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Vedolizumab in Ulcerative Colitis and Crohn's Disease-A Systematic Review

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Abstract

Background: *Vedolizumab is a fully humanized monoclonal IgG-1 antibody that selectively inhibits the interaction between α4β7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). It prevents lymphocyte translocation from the blood into the inflamed gut tissue, resulting in a reduction in local inflammation. Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory conditions of the bowel affecting approximately 1.4 million people in the US. The efficacy of the drug was studied.*

Methods: *The outcome measures for Phase 3 and randomized clinical trials in ulcerative colitis and Crohn's disease, was as per GEMINI 1, 2, and 3 for its efficacy.*

Results: *A total of 309 out of 499 reported vedolizumab AEs. In comparison with all other drugs, 3PRR signals were detected including joint-related symptoms like arthralgia, upper respiratory tract infections like nasopharyngitis and sinusitis, and upper respiratory tract symptoms like oropharyngeal pain. Among the vedolizumab-associated reports with serious outcomes, the drug was used for CD in 52.5% and UC in 27.4% compared with 86.1% and 13.9% for the anti-TNFs-associated reports. Although safety data from both these studies suggest VDZ is safe, larger studies with longer follow-up will be necessary to determine the potential risk for the development of PML.*

Conclusion: *There is limited information on other potential confounders, such as co-morbidities, duration, and severity of disease, disease phenotype, surgical history, smoking, and concurrent IBD treatment. The benefit and risk profile of combining Vedolizumab with anti-TNF-α agents in the treatment of IBD will need to be examined. Vedolizumab is revolutionary in the community of inflammatory bowel disease, especially with the potential advantage for VDZ's selectivity to the gastrointestinal immune system. Vedolizumab provides an alternate class to biologic therapy with an encouraging response and safety profile.*

Keywords: *Ulcerative colitis; Vedolizumab; Inflammatory bowel disease; Crohn's disease*

Introduction

Inflammation is a technique that includes cytokines that assign the lymphocytes to regions with new drug remedies focused on the inflammatory technique. Both Crohn's ailment (CD) and ulcerative colitis (UC) fall below inflammatory bowel ailment (IBD) with the immune device sharing signs and symptoms of the body's bizarre response. The number one area is the gastrointestinal (GI) tract and with the aid of using the age of 30 years identified with IBD. In addition, sufferers with UC regularly gift with rectal bleeding

(RB) and record stomach pain (AP) in CD (Figure 1) [1,2].

In human beings with IBD, GI errors food or microorganism for overseas materials ensuing in continual irritation because the lining of the bowel is with the aid of using activating the immune device (Figure 1). Inflammation process in IBD.

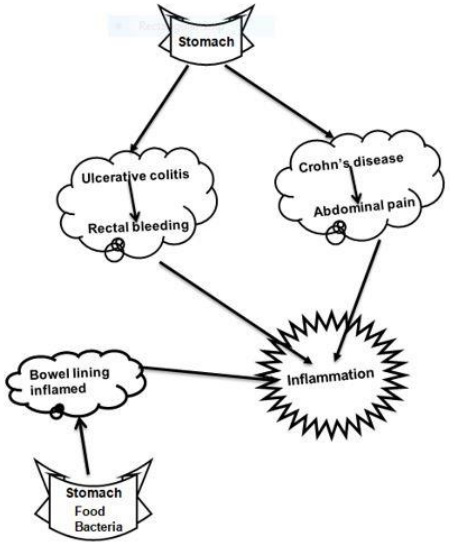

Figure 1: Inflammation process in IBD.

The pathophysiology of inflammatory bowel ailment (IBD) is not always absolutely understood, however, there appears to be a genetic predisposition to IBD with over one hundred sixty unmarried nucleotide polymorphisms (SNPs) mapped to be related to the ailment with the aid of using the genome-extensive affiliation study [3,4]. Several research studies have recognized the decision of RB and the normalization of bowel behaviour as the number one PRO goals for UC therapy. In CD, Khanna et al endorsed the decision of AP and the normalization of bowel dependency because the number one PROs for the assessment of CD remedy efficacy in scientific trials. It is normally located in human beings in better socioeconomic repute and in whites. Treatment of IBD is handling signs and symptoms with an intention to acquire remission as it's also lifelong and can sufferers be having trade durations of remission and flare-up. Modern remedies, however, permit human beings to stay pretty every day and efficient lives and IBD needs to now no longer be pressured with irritable bowel syndrome (IBS) [5-7].

