SĘK, Michał, DUCHNEVIČ, Olgerd, GALASIŃSKA, Iwona, HAJDUK-MAŚLAK, Katarzyna, SZYPUŁA, Aleksandra, MICHALIK, Beniamin and SKÓRA, Adrianna. Latest Treatment Perspectives for IBD-related Arthritis - a review. Journal of Education, Health and Sport. 2024;61:55-72. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2024.61.004
https://apcz.umk.pl/JEHS/article/view/48325
https://zenodo.org/records/10672425

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 24.01.2023. Revised: 08.02.2024. Accepted: 16.02.2024. Published: 16.02.2024.

Latest Treatment Perspectives for IBD-related Arthritis - a review

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Abstract

Introduction: IBD-related arthritis (spondyloarthropathy) is the most common extraintestinal manifestation (EIM) of inflammatory bowel disease (IBD) and is often considered a formidable clinical challenge. Emergence of TNFα-antagonists has revolutionised the clinical approach to management of IBD-related arthritis and remains the mainstay of the therapy. However, its use presents several limitations, underscoring the need for new treatment modalities. Recently, new agents have been approved for the management of IBD, although their influence on IBD-related arthritis has been scarcely investigated.

Aim of the Study: The aim of the study was to collect and analyse current literature regarding the efficacy of new agents used for treating IBD-related arthritis.

Methods and Materials: Extensive research was conducted using the PubMed, ScienceDirect database and Google Scholar, with the primary focus on literature from the past 5 years. Firstly, potential novel treatment options for IBD-related arthritis were obtained. The names of the drugs were juxtaposed with terms related to “IBD-related arthritis” to gather data regarding their efficacy in said condition. Additionally, references from selected articles were included in the analysis.

Results: Emerging treatment options show promising results in achieving remission of IBD-related arthritis. However, our study revealed research gap as the current literature lacks large-scale, prospective studies that assess the efficacy of the aforementioned agents in achieving a resolution of IBD-related arthritis. Therefore, the results of our study encourage further research, with special emphasis on large-scale randomised controlled trials.

Keywords: Gastroenterology, Rheumatology, Arthritis, Extraintestinal manifestations, IBD, Treatment

Introduction

Inflammatory bowel diseases is a group of conditions consisting of Crohn's disease (CD) and Ulcerative colitis (UC), caused by dysregulation of intestinal mucosae, leading to an immunological overresponse to luminal contents. An inappropriate immune reaction causes damage to the intestinal lining [1]. Chronic and relapsing inflammation within the gastrointestinal tract is a predominant feature of IBD. However, extraintestinal manifestations (EIM) may occur, including articular, ocular, cutaneous, hepatopancreatobiliary, pulmonary, hematologic, renal and neurological conditions. Inflammatory arthropathies are the most common EIMs, with an estimated prevalence of 10–35% [2]. Articular EIMs exert a substantial negative impact on the quality of life associated with the health of affected patients [3]. IBD-related arthropathies can be divided into two subgroups: peripheral and axial spondyloarthropathies (axSpA). Peripheral spondyloarthropathies, with a prevalence of 5–20%, are classified as pauciarticular (oligoarticular, type I arthropathy) or polyarticular (type II arthropathy). The activity of type I arthropathy correlates with inflammation in GI tract, hence the treatment of underlying IBD is pivotal for the resolution of this specific type of arthritis. Type I arthropathy involves less than five joints. Type II arthropathy affects five or more joints and is independent of the course of IBD. Axial spondyloarthropathies manifest as isolated sacroiliitis, ankylosing spondylitis and inflammatory back pain. These arthropathies affect 5-22% of patients with CD and 2-6% of patients with UC and do not correlate with activity of underlying IBD [4,5]. The pathophysiology of EIMs, including articular manifestation, is still unclear, however, there are two dominant theories that explain the pathophysiology of extraintestinal inflammation in IBD. The first theory assumes a

translocation of antigen-specific immunological response from the GI tract to extraintestinal locations. Possible mechanisms include ectopic expression of gut-specific chemokines and adhesion molecules, upregulation of non-specific adhesion molecules for T-cells, translocation of microbial antigen and presence of circulating autoantibodies. The second theory explains the development of EIMs as an independent inflammation driven by systemic alteration of immunological response and a shift in inflammatory tone [5].

Management of axial spondyloarthropathy

NSAIDs are first line of treatment in axSpA without concomitant IBD [6]. However, due to well-established gastrointestinal toxicity of NSAIDs, long-term use in IBD should be avoided [7]. There is no evidence of correlation between use of NSAIDs and the exacerbation of UC, but there is a potentially increased risk of CD flare up in patients using NSAIDs [8,9]. The ECCO guidelines recommend implementing a case-by-case decision model before starting NSAID treatment, carefully considering the pros and the cons of such treatment. In cases refractory to standard treatment, the use of TNFα-antagonists is recommended, with the exclusion of etanercept, due to reported cases of paradoxical gastrointestinal inflammation [10,11]. ECCO guidelines state that JAK inhibitors may be used in axSpA due to their efficacy in ankylosing spondylitis [10].

