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DRUG SAFETY EVALUATION

An update on the safety of long-term vedolizumab use in inflammatory bowel disease

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ABSTRACT

Introduction: Vedolizumab (Entyvio) is a humanized monoclonal antibody that disrupts the interaction between α4β7 integrin on circulating T-lymphocytes and MAdCAM-1 on the vascular endothelium to prevent their egress to sites of gut inflammation. It has proven therapeutic efficacy for the treatment of moderate-to-severe Crohn's disease, ulcerative colitis, and pouchitis.

Areas covered: This narrative review assesses the safety profile of vedolizumab from the registration trial programs, open-label extension studies, observational real-world data, and pooled safety analyses. This includes an evaluation of the long-term overall safety in special populations typically under-represented in clinical trials.

Expert opinion: Vedolizumab is an effective therapy for inflammatory bowel disease with a well-established safety profile. No unexpected long-term safety signals have been identified. Safety data in pregnancy, in pediatric and elderly populations, in patients undergoing surgery, and in patients with a prior history of cancer are reassuring. Due to its safety merits, we propose that vedolizumab is an excellent candidate for advanced combination treatment with an anti-cytokine approach using another biologic or novel small molecule inhibitor. This is important in patients with medically refractory IBD, in patients at high risk of developing disease-related complications, or in patients with concomitant uncontrolled immune-mediated inflammatory diseases.

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1. Introduction

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), are chronic, immune-mediated inflammatory diseases (IMID) that have a profound impact on patient quality of life. With an increasing incidence and prevalence worldwide, UC and CD follow a relapsing and remitting disease course, which untreated leads to cumulative intestinal damage and a significant risk of long-term burdensome complications. The panoply of drugs currently available for the treatment of IBD aim to achieve induction and maintenance of durable remission. This expansive array of biologics and small molecule inhibitors, broadly speaking, works in two main ways; to attenuate the signaling of one or more pro-inflammatory cytokines, or to prevent leukocyte migration to sites of inflammation.

Vedolizumab (previously known as MLN0002), is a gut selective anti-lymphocyte trafficking anti-integrin. It has demonstrated efficacy for the treatment of moderate-to-severe UC, CD, and most recently pouchitis. It first obtained its regulatory approval just under a decade ago following the successful GEMINI phase III clinical trial program [1,2]. The gut-selective mechanism of vedolizumab has been the focus of significant interest since it was first launched given the advantages conferred over other systemically acting advanced therapies in this arena. This review provides a detailed update and overview on the long-term safety profile of vedolizumab, particularly in special populations.

2. Mechanism of action and pharmacology

Vedolizumab is a recombinant humanized monoclonal antibody (mAb) directed against the α4β7 integrin on circulating leukocytes. This prevents the interaction with cell adhesion molecules on the vascular endothelium and subsequent infiltration into inflamed intestinal tissues, a key pathogenic mechanism in IBD (Figure 1) [3]. Integrins are transmembrane glycoprotein receptors with an extracellular ligand-binding adhesion site and an intracellular cytoplasmic receptor, which facilitate bi-directional cellular signaling [4]. Integrins consist of a heterodimeric, non-covalent complex of an α- and β-subunit; in total, there are 18 α-subunits and eight β-subunits, which can pair to form any one of the 24 known

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Article highlights

- The gut-selective mechanism offers a safer alternative to most of the other available advanced therapies, which act systemically by targeting one or more cytokines.
- Long-term safety has been demonstrated through the GEMINI long-term safety study over 8 years, a global four-year post-marketing surveillance study with >200,000 patient-years of vedolizumab exposure, and a multitude of real-world observational cohort studies.
- Comparative safety data against other advanced therapies in clinical trials and the real world appear to favor vedolizumab as the safer agent.
- Vedolizumab has also demonstrated a favorable safety profile in special populations that are under-represented or excluded from clinical trials. No safety signals were identified with the use of vedolizumab in elderly patients, and there were no adverse pregnancy outcomes in vedolizumab-treated patients and their infants.
- Patients with a history of prior malignancy do not have an increased risk of *de novo* cancer or cancer recurrence with vedolizumab, although there are insufficient data to draw any conclusions on its use in those with active malignancy.
- Given the robust safety profile, vedolizumab has been proposed as an excellent candidate for advanced combination treatment (alongside another biologic or novel small molecule) in patients with refractory IBD, in those patients at high risk of developing complications, or in patients with concomitant uncontrolled immune-mediated inflammatory disease(s).
- The IBD-Cancer And seRious infections in Europe (I-CARE) study is a pan-European, prospective observational study that seeks to assess the long-term safety of advanced IBD therapies and has enrolled >10,206 patients to date. Safety outcomes from this large-scale trial, which includes 894 vedolizumab-treated patients, are eagerly awaited.

