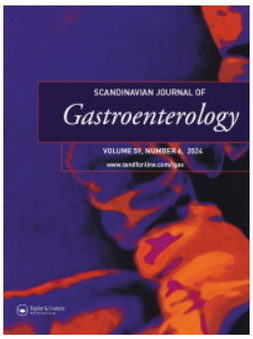

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REVIEW ARTICLE

Acute interstitial nephritis in patients with inflammatory bowel disease treated with vedolizumab: a systematic review

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ABSTRACT

Background: Acute interstitial nephritis (AIN) is a complication of drugs that may cause permanent kidney injury. AIN has been reported in patients with inflammatory bowel disease (IBD) treated with the integrin inhibitor vedolizumab. Through systematic review of existing literature, we aimed to identify and describe cases of AIN in patients with IBD treated with vedolizumab.

Methods: We searched Medline, Embase, Cochrane, and Web of Science Core Collection between 1 January 2009 and 25 April 2023. The search yielded 1473 publications. Titles and abstracts were screened by two independent reviewers. Seventy publications were reviewed in full-text. Eight met the inclusion criteria. Clinical characteristics of AIN cases were extracted. Case causality assessment was performed according to two international adverse drug reaction probability assessment scales. Results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: Nine biopsy-confirmed cases of AIN were reported in six patients with ulcerative colitis and three with Crohn's disease. Mean age at AIN onset was 36 years (range = 19–58) and the majority of patients were females ($n = 6/9$). Time from vedolizumab treatment initiation to AIN onset spanned from hours to 12 months. Common symptoms were fever and malaise. Creatinine levels were elevated in all patients. Five patients sustained permanent kidney injury.

Conclusion: Our findings suggest that vedolizumab, although rarely, could cause AIN in patients with IBD. Awareness of laboratory findings and symptoms consistent with AIN, along with monitoring of the kidney function, could be warranted in patients with IBD treated with vedolizumab.

Abbreviations: AIN: acute interstitial nephritis; anti-TNF: anti-tumor necrosis factor; CD: Crohn's disease; CRP: C-reactive protein; IBD: inflammatory bowel disease; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; UC: ulcerative colitis; WBC: white blood cell count; WHO-UMC: World Health Organization-Uppsala Monitoring Centre

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Introduction

The number of treatment options in inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is continuously increasing. Anti-tumor necrosis factor (anti-TNF) agents have become the mainstay of therapy in patients failing conventional treatment. A sizeable number of patients with IBD do not respond, lose response or do not tolerate anti-TNF treatment [1–5]. For these patients, and also for anti-TNF naïve patients, other treatment options are more recent biological agents such as vedolizumab. Vedolizumab is a humanized monoclonal antibody targeting the α4β7-integrin expressed on gut lymphocytes. By binding to α4β7-integrin, leukocyte migration from the blood to the intestinal mucosa is inhibited. Vedolizumab is approved for treatment of patients with moderate to severe CD and UC, and, in the European Union, also for chronic pouchitis after proctocolectomy with ileal pouch anal anastomosis. Compared with anti-TNF treatment, vedolizumab is believed to have an overall lower risk of adverse drug reactions [6,7]. However, as a comparably new contribution to the advanced treatment options in IBD, less frequent and unexpected adverse drug reactions may unfold over time.

Acute interstitial nephritis (AIN) is a feared treatment complication of pharmacological therapies that may cause permanent kidney injury. The classical clinical presentation consists of fever, rash, and eosinophilia but can be highly variable. Increased creatinine levels are present in most cases [8]. Except from a few case reports [9–11] on AIN in patients treated with vedolizumab for IBD, little is known about occurrence and clinical features of AIN associated with vedolizumab.

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Hence, there is a need to systematically investigate reported cases of AIN in vedolizumab treated patients with IBD through systematic review of existing literature.

Methods

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. A prespecified protocol was registered in the PROSPERO database (Protocol ID: CRD42023400647).