Management of non-axial spondyloarthropathy

The 2016 ECCO guidelines suggest that effective treatment of underlying gut inflammation is often sufficient to treat peripheral spondyloarthritis. Short-term NSAIDs, short-term corticosteroids and local steroid injections are indicated for achieving reduction of symptoms of peripheral SpA [7]. Recent ECCO guidelines recommend the use of TNFα-antagonists in IBD-related non-axial SpA. Methotrexate, sulfasalazine, ustekinumab and JAK-inhibitors may be used as additional treatment options [10].

Limitations of TNFα-antagonists

TNFα-antagonists bind and neutralise soluble TNFα, a major pro-inflammatory cytokine, and demonstrate additional effect against transmembrane TNFα and Fc receptor-expressing cells [12]. Due to their efficacy in inducing and maintaining remission in IBD as well as in resolving numerous extraintestinal manifestations, TNFα-antagonists are currently the mainstay of treatment for patients with EIMs [10,13,14]. TNFα-antagonists are often started to treat EIMs rather than the underlying IBD and are characterised by superior efficacy in

improving symptoms of overall EIMs [15]. However, these agents have several limitations. Approximately 13-30% of patients with IBD does not respond to the therapy and 23-46% of initial responders may lose response over time [16]. Therapy with TNFα-antagonists may also be discontinued due to adverse effects, including serious infections, lupus-like syndrome, and allergic reactions [13]. Consequently, there is need for alternative treatment options for patients who do not tolerate or are refractory to TNFα-antagonist treatment.

Methods and Materials

Extensive research was conducted using PubMed, ScienceDirect database and Google Scholar, with the primary focus on literature from the past 5 years. Firstly, ustekinumab, upadacitinib, tofacitinib and vedolizumab were recognised as potential novel treatment options for IBD-related arthritis. The names of the drugs were juxtaposed with terms related to "IBD-related arthritis" to gather data regarding their efficacy in said condition. Additionally, references from selected articles were included in the analysis.

Novel treatment options

Janus kinases inhibitors - Tofacitinib and Upadacitinib

Janus kinase inhibitors (Jakinibs) are oral agents that have been shown to be effective in controlling intestinal inflammation. Jakinibs inhibit the activity of JAKs, intracytoplasmic proteins responsible for activation of STAT proteins, which are recognized as central mediators of inflammatory cytokine signalling. Activated STAT acts as pro-inflammatory transcription factors in the nucleus [17].

Tofacitinib was approved by the US Food and Drug Administration (FDA) for the treatment of UC. Upadacitinib received FDA approval for the treatment of UC by the European Medicines Agency (EMA) and FDA, but its use in CD has only been approved by EMA. Recent ECCO guidelines suggest the use of Jakinibs in both axial and non-axial spondyloarthropathies [10].

Tofacitinib

Tofacitinib is a selective inhibitor of JAK-1 and JAK3 proteins. approved for the treatment of UC. Tofacitinib is also effective in managing other chronic inflammatory conditions, such as rheumatoid arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, and

psoriatic arthritis. Considering its proven efficacy in managing autoimmune diseases, there is potential for it to be a viable treatment for IBD-related arthritis [18–20].

Several case reports seem to support this theory. In their 2019 case study, Wang et al. have reported remission of synovitis and underlying IBD in patient with UC after the combined use of tofacitinib and vedolizumab (VDZ). Prior use of vedolizumab was ineffective in achieving long-lasting remission of arthritis [21]. Similar findings by Le Berre et al. further support the efficacy of combined therapy with VDZ and tofacitinib in a UC patient with axial and peripheral arthropathy [22]. Majumder et al. report remission of IBD-related arthritis in joints of the lower extremity and UC after combined therapy with tofacitinib, methotrexate (MTX) and mesalazine. The prior use of sulfasalazine, etanercept, adalimumab and infliximab was ineffective in achieving remission of abdominal and joint symptoms. The authors have also reported a case of a patient with CD and CD-related arthritis of the lower extremities and hands, who after unsuccessful treatment with naproxen, prednisolone, sulfasalazine and MTX experienced a significant improvement after starting tofacitinib treatment [23]. Another case study showcased the efficacy of tofacitinib in patient with IBD-related, steroid refractory peripheral arthritis, in whom treatment attempts with salazopyrine and golimumab were discontinued [24].