heterodimers. Of these, eight are leukocyte cell-adhesion integrins, which have a pivotal role in regulating inflammation and infection. Circulating leukocytes expressing this integrin subclass adhere to ligands on vascular endothelial cells and migrate across this barrier, thereby mediating the inflammatory response at the site of inflammation [5]. Leukocyte cell-adhesion integrins have been the focus of therapeutic blockade over the past two decades and have led to regulatory approval of several drugs across a range of immune-mediated and non-immune mediated diseases [6].

The integrins involved in immune cell homing to the gastrointestinal tract include α4β1, α4β7, and αEβ7 (Figure 1). Effector and regulatory T-cells expressing the α4β7 integrin binds to MAdCAM-1, whereas those expressing α4β1 interact with vascular cell adhesion molecule-1 (VCAM-1) [7,8]. Antagonists of integrin–adhesion molecule interactions can target either the α4β7 integrin heterodimer, the α4 integrin, the β7 integrin, or MAdCAM-1. Natalizumab, a pan-α4 antagonist inhibiting ligand binding to α4β1 and α4β7, was first approved in 2004, but widespread use has been limited by the potential risk of progressive multifocal leukoencephalopathy (PML). More recently, carotegrast methyl (AJM300), an orally administered small molecule α4 integrin antagonist, received approval in Japan for the treatment of moderate UC [9]. However, the most widely used anti-integrin for moderate-to-severe IBD over the past decade is vedolizumab, which first received regulatory approval in May 2014. Vedolizumab binds exclusively to α4β7 and not to other α4 or β7 heterodimers and therefore lymphocyte trafficking to other tissues, e.g. the central nervous system, is unaffected.

Vedolizumab is administered by intravenous infusion at the licensed dose of 300 mg every 8 weeks following three induction doses over 6 weeks in both UC and CD. Maintenance treatment with a 108 mg subcutaneous injection every 2 weeks is also effective after two intravenous induction

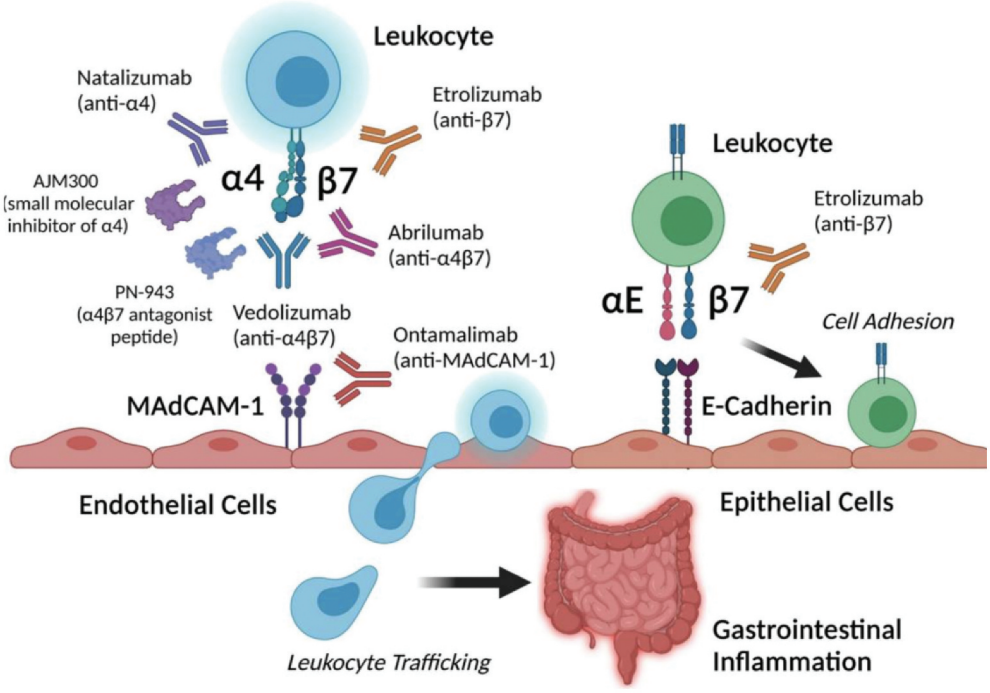

Figure 1. Overview of available and investigational anti-integrin therapies for the treatment of inflammatory bowel disease.