Search

A search was conducted of Medline, Embase, Cochrane, and Web of Science Core Collection from 1 January 2009 up to 25 April 2023 including the terms: 'antibodies, monoclonal', 'gastrointestinal agents', 'colitis, ulcerative', 'Crohn's disease', 'kidney disease', and 'interstitial nephritis'. Detailed search strategies for each database are presented in supplementary Figure S1. The search strategies were elaborated in collaboration with the University Library at Karolinska Institutet (Stockholm, Sweden). The search was limited to publications in English but no restriction to type of study design was applied. Search results were reviewed independently by two reviewers. Disagreement about interpretation and inclusion/exclusion of publications were resolved by discussion between the reviewers. After initial search and removal of duplicates, a total of 1473 publications were identified. Titles and abstracts of these were screened for inclusion in full-text review (Figure S1).

To contrast our literature search, we searched the World Health Organization pharmacovigilance database, VigiBase (accessed 4 April 2023) for Medical Dictionary for Regulatory Activities (MeDRA) System Organ Classes (SOC) 'renal and urinary disorders', including tubulointerstitial nephritis [13]. An equivalent search was performed in the Swedish pharmacovigilance database (BiSi, accessed 1 April 2023) where the search terms used were ATC-code L04AA33 (vedolizumab) AND MeDRA-term 'renal and urinary disorders' [14].

Identification of patients, treatment and clinical data

IBD and treatment with vedolizumab

We only included studies where the IBD diagnosis was reported as either CD or UC. Treatment with vedolizumab, including treatment duration, dose and dosing interval, along with clinical patient characteristics were ascertained from data reported in each reviewed publication.

AIN

For the diagnosis of AIN, we required reporting of a kidney biopsy consistent with AIN. We also considered cases where the diagnosis was not biopsy-confirmed, but where there was a high clinical suspicion of AIN.

Data items and risk of bias

We systematically extracted data to a study specific form on the following variables: (1) first author and year of publication; (2) country; (3) sample size (including age and sex of study participants); (4) number of AIN cases; (5) laboratory findings, including C-reactive protein (CRP), creatinine, white blood cell count (WBC), and urine analysis; (6) previous biologics and concomitant treatment; (7) details on vedolizumab treatment, such as dose, dosing interval and route of administration; (8) symptoms of AIN; (9) treatment of AIN and whether the patient was rechallenged with vedolizumab or not; and (10) if kidney biopsy was performed and main histological biopsy findings (extracted data is presented in Tables 1 and 2).

The Newcastle–Ottawa quality assessment scale [15,16] was planned to be used to grade the quality of included publications. However, our systematic review only identified case reports for which this, and other quality assessment tools, are

Table 1. Clinical characteristics of cases included in systematic review of AIN in patients with IBD treated with vedolizumab.

Author, year	Country	IBD	Sex	Age at AIN (years)	Time since start VZB (months)	Cr/eGFR at AIN (μmol/L; ml/min)	Biopsy verified AIN (yes/no)	Treatment AIN	Cr/eGFR after AIN[a] (μmol/L; ml/min)	Permanent kidney injury (yes/no)	Rechallenge/ successful (yes/no)	Naranjo[b]/WHO[c] scale
Bailly, 2018	France	CD	F	55	0	410/10	Yes	CS	88/63	No	Yes/yes	Possible/possible
Jahan, 2022	Australia	UC	F	19	2	280	Yes	CS	NA	Yes	No/–	Possible/unlikely
Kepley, 2021	USA	UC	M	33	NA	NA	Yes	CS	NA	Yes	Yes/no	Probable/unlikely[d]
Kepley, 2021	USA	UC	F	45	NA	NA	Yes	NA	NA	NA	NA	Possible/unclassified[e]
Muzib, 2020	USA	UC	F	58	12	199	Yes	CS	97/58[f]	NA	NA	Possible/possible
O'Leary, 2022	Australia	UC	M	21	>6	133	Yes	CS	108/86[f]	Yes	Yes/no	Probable/probable
Simpson, 2023	UK	CD	F	44	12	165/29	Yes	CS	130/39	Yes	No/–	Possible/possible
Subhaharan, 2022	Australia	UC	M	20	10	171/49	Yes	CS	89/>90	No	No/–	Possible/probable
Zhang, 2020	USA	CD	F	33	2	177	Yes	CS	150/40[f]	Yes	No/–	Possible/possible

AIN, acute tubulointerstitial nephritis; CD, Crohn's disease; Cr, creatinine; CS, corticosteroids; F, female; IBD, inflammatory bowel disease; M, male; NA, data not available; UC, ulcerative colitis; VZB, vedolizumab.
[a]After treatment with corticosteroids.
[b]According to Naranjo scale initially described in Naranjo et al. [19].
[c]According to WHO-UMC system described in World Health Organization (WHO)-Uppsala Monitoring Centre [18].
[d]Due to a later positive rechallenge with aminosalicylates.
[e]More data needed for proper assessment.
[f]eGFR calculated with the CKD-EPI 2021 equation.