Vedolizumab (VDZ), is a gut-selective integrin blocker that is a fully humanized monoclonal IgG-1 antibody indicated for Crohn's disease (CD) and ulcerative colitis (UC) that selectively inhibits α4β7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) interaction, thus preventing the lymphocyte translocation from the blood into the inflamed gut tissue, resulting in a reduction in inflammation [8,9]. The study aims at using the FDA Adverse Event Reporting System (FAERS) database to examine the adverse events (AEs) of vedolizumab compared to anti-tumor necrosis factors (anti-TNFs) indicated for CD and UC [10]. Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory condition of the bowel affecting approximately 1.4 million people in the US [11]. The genetic, immunologic, and environmental factors for UC could be associated with either smoking or gut microbiome but the treatment for UC and CD are similar, with the aim of mainly reducing the inflammation either by suppressing the adaptive immune system or by inhibiting leukocyte trafficking. Immunosuppressants, such as methotrexate, azathioprine, or mercaptopurine are used as maintenance therapy for both CD and UC. TNF-α antagonists, such as infliximab, adalimumab, certolizumab, and golimumab, have been shown to be effective for both induction and maintenance of UC (excluding certulizumab) and CD (excluding golimumab) [12-17]. While TNF-α antagonists hamper lymphocyte maturation, newer drug therapies are aimed at targeting the other steps in the inflammatory process, such as other cytokines (secukinumab),

lymphoid differentiation (ustekinumab) and leukocyte trafficking (VDZ, natalizumab). α4β7-integrin is expressed on lymphocytes that are specific for the gastrointestinal tract. The interaction of α4β7-integrin and MAdCAM-1 on endothelial cells are responsible for the arrest phase of leukocyte trafficking [18-21]. Recently biologic remedies with novel mechanisms of movement along with vedolizumab the primary intestine-focused integrin blocker, have entered the marketplace and offer opportunity remedy alternatives for IBD patients, demonstrating protection in randomized medical trials and in early real-international studies, its protection has now no longer been in comparison with anti-TNF remedies. Vedolizumab is a fully humanized monoclonal IgG-1 antibody that selectively inhibits the interplay among α4β7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) (MAdCAM-1). It prevents lymphocyte translocation from the blood into the infected intestine tissue, ensuing in a discount in nearby inflammation [9,22]. Inflammation is a highly regulated process involving cytokines and adhesion molecules to signal lymphocytes to area of local insult. While TNF-α antagonists hamper lymphocyte maturation, newer drug therapies are aimed at targeting the other steps in the inflammatory process, such as other cytokines, lymphoid differentiation, and leukocyte trafficking.

People are confused when it comes to inflammatory bowel diseases (IBD), Crohn's disease, and ulcerative colitis (UC). In short both Crohn's disease and UC fall under IBD. Both Crohn's and UC are marked by abnormal response by the body's immune system and share some symptoms. These primarily include the location of the maladies in the gastrointestinal (GI) tract and the way each disease responds to treatment. Many with IBD are diagnosed before the age of 30 years. Like other autoimmune and allergic disorders, in people with IBD, the immune system mistakes food, bacteria, or other materials in the GI tract for foreign substances and responds by sending white blood cells into the lining of the bowels resulting in chronic inflammation. IBD may strike at any age but can be diagnosed later in life. It is more common in people in higher socioeconomic brackets, people who are white, people who eat high-fat diets. It's also more common in the following environments like industrialized countries, northern climates, and urban areas. For many forms of IBD, there is no cure. Treatment is centred on management of symptoms with remission as a goal. For most, it's a lifelong disease, with alternating periods of remission and flare-up. Modern treatments, however, allow people to live relatively normal and productive lives and IBD should not be confused with irritable bowel syndrome (IBS). Ulcerative colitis (UC) and Crohn's sickness (CD) are inflammatory situations of the bowel affecting about 1.4million humans withinside the US [11]. Vedolizumab (VDZ) selectively inhibits α4β7-integrin, with the intention of leukocyte trafficking within the gastrointestinal tract (GIT). The pathophysiology of inflammatory bowel sickness (IBD) isn't absolutely understood; however, maximum consider that is a technique from the dysregulated immune response. There is a genetic predisposition to IBD with over a hundred and sixty unmarried nucleotide polymorphisms (SNPs) mapped to be related to the sickness through the genome-extensive affiliation study [3,4]. UC is a outcome of interactions among genetic, immunologic, and environmental elements consisting of smoking or microbiome, and remedy for UC and CD are similar, particularly aimed to lessen the inflammatory nation through suppressing the adaptive immune machine or extra recently, through blockading leukocyte trafficking. One anti-inflammatory, consisting of 5-ASA, is particularly used as induction and protection remedy for mild-to-slight UC. Immunosuppressants, consisting of methotrexate, azathioprine, or mercaptopurine are used as protection remedy for each CD and UC (aside from methotrexate). Biologics refers to recombinant antibodies that block cytokines or adhesion molecules which have been observed to play an essential function in controlling the inflammatory pastime of IBD. TNF-α antagonists, consisting of infliximab, adalimumab, certulizumab, and golimumab, had been proven to be powerful for each induction and protection of UC (aside from certulizumab) and CD (aside from golimumab) [17,23,24]. GEMINI is a Phase 3, randomized, placebo-controlled, parallel trial to assess the efficacy of vedolizumab (VDZ), a α4β7-integrin antagonist, in induction and maintenance of moderately to severely active UC (GEMINI 1) [25] and CD (GEMINI 2) [26]. In this study between 2008–2012, patients were recruited in over 200 centres across more than 30 countries.