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infusions [10,11]. Single dose and multiple dose pharmacokinetics and pharmacodynamics have been analyzed in healthy volunteers and those with IBD [12,13]. Vedolizumab is predominantly cleared through a linear elimination pathway by proteolytic degradation and nonspecific endocytosis and has a serum half-life of 26 days. It maximally saturates α4β7 receptors on peripheral serum lymphocytes at all measurable serum concentrations [14]. Long-term vedolizumab use is associated with low rates of anti-drug antibody formation and negligible clinical significance [15].

3. Overview of vedolizumab safety data

3.1. Clinical trials

Safety is an essential factor when selecting an advanced therapy in patients with IBD. The two factors that determine safety of a drug include the intrinsic immunosuppressive properties of the drug and its therapeutic efficacy in achieving disease control to obviate the need for corticosteroids and minimize disease-related complications. The safety of vedolizumab has been assessed in randomized placebo-controlled trials, post-marketing surveillance analyses, and in real-world observational cohorts. Table 1 provides a safety overview from the GEMINI clinical trial program.

The short-term safety and tolerability of vedolizumab was first confirmed in the phase III GEMINI registration trials for up to 1 year [1,2]. This was followed by integrated analyses of six clinical trials of vedolizumab; two phase II studies and four phase III studies, which included interim results from the GEMINI long-term safety (LTS) study [16]. This included 2830 patients and 4811 person-years (PYs) of vedolizumab exposure between 2009 and 2013 and showed low incidence rates of serious infections, infusion-related reactions, and malignancies [16]. The final results from the GEMINI LTS study, an open-label phase III study of patients receiving four weekly vedolizumab, were published in September 2020 [17]. This is the largest trial of vedolizumab-treated patients with the longest follow-up duration to date and included 2243 IBD patients (1349 CD, 894 UC) between 2009 and 2017 with 7999 PYs of vedolizumab exposure [17]. Serious adverse events (SAE) in UC and CD were reported in 31% and 41% of patients with treatment discontinuation due to adverse events (AE) occurring in 15% and 17%, respectively. Most of SAEs were related to complications of the underlying disease and only a small proportion overall (UC 4.1%, CD 5.9%) were treatment-related SAEs. No cases of PML attributed to vedolizumab were seen. There were no new safety concerns following the interim analysis, and the findings from this study supported the long-term safety profile of vedolizumab [17]. The VISIBLE clinical trials assessing the subcutaneous preparation as maintenance treatment in UC and CD conducted between 2015 and 2018 identified injection-site reactions in those receiving the drug as the only new safety finding [10,11]. A systematic review and meta-analysis patients of nine vedolizumab RCTs including 4268 patients concluded that vedolizumab was as safe as placebo in terms of risk of SAEs [18].

There is a dearth of head-to-head clinical trials in IBD. VARSITY was a head-to-head study in which the safety and efficacy of vedolizumab was compared against adalimumab [19]. This trial demonstrated that vedolizumab had a lower rate of AEs (63% vs. 69%), SAEs (11% vs 14%), exposure-adjusted incidence rates of infections/100 PYs (23 vs. 35), and serious infections (1.6 vs. 2.2); the only exception was Clostridium difficile infection (1.1 vs. 0.6) where the rate was higher in the vedolizumab treated group [19]. In the absence of head-to-head comparator studies, network meta-analyses of randomized trials can be informative and provide indirect comparisons. For the treatments for UC but not CD, vedolizumab has repeatedly been ranked as the safest drug in terms of AEs and SAEs [20–22].

3.2. Real-world observational studies

Due to stringent inclusion criteria, among other factors, clinical trials have poor external validity and may not be suitable for effectiveness research, highlighting the importance of complementary real-world data [23,24]. A post-marketing study of all adverse events received by Takeda after drug approval in 2014 were held on the Vedolizumab Global Safety Database and later analyzed [25]. With 208,050 PYs of vedolizumab exposure in 32,752 patients, there were 3580 (10%) SAEs reported for UC and 5230 (14%) SAEs for CD. SAEs related to active IBD, Clostridium difficile infection, and pneumonia were the most frequently recorded. Again, no cases of PML were reported. Of all reported AEs, 87% were non-serious and vedolizumab was continued in 81% of these cases, indicating high treatment persistence and suggested AEs were non-treatment related or transient. The most frequently reported AEs included symptoms related to active IBD, disease progression due to drug ineffectiveness, and expected side effects listed on the product label, including headache, arthralgia, and fatigue [25]. The AE profile from this study was consistent with the GEMINI LTS study.

