Aliment Pharmacol Therap* 2018;47:485-493.
41. Fleisher M, Marsal J, Lee SD, *et al.* Effects of vedolizumab therapy on extraintestinal manifestations in inflammatory bowel disease. *Dig Dis Sci* 2018;63:825-833.
42. Sheth T, Pitchumoni CS, Das KM. Management of musculoskeletal manifestations in inflammatory bowel disease. *Gastroenterol Res Practice* 2015;5:1-12.
43. Dupre A, Collins M, Nocturne G, *et al.* Articular manifestations in patients with inflammatory bowel disease treated with vedolizumab. *Rheumatol* 2020;59:3275-3283.
44. Dubash S, Marianayagam T, Tinazzi I, *et al.* Emergence of severe spondyloarthropathy-related enthesal pathology following successful vedolizumab therapy for inflammatory bowel disease. *Rheumatol* 2019;58:963-968.
45. Ramos GP, Dimopoulos C, McDonald NM, *et al.* The impact of vedolizumab on pre-existing extraintestinal manifestations of inflammatory bowel disease: A multicenter study. *Inflamm Bowel Dis* 2021;27:1270-1276.
46. Gottlieb A, Menter A, Mendelsohn A, *et al.* Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: Randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009;373:633-640.
47. Helliwell PS, Gladman DD, Chakravarty SD, *et al.* Effects of ustekinumab on spondylitis-associated endpoints in tnfi-naive active psoriatic arthritis patients with physician-reported spondylitis: Pooled results from two phase 3, randomised, controlled trials. *RMD open* 2020;6:1-8.

48. Tursi A, Mocci G, Maconi G. Effect of ustekinumab on extraintestinal diseases in refractory crohn's disease. *J Crohn's Colitis* 2021;1:1399-1400.
49. Guillo L, D'Amico F, Danese S, Peyrin-Biroulet L. Ustekinumab for extra-intestinal manifestations of inflammatory bowel disease: A systematic literature review. *J Crohn's Colitis* 2021;15:1236-1243.
50. Singh A, Khan F, Lopez R, Shen B. Ustekinumab for moderate to severe crohn's disease and its extraintestinal manifestations. *Am J Gastroenterol* 2017;112:1482-1483.
51. Jansens Cilag SAS. Real-world effectiveness of ustekinumab in participants suffering from inflammatory bowel disease (crohn's disease or ulcerative colitis) with extra-intestinal manifestations or immune-mediated inflammatory diseases (tenor) - clinicaltrials.Gov identifier: Nct03606499.
<https://clinicaltrials.gov/ct2/show/NCT03606499?term=tenor&cond=Crohn+Disease&draw=2&rank=1> Accessed 23/03/2022, 2018.
52. Matsumoto S, Mashima H. Efficacy of ustekinumab against infliximab-induced psoriasis and arthritis associated with crohn's disease. *Biologics : Targets & Therapy* 2018;12:69-73.
53. Macaluso FS, Fries W, Viola A, *et al.* Effectiveness of ustekinumab on crohn's disease associated spondyloarthritis: Real-world data from the sicilian network for inflammatory bowel diseases (sn-ibd). *Expert Opin Biol Ther* 2020;20:1381-1384.
54. Deodhar A, Gensler LS, Sieper J, *et al.* Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol* 2019;71:258-270.
55. Schett G, McInnes IB, Neurath MF. Reframing immune-mediated inflammatory diseases through signature cytokine hubs. *N Engl J Med* 2021;385:628-639.