While TNF-α antagonists hamper lymphocyte maturation, newer drug therapies are aimed at targeting

the other steps in the inflammatory process, such as other cytokines (secukinumab, vidofludimus), lymphoid differentiation (ustekinumab) and leukocyte trafficking (VDZ, natalizumab). α4β7-integrin is expressed on lymphocytes that are specific for the gastrointestinal tract. The interaction of α4β7-integrin and MAdCAM-1 on endothelial cells are responsible for the arrest-phase of leukocyte trafficking [18,19]. Vedolizumab is the primary gut-selective integrin blocker indicated for sufferers with Crohn's disease (CD) and ulcerative colitis (UC). The study aimed to look at the destructive events (AEs) profile of vedolizumab as compared to anti-tumor necrosis factors (anti-TNFs) indicated for CD and UC the usage of the FDA Adverse Event Reporting System (FAERS) database. Biologic capsule's goal unique additives of the immune gadget and feature revolutionized the remedy of inflammatory bowel disease (IBD) [27-31]. New biologic therapies with novel mechanisms of action such as vedolizumab the first gut-targeted integrin blocker, have entered the market and provide alternative treatment options for IBD patients, demonstrated a favourable safety profile in randomized control trials but its safety profile has yet to be compared with anti-TNF therapies. New therapies with novel mechanisms of action and safety are crucial to patients, of IBD. Vedolizumab mainly acts via alpha4-beta7 integrin on the surface of memory T cells. In May 2014 vedolizumab was approved for the treatment of moderate-to-severe IBD and is approved in the US for the treatment of both UC and CD due to its gut-selective leukocyte migration inhibition action [32-35].

Balance between clinical benefit and possible risks is essential in determining optimal treatment choice [12–14]. While the safety profiles of anti-TNF drugs are well-established from both randomized clinical trials (RCTs) [36,37] and real-world studies [38] to date, information on possible adverse events (AEs) after treatment with vedolizumab comes mainly from clinical trials such as the two Phase III trials for vedolizumab in patients with UC and CD (GEMINI 1 and 2) [39,40]. While RCTs are the gold standard for assessing the efficacy of drugs, they are not ideal for detecting rare safety events [41]. The main shortcoming of the RCT study design is its limited external validity namely due to its often short duration of follow-up, limited study population size, stringent entry criteria that often exclude patients with significant comorbidities, older age, real-world population heterogeneity, and an artificially high level of adherence to treatment [42]. As a result, infrequent serious adverse events (SAEs) are often discovered through voluntary reporting systems or from nonrandomized post-marketing studies.

The FDA Adverse Event Reporting Systems (FAERS) is a voluntary reporting system developed by the FDA for the purpose of post-marketing surveillance for all approved drugs and therapeutic biologics. It gathers reports of AEs voluntarily submitted by health care professionals and consumers (directly or through the manufacturer of the drug), which may contain AEs that were already observed in RCTs and others that may not have been detected during RCTs. The targets of this look have been to evaluate the costs of real-international AE reporting related to vedolizumab the usage of the FAERS database. Three unique targets have been addressed. The first goal becomes to discover the real-international profile of suggested AEs with vedolizumab because the precise mechanism of action (MOA) of vedolizumab presents the possibility to evaluate gut-selective with systemic immunosuppressive tablets. The second goal was whether there are any suggested AEs that are disproportionately related to vedolizumab relative to anti-TNFs for the remedy of UC and CD. The third goal was whether there are any suggested AEs disproportionately related to vedolizumab relative to all different tablets suggested within the FAERS database.

Literature search

The author searched key words like ulcerative colitis, crohn's disease, vedolizumab in FDA Adverse Event Reporting System(FAERS), PubMed, Clinical investigation, World journal of Gastroenterology, Clinical Gastroenterology and Hepatology, Gastroenterology & Hepatology, Gut, World Journal of Gastrointestinal Pharmacology and Therapeutics, PLOS, Immunotherapy , Inflammatory Bowel Disease, Gastrointestinal /Endocrine and metabolic diseases, Alimentary Pharmacology & Therapeutics, Clinical Investigation, Journal of Gastroenterology Research. The articles between 2005 to 2019 were searched, of which the author selected six articles for this review.

Materials and methods

The FDA Adverse Event Reporting System (FAERS) is a spontaneous reporting database maintained by the FDA [43] whose aim is to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products by collecting information on adverse drug reactions from two principal sources: (1) mandatory reports from pharmaceutical companies (who must report any AE within 14 days of becoming aware of the AE), and (2) voluntary AE reports from healthcare professionals, consumers, and manufacturers. In the database, AE names and indications for drug use are coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms [43,44].