Macaluso et al. recently assessed the safety and effectiveness of vedolizumab in a comprehensive systematic review

Table 1. Vedolizumab safety overview from pooled analyses of real-world studies[26] and the GEMINI clinical trial program[16].

Outcome	Real World Studies IR/100 PY (95% CI)	GEMINI Clinical Trials IR/100 PY (95% CI)
Patients studied, n	Total: 25678 UC: 12015 CD: 13663	Total: 2,884 UC: 1,114 CD: 1,770
Adverse events	34.6 (29.5–39.8)	247.8 (229.8 to 265.8)
Serious adverse events	8.1 (6.3–9.8)	2.0 (18.5 to 21.5)
Any infection	7.7 (6.4–8.9)	63.5 (59.6 to 67.3)
Malignancies	0.3 (.2–.4)	0.1 (18 malignancies total)

and meta-analysis of 88 observational studies including 25,678 patients (UC 12 015, CD 13 663) [26]. Safety data were extractable in 46 studies, and the pooled estimate of incidence rate of AEs was 34.6 per 100 PYs. However, the pooled estimated incidence rate of SAEs was much lower at 8.1 per 100 PYs, and not too dissimilar from the GEMINI clinical trial program [26]. Meta-regression did not identify variables associated with safety outcomes. Expectedly, the pooled results had a high degree of heterogeneity due to the varied methods and rigorousness of collecting safety data across studies, which in turn impacts data reliability. Nonetheless, the safety data were consistent with the known safety profile of vedolizumab with low rates of serious infections and malignancy. These findings were consistent with those of an earlier systematic review and meta-analysis of real-world data [27]. There are a number of real-life comparator studies comparing the safety and effectiveness of vedolizumab against other advanced therapies and these will be below.

4. Safety outcomes

4.1. Infection

In an integrated analysis of the phase II, III, and IV GEMINI clinical trials, there was no increased risk of any infection or serious infection associated with vedolizumab exposure [16]. The incident rate of serious infection was 4.3 per 100 PYs for the vedolizumab-exposed group and 3.8 per 100 PYs for the placebo group. No associated link between vedolizumab and tuberculosis has been identified, and the requirement for screening was proposed by extrapolating recommendations for anti-TNF agents [28]. Enteric infection incidence rates, including clostridium difficile, were all ≤0.8/100 PYs. In the final analysis of the open-label GEMINI LTS study of 2243 patients, no new infection trends were recognized with low rates of serious systemic and enteric infections [17]. Table 2 provides a summary of the incidence of infections in the clinical trial program, stratified by disease type. These reassuring findings contrast with other agents such as adalimumab, where rates of serious infection in the clinical trial program were approximately twice that reported for vedolizumab. Indeed, in VARSITY, a double-blind, head-to-head study of patients treated with vedolizumab or adalimumab, vedolizumab was associated with lower rates of overall and serious infections than adalimumab (23.4 vs 34.6/100 PYs and 1.6 vs 2.2/100 PYs, respectively), although these changes did not reach significance [19]. In the absence of other head-to-head studies of vedolizumab, indirect comparisons in network meta-analyses did not show that vedolizumab was more or less likely to lead to infections compared to other advanced therapies [22].

Comparative safety data across advanced therapies were assessed in a systematic review and meta-analysis comprising 20 head-to-head studies, including two RCTs [29]. This showed that vedolizumab was associated with a 32% reduced risk of serious infection compared to anti-TNFα agents in patients with UC (11 cohorts; OR, 0.68; 95% CI, 0.56–0.83) but not CD (9 cohorts; OR, 1.03; 95% CI, 0.78–1.35) [29]. In CD, ustekinumab appeared to be more favorable vs. vedolizumab and had a 60% lower risk of infection, although only three cohorts were studied (OR, 0.40; 95% CI, 0.17–0.93). There were insufficient data to make reach a conclusion for the risk of serious infection between ustekinumab and vedolizumab for the treatment of UC. While not comparative in nature, other real-world data were comprehensively summarized in an up-to-date meta-analysis of observational studies published in 2023, which demonstrated low rates of infection; the pooled estimates of incidence rate of infections (reported by 50 studies) was 7.7 (95% CI 6.4–8.9).