56. Liefverinckx C, Verstockt B, Gils A, *et al.* Long-term clinical effectiveness of ustekinumab in patients with crohn's disease who failed biologic therapies: A national cohort study. *J Crohn's Colitis* 2019;13:1401-1409.
57. Ito T, Maemoto A, Katsurada T, *et al.* Long-term clinical effectiveness of ustekinumab in patients with crohn's disease: A retrospective cohort study. *J Crohn's Colitis* 2020;2:1-9.
58. Narula N, Aruljothy A, Wong EC, *et al.* The impact of ustekinumab on extraintestinal manifestations of crohn's disease: A post hoc analysis of the uniti studies. *United Eur Gastroenterol J* 2021;5:581-589.
59. Carron P, Varkas G, Renson T, *et al.* High rate of drug-free remission after induction therapy with golimumab in early peripheral spondyloarthritis. *Arthritis Rheumatol* 2018;70:1769-1777.
60. Brandt J, Khariouzov A, Listing J, *et al.* Successful short term treatment of patients with severe undifferentiated spondyloarthritis with the anti-tumor necrosis factor-alpha fusion receptor protein etanercept. *J Rheumatol* 2004;31:531-538.
61. Landewé R, Sieper J, Mease P, *et al.* Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ability-3): A multicentre, randomised, double-blind study. *Lancet* 2018;392:134-144.
62. Vavricka SR, Brun L, Ballabeni P, *et al.* Frequency and risk factors for extraintestinal manifestations in the swiss inflammatory bowel disease cohort. *American J Gastroenterology* 2011;106:110-119.
63. Basu D, Lopez I, Kulkarni A, Sellin JH. Impact of race and ethnicity on inflammatory bowel disease. *LWW*, 2005: 2254-2261.

TABLES

Table 1: Baseline characteristics of study population dependent of treatment

	VDZ n=584	UST n=327	<i>p</i>
Age (years), median [IQR]	43 [33-57]	43 [32-55]	0.577
Sex , n [%]			
Female	289 [49.5]	182 [55.7]	0.074
Male	295 [50.5]	145 [44.3]	
Body mass index (kg/m ²), median [IQR]	n=471	n=259	
	24.0 [21.1-27.3]	23.6 [21.3-26.8]	0.414
IBD type , n [%]			
Ulcerative colitis	301 [51.5]	38 [11.6]	<0.001
Crohn's disease	283 [48.5]	289 [88.4]	
Montreal score (location) for CD , n [%]*	n=280	n=287	
L1	88 [31.4]	80 [27.9]	0.060
L2	78 [27.9]	61 [21.3]	
L3	109 [38.9]	135 [47.0]	
L3 + L4	5 [1.8]	11 [3.8]	
Montreal score (behaviour) for CD , n [%] [§]	n=281	n=289	
B1	127 [45.2]	110 [38.1]	0.075
B2	95 [33.8]	96 [33.2]	
B3	59 [21.0]	83 [28.7]	
Perianal disease , n [%] ⁰	66 [11.3]	89 [27.2]	<0.001

Montreal score for UC, n [%] ^o	n=300	n=38	
E1	21 [7.0]	1 [2.6]	0.157
E2	141 [47.0]	19 [50.0]	
E3	119 [39.7]	12 [31.6]	
Pouchitis	19 [6.3]	6 [15.8]	
Disease duration (years), median [IQR]	8 [3-15.5]	10 [5-19]	<0.001
Previous intestinal surgery , n [%]	153 [26.2]	130 [39.8]	<0.001
Previous treatments , n [%]			
TNF α inhibitors	404 [69.2]	300 [91.7]	<0.001
Vedolizumab	-	113 [34.6]	NA
Ustekinumab	20 [3.4]	-	NA
Steroid use , n [%]			
No	276 [47.3]	219 [67.0]	<0.001
Systemic ((methyl)prednisolone)	143 [24.5]	32 [9.8]	
Local (budesonide/beclomethasone)	165 [28.3]	76 [23.2]	
Concomitant immunomodulator use , n [%]	131 [22.4]	70 [21.4]	0.720
Concomitant 5-ASA treatment , n [%]	185 [31.7]	33 [10.1]	<0.001
Smoking , n [%]	n=548	n=307	
No	453 [82.7]	223 [72.6]	<0.001
Current smoker	95 [17.3]	84 [27.4]	

IBD: inflammatory bowel diseases; NA: not applicable; UST: ustekinumab; TNF α : Tumour Necrosis Factor alpha;

VDZ: vedolizumab; *Missing data: n=5, ^sMissing data: n=2 ^oMissing data: n=1.

