[redacted] ABSTRACT

Title

Entyvio® (vedolizumab) long-term safety study: An international observational prospective cohort study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's disease.

Keywords

Ulcerative colitis, Crohn's disease, vedolizumab, post-authorization safety study

Rationale and Background

Ulcerative colitis (UC) is a chronic, relapsing, remitting inflammatory disease of the colonic mucosa and submucosa. Crohn's disease (CD) is a chronic, relapsing, remitting inflammatory disease that may involve any portion of the gastrointestinal (GI) tract, from mouth to anus, in a transmural fashion from mucosa to serosa. The highest reported annual prevalence of UC and CD in North America was 286/100,000 persons and 319/100,000 persons, respectively. However, in Europe, the highest annual reported prevalence of UC and CD was 505/100,000 persons and 322/100,000 persons, respectively [1]. UC and CD are lifelong diseases that cause considerable morbidity in a relatively young patient population.

Pharmacologic treatments for UC and CD included 5-aminosalicylates (5-ASAs), corticosteroids, immunomodulators (thiopurines, such as azathioprine and 6-mercaptopurine [6-MP], and methotrexate), and biologic agents (infliximab and adalimumab). Other biologic agents were approved for CD only (certolizumab pegol, natalizumab and ustekinumab).

Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody (mAb) directed against the human lymphocyte integrin α4β7. The α4β7 integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue through adhesive interactions with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa.

Vedolizumab exclusively targets the α4β7 integrin, antagonizing its adherence to MAdCAM-1 and hence impairing the migration of leukocytes into GI mucosa. Therefore, by virtue of its gut-selective mechanism of action, vedolizumab is expected to have anti-inflammatory activity without the generalized immunosuppression found with other biologic treatments for UC and CD.

This study was a post marketing requirement for the Food and Drug Administration (FDA) and a category 3, required additional pharmacovigilance activity in the EU risk management plan (RMP), for the European Medicines Agency (EMA). This was a prospective observational study to assess the safety of vedolizumab versus other biologic agents in the real-world clinical setting. The participating physicians were expected to be representative of the gastroenterologists who prescribe vedolizumab, or other biologic agents, per the local prescribing information in the participating countries.

The patients enrolled in this study corresponded to the target population of UC or CD patients initiating vedolizumab or similar patients initiating other biologic agents in the participating countries. This study was designed to accommodate the use of products according to approved product labels in all participating countries.

This study report presents the results of the final statistical analysis.

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Research Question and Objectives

Primary Objective:

- Assessed the long-term safety of vedolizumab versus other biologic agents in patients with UC or CD.

Secondary Objective:

- Described changes in UC/CD disease activity, using disease activity scores, health resources used, and patient reported quality of life (QoL) assessments, during the course of the study.

Study Design

Design

This was a prospective, observational, multi-center, cohort study designed primarily to assess the long-term safety of vedolizumab versus other biologic agents in patients with UC or CD. The study had two cohorts: a vedolizumab cohort and a cohort of patients receiving other biologic agents.

The study was non-interventional. All decisions on clinical management were made by the Investigator as part of routine standard of care, and independent of participation in the study. The study design allowed the Investigator to modify or change patients' treatment at any time during the study period without having to withdraw the patients from the study.

Study Procedures

Cohort Entry Criteria

Patients with UC or CD who were initiating vedolizumab therapy were recruited into the vedolizumab cohort. Patients may have had prior exposure to biologics or were naïve to biologics. Patients were to be naïve to vedolizumab at study entry.

Patients with UC or CD who initiated therapy with another biologic agent indicated for UC or CD were recruited into the other biologic agents cohort. Patients may have had prior exposure to biologic agents or were naïve to biologics. Patients may not have had prior exposure to vedolizumab at study entry.

This study was designed to permit interested physicians within participating countries to participate as Investigators, and all interested eligible patients within investigator sites to participate as patients.

Data Collection and Follow-up

Study assessments were collected at baseline and at least every 6 months by their treating physician, as part of routine care. Adverse Events of Special Interest, other serious adverse events (SAEs), and adverse drug reactions were to be recorded at all visits.

Safety was evaluated through:

- Adverse Events of Special Interest:
    - Serious infections (infections that were SAEs, and opportunistic infections such as progressive multifocal leukoencephalopathy [PML])
    - Gastrointestinal infections
    - Lower and upper respiratory infections

  - Other clinically significant infections (infections that were not SAEs, were classified as moderate or severe, and require anti-infective treatment)
  - Malignancies
  - Infusion-related reactions and hypersensitivity
  - Hepatic injury
- All other SAEs
- Adverse drug reactions
- Pregnancy outcomes

Data on UC/CD disease activity, medication use, health resource use, and QoL were also collected.

The Sponsor ensured the routine reporting of aggregate and individual safety information in study progress reports as required by local competent authorities.

Duration of Study

The cohort follow-up period ran for up to 7 years.

Setting

The study was conducted in the following countries: Austria, Belgium, Canada, Croatia, Denmark, Estonia, France, Germany, Greece, Ireland, Israel, Italy, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, United Kingdom (UK), and United States of America (USA).