Table 2. Clinical characteristics of cases included in systematic review of AIN in patients with IBD treated with vedolizumab.

Author, year	Dose/dose interval vedolizumab (mg/w)	Aminosalicylates[a] (yes/no)	Other concomitant drugs	Symptoms	Biopsy findings	Main laboratory findings
Bailly, 2018	300/NA	No	None	Vomiting, asthenia, fever, myalgia, pyoderma gangrenosum	AIN with interstitial edema, interstitial infiltrate of lymphocytes, plasma cells, histiocytes, granuloma formation.	CRP 130 mg/L, WBC 14.2×10^3/µL Eosinophilia, neutrophilia
Jahan, 2022	NA	Yes	None	Calf pain	AIN	NA
Kepley, 2021 (M)	NA	Yes	Budesonide, PPI	Fever and chills	Acute and chronic TIN with severe interstitial fibrosis, tubular atrophy and focal global glomerulosclerosis.	NA
Kepley, 2021 (F)	NA	Yes	Losartan, PPI	NA	Acute and chronic TIN with eosinophils	NA
Muzib, 2020	300/8	No	NA	None	Focal degenerative changes in tubules consistent with mild ATN. AIN with interstitial infiltrates with mononuclear cells and frequent eosinophils	Hematuria and leukocyturia, nitrite negative.
O'Leary, 2022	NA	No	None	Fever, malaise, nausea	AIN with interstitial infiltrate of lymphocytes	NA
Simpson, 2023	300/6	No	Budesonide, calcium + vitamin D	Fever, malaise, myalgia	AIN with interstitial fibrosis and tubular atrophy. Interstitial infiltrate of lymphocytes, plasma cell, macrophages	WBC 14.3×10^3/µL Erythro- and leukocyturia.
Subhaharan, 2022	NA/8	No	None	Right flank pain	AIN with interstitial infiltrates of lymphocytes and occasional eosinophils.	CRP 74 mg/L, WBC 103×10^3/µL, neutrophilia, Hb 166 g/L, elevated ANCA.
Zhang, 2020	300/8	No	NA	NA	AIN with interstitial infiltrate of lymphocytes with tubulitis.	NA

AIN, acute tubulointerstitial nephritis; ANCA, anti-neutrophil cytoplasmic antibody; ATN, acute tubular necrosis; CD, Crohn's disease; Cr, creatinine; CRP, C-reactive protein; CS, corticosteroids; F, female; IBD, inflammatory bowel disease; M, male; NA, data not available; PPI; proton pump inhibitor; TIN, tubulointerstitial nephritis; UC, ulcerative colitis; VZB, vedolizumab; WBC, white blood count; W, weeks.
[a]Concomittant treatment with any of the following: mesalamine (mesalazine, 5-aminosalicylate), sulfasalazine.

not primarily designed to evaluate. For this reason we did not use any quality assessment tool and instead commented quality and completeness of the case reports in the 'Discussion' section.

Analysis methods

This study was a systematic review of existing literature without meta-analysis of collected data. Results were presented as systematized descriptive clinical data on individual cases, or when applicable, on a generalized level. Laboratory data were reported with different units in different studies. To make measurements comparable, we converted mg/dL to mg/L or µmol/L by using a converting factor based on molecular weight [17]. The causality of the adverse drug reaction in relation to vedolizumab was evaluated in each reported case by the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system [18] and the Naranjo Adverse Drug Reaction (ADR) Probability Scale [19]. The WHO-UMC-system has been developed as a practical tool for causality assessment of case reports in pharmacovigilance. It takes into account clinical and pharmacological aspects of each reported case, as well as quality of the presented documentation [18]. The Naranjo ADR probability scale was developed to standardize the causality assessment of ADRs and is used in clinical trials and routine clinical practice [19,20].