Post-hoc analysis of OCTAVE trials, which evaluated the efficacy of tofacitinib in patients with concomitant EIMs, reported an improvement in arthritis symptoms in several patients with UC and SpA. The OCTAVE trials consisted of OCTAVE induction 1 and 2, which were phase III, double blinded RCTs, evaluating the efficacy and safety of tofacitinib as induction therapy in UC, while OCTAVE Sustain, a phase III, double blinded RCT, evaluated the efficacy and safety of tofacitinib maintenance therapy in UC after a successful induction phase. At the beginning of the OCTAVE induction study, 127 (11.2%) patients had active peripheral arthritis. At week 8, a similar proportion of patients in the placebo and tofacitinib treatment group had an improvement of arthritis symptoms, 14.3% and 15.6%, respectively. In contrast, at week 52 of the OCTAVE sustain study, only patients allocated to the tofacitinib treatment group showed improvement in arthritis symptoms, 1 (16.7%) treated with 5 mg of tofacitinib and 1 (33.3%) treated with 10 mg of tofacitinib. The remaining subgroups reported no change in symptoms. Of the placebo group, 2 study subjects (18.2%) have experienced a worsening of SpA symptoms, and 9 study subjects (81.8%) reported no change [25]. Owing to a low number of patients with SpA at baseline of OCTAVE Sustain, presented results should be treated with caution. The presented results, combined with the abundance of case reports

and the common use of tofacitinib in treating other autoimmunological conditions, make tofacitinib a reasonable candidate for further studies as a potential treatment option for articular EIMs.

Upadacitinib

Upadacitinib is an oral selective JAK-1 inhibitor, approved for use in UC by both the FDA and the EMA, and gained the approval of EMA for CD. Upadacitinib is effective in treating rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, thus it potentially may be used in the treatment of articular EIMs [26–28].

U-ENDURE, a randomized, double blinded trial assessing the efficacy of upadacitinib in maintenance therapy of CD, revealed that subjects on a 30 mg/day upadacitinib regimen were significantly more likely to achieve a resolution of EIMs than patients in the placebo group. A total of 26 out of 73 patients (35.6%) experienced a resolution of EIMs. This dependence was not statistically significant in a group treated with a lower dose of upadacitinib (15 mg). This finding may potentially be explained by the presence of a dose-response relationship. Due to lack of precise information on the exact type of EIMs in each patient, no definitive conclusions can be drawn. However, when considering the high prevalence of arthritis among EIMs, it may be assumed that upadacitinib was effective in some cases of arthritis resolvement [29].

Data collected from U-ACHIEVE induction, U-ACHIEVE maintenance and U-ACCOMPLISH studies (phase III, multicentre, double blinded RCTs) support assumption that upadacitinib is effective in resolving EIMs, including articular manifestations in patients with UC. In the induction phase, 41 out of 75 patients (54.7%) treated with upadacitinib on a 45 mg/day regimen, achieved resolution of peripheral or axial arthropathy. In comparison, only 16 out from 38 patients (42.1%) in placebo group achieved resolution. In the maintenance study, 10 out of 15 patients (66.7%) patients treated with UPA on a 30 mg/day regimen and 5 out of 13 patients (38.5%) receiving UPA 15 mg/day regimen achieved a resolution of peripheral or axial arthropathies, compared the placebo group where only 4 out of 18 patients (22.2%) had a remission [30].

Similarly, an analysis of data from the CELEST study (phase II, multicentre, double-blinded RCT) suggests a beneficial influence of UPA on articular EIMs in patients with CD. After 16 weeks of induction therapy 10 out of 24 (41.7%), 3 out of 12 (25.0%), 3 out of 7 (42.9%), 9 out of 16 (56.3%), 6 out of 11 (54.5%) patients treated with 3 mg/day, 6 mg/day, 12 mg/day,

24 mg twice daily, 24 mg once daily regimens, respectively, achieved a resolution of arthropathy [31].

In summary, while the current data supporting the efficacy of JAK inhibitors in the treatment of IBD-related arthritis is limited, both tofacitinib and upadacitinib emerge as a promising candidates for inclusion in the future armamentarium for articular EIMs. Notably, more selective JAK inhibitors are tested in IBD (Filgotinib) and rheumatological disorders (Baricitinib) [32,33]. Such discoveries may further broaden the future perspectives of IBD-related arthritis treatment. Further research consisting of large prospective studies, including RCTs, will be crucial for placing JAK inhibitors in treatment algorithms for articular EIMs.

Ustekinumab

Ustekinumab is a fully human monoclonal antibody that binds the p40 subunit, common for IL-12 and IL-23, which are involved in Th1 and Th17-mediated immune responses [34]. Ustekinumab has been approved by the FDA for the treatment of moderate to severe, TNFα-refractory CD, and moderate to severe UC. Ustekinumab is also approved by the FDA for the use in psoriatic arthritis and plaque psoriasis, which exhibit pathogenesis similar to IBD [35].