Cohort 1 was a randomized induction trial, while cohort 2 an open-labeled induction and was randomized for maintenance trial. Cohort 1 was randomized 3 to 2 where VDZ 300 mg or placebo was given at week 0 and week 2. Cohort 2 received open-labeled VDZ 300 mg at week 0 and week 2. Response to therapy was assessed at week 6.

Responders from the treatment arm in both cohorts were randomized to VDZ 300 mg every 8 weeks, VDZ 300 mg every 4 weeks or placebo. Non responders from the treatment arm received VDZ every 4 weeks. Placebo arm from the induction trial received placebo during the maintenance trial.

In over 34 countries, over 211 centres enrolled 374 patients into cohort 1 and 521 patients into cohort 2 for GEMINI 1. The primary end point in the induction trial was clinical response at week 6, defined by reduction in Mayo Clinical score of at least 3 points and decrease of at least 30% from the baseline score, with decrease of at least 1 point from the rectal bleeding subscale or absolute rectal bleeding score of 0 or 1. The secondary end points in the induction trial were clinical remission at week 6 as defined by Mayo Clinical score of 2 or lower and no subscore higher than 1 and mucosal healing defined by endoscopic subscore of 0 or 1. The primary end point in the maintenance trial was clinical remission at week 52. The secondary end point in the maintenance trial was durable clinical response, durable clinical remission, mucosal healing at week 52 in patients. Response or remission was defined as response or remission at both weeks 6 and 52. In 39 countries from 285 centres 368 patients were enrolled into cohort 1 and 747 patients into cohort 2 in GEMINI 2. The primary end points in the induction trial were clinical remission as defined a CDAI score of less than or equal to 150 and CDAI-100 response at week 6 as defined as a reduction of CDAI score by at least 100 points. The secondary end point in the induction trial was change in CRP from baseline. The primary end point in the maintenance trial was clinical remission at week 52. The secondary end point in the maintenance trial was CDAI-100 response, with clinical remission at week 52.

Inclusion and exclusion criteria

Inclusion criteria

Adult patients with active UC, defined by Mayo Clinical score≥6 and sigmoidoscopy subscore of ≥2 and ≥15cm of disease from anal verge. GEMINI 2 inclusion criteria select for adult patients with active CD, defined by CD for at least 3 months with Crohn's disease activity index (CDAI) of 220–450, and either CRP > 2.87 mg/l, colonoscopy findings ≥3 large ulcers or ≥10 aphthous ulcers or fecal calprotectin >250 μg/g with evidence of ulcers on imaging.

Exclusion criteria

Patients previously exposed to natalizumab, VDZ, efalizumab and rituximab. Glucocorticoids were tapered in patients who had response at week 6 according to a pre specified regimen. Immunosuppressants were maintained at stable dose except for the US sites, where these agents were discontinued after VDZ induction period.

Results

The average duration of disease was 7.1 ± 7.2 years with Mayo Clinic score in the placebo group was 8.6 ± 1.7 the average duration of disease in years was 6.8 ± 6.2 with Mayo Clinic score at 8.6 ± 1.8 in the cohorts treated combined in GEMINI 1. 49.0% with the placebo group and 48.0% in combined cohorts who received TNF-α antagonist. The primary non-responders were 46.0 and 48.4%. The average CDAI score was 325 ± 78 in GEMINI 2, with the placebo group had average disease duration of 8.2 ± 7.8 years while in the combined treatment cohorts, the average CDAI score was 323 ± 68 with an average duration of disease at 9.2 ± 7.8 years. 14.2% of participants reported only ileal disease and 56.8% reported both ileum and colonic disease in the placebo group. In the combined treatment cohorts around 16.5% had the only ileal disease while ileum and colonic disease was reported in 55.2% of participants. Current smokers were 23.0% in the placebo group and the combined treatment cohorts had 27.3%. Those who received

prior TNF-α antagonist in placebo was 48.6 and 63.8% in combined cohorts, of those, primary non responders were 58.6 and 48.5%. The primary and secondary endpoints in GEMINI 1, in the induction trial, at 6 weeks showed statistical significance. 25.5% of the placebo group and 47.1% of the VDZ treatment group showed a clinical response. The placebo group and VDZ treatment group achieved clinical remission at 5.4 and 16.9%. Participants showed 24.8% of the placebo group and 40.9% of the VDZ treatment group displayed mucosal healing. Clinical response of 44.3%, clinical remission of 19.2%, and mucosal healing of 36.7% in cohort 2 were achieved. In prior anti-TNF-α failure patients, 20.6% in placebo and 39.0% in the VDZ group displayed statistically significant clinical response by 6 weeks. GEMINI 1 achieved statistically significant primary and secondary endpoints in the maintenance trial by 52 weeks. In the VDZ every 8 weeks and every 4 weeks arm clinical remission of 41.8% and 44.8% was displayed in comparison to the placebo arm that displayed 15.9%. With mucosal healing VDZ every 8 weeks displayed 51.6% and VDZ every 4 weeks displayed 56.0% in treatment arms, as compared to the placebo arm displaying 19.8% with a relative risk of 3.3 and 3.8 in GEMINI 1. Statistically significant clinical remission in prior anti-TNF-α failure patients was achieved with 5.3% in the placebo group compared with 37.2% in VDZ every 8-week group and 35.0% in VDZ every 4-week group. Statistically significant clinical remission was displayed in patients without anti-TNF-α failure in 20.5% of the placebo group compared to 44.3% in VDZ every 8 weeks. In the induction and maintenance trial, GEMINI 1 displayed an improved quality of life compared to placebo. In GEMINI 2, one of the primary endpoints was not met in the induction trial by 6 weeks. The CDAI-100 response displayed no statistical difference between VDZ and placebo, with 14.5% in the treatment arm displaying a statistically significant difference compared to 6.8% in the placebo arm, in clinical remission at 6 weeks.