Ethics

This was a study of existing literature and therefore no ethical permission was needed.

Results

We screened titles and abstracts for 1473 publications (Figure S1). A total of 32 publications were identified as relevant for inclusion and read in full-text [9–11,21–49]. Additionally, 38 publications were identified from the publications reference lists of these [7,50–86]. The majority of these were pivotal or observational efficacy and safety studies of vedolizumab. None of them were included after full-text screening. A total of 62 publications were excluded (reasons for exclusion: no data on AIN, $n=55$ [7,21,23–27,29–32,35–39,42–44,46,47,50–52,55,56,58–86]; insufficient data on AIN, $n=2$ [45,64]; overlapping population, $n=4$ [22,48,53,54]; and article not retrievable, $n=1$ [57]. Remaining eight publications [9–11,33,34,40,41,49], all case reports, comprised a total of nine cases of potentially vedolizumab-associated AIN which were included in descriptive analysis. Three patients had CD and six UC. The majority were females ($n=6$). Mean age at AIN onset was 36 years (range: 19–58). IBD disease duration ranged between 1 and 17 years (missing data, $n=5$). No kidney disease prior to AIN onset was reported, except for two patients with nephrolithiasis

before AIN (missing data, $n=3$). All nine cases of AIN were biopsy-confirmed. Detailed information on included studies and clinical characteristics of each case are reported in Tables 1 and 2.

Four patients received the dosage of 300 mg per administration (missing data, $n=5$) with dose intervals of 6 ($n=1$) [9] or 8 weeks ($n=3$) [10,40,49] (Table 2). Five patients received intravenous vedolizumab [9,11,33,40,49] (missing data, $n=4$). Onset of AIN after first administered dose of vedolizumab ranged from a few hours to 12 months (mean = 7 months), (missing data, $n=2$ [34] (Table 1). Concomitant medical treatment was reported in seven patients (missing data, $n=2$ [40,49]. Three out of nine had concomitant treatment with aminosalicylates, and two with proton pump inhibitors (PPIs) when AIN occurred (Table 2). Four patients had previously been treated with anti-TNF agents and/or ustekinumab [9–11,33], while two patients had no previous exposure at all to biological therapies [34] (missing data, $n=3$).

Symptoms reported included fever, malaise, myalgia, nausea, vomiting, and flank pain. Fever was the most common symptom, present in four out of nine patients [9,11,34,41]. In three patients, systemic or other symptoms [10,33,40] were absent (Table 2). In addition to systemic symptoms, pyoderma gangrenosum was reported in one patients [11]. In two cases, absence or presence of symptoms were not reported [34,49].

Laboratory findings were heterogeneously reported. CRP and WBC was only reported in three cases, with a mean CRP of 92 mg/L (range: 71–130 mg/L) and mean WBC of $12.9\times10^3/\mu$L (range = $10.3–14.3\times10^3/\mu$ L) [9–11]. Mean creatinine level at time of suspicion of AIN was 210… mol/L (range = 105–410… mol/L). Elevated eosinophils was found in one patient (0.6×10^3/… L) [11], not elevated in two patients [9,10], and not reported in the remainder of patients. Leucocyturia was observed in four out of nine patients [9,11,40,41].

Eight patients were treated with corticosteroids for AIN [9–11,33,34,40,41,49]. Most frequently reported dose ($n=2$) [9,10] was prednisone 40 mg, tapered over weeks to months (missing data, $n=5$). Three patients were rechallenged with vedolizumab. Of these, two were rechallenged while on corticosteroids [11,41]. One did not relapse with AIN after seven subsequent doses of vedolizumab [11], while one relapsed [41]. One patient did not receive corticosteroids during rechallenge and relapsed with AIN after one year on vedolizumab [34].

Permanently impaired kidney function was reported in five out of nine patients [9,33,34,41,49] (missing data, $n=2$). None required dialysis or kidney transplantation during the reported follow-up. Full renal recovery within four weeks was observed in two out of nine patients [10,11]. A summary of each reported case is included in the Supplementary material.