The I-CARE study (IBD-Cancer And seRious infections in Europe) is a pan-European, prospective observational study that seeks to assess the long-term safety of advanced IBD therapies and has enrolled 10,206 patients over a 3 year period [30,31]. With a longitudinal standardized follow-up, the findings from this large-scale collaborative endeavor of 15 countries are likely to have practice changing implications. In total, there were 894 patients that were established on vedolizumab at baseline and outcomes with respect to safety, including infections, are eagerly awaited [30,31].

4.2. Cancer

The topic of malignancy and IBD therapy raises two issues that need careful assessment. Firstly, the risk of cancer attributed to the drug used to manage IBD and secondly, the safety of using the treatment in IBD patients with previous or active malignancy.

Current evidence does not show an increased risk of malignancy with vedolizumab. The GEMINI LTS study, together with the global post-marketing data, recorded a low number of malignancies for patients treated with vedolizumab and the observed malignancy rate of 0.1/100 PY was consistent with the background IBD patient population [32]. With >200,000 PYs of vedolizumab exposure, the most frequent malignancy reported were those arising from the lower gastrointestinal tract [32]. Findings in this regard from 53 observational cohort

Table 2. Incidence of infections in the GEMINI clinical trial program stratified by disease type[17].

Outcome	UC, $n = 894$ N (%), IR/100 PY	CD, $n = 349$ N (%), IR/100 PY
Total infections	591 (66), 38.9	937 (70), 49.2
Serious infections	61 (7), 1.8	146 (11), 3.4
Nasopharyngitis	252 (28), 9.4	342 (25), 9.4
Upper respiratory tract infections	166 (19), 5.6	213 (16), 5.3
Abdominal/GI infection	122 (14), 4.7	162 (12), 4.6
Clostridium infections	26 (3), 0.9	21 (2), 0.5

studies were similar; the pooled estimates of incidence rate of malignancy per 100 PY was 0.3 (95% CI: 0.2–0.4, $I^2 = 0\%$) [26].

Vedolizumab does not appear to increase the risk of cancer recurrence in patients with prior malignancy. The largest study investigating this was a retrospective review by Vedamurthy et al., which included 96 patients with current or prior malignancy who were subsequently commenced on vedolizumab [33]. There was no increased risk of new or recurrent cancers in the vedolizumab group when compared with prior malignancy patients who received anti-TNFα agents or no advanced therapy [33]. Additional reassurance is provided by two smaller studies of patients with prior malignancy, which also do not report increased risks of new or recurrent cancers [34,35]. The ongoing I-CARE study described above will provide unique insights into the long-term risks of cancer with biologics in IBD [30,31]. At present, there are insufficient data regarding the use of vedolizumab in active malignancy and decisions should be made on a case by case basis involving the wider multi-disciplinary team. These studies highlight the safety of vedolizumab in this setting and are in line with recently published ECCO guidelines, which state that current evidence does not show an increased risk of malignancy in patients with IBD treated with vedolizumab but acknowledges that longer-term data are lacking. Further, the guidelines also state that IBD patients with a history of prior malignancy do not appear to have an increased risk of cancer recurrence or new cancer when treated with vedolizumab [36].

4.3. Post-operative complications

Surgical intervention for patients with IBD is common and indicated invariably for disease progression and disease-related complications. Post-operative complications can result in morbidity, mortality, increased length of hospitalization, and costs. Pre-operative use of certain drugs for IBD, such as corticosteroids for example, has been shown to increase the risk of post-operative complications [37].

For vedolizumab, several studies have reported conflicting results. In two studies, Lightner et al. previously found that vedolizumab administered within 12 weeks of treatment led to significantly higher rates of surgical site infections, compared to patients who received anti-TNFα agents or no advanced therapy [38,39]. Furthermore, Novello et al. found that when compared to pre-treatment with ustekinumab, vedolizumab-treated patients had an overall higher post-operative complication rate, including rates of ileus and need for re-operation. While the largest published recent systematic review and meta-analysis of 709 vedolizumab-treated patients did not show an overall difference in post-operative complications (OR = 1.25, $p = 0.43$), there was an increased risk of surgical site infections (OR = 2.24, $p = 0.02$), mucocutaneous separation (OR = 4.69, $p = 0.03$), and post-operative ileus (OR = 2.16, $p < 0.001$) [40]. Conversely, several studies show no increase in post-operative complication rates for patients who received vedolizumab prior to surgery, which includes the post-marketing experience from the GEMINI trials [41–43]. Two meta-analyses, albeit with fewer studies and number of vedolizumab-treated patients than the aforementioned meta-analysis, supported this encouraging finding and showed no difference in complication rates.