No statistically significant difference was found in CRP from baseline to 6 weeks in the two groups. The change in CRP from baseline to 6 weeks was not statistically different between the two groups. In cohort 2, 17.7% displayed clinical remission and 34.4% displayed CDAI-100 response. There was not statistically significant difference in clinical remission in prior anti-TNF-α failure patients with 4.3% of placebo group compared with 10.5% of VDZ group, an estimated difference of 6.2%. As well, CDAI-100 response in prior anti-TNF-α failure patients did not achieve statistically significant difference with 22.9% of placebo group compared with 23.8% of VDZ group, an estimated difference of 1.0%. In patients without anti-TNF-α failure, clinical remission and CDAI-100 response were not achieved with 9.0 and 28.2% in placebo group compared with 18.3 and 38.3% VDZ group, respectively, with an estimated difference of 9.3% and 10.1%, respectively. GEMINI 2 achieved the primary end point and most of the secondary end points by week 52 in the maintenance trial. A total of 39.0% and 36.4% of patients receiving VDZ every 8 weeks and every 4 weeks, respectively, were in clinical remission, compared with 21.6% in the placebo arm. Similarly, 31.7% VDZ every 8 weeks and 28.8% VDZ every 4 weeks of treatment arms achieved glucocorticoid-free remission, compared with 15.9% of placebo arm. Durable clinical remission did not reach statistical significance in this study. Both GEMINI 1 and GEMINI 2 studies highlighted that in the induction trial, a higher VDZ correlation to clinical response was observed. In the maintenance trial, >95% of the population achieved saturation of α4β7 on peripheral T-cell lymphocytes over 95% in both doses of VDZ. No incidence of PML was reported in safety data from both studies. VDZ and placebo groups displayed no difference in the adverse effects in GEMINI 1. An acute coronary event leads to the death of one participant in the VDZ group. The exposure-adjusted relative risk for patients receiving VDZ versus placebo group was identified for serious adverse events 0.71, for serious infections 0.56, and for malignancies 0.09 viz colon cancer. In GEMINI 2, 12.3% incidence of nasopharyngitis in the VDZ arm was detected compared to 8.0% with placebo. 24.4% incidence of serious infections in the VDZ arm compared to 15.3% with placebo. The exposure-adjusted relative risk for patients receiving VDZ compared to placebo was 1.30 for serious adverse events, 1.48 for serious infections, and for malignancies. Four deaths occurred in the treatment arm from GEMINI 2 due to culture-negative sepsis with extensive thromboemboli, intentional drug overdose, and myocarditis from intravenous drug use. A comparable kind of effects became located with the GEMINI 3, which evaluated the efficacy of vedolizumab in 315 sufferers with reasonably to significantly lively CD and insufficient reaction, lack of reaction, or intolerance to preceding TNFα antagonists 44. Patients assigned randomly to acquire vedolizumab 300mg iv or placebo at 0, 2, and six weeks. Clinical remission at 6 weeks was 15.2% of vedolizumab in comparison to 12.1% with the placebo group. The number one endpoint of the examination

became now no longer met. Clinical remission at 10 weeks became drastically better in sufferers handled with vedolizumab this is 26.6% vs. 12.1% with the placebo group. The gain became visible at 10 weeks, suggesting a not-on-time reaction in acquiring clinical remission.

Discussion

From May 20, 2014, to June 30, 2015, the date of FDA approval, vedolizumab reports were included. The anti-TNFs (i.e., adalimumab, certolizumab pegol, golimumab, and infliximab) reports were looked into from August 24, 1998 to June 30, 2015, the date of approval of infliximab—the first anti-TNF drug for CD. Only 88% of reports for vedolizumab and 97.6% of reports for anti-TNFs, as the primary suspect reports were kept. All vedolizumab reports were included without respect to indication because vedolizumab is only indicated for IBD. As anti-TNFs are indicated for multiple non-IBD inflammatory conditions, only reports where these drugs were indicated for UC or CD were included to ensure a homogeneous comparison with vedolizumab. Reports satisfying the above inclusion criteria and those associated with serious outcomes were studied for the subgroup analyses. Study outcomes Grouped AEs associated with vedolizumab were analyzed. Specifically, all individual AEs based on MedDRA preferred terms 43 recorded on vedolizumab reports were first identified, and then the preferred terms belonging to the same MedDRA High Level Term (HLT) class were grouped to form 254 grouped AEs.