We assessed the potential causality between treatment with vedolizumab and AIN according the Naranjo scale [18] and WHO-UMC system [17] for adverse drug reactions. We found that according to the Naranjo scale, all nine cases were estimated as 'possible' or 'probable' adverse drug reactions, while according to the WHO-UMC system six cases [9–11,40,41,49] were estimated as 'possible' or 'probable'. In the WHO-UMC system two cases were assessed as 'unlikely' [33,34], and one case [34] was 'unclassifiable' (due to lack of data to allow complete assessment) (Table 1).

Additionally, we searched the WHO pharmacovigilance database VigiBase [13] for adverse drug reaction reports related to interstitial nephritis. The search yielded 56 reports of tubulointerstitial nephritis (out of a total 32,220 adverse drug reaction reports for vedolizumab) up until 4 April 2023. These reports do not always include assessment of potential causality between treatment and adverse drug reactions, and it is unknown if the nine cases we report are included among them. In the Swedish pharmacovigilance database BiSi [14] we identified six reports of kidney and urinary disorders of which five cases were reported as AIN potentially associated with vedolizumab up until 1 April 2023. In two of six reports from BiSi the patients had concomitant treatment with aminosalicylates. All reports from BiSi are included in the 56 reports in VigiBase. Of note, it is not possible to determine whether any of the reports in VigiBase and BiSi include patients with other treatment indications than IBD.

Discussion

To the best of our knowledge, this is the first systematic review to report about AIN in patients with IBD treated with vedolizumab. We identified nine cases of AIN potentially associated with vedolizumab published up until early 2023.

Pathophysiology of drug-induced AIN

It is estimated that up to one fifth of all cases of acute kidney injury is caused by AIN [87,88] Of all AIN cases, approximately 70% are attributable to drugs and the remainder to autoimmune disease, infection or idiopathic. Common culprit drugs in AIN are antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs). However, in IBD, aminosalicylates are the drugs most commonly associated with AIN [8,89]. The prevalence of AIN have been estimated to between 3-10% in general kidney biopsies [87]. To our knowledge, there is no data on the overall incidence and prevalence of AIN in the IBD population. Studies of IBD patients undergoing kidney biopsy show that about 10% are diagnosed with AIN [90–92] and approximately 5% of kidney biopsies in IBD patients showed signs of granulomatous interstitial nephritis linked to aminosalicylates [93].

The development of drug-induced AIN represent a type B adverse drug reaction (i.e., idiosyncratic reaction) that is not believed to be dose-dependent [8]. One theory behind the mechanism of drug-induced AIN is that the drug forms haptens with the tubular basement membrane, or mimicks an antigen normally present in basement membrane, that in turn elicit an immune response. The drug itself could also possibly deposit in the interstitium and cause an immune reaction [89].

AIN resembles a type IV (delayed) hypersensitivity reaction mediated by T-cells. In AIN there is an absence of immunofluorescence stainings for immunoglobulins or complements, which makes the humoral immune response less likely to be involved [8,89]. In rare cases, active IBD has

itself been linked to AIN, which has sometimes been described as an extraintestinal manifestation of IBD in patients that are aminosalicylate-naïve [93–95].

Among biological agents, mainly immune checkpoint inhibitors have been associated with AIN [96,97]. Although widely used in IBD, only a few cases of AIN linked to the anti-TNF agents adalimumab [98,99] and infliximab [100,101] have been reported in the literature. For these agents, around 100 and 50 cases of tubulointerstitial nephritis have been reported in VigiBase, respectively [13]. To date, the sphingosine-1-phosphate receptor agonist ozanimod used in UC, which partly share mechanism of action with vedolizumab by controlling leukocyte trafficking to the intestine, does not have any cases of AIN reported in literature or in VigiBase [102]. No reports of AIN associated with ustekinumab or Janus kinase inhibitors were found in the literature, although a few cases have been reported in VigiBase [13]. It is important to note that reports in VigiBase have not always undergone a full case causality assessment and should therefore be interpreted with caution.

The emergence of AIN cases associated with immune checkpoint inhibitors suggests a possible loss of tolerance to a native antigen expressed by tubular or other renal cells [97]. Since AIN has been reported in cases with both chimeric monoclonal antibodies like infliximab [101] and human antibodies like adalimumab [99], the degree of humanization of the antibody possibly plays less of a role in AIN.