Although current data indicate that clinicians should be attentive of protecting the surgical site and monitoring for post-operative ileus, overall, vedolizumab appears to be safe with the most recent ECCO guidelines stating that cessation of vedolizumab prior to surgery is not mandatory [44]. Larger, randomized studies including perioperative drug monitoring are important to provide robust safety evidence for vedolizumab in the surgical context.

5. Special populations

5.1. Pregnancy and lactation

The incidence of IBD is highest during reproductive years, and pregnant patients with active IBD are at an increased risk of spontaneous abortion, preterm birth, low birth weight, and complications during labor [45,46]. This highlights the importance of understanding the safety of IBD therapies in pregnancy to facilitate their use to induce and maintain remission. Vedolizumab, like other mAbs used in IBD, is an immunoglobulin G1 antibody and placental transfer starts at week 16 gestation via the neonatal Fc receptor. Pre-clinical studies in rabbits and primates showed no adverse developmental effects, even when used at supratherapeutic doses [47]. Vedolizumab has also been detected in human breast milk; however, this was only 0.4% to 2.2% of maternal serum concentrations and no adverse findings have been seen in breast-feeding infants [48,49]. Vedolizumab has a molecular weight of 147kD and is thought that this will be destroyed by proteolysis by the infant gastrointestinal tract thereby exerting a negligible impact on the infant.

To date, there have been two prospective and two retrospective studies examining pregnancy outcomes of vedolizumab-treated patients and their infants with reassuring safety outcomes (Table 3). An Israeli study and the US-based PIANO study prospectively examined 24 and 41 patients, respectively,

Table 3. Summary of studies assessing risk of vedolizumab in pregnancy.

Study	Study Type	Pregnancies Studied	Live Births (%)	Stillbirths (%)	Spontaneous Abortion (%)	Medical Interruption (%)	Pre-term Births (%)	Congenital Abnormality (%)
Bar-Gil Shitrit[50]	Prospective	24	63	0	21	8	20	4
Mahadevan**[51]	Prospective	41	75	<1	7	-	10	9
Moens[52]	Retrospective	79	78	1	16	5	16	5
Wils[53]	Retrospective	44	86	0	11	3	16	5

Note: **Data from this study could not be extracted specifically for vedolizumab and are presented for all 869 biologic-treated patients. In this study, biologic, thiopurine, or combination therapy exposure during pregnancy was not associated with increased adverse maternal or fetal outcomes at birth or within the first year of life.

and showed no increase in drug-related AEs to mothers or neonates [50,51]. In the CONCEIVE study, 79 pregnancies were studied in 73 vedolizumab-treated patients and compared to both anti-TNFα-treated and advanced therapy naïve pregnant patients [52]. No significant differences were seen between the groups with respect to spontaneous abortions, live birth rates, birthweight, congenital abnormalities, or neonate infection risk during the first year of life [52]. A retrospective review of French GETAID centers identified 44 patients exposed to vedolizumab which did not identify a negative signal on maternal or neonatal outcomes when compared to those exposed to anti-TNFα drugs [53]. While a systematic review and meta-analysis including studies of vedolizumab-exposed patients suggested increased odds of adverse pregnancy outcomes (OR 2.18, 95% CI 1.52–3.13), it is likely these findings were confounded by disease activity. Final results from the prospective OTIS Vedolizumab Pregnancy Exposure Registry, which seeks to enroll, analyze, and compare 100 vedolizumab-treated pregnant patients against disease and healthy controls, are awaited [54]. The preliminary results for major birth defects presented in abstract form are reassuring [55]. In the most recent ECCO guidelines on pregnancy and lactation, it is advised that patients with active IBD prior to pregnancy, or those with difficult to control disease, vedolizumab should be continued throughout pregnancy. For those in remission, decisions regarding discontinuation should be made on a case-by-case basis [56].