A prospective cohort study by Biemans et al. describing the efficacy and safety of Ustekinumab in patients with CD revealed that 44 out of 221 enrolled patients reported arthralgia. During the follow-up period 24 out of 44 patients (54.5%) experiencing symptoms at baseline achieved remission. However, in 37 patients new onset of arthralgia was observed, predominantly in patients who did not achieve clinical remission of underlying CD [36]. The prospective design of this study, substantial cohort size and extended follow-up period are notable strengths of this study in evaluating the impact of Ustekinumab on articular EIMs. On the other hand, the limitation of the study lies in the absence of differentiation between arthralgia without arthritis and arthralgia as a symptom of IBD-related arthritis, thereby limiting the possibility of drawing definitive conclusions about the efficacy of ustekinumab in treating articular EIMs.

A retrospective study by Liefferinckx et al. evaluated the efficacy of Ustekinumab in patients with CD refractory to biology treatment. The study reported complete resolution of arthralgia in 34 out of 44 patients (82.6%) who experienced arthralgia at baseline after 52 weeks of ustekinumab treatment. Notably, effectiveness in ankylosing spondylitis was not observed [37]. While the results suggest the efficacy of ustekinumab in resolving arthralgia, caution is advised due to the lack of a clear distinction between arthralgia and IBD-related arthritis, the

absence of an evaluation by a rheumatologist, and an omission of an assessment of arthritis intensity based on a VAS scale.

Post-hoc analysis of the UNITY trials, which evaluated the use of ustekinumab as induction and maintenance therapy of moderate to severe CD, did not reveal a superior efficacy of ustekinumab in the resolution of overall EIMs compared to placebo. However, in the maintenance phase, 89 out of 129 patients (68.99%) with arthritis or arthralgia at baseline experienced a resolution of symptoms [38]. Due to the lack of distinction between arthritis and arthralgia in this study, the interpretation of the results is not unequivocal.

A case report by Matsumoto et al. described a patient with CD-related sacroiliitis and peripheral arthritis with IBD-related skin rash and scleritis, who after unsuccessful treatment with NSAIDs was started on ustekinumab. The authors reported a rapid resolution of cutaneous and ocular EIMs, and a gradual remission of articular manifestations [39]. Notably, treatment with ustekinumab led to resolvement of sacroiliitis, which is one of the presentations of axial SpA. It is particularly interesting, as ustekinumab is not recommended in treatment of IBD-related axial-SpA [10]

Another case study by Matsumoto et al. presented a patient with paradoxical psoriasis as a result of infliximab treatment and simultaneous peripheral IBD-related arthritis of the knee joint. Treatment with ustekinumab led to a rapid remission of arthritis and the resolvement of cutaneous symptoms within 2 months of treatment [40].

Vedolizumab

Vedolizumab (VDZ) is a humanized monoclonal antibody against integrin $\alpha_4\beta_7$, approved by FDA for maintenance treatment of Crohn's disease (CD) and Ulcerative Colitis (UC) [41]. VDZ binds to the integrin $\alpha_4\beta_7$ expressed on gut-homing T lymphocytes, blocking its interaction with mucosal addresin cell adhesion molecule 1 (MAdCAM-1). Due to preferential expression of MAdCAM-1 on mucosal endothelial cells VDZ allows for a targeted therapy of the gastrointestinal tract [42]. However, it is currently unknown whether gut-selective mechanism of action is optimal for controlling EIMs, including IBD-related arthritis [43,44]. Based on assumption that development of IBD-related arthritis is caused by inflammation of intestinal mucosa, selective treatment targeting mucosal inflammation with VDZ could be potentially effective. On the other hand, if IBD-related arthritis is driven by

systemic immune activation, TNF antagonists or corticosteroids might prove more effective than VDZ [43].

The 2023 ECCO guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease do not recommend use of VDZ in both Axial and non-axial spondyloarthropathy due to occurrence of paradoxical arthritis and deterioration of existing arthropathy [10,45–47]. Our literature review on the efficacy and safety of VDZ in treatment of IBD-related arthritis has identified studies with conflicting results.

A multicentre cohort study nested in the OBSERVE-IBD cohort by S. Tadbri et al. suggests potential benefit of VDZ treatment in patients with IBD-related arthritis [44]. At baseline, 47 of 294 enrolled patients presented arthritis or arthralgia. At week 52 of VDZ therapy, 21 (44,7%) patients achieved complete remission, 10 patients (21,3%) were symptomatic and 16 (34%) discontinued VDZ due to lack of response. Multivariate analysis revealed significant association of arthritis or arthralgia remission with clinical remission of IBD (OR=1.89 IC95% [1.05-3.41], P = 0.03)) and recent onset of inflammatory arthralgia/arthritis (OR=1.99 IC95% [1.12-3.52], P = .02) [44]. Such outcomes may support the theory, that active inflammation of mucosae is the driving factor of articular EIM, therefore VDZ may prove efficient in their treatment. On the other hand, the same study reports that in 34 patients (after excluding 47 patients with inflammatory arthritis or arthralgia at baseline) symptoms of arthritis or arthralgia were observed, of whom 22 (64,7%) suffered from arthralgia without arthritis. Occurrence of new onset arthritis or arthralgia may indicate that use of VDZ in treatment of IBD-related arthritis is not safe.