The expression of antigens in the renal tubulointerstitium that may induce nephritis is likely counterbalanced by protective mechanisms, mainly involving suppressor T-cells [89]. A possible theoretical explanation to AIN when drugs alter the immune response, is modulation of T-cell activity decreasing the immunologically protective effects that otherwise counteract the effects of drugs with AIN-inducible properties, for example aminosalicylates and PPIs. However, as vedolizumab mainly is a gut-selective drug with limited or no effect on levels of circulating T-cells, granulocytes [103], nor on T-cell-dependent antigen response in animal studies [104], this mechanism seems less likely. In our study, three out of nine patients had concomitant treatment with mesalazine and/or PPI during time of AIN diagnosis. However, because vedolizumab was the sole treatment in three out of nine patients in this review, we believe that vedolizumab by yet unknown mechanisms could potentially induce AIN in susceptible individuals.

Diagnosis and patient characteristics

AIN is a histopathological diagnosis, thus a kidney biopsy is required for diagnosis. Histopathological features of AIN include interstitial edema, inflammation, and tubular disruption with a predominance of T lymphocytes, macrophages and a smaller number of eosinophils and plasma cells [8,89]. Interstitial fibrotic changes have been observed already after 7–10 days of inflammation [89]. This could explain why kidney impairment persisted even though vedolizumab was rapidly withdrawn in most of patients in this study. Kidney biopsy findings of patients included in our review were mainly consistent with the histological features seen in AIN, although one patient also had concomitant acute tubular necrosis (ATN) [40] (Table 2).

Symptoms and laboratory findings

The clinical presentation of AIN is heterogenous which was illustrated by the varying symptoms of patients included in our study. According to literature, some patients may be asymptomatic, while others present with distinct symptoms such as nausea, vomiting, and malaise [8]. The classic triad of clinical signs and symptoms comprises rash, fever and eosinophilia, although rarely seen together in the same patient. In our review, this triad was only present in one patient [11], while four patients had fever and/or eosinophilia [9,11,34,41].

In cases of AIN, creatinine is most often elevated and the patient is typically non-oliguric [8]. Elevated levels of creatinine were seen in the majority of cases in our review at AIN onset. After treatment for AIN, levels decreased but remained above normal levels in several patients, although follow-up time in some studies was not long enough to capture the long-term effects on creatinine levels. Eosinophilia, elevated WBC, and increased CRP was seen in a few patients. In all, the laboratory findings are consistent with what could be anticipated in AIN.

Treatment and outcome

Eight cases of AIN were treated with corticosteroids. It seems like the mainstay treatment for AIN with corticosteroids was effective also in AIN caused by vedolizumab with a decrease of creatinine levels, although the majority of patients sustained permanent kidney injury. Immediate termination of vedolizumab and other potential culprit drugs, and prompt initiation of corticosteroids, is of major importance to limit potential permanent reduction of the kidney function. Three patients in our review were rechallenged with vedolizumab, and two were on concomitant corticosteroid treatment at time of rechallenge. One rechallenge was successful [11] while the other two resulted in a rise in creatinine [34,41]. Whether rechallenge could be performed or not depends on several clinical aspects related to the individual case, such as remaining treatment options and the initial response to treatment of AIN. No clear conclusions can be made from the three cases of rechallenge in our study.

Case causality and predictors of AIN

It can be challenging to establish causality between treatment and AIN, especially in case of concomitant treatment with drugs known to cause AIN. To establish a causal link, several factors must be examined, such as the temporal relationship between drug exposure and AIN onset, and exclusion of alternative explanations.

Generally, time to onset of acute kidney injury in AIN after drug exposure seem to vary between causative agents. Time to onset of AIN after first exposure of antibiotics is usually short, days to weeks, while time to onset is longer for PPIs and NSAIDS, usually one week to 9 months for PPIs and 6 to 18 months for NSAIDs

[8,97]. For aminosalicylates, AIN onset usually occur during first year of treatment [8] but cases after 4 years have been described [105]. In our review, the seven publications reporting time to onset, the mean time was 7 months (range 0–12 months) which is consistent with reports of AIN associated with other drugs.