Two FDA-recommended algorithms for the analysis of spontaneous reports were used in this study: the proportional reporting ratio (PRR) and the empirical Bayesian geometric mean (EBGM) [45,46]. The PRR is one of the most commonly used method for reporting disproportionality. In this study, the PRR was calculated as the ratio of the reporting proportion of AEs associated with vedolizumab divided by the reporting proportion of AEs associated with the comparator i.e., anti-TNF drugs or all the other drugs in the FAERS database. The same two disproportionality analysis measures (PRR and EBGM) were calculated to examine the presence of signals of disproportionate reporting for reports associated with serious outcomes only. In total, 2830 patients had 4811 persons per years (PYs) of vedolizumab exposure (median exposure range, 1–1977 days). No increased risk of any infection or serious infection was associated with vedolizumab exposure. Serious infections with clostridia, sepsis and tuberculosis were reported in ≤0.6% of patients. No cases of progressive multifocal leukoencephalopathy (PML) were observed. Independent risk factors for serious infection in UC were prior failure of a tumour necrosis factor α (TNF α) antagonist and in CD were younger age. In ≤5% of patient's infusion-related reactions were reported in each study with <1% of vedolizumab-exposed patients diagnosed with malignancy. Thus, concluding that vedolizumab had a good safety profile, with lower incidence of serious infections, reactions related to infusions and malignancies over the period of treatment [47]. The safety profile of vedolizumab that has emerged from the analysis of clinical trial data in over 3,000 patients suggests an increased susceptibility to upper respiratory infections like nasopharyngitis, sinusitis, and other serious and opportunistic infections as well as non-specific AEs like nausea, fatigue, headache, arthralgia, rash, and pruritus. However, data from RCTs may underestimate the occurrence of rare but SAEs for which clinical trials have no adequate detection power due to sample size and relatively short-duration. Post-marketing surveillance is currently required for all FDA-approved drugs so that rare AEs or AEs undetected in RCTs can be detected sooner after use in the real-world clinical setting [48]. The assessment of long-term safety of a drug is of the upmost importance to better educate patients and healthcare providers regarding the risks and benefits of treatment. Therefore, in the current study we have investigated the real-world safety profile of vedolizumab compared to anti-TNF and other drugs using the FAERS database. In this study, no signals were detected for known AEs listed in vedolizumab's prescribing information relative to anti-TNF use. However, signals were detected for arthralgia, nasopharyngitis, sinusitis, and oropharyngeal pain when comparing vedolizumab with all other drugs reported in the FAERS database. Among the 254 grouped AEs identified for vedolizumab in the FAERS database, 22 and 34 were identified with signals of disproportionate reporting compared with anti-TNF drugs and all other drugs in the database, respectively. Grouped AEs with a PRR signal include AEs related to cardiovascular disease and AEs that had been reported in vedolizumab clinical trials and discussed in the

warnings and precautions section of vedolizumab's prescribing information that included infusion site reactions, infections, liver abnormalities, and colorectal neoplasms. AE signals detected in both comparisons include pulmonary edemas, infusion site reactions, infections, liver abnormalities, and colorectal neoplasms.

First, the reported cardiovascular disease AEs may be related to the different mechanisms of action of vedolizumab and anti-TNFs. Second, cardiovascular disease signals are commonly missed in IBD clinical trials as they are uncommon [49]. In the case of IBD, cardiovascular AEs may be linked to the underlying IBD: Chronic low-grade inflammation has been associated with both venous and arterial thromboembolic events and, overall, the development of cardiovascular disease [50-55]. An alternative explanation for the reported cardiovascular disease AEs could be that vedolizumab would be utilized in moderately to severely active CD and UC patients with who have had an inadequate response or intolerance to a TNF inhibitor or corticosteroids as indicated by the FDA.

The nature of the voluntary AE reporting system and the types of data it collects, the study could not examine or control for various potential confounding factors which could influence the incidence of cardiovascular disease-related AEs. Such confounding factors include patient's lifestyle habits (smoking, daily physical activity levels, diet), prior or concurrent treatments (e.g., NSAIDs), and other comorbidities (e.g., obesity, diabetes), among others.