In contrary to study above, a real life, multicentric cohort study, by Cara De Galan et al. which evaluated impact of vedolizumab and ustekinumab on articular EIM in UC and CD, suggests that use of VDZ is safe for patients with IBD-related arthritis. In total, 584 patients received treatment with VDZ, of whom 39 had pre-existing arthropathy. Condition deteriorated in 14 patients (35,9%) during 2 year follow-up, however a multivariate regression model did not reveal a statistically significant association between received treatment and deterioration (aOR VDZ: 1.95 IC95%: [0.61-6.21]; p=0.258). New onset of arthropathy was diagnosed in 11 patients (2%) receiving VDZ, but neither was it identified as risk factor in a multivariate regression model, assessing new onset arthropathy during the 2-year follow-up (aOR: 0.82 IC95%: [0.30-2.29]; p=0.708). The authors conclude, that patients with articular EIMs can be treated safely with VDZ [48]. The large sample size, a long-follow up period, a

clear distinction between arthritis and arthralgia and careful consideration of numerous confounders in multivariate regression model contribute to the high quality of the study.

A prospective, observational study by Macaluso et al. indicates effectiveness of VDZ in reducing symptoms of articular EIMs. After 10 weeks of treatment, a response on arthritis was reported in 17 out of 43 (39.5%), 2 out of 4 (50%) and 2 out of 11 (18.2%) study subjects diagnosed with peripheral SpA, axial SpA and both peripheral and axial SpA, respectively. Of the 22 patients with articular EIMs who reached 22 weeks of follow-up, 8 out of 14 (57.1%) with peripheral SpA and 2 out of 8 (25.0%) patients with both peripheral and axial SpA, achieved an improvement of symptoms. A univariate logistic regression analysis indicated statistically significant correlation between the resolution of articular manifestations and the improvement of intestinal symptoms after VDZ treatment [49]. This correlation further supports theory, that mucosal inflammation is driving factor of EIMs, however does not exclude possible direct effect of VDZ on joints. The study was limited in several ways. Firstly, the follow-up period was short, spanning only 22 weeks. Furthermore, at week 10, 47% of patients with articular manifestations required the simultaneous use of concomitant steroids. Although none of the patients were still on steroids by week 22, previous use of steroids may have had a bearing on results, especially taking length of follow up into consideration.

A chart review study by Uri Kopylov et al. demonstrates efficacy of VDZ in achieving resolution or improvement in peripheral spondyloarthritis. After 12 months of treatment with VDZ, resolution of symptoms was observed in 7 of 21 patients (33.3%) with peripheral spondyloarthritis. On the contrary, in a group of 10 patients with axial spondyloarthritis, no resolution has been observed. Additionally, in a group of 69 patients diagnosed with arthralgia, resolution was observed in 18 patients (26.1%) after 12 months of treatment with VDZ. The data presented in this study are not sufficient to draw definitive conclusions due to a small number of study subjects. The use of concomitant medications for peripheral arthritis (COX-2 inhibitors and aspirin) can further limit the interpretation of the results [50].

Several case studies have demonstrated therapeutical success in the treatment of articular EIMs. Treatment with VDZ led to resolution of ankylosing spondylitis (SpA) and sacroiliitis in CD, polyarthritis in CD, joint and back pain in UC and polyarticular arthropathy in UC [42]. The resolution of articular EIMs corresponded to good control of luminal IBD in all presented patients. The reported resolution of SpA is particularly notable, as this condition is thought to be uncorrelated with the activity of luminal IBD. Although case reports are considered the

have the lowest level of evidence, they may unveil the potential efficacy of VDZ in treating articular EIMs.

In summary, available data suggest that VDZ may be potentially beneficial in treatment of patients with IBD-related arthritis, especially patients who achieve resolution of luminal disease with VDZ. However, currently available literature does not allow to formulate clear conclusions about efficacy and safety of VDZ in articular EIMs. Conflictive data in retrospective cohort studies and lack of large prospective studies including RCTs highlights need of further research.