In cases of concomitant use of common culprit drugs causing kidney complications causality between one of these treatments and AIN could be a challenge to establish. Three out of nine patients in our study had concomitant treatment with PPI or aminosalicylates at the time of AIN onset. Whether PPI or aminosalicylates alone or in combination with vedolizumab caused AIN is difficult to determine.

The causality assessments according to the Naranjo scale and WHO-UMC system were disconcordant in several of the reported cases. According to the Naranjo scale, all cases were assessed as 'possible' or 'probable'. In general, the WHO-UMC system resulted in a more heterogenous causality assessment between the cases, where three cases were classified as 'unlikely' or 'unclassifiable'. As an illustration of this, assessment of one of the cases reported by Kepley et al. resulted in 'probable' according to the Naranjo scale, while the WHO-UMC system resulted in 'unlikely'. Studies have found low agreement between the two scales [20]. The WHO-UMC system has an inherent tendency for subjective variations in causality assessments while Naranjo scale is designed to reduce dissimilarity between causality assessments but lacks the possibility to take confounding variables into consideration, e.g., concomitant medications or underlying disease [20]. After assessment of all available data in each case, our impression is that the WHO-UMC scale reflects a more accurate case causality assessment of included cases.

The limited number of cases in this review did not allow statistical analyses of potential predictors of AIN in patients treated with vedolizumab. When looking for commonalities between the cases, we were not able to identify any specific patient characteristics, such as age, sex, IBD subtype, dosage or dosing interval of vedolizumab that could predict AIN. In previous studies of kidney complications in patients with IBD that have undergone kidney biopsy, higher risk of tubulointerstitial nephritis has been indicated to be linked to older age, higher baseline eGFR [92] and possibly also female sex [91]. However, these findings should be interpreted with caution due to comparably small sample sizes of the studies. Nevertheless, it seems reasonable to assume these factors also could play a role in the risk of developing AIN caused by vedolizumab, although evidence for such claim currently is lacking.

Strengths and limitations

Our study has some strengths, such as the comprehensive search of four major medical literature databases and the structured and systematized extraction of data from included studies. We also searched pharmacovigilance databases to contrast our findings and used established causality assessment scales to assess to what degree of certainty vedolizumab was the causative agent in each case. We acknowledge some limitations. First, some studies included in our review were only published as abstracts, thus in some cases lacking granular clinical information. Second, we only performed descriptive analysis since any meaningful statistical analysis was not possible due to the low number of cases. Third, our assessment of case causality based on the WHO-UMC and Naranjo scales was limited by lack of available data. Finally, due to underreporting of adverse drug events we cannot draw any conclusion about the real-world prevalence of AIN associated with vedolizumab based on our findings and reported cases in pharmagovigilance databases.

Conclusions

After reviewing existing literature, we found nine cases of AIN in patients with IBD during treatment with vedolizumab. Most cases were assessed to be possible or probable adverse drug reactions according to the Naranjo and WHO-UMC scales. When searching pharmacovigilance databases, roughly 50 reports of AIN during treatment with vedolizumab were found, which lends support to the notion of vedolizumab as a potential causative agent of AIN. In all, our findings suggest that vedolizumab, although rarely, can potentially cause AIN in patients with IBD. Based on the cases described in this systematic review, we cannot identify any clear patterns, neither in patient characteristics, such as age and sex, nor in factors related to dosage or dosing interval of vedolizumab. Nevertheless, we believe that awareness of laboratory findings and symptoms consistent with AIN, along with monitoring of the kidney function, could be warranted in patients with IBD treated with vedolizumab.

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Author contributions

Guarantor of the article: AF and PF had full and unrestricted access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analyses.

AF: Drafting study protocol, data collection and review of publications, analysis and interpretation of collected data, and drafting of the manuscript; PF: Review of study protocol, data collection and review of publications, analysis and interpretation of collected data, and drafting of the manuscript; AS: Database search, review of study protocol, analysis and interpretation of collected data, and critical revision of the manuscript; MK: Review of study protocol, analysis and interpretation of collected data, and critical revision of the manuscript. SR: Study supervision, review of study protocol, analysis and interpretation of collected data, and critical revision of the manuscript.

Disclosure statement

AF served as speaker and advisory board member for Janssen Corporation and Tillotts Pharma. PF, AS, MK and SR declares no conflicts of interest related to this study.

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