Table 2: Baseline objective disease activity assessment

	VDZ	UST	p
	n=584	n=327	
Baseline CRP, median [IQR]	n=522	n=302	
	4.9 [2-12.6]	5.8 [2.0-15.0]	0.243
Baseline faecal calprotectin, median [IQR]	n=273	n=163	
	650 [213-1725]	478 [172-1300]	0.154
Baseline endoscopic activity, n [%]*	n=432	n=181	
Remission	13 [3.0]	9 [5.0]	
Mild	62 [14.4]	16 [8.8]	0.088
Moderate	211 [48.8]	82 [45.3]	
Severe	146 [33.8]	74 [40.9]	

CRP: C-reactive protein; VDZ: vedolizumab; UST: ustekinumab. *Endoscopic disease activity: physician's assessment

Table 3: Baseline EIMs dependent of treatment

	VDZ n=584	UST n=327	<i>p</i>
Joint EIMs, n [%]			
Arthropathy	39 [6.7]	40 [12.2]	0.004
Axial arthropathy	22 [3.8]	22 [6.7]	
Peripheral arthritis	13 [2.2]	8 [2.4]	
Axial + peripheral disease	4 [0.7]	10 [3.1]	
Arthralgia	33 [5.7]	30 [9.2]	0.044
Axial arthralgia	5 [0.9]	3 [0.9]	
Peripheral arthralgia	27 [4.6]	25 [7.6]	
Axial + peripheral arthralgia	1 [0.2]	2 [0.6]	
Skin EIMs, n [%]			
Erythema nodosum	10 [1.7]	12 [3.7]	
Pyoderma gangrenosum	2 [0.3]	1 [0.3]	
Sweet syndrome	3 [0.5]	1 [0.3]	
Pyoderma gangrenosum + erythema nodosum	1 [0.2]	2 [0.6]	
Eye EIMs, n [%]			
Episcleritis	4 [0.7]	2 [0.6]	
Scleritis	2 [0.3]	0 [0.0]	
Uveitis	1 [0.2]	3 [0.9]	
Hepatic EIMs, n [%]			
PSC	14 [2.4]	5 [1.5]	

AIH	3 [0.5]	1 [0.3]	
PSC/AIH overlap	2 [0.3]	1 [0.3]	
Psoriasis, n [%]	26 [4.5]	35 [10.7]	<0.001

AIH: autoimmune hepatitis; EIM: extraintestinal manifestations; PSC: Primary sclerosing cholangitis; UST: ustekinumab; VDZ: vedolizumab.

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Table 4: Multivariate regression model assessing risk factors for worsening of arthropathy

	Arthropathy worsening at 6 months		Arthropathy worsening at 1 year	
	aOR [95% CI]	p-value	aOR [95% CI]	p-value
Studied biological (VDZ)	1.45 [0.27-7.78]	0.667	0.62 [0.08-4.81]	0.643
anti-TNF α use before start of VDZ/UST	0.78 [0.14-4.49]	0.784	7.95 [0.66-96.48]	0.104
Corticosteroid free remission	0.61 [0.10-3.61]	0.586	0.16 [0.01-1.72]	0.130
Disease duration	0.99 [0.91-1.09]	0.891	1.01 [0.92-1.10]	0.850
Smoking (yes)	1.07 [0.17-6.58]	0.945	1.19 [0.14-10.04]	0.873
Country (Spain)	0.68 [0.12-3.83]	0.661	0.95 [0.11-8.16]	0.959

VDZ: vedolizumab; UST: ustekinumab; aOR = adjusted odds ratio; 95% CI = 95% confidence interval

Table 5: Multivariate regression model assessing risk factors for arthropathy development

	Arthropathy development up to 6 months		Arthropathy development up to 1 year	
	aOR [95% CI]	p-value	aOR [95% CI]	p-value
Studied biological (VDZ)	1.02 [0.09-11.72]	0.989	0.46 [0.11-1.89]	0.278
anti-TNF α use before start of VDZ/UST	5.05 [0.51-50.29]	0.167	2.02 [0.49-8.35]	0.333
Corticosteroid free remission	3.94 [0.38-40.70]	0.250	0.89 [0.22-3.56]	0.866
Disease duration	0.94 [0.81-1.10]	0.443	0.98 [0.90-1.06]	0.570
Smoking (yes)	1.42 [0.13-15.37]	0.771	2.43 [0.62-9.59]	0.204
Country (Spain)	0 [0-0]	0.995	0.77 [0.18-3.25]	0.719