Conclusions

Articular manifestations are a frequent challenge for physicians managing patients with IBD. Although TNFα-antagonists are effective for the treatment of IBD-related arthritis, alternative treatment modalities are needed, especially for refractory and severe cases. Novel biological agents (vedolizumab, ustekinumab) and small-molecule JAK-inhibitors (tofacitinib, upadacitinib) have proven effective in the treatment of IBD, suggesting a potential for their application beyond current indications. Tofacitinib and upadacitinib have demonstrated efficacy in the treatment of IBD-related axSpA and peripheral spondyloarthropathies, whereas ustekinumab has shown potential in the treatment of IBD-related peripheral arthropathies. Although potentially effective in both IBD-related axSpA and peripheral arthropathies, the use of vedolizumab remains controversial due to the possible occurrence of paradoxical arthritis. However, the majority of available data stems from post-hoc analyses of retrospective cohort studies, which may be riddled with inherent limitations. Our research revealed a gap in the existing literature, particularly the absence of large, prospective studies assessing the efficacy of new agents in IBD-related arthritis. Therefore, conducting further research, with a particular emphasis on large-scale RCTs, is crucial for resolving the controversies regarding vedolizumab and in confirming the efficacy of ustekinumab, upadacitinib, and tofacitinib.

Disclosure

Supplementary materials

Not applicable.

Authors contribution:

Conceptualization, Michał Sęk; methodology, Beniamin Michalik; software, Katarzyna Hajduk-Maślak; check, Olgerd Duchnevič, Iwona Galasińska and Aleksandra Szypuła; formal analysis, Michał Sęk and Beniamin Michalik; investigation, Adrianna Skóra; resources, Michał Sęk; data curation, Iwona Galasińska and Aleksandra Szypuła; writing - rough preparation, Iwona Galasińska; writing - review and editing, Michał Sęk and Olgerd Duchnevič; visualization, Adrianna Skóra; supervision, Olgerd Duchnevič; project administration, Katarzyna Hajduk-Maślak; All authors have read and agreed with the published version of the manuscript.

Funding Statement

The authors did not receive funding for this project.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Acknowledgements

Not applicable.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Data Availability Statement

The data presented in this study are available upon request from the correspondent author.

References

1. Winter MW, Weinstock JV. Inflammatory Bowel Disease. In: *The Autoimmune Diseases*. Elsevier; 2020:871-894. doi:10.1016/B978-0-12-812102-3.00046-4

2. Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: Epidemiology, diagnosis, and management. *Ann Med*. 2010;42(2):97-114. doi:10.3109/07853890903559724

3. Palm Ø, Bernklev T, Moum B, Gran JT. Non-inflammatory joint pain in patients with inflammatory bowel disease is prevalent and has a significant impact on health related quality of life. *J Rheumatol*. 2005;32(9):1755-1759.

4. Ott C, Schölmerich J. Extraintestinal manifestations and complications in IBD. *Nat Rev Gastroenterol Hepatol*. 2013;10(10):585-595. doi:10.1038/nrgastro.2013.117

5. Hedin CRH, Vavricka SR, Stagg AJ, et al. The Pathogenesis of Extraintestinal Manifestations: Implications for IBD Research, Diagnosis, and Therapy. *J Crohns Colitis*. 2019;13(5):541-554. doi:10.1093/ecco-jcc/jjy191

6. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis*. 2023;82(1):19-34. doi:10.1136/ard-2022-223296

7. Harbord M, Annese V, Vavricka SR, et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. *J Crohns Colitis*. 2016;10(3):239-254. doi:10.1093/ecco-jcc/jjv213

8. Moninuola OO, Milligan W, Lochhead P, Khalili H. Systematic review with meta-analysis: association between acetaminophen and nonsteroidal anti-inflammatory drugs (NSAID s) and risk of Crohn's disease and ulcerative colitis exacerbation. *Aliment Pharmacol Ther*. 2018;47(11):1428-1439. doi:10.1111/apt.14606

9. Long MD, Kappelman MD, Martin CF, Chen W, Anton K, Sandler RS. Role of Nonsteroidal Anti-Inflammatory Drugs in Exacerbations of Inflammatory Bowel Disease. *J Clin Gastroenterol*. 2016;50(2):152-156. doi:10.1097/MCG.0000000000000421

10. Gordon H, Burisch J, Ellul P, et al. ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. *J Crohns Colitis*. Published online June 23, 2023:jjad108. doi:10.1093/ecco-jcc/jjad108

11. Iriarte A, Zaera C, Bachiller-Corral J, López-Sanromán A. Enfermedad inflamatoria intestinal como efecto paradójico del tratamiento con anti-TNF-α. *Gastroenterol Hepatol*. 2017;40(2):117-121. doi:10.1016/j.gastrohep.2016.01.011

12. Mitoma H, Horiuchi T, Tsukamoto H, Ueda N. Molecular mechanisms of action of anti-TNF-α agents – Comparison among therapeutic TNF-α antagonists. *Cytokine*. 2018;101:56-63. doi:10.1016/j.cyto.2016.08.014