A systematic review and meta-analysis of the aforementioned RCTs confirmed that vedolizumab was superior to placebo for induction of clinical remission, clinical response, and endoscopic remission in patients with active UC and CD. Furthermore, maintenance therapy with vedolizumab was superior to placebo for achieving clinical remission and endoscopic remission [56]. From GEMINI 1, VDZ is effective for induction and maintenance of moderately to severely active ulcerative colitis in patients who are treatment naïve and treatment failure to TNF-α antagonist. GEMINI 2 did not meet one of the co-primary end points in the induction trial, the CDAI-100 response criteria, but did meet the other primary end point, clinical remission. The totality of the GEMINI 2 trial suggests that indeed VDZ is an effective agent for the treatment of CD. VDZ is effective for maintenance of moderately to severely active CD with promising induction data. The data from the maintenance trial in GEMINI 2 showed significant clinical remission, clinical response, and glucocorticoid-free remission. The response to therapy became more evident by week 28, demonstrating a slower response to VDZ compared with other therapies (such as TNF-α antagonists) in CD. The sub analysis with plot of risk differences from patient characteristic in GEMINI 2 is less cohesive and meaningful interpretation cannot be drawn from them at this time. It is interesting to note that despite similar baseline characteristics between cohorts 1 and 2, cohort 2 responded better than cohort 1 in the maintenance trial, which can likely be explained by a lack of a placebo group in cohort 2 (GEMINI 2)19. VDZ is demonstrated to be an effective maintenance therapy for CD, but because of the longer time to produce effect, VDZ may not be an ideal option for CD induction therapy.

GEMINI 3 is a multicenter randomized, double-blinded, placebo-controlled trial on VDZ induction therapy for patients with CD and prior anti-TNF-α antagonist failure. Patients were randomized 1:1 into VDZ 300 mg IV for induction at week 0, 2 and 6 or placebo. The primary end point was clinical remission at week 6 in prior anti-TNF-α failure patients. Secondary end points are clinical remission at week 6 in overall population (both anti-TNF-α failure and anti-TNF-α naive populations), clinical remission at week 10 in both populations, durable clinical remission defined by remission at both weeks 6 and 10 in both populations and CDAI-100 response at week 6 in prior anti-TNF-α failure patients. This study did not meet statistical significance in the primary end point; however, extrapolation to secondary end point showed clinical remission in overall population in week 6 did meet statistical significance of 26.6% in VDZ group compared with 12.1% in placebo group [57] (Table 1).

Although safety data from both these studies suggests VDZ is safe, larger studies with longer follow up will be necessary to determine the potential risk for development of PML. From all VDZ trials combined for a median exposure of 18.8 months, no cases of PML have been reported as of February 2013, suggesting that the selectivity of VDZ is specific and does not interfere with CNS leukocyte trafficking [58].

As such, current evidence suggests that VDZ does not affect the immune surveillance of CNS and may not have similar risks of PML as natalizumab [59].

Table 1: Percentage of Clinical response, remission, and mucosal healing of vedolizumab (VDZ) in patients with Ulcerative colitis and Crohn's disease in GEMINI 1, 2, 3.

Study	n	Induction/ Maintenance	Dose (mg)	Clinical response (%)	Clinical remission (%)	Mucosal healing (%)
GEMINI 1	374	Induction	300 mg	47.1	16.9	40.9
			Placebo	25.5	5.4	24.8
		Maintenance	300 mg 4 weekly	-	44.8	56
			300 mg 8 weekly		41.8	51.6
			Placebo		15.9	19.8
GEMINI 2	368	Induction	300 mg	31.4	14.5	-
			Placebo	25.7	6.8	
		Maintenance	300 mg 4 weekly	45.5	36.4	-
			300 mg 8 weekly	43.5	39	
			Placebo	30.1	21.6	
GEMINI 3	315	Induction	300 mg	-	15.2	-
			Placebo		12.1	

Clinical response was defined as a reduction in the Mayo score of at least 3 points plus a decrease of at least 30% from the baseline score, with a decrease in the rectal bleeding subscore ≥ 1, an absolute rectal bleeding subscore ≤ 1 (GEMINI 1), or as a ≥ 100-point decrease in the CDAI score (GEMINI 2). Clinical remission defined as a Mayo score of ≤ 2 and no subscore > 1 (GEMINI 1) or as a CDAI score ≤ 150 points (GEMINI 2, GEMINI 3)

Authors from GEMINI 1 have pointed out that the study was not designed to identify the time of maximal effect of VDZ as induction therapy, or a minimal effective VDZ dose regimen as maintenance therapy in UC. Future study into dosing data may be useful from a cost-analysis point of view once the cost of this therapy is known. As well, an important question that will need to be addressed is the use of VDZ in the hospitalized severe UC patient. Will VDZ be effective. In the time frame required for induction for such patients, or will the safety of this drug allow us to use it in combination with another agent to induce remission? A useful predictor of drug response and the mechanisms behind the loss of response to VDZ will need to be understood. Though the blood saturation of α4β7 on peripheral T-cell lymphocytes was >95% in most patients studied, the variable response to VDZ may be more related to the saturation of these receptors on the T-cell lymphocytes at the site of inflammation. The correlation between the serum drug levels to response, and to the saturation of α4β7 T-cell lymphocytes at the site of inflammation should be evaluated. Finally, the benefit and risk profile of combining VDZ with anti-TNF-α agents in the treatment of IBD will need to be examined. VDZ is revolutionary in the community of inflammatory bowel disease, especially with the potential advantage for

VDZ's selectivity to gastrointestinal immune system. VDZ provides an alternate class to biologic therapy with encouraging response and safety profile.