5.2. Pediatrics

Vedolizumab is a safe and effective therapy for adult IBD patients, but its use in pediatric patients remains off-label despite receiving regulatory approval for adults in 2014. Therefore, outcome data in pediatrics are scant and limited to small retrospective cohorts only.

A systematic review of 10 studies, which incorporated 455 pediatric patients, highlighted a safety profile consistent with adult populations [57]. Six percent of patients reported AE with respiratory tract infections, nausea and vomiting, headaches, and fatigue the most commonly reported, in decreasing order of frequency [57].

VEDOKIDS is a prospective, multicenter study that seeks to evaluate the safety, effectiveness, and dosing of vedolizumab in 142 enrolled children with a planned three-year follow-up [58]. So far, only week 14 outcomes have been published and overall, AEs thought 'possibly' or 'definitely' related to vedolizumab were reported in 15% of children with headache, myalgia, and fever the commonest. The vast majority of AEs were mild and only two discontinued therapy due to AEs; one patient had an infusion reaction and one patient had a leukocytoclastic vasculitis, which both recovered after vedolizumab cessation [58]. Long-term data from this study is awaited.

Available data thus far suggest safety of vedolizumab is comparable to adults. Further prospective pediatric studies are needed to assess long-term effectiveness and durability, clinical predictors of clinical and endoscopic remission, and to identify optimum dosing strategies, particularly for those weighing less than 30 kg.

5.3. Elderly IBD population

The increasing incidence and compounding prevalence of IBD in the elderly warrants a careful analysis of the safety of advanced therapies in this age group [59]. Managing older patients with IBD is challenging due to, among other factors, an increased prevalence of age-related co-morbidities, higher risk of malignancy, and polypharmacy with unpredictable adverse events. Further, the evidence base for the safety and efficacy of IBD treatments is limited as less than 6% of patients older than the age of 65 are included in clinical trials [60,61].

Several observational studies have been conducted to assess the safety profile of vedolizumab in the elderly population [62–67]. The frequency of infections in the elderly (>60 years) appears to be increased when compared to younger vedolizumab-treated patients (<40 years) (2% vs. 12%,$p < 0.01$) [67]. The risk of AE also increases in those with more comorbidities (Charlson comorbidity index >2) [65]. A systematic review and meta-analysis pooled these data and included 15 real-world studies of 1978 elderly (aged >60 years) IBD patients on biologics, of which 816 were treated with vedolizumab [68]. The study showed that the adverse event and infection rates were not statistically significantly different among the studied biologics, although a higher rate of infusion/injection site reactions were seen with anti-TNF agents [68]. A more updated meta-analysis including 1314 elderly and 2232 younger patients showed that vedolizumab was equally safe and effective for both populations with no difference in overall infection rates between the two [69].

There are also some comparator studies to be noted, although outcomes with respect to serious infection are mixed. Singh et al. performed a nationwide propensity score – matched comparative study of vedolizumab and anti-TNFα treatment in 754 IBD patients ≥50 years of age and found that vedolizumab was associated with a higher risk of treatment failure (hospitalization and need for surgery) at 1 year, 45.4% vs 34.7%, adjusted hazard ratio [HR] 1.31 (95% CI 1.02–1.69). This study, however, did not demonstrate an additional safety advantage for vedolizumab in older patients as the one-year serious infection risk was insignificant between the two groups, 8.2% vs 8.7%, adjusted HR 1.04 (95% CI 0.58–1.85) [70]. These findings are in direct contrast from those of Kochar et al. who found no difference in treatment effectiveness but a reduced risk of infection-related hospitalizations in those treated with vedolizumab, HR 0.47 (95% CI 0.25–0.86) [71]. Smaller retrospective comparator studies by Pabla et al. and Adar et al. showed no difference in adverse events between the anti-TNFα-treated and vedolizumab-treated cohorts. Despite conflicting comparative data, these data nonetheless affirm the safety profile in an elderly patient group and can be considered a valid option to induce and maintain remission.