VDZ: vedolizumab; UST: ustekinumab; aOR = adjusted odds ratio; 95% CI = 95% confidence interval

Table 6: Multivariate regression model assessing risk factors for new onset arthralgia

	New onset arthralgia up to 6 months		New onset arthralgia up to 1 year	
	aOR [95% CI]	p-value	aOR [95% CI]	p-value
Studied biological (VDZ)	2.28 [1.01-5.15]	0.047	1.61 [0.80-3.23]	0.178
anti-TNF α use before start of VDZ/UST	1.39 [0.72-2.67]	0.322	0.73 [0.40-1.33]	0.309
Corticosteroid free remission	1.03 [0.55-1.92]	0.935	1.03 [0.57-1.86]	0.913
Disease duration	0.97 [0.93-1.01]	0.094	0.99 [0.97-1.02]	0.663
Age at treatment initiation	1.02 [1.00-1.05]	0.033	1.02 [1.00-1.04]	0.060
Sex (female)	1.50 [0.79-2.84]	0.215	1.33 [0.75-2.36]	0.329
Smoking (yes)	1.34 [0.63-2.84]	0.450	0.76 [0.36-1.62]	0.478
Country (Spain)	0.39 [0.18-0.87]	0.020	0.47 [0.23-0.95]	0.036

VDZ: vedolizumab; UST: ustekinumab; aOR = adjusted odds ratio; 95% CI = 95% confidence interval

Figure 1

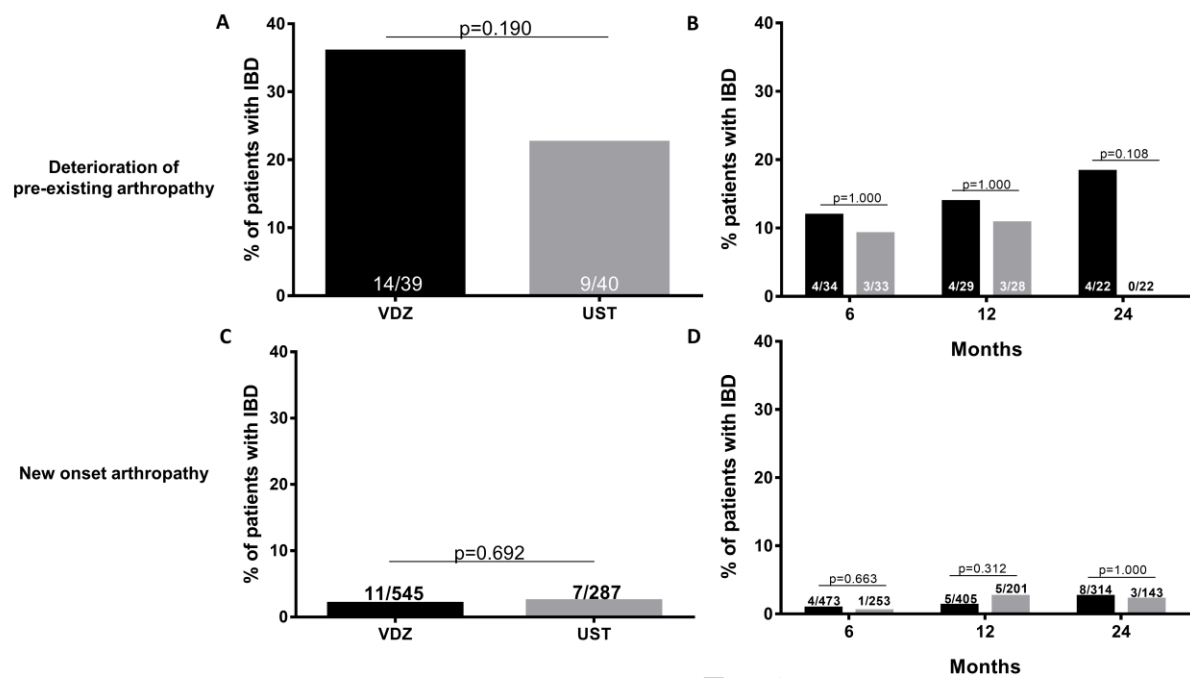


Figure 2