Although safety data from both these studies suggests VDZ is safe, larger studies with longer follow up will be necessary to determine the potential risk for development of PML. From all VDZ trials combined for a median exposure of 18.8 months, no cases of PML have been reported as of February 2013, suggesting that the selectivity of VDZ is specific and does not interfere with CNS leukocyte trafficking [58]. As such, current evidence suggest that VDZ does not affect the immune surveillance of CNS and may not have similar risks of PML as natalizumab [59].

Given these limitations, it is important to consider our results as hypothesis-generating and deserving of further study. Taken together, findings from these the chronic inflammatory bowel diseases (IBDs), comprised of ulcerative colitis (UC) and Crohn's disease (CD), are idiopathic conditions that typically affect younger people. Given that the cause of IBD is unknown, treatment is directed towards suppression of pathological inflammation in the gut. In UC, therapy consists of a step-care approach that features sequential use of aminosalicylates, corticosteroids, tumour necrosis factor (TNF)-α antagonist, and the oral small molecule JAK1/3 inhibitor tofacitinib. Although corticosteroids remain the standard induction therapy for most patients with CD, incremental step-care approach has fallen out of favour, with current algorithms specifying early use of highly effective treatment in high-risk patients. Specifically, this strategy involves the use of biologics such as TNF antagonists, anti-integrins or the interleukin (IL)-12/23 antagonist ustekinumab [60]. Natalizumab monoclonal antibody directed to the α4 subunit shared by the α4β1- and α4β7-integrins on T cells was the first anti integrin therapy for CD. Although natalizumab was effective as induction and maintenance therapy for moderate to severe CD [61], use was limited by the risk of progressive multifocal leukoencephalopathy (PML), a rare viral disease with a high mortality rate.

Inhibition of α4β1-integrin and vascular cell adhesion molecule-1 (VCAM-1) interaction by targeting α4 impairs immune surveillance in the kidney, allowing the John–Cunningham (JC) virus to replicate and become genetically diverse and the mutated virus invades the central nervous system, where it infects glial cells and causes PML [62,63]. The viral replication in the central nervous system cannot be controlled by the immune system because cytotoxic T-cell trafficking to the brain is dependent on α4β1 VCAM-1 interactions.

The mechanism of action of vedolizumab is distinct from natalizumab because the former only targets the α4β7 integrin heterodimer that governs trafficking of T lymphocytes, though interaction with mucosal vascular addressin cell adhesion molecule (MAdCAM-1) [20]. Vedolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that binds to α4β7 with no affinity for α4. Accordingly, the drug does not block α4β1-VCAM interactions, nor does it affect T-cell trafficking to either the kidney or brain. Therefore, there is no theoretical risk of PML [20,64,65]. Vedolizumab received approval from the European Medicines Agency (EMA) and US FDA in 2014 for the treatment of moderate to severe UC and CD. Guidelines currently recommend vedolizumab in both diseases as a first-line biologic agent or for patients who are refractory to a TNF antagonist [66-74].

Limitations

Incomplete and inconsistent reporting from database was relied on as well as ascertainment bias. Increased reporting was found to be spontaneous reporting in the early years of a VDZ launch. The spontaneous reporting systems did not provide how many patients used the drug.

This was a major limitation to find out actual utilization of the drug and calculate incidence rates from FAERS. Adverse effects that reported with exceedingly small numbers, using the PRR approach reported large variations, resulting in false-positive signals. PRR approach, the EBGM approach, were used. It should be noted that there is no gold standard for data mining algorithms. Reporting odds ratio (ROR) in comparison to PRR was used as an alternative method. The study detected signals of vedolizumab with a severe increase reporting of adverse effects, related to cardiovascular and thromboembolic disease, IBD patients compared to anti-TNFs. further studies are required to confirm them.

Conclusion

For patients with UC and CD, vedolizumab may be considered as treatment over conventional or TNFα inhibitors. GEMINI studies have displayed the efficacy and safety of vedolizumab in patients with IBD. However, the stringent and restrictive inclusion and exclusion requirements with the check designs also can moreover restrict the translation of medical trial outcomes into patients generally seen in the clinic. Patients enrolled in RCTs only in components

represent the IBD population encountered in some unspecified time in the future of the routine medical practice. Mucosal restoration is a relevant restoration purpose in patients with IBD because of the reality its miles associated with a reduction in hospitalization, IBD-related surgery, bowel damage, and the threat of colonic dysplasia. mucosal healing can favour patients with IBD. Safety statistics from all the GEMINI studies showed a similarity of adverse events in the placebo group. As vedolizumab has shown efficacy and safety in patients who failed TNF-α antagonists and must therefore be considered for treatment.

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