13. Atreya R, Neurath MF. IL-23 Blockade in Anti-TNF Refractory IBD: From Mechanisms to Clinical Reality. *J Crohns Colitis*. 2022;16(Supplement_2):ii54-ii63. doi:10.1093/ecco-jcc/jjac007

14. Peyrin-Biroulet L, Van Assche G, Gómez-Ulloa D, et al. Systematic Review of Tumor Necrosis Factor Antagonists in Extraintestinal Manifestations in Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol*. 2017;15(1):25-36.e27. doi:10.1016/j.cgh.2016.06.025

15. Vavricka SR, Gubler M, Gantenbein C, et al. Anti-TNF Treatment for Extraintestinal Manifestations of Inflammatory Bowel Disease in the Swiss IBD Cohort Study: *Inflamm Bowel Dis*. 2017;23(7):1174-1181. doi:10.1097/MIB.0000000000001109

16. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*. 2016;7(1):e135. doi:10.1038/ctg.2015.63

17. Nielsen OH, Boye TL, Gubatan J, Chakravarti D, Jaquith JB, LaCasse EC. Selective JAK1 inhibitors for the treatment of inflammatory bowel disease. *Pharmacol Ther*. 2023;245:108402. doi:10.1016/j.pharmthera.2023.108402

18. Gratacós Masmitjà J, González Fernández CM, Gómez Castro S, Rebollo Laserna FJ. Efficacy of Tofacitinib in the Treatment of Psoriatic Arthritis: A Systematic Review. *Adv Ther*. 2021;38(2):868-884. doi:10.1007/s12325-020-01585-7

19. Harrington R, Harkins P, Conway R. Janus Kinase Inhibitors in Rheumatoid Arthritis: An Update on the Efficacy and Safety of Tofacitinib, Baricitinib and Upadacitinib. *J Clin Med*. 2023;12(20):6690. doi:10.3390/jcm12206690

20. Herrera-deGuise C, Serra-Ruiz X, Lastiri E, Borruel N. JAK inhibitors: A new dawn for oral therapies in inflammatory bowel diseases. *Front Med*. 2023;10:1089099. doi:10.3389/fmed.2023.1089099

21. Wang W, Cleveland NK, Ollech J, Rubin DT. Use of Tofacitinib for the Treatment of Arthritis Associated With Ulcerative Colitis. *ACG Case Rep J*. 2019;6(9):e00226. doi:10.14309/crj.0000000000000226

22. Le Berre C, Loeuille D, Peyrin-Biroulet L. Combination Therapy With Vedolizumab and Tofacitinib in a Patient With Ulcerative Colitis and Spondyloarthropathy. *Clin Gastroenterol Hepatol*. 2019;17(4):794-796. doi:10.1016/j.cgh.2018.08.017

23. Momen Majumder MS, Haq SA, Rasker JJ. Tofacitinib for the treatment of inflammatory bowel disease-associated arthritis: two case reports. *J Med Case Reports*. 2023;17(1):71. doi:10.1186/s13256-023-03796-2

24. Lomborg N, Jensen MD. Effect of tofacitinib in a patient with inflammatory bowel disease–related arthritis. *Mod Rheumatol Case Rep*. 2022;6(2):171-172. doi:10.1093/mrcr/rxac021

25. Rubin DT, Reinisch W, Greuter T, et al. Extraintestinal manifestations at baseline, and the effect of tofacitinib, in patients with moderate to severe ulcerative colitis. *Ther Adv Gastroenterol*. 2021;14:175628482110057. doi:10.1177/17562848211005708

26. Fonseca D, Nogueira M, Torres T. Upadacitinib for the treatment of psoriatic arthritis. *Drugs Context*. 2023;12:1-13. doi:10.7573/dic.2022-11-6

27. Sanmartí R, Corominas H. Upadacitinib for Patients with Rheumatoid Arthritis: A Comprehensive Review. *J Clin Med*. 2023;12(5):1734. doi:10.3390/jcm12051734

28. Baraliakos X, Van Der Heijde D, Sieper J, et al. Efficacy and safety of upadacitinib in patients with ankylosing spondylitis refractory to biologic therapy: 1-year results from the open-label extension of a phase III study. *Arthritis Res Ther*. 2023;25(1):172. doi:10.1186/s13075-023-03128-1

29. Loftus EV, Panés J, Lacerda AP, et al. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. *N Engl J Med*. 2023;388(21):1966-1980. doi:10.1056/NEJMoa2212728

30. Colombel JF, Cao Q, Ghosh S, et al. Tu1455: EFFECT OF UPADACITINIB (UPA) TREATMENT ON EXTRAINTESTINAL MANIFESTATIONS (EIMS) IN PATIENTS WITH MODERATE-TO-SEVERE ULCERATIVE COLITIS (UC): RESULTS FROM THE UPA PHASE 3 PROGRAMME. *Gastroenterology*. 2022;162(7):S-968. doi:10.1016/S0016-5085(22)62293-5