6. Expert opinion

The goal of our review was to provide a contemporaneous overview of the long-term safety of vedolizumab using randomized controlled trials and real-world observational data. Further, we wanted to provide a focus on the groups that

are typically underrepresented in clinical trials to help inform everyday clinical practice. Our review verifies the known safety merits of vedolizumab with no new concerning signals identified. Vedolizumab has been granted marketing authorization in over 70 countries, including Canada, the United States, and the European Union, with more than 1,000,000 patient years of exposure to date [72]. Vedolizumab has a unique pharmacological profile of modulating gut inflammation without inducing systemic immunosuppression. This is largely due to its selective inhibition of α4β7 via MAdCAM-1 without affecting other α4 or β7 heterodimers and lymphocyte trafficking to other tissues. For example, unlike natalizumab which also affects ligand binding to α4β1, not a single case of PML due to vedolizumab use has been reported [73]. Due to the restricted expression of α4β7 to a subset of leukocytes, vedolizumab does not bind to nor interfere with the trafficking of most white cells in the gastrointestinal vasculature [74]. In this review, we demonstrate that these features confer a highly favorable safety profile and consequently, there are evolving treatment paradigms that should be considered for vedolizumab use in clinical practice that we discuss here.

Vedolizumab is an attractive option when combined with an anti-cytokine approach using another biologic or a novel small molecule inhibitor due to its safety merits [75]. Despite the rapid expansion of therapies for the treatment of moderate-to-severe IBD, most advanced therapies, including vedolizumab, result in 1 year remission rates that do not exceed 30–40%, with treatment differences typically no greater than 15–20% between drug and placebo [76]. One way to break this apparent therapeutic ceiling and make strides to resolving the unmet need is to harness the potential synergistic effect of combining biologics. While phase III trials investigating dual biologics are underway, many have started to adopt the off-label prescribing of dual advanced therapy in clinical practice, mainly for highly resistant disease or where treatment is required to control IBD and extra-intestinal manifestations/concurrent IMIDs [77]. Vedolizumab has invariably been the favored combination biologic given its safety data, and we feel that studies that prioritize this approach of a baseline biologic with potent inhibition of cytokine signaling are desperately needed. The lack of RCT data and a tentative approach taken by many regarding safety of dual biologic/small molecule immunosuppression are contributory factors inhibiting widespread adoption in clinical practice. This is further compounded by cost implications given the lack of a vedolizumab biosimilar.

Treatment positioning in IBD is a topic of perpetual debate with therapeutic efficacy and safety as the key determinants, among others, when tailoring individual treatment. Advanced therapies with a robust safety profile are likely to increasingly be positioned earlier in the treatment algorithms given the burgeoning prevalence in the elderly and co-morbid populations. Emerging data from numerous observational studies highlight that vedolizumab use in biologic-naïve patients confers a better safety profile, though controlled data is needed to influence treatment guidelines [78]. Positioning is also influenced by the presence of cancer risk factors and while vedolizumab does not appear to affect the risk of cancer recurrence in patients with prior cancer, we agree that more studies are needed to make recommendations in those with active cancer. Ongoing studies of vedolizumab in patients with checkpoint inhibitor-induced enterocolitis for active cancer may provide additional answers.

Therapeutic drug monitoring (TDM) has the potential to improve outcomes in vedolizumab-treated patients, although the exposure–response relationship is less consistent than that for anti-TNFα agents. For example, even at low vedolizumab doses, there is maximal saturation of α4β7 receptors on peripheral serum lymphocytes [14]. A positive exposure–efficacy relationship has been reported with higher vedolizumab serum concentrations associated with higher remission rates after induction [79,80]. While the clinical trial program did not find a difference in drug efficacy between four weekly and eight weekly dosing for either UC or CD in the maintenance phase, this has been observed in several real world, largely retrospective studies [1,2,81–84]. We believe that prospective studies are needed to better evaluate the effect of vedolizumab dose optimization before the positioning of vedolizumab TDM in therapeutic algorithms is to be defined.

In conclusion, α4β7 blockade by vedolizumab is well tolerated and no deleterious adverse events have been noted since receiving regulatory approval in 2014. Accumulating safety supports its use in pregnancy, lactation, in those with prior cancer, and in pediatric patients. Although there has only been one head-to-head vedolizumab RCT that has assessed safety, there are several lines of evidence to suggest that vedolizumab is one of the safest of the licensed advanced therapies available for IBD. As a result, vedolizumab has been proposed as an excellent candidate for advanced combination treatment in patients with refractory IBD, in those patients at high risk of developing complications, or in patients with concomitant uncontrolled IMIDs. Overall, the long-term safety of vedolizumab is well established and its unique gut-selective mechanism of action provides an invaluable option where systemically acting immunosuppressive treatments are less preferred.

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Scientific accuracy review

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Author contributions

S Honap drafted the manuscript. P Netter, S Danese, and LP Biroulet critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Articles of special interest have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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