31. Peyrin-Biroulet L, Danese S, Louis E, et al. DOP50 Effect of upadacitinib on extra-intestinal manifestations in patients with moderate to severe Crohn's disease: data from the CELEST study. *J Crohns Colitis*. 2019;13(Supplement_1):S057-S057. doi:10.1093/ecco-jcc/jjy222.084

32. Smolen JS, Xie L, Jia B, et al. Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis with 3 years of treatment: results from a long-term study. *Rheumatology*. 2021;60(5):2256-2266. doi:10.1093/rheumatology/keaa576

33. Feagan BG, Danese S, Loftus EV, et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *The Lancet*. 2021;397(10292):2372-2384. doi:10.1016/S0140-6736(21)00666-8

34. Pugliese D, Daperno M, Fiorino G, et al. Real-life effectiveness of ustekinumab in inflammatory bowel disease patients with concomitant psoriasis or psoriatic arthritis: An IG-IBD study. *Dig Liver Dis*. 2019;51(7):972-977. doi:10.1016/j.dld.2019.03.007

35. Freuer D, Linseisen J, Meisinger C. Association Between Inflammatory Bowel Disease and Both Psoriasis and Psoriatic Arthritis: A Bidirectional 2-Sample Mendelian Randomization Study. *JAMA Dermatol*. 2022;158(11):1262-1268. doi:10.1001/jamadermatol.2022.3682

36. Biemans VBC, 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 Crohns Colitis*. 2020;14(1):33-45. doi:10.1093/ecco-jcc/jjz119

37. Liefferinckx 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 Crohns Colitis*. 2019;13(11):1401-1409. doi:10.1093/ecco-jcc/jjz080

38. Narula N, Aruljothy A, Wong ECL, 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;9(5):581-589. doi:10.1002/ueg2.12094

39. Matsumoto S, Matsumoto K, Takaya H, Otake H, Mashima H. Efficacy of Ustekinumab Against Spondyloarthritis Associated with Crohn's Disease: A Case Report and Review of the Literature. *Open Access Rheumatol Res Rev*. 2020;Volume 12:133-137. doi:10.2147/OARRR.S263259

40. Matsumoto S, Mashima H. Efficacy of ustekinumab against infliximab-induced psoriasis and arthritis associated with Crohn’s disease. *Biol Targets Ther*. 2018;Volume 12:69-73. doi:10.2147/BTT.S169326

41. Brüner M, Dige A, Loft AG, et al. Spondylitis-psoriasis-enthesitis-enterocolitis-dactylitis-uveitis-peripheral synovitis (SPEED-UP) treatment. *Autoimmun Rev*. 2021;20(2):102731. doi:10.1016/j.autrev.2020.102731

42. Fleisher M, Marsal J, Lee SD, et al. Effects of Vedolizumab Therapy on Extraintestinal Manifestations in Inflammatory Bowel Disease. *Dig Dis Sci*. 2018;63(4):825-833. doi:10.1007/s10620-018-4971-1

43. 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 Crohns Colitis*. 2019;13(1):50-57. doi:10.1093/ecco-jcc/jjy125

44. 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 Ther*. 2018;47(4):485-493. doi:10.1111/apt.14419

45. Dubash S, Marianayagam T, Tinazzi I, et al. Emergence of severe spondyloarthropathy-related entheseal pathology following successful vedolizumab therapy for inflammatory bowel disease. *Rheumatology*. 2019;58(6):963-968. doi:10.1093/rheumatology/key267

46. 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 Rheum Dis*. 2017;76(5):878-881. doi:10.1136/annrheumdis-2016-210233

47. 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(8):1270-1276. doi:10.1093/ibd/izaa293

48. De Galan C, Truyens M, Peeters H, et al. The Impact of Vedolizumab and Ustekinumab on Articular Extra-Intestinal Manifestations in Inflammatory Bowel Disease Patients: A Real-Life Multicentre Cohort Study. *J Crohns Colitis*. 2022;16(11):1676-1686. doi:10.1093/ecco-jcc/jjac058

49. Macaluso FS, Orlando R, Fries W, et al. The real-world effectiveness of vedolizumab on intestinal and articular outcomes in inflammatory bowel diseases. *Dig Liver Dis*. 2018;50(7):675-681. doi:10.1016/j.dld.2018.02.013

50. Kopylov U, Burisch J, Ben-Horin S, et al. Impact of Vedolizumab on Extraintestinal Manifestations in Inflammatory Bowel Disease: Results From a Descriptive, Retrospective, Real-world Study. *Inflamm Bowel Dis*. 2023;29(11):1713-1722. doi:10.1093/ibd/izad075