The study aimed to recruit 2,500 patients in the vedolizumab cohort and 2,500 patients in the other biologic agents cohort.

Patients and Study Size (Including Dropouts)

Inclusion Criteria:

- Signed informed consent, by the patient or a legally acceptable representative, obtained before any study-related activities were undertaken.
- Male and female patients, aged at least 18 years.
- Initiated vedolizumab or initiated a biologic agent for UC or CD (where possible patients were recruited on or before day of first dose of vedolizumab or other biologic agent. To help fit recruitment around busy clinics, patients were recruited up to 2 weeks after first dose of vedolizumab or other biologic).
- Signed release form, by the patient or a legally acceptable representative, that permitted abstraction of the patient's medical records at baseline and during participation in the study.

Exclusion Criteria:

- The patient was enrolled in a clinical trial in which treatment for UC or CD was managed through a protocol.
- Prior treatment with vedolizumab.

Study Size:

A total of 5,208 patients were enrolled in the study.

Variables

Safety

- Adverse Events of Special Interest:
  - Serious infections (infections that were SAEs, and opportunistic infections such as PML)
  - Gastrointestinal infections
  - Lower and upper respiratory infections
  - Other clinically significant infections, not SAEs, that were classified as moderate or severe and required anti-infective treatment
  - Malignancies
  - Infusion-related reactions and hypersensitivity
  - Hepatic injury
- All other SAEs
- Adverse drug reactions
- Pregnancy outcomes

Disease Activity

- UC and CD activity assessment:
  - Partial or full Mayo score for patients with UC
  - Harvey-Bradshaw Index (HBI) score for patients with CD
  - Fecal calprotectin (if measured)
  - C-reactive protein (if measured)
  - Presence/site of extra-intestinal manifestations
- Health resources used (eg, surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC or CD)

Patient Reported QoL Assessments:

- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
- 12-Item Short Form Health Survey (SF-12)

Data Sources

Baseline Data Collected at Study Enrollment

The following data were collected at study enrollment:

- Demographic data

- Medical history:
  - General, including co-morbid conditions and other autoimmune disease(s)
  - Prior serious and atypical infections and dates
  - Malignancies
  - Organ transplantation, including bone marrow or stem cell transplants
  - Infusion-related reactions
  - Hepatic injury
- UC/CD history
  - Dates and age of onset / diagnosis
  - Disease location(s)
  - Surgical history / disease management
- Health resources used within 1 year before study enrollment (eg, surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC or CD)
- UC and CD activity assessment:
  - Partial or full Mayo score for patients with UC
  - HBI score for patients with CD
  - Fecal calprotectin (if measured)
  - C-reactive protein (if measured)
  - Presence/site of extra-intestinal manifestations
- Any prior use of the following drugs, including specific drug used, indication, dose received, route of administration, and dates of use:
  - Tumor necrosis factor alpha (TNF-α) antagonists, azathioprine, 6-MP, methotrexate, or 5-ASA
  - Drugs with known association with PML (eg, alemtuzumab, belatacept, brentuximab vedotin, efalizumab, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)
  - Other immunomodulatory, anti-neoplastic, or immunosuppressive agents for UC or CD in 5 years before study enrollment
  - Other immunomodulatory, anti-neoplastic, or immunosuppressive agents for other indications in 5 years before study enrollment
  - Systemic corticosteroids in 6 months before study enrollment
  - Antibiotics to treat UC/CD in 5 years before study enrollment
- Patient reported QoL assessment:
  - SIBDQ

- SF-12

Prospective Data Collection

The following data were collected at least every 6 months during the follow-up period. If additional, unscheduled visits were performed, the minimum data to be recorded were SAEs, Adverse Events of Special Interest, and adverse drug reactions.

- UC and CD activity assessment:
  - Partial or full Mayo score for patients with UC
  - HBI score for patients with CD
  - Fecal calprotectin (if measured)
  - C-reactive protein (if measured)
  - Presence of extra-intestinal manifestations
- Vedolizumab infusions, including dose and dates
- Any use of the following drugs, including specific drug used, indication, dose received, route of administration, and dates of use:
  - TNF-α antagonists, azathioprine, 6-MP, methotrexate, or 5-ASA
  - Other immunomodulatory, anti-neoplastic, or immunosuppressive agents
  - Drugs with known association with PML (eg, alemtuzumab, belatacept, brentuximab vedotin, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)
  - Systemic corticosteroids
  - Antibiotics to treat UC/CD
- Health resources used (eg, surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC or CD)
- Patient reported QoL assessment:
  - SIBDQ
  - SF-12
- Adverse Events of Special Interest:
  - Serious infections (infections that were SAEs, and opportunistic infections such as PML)
  - Gastrointestinal infections
  - Lower and upper respiratory infections
  - Other clinically significant infections, not SAEs, that were classified as moderate or severe and require anti-infective treatment
  - Malignancies
  - Infusion-related reactions and hypersensitivity

- Hepatic injury

- All other SAEs
- Adverse drug reactions
- Pregnancy outcomes

Results

Analyses reflect data collected between 24 March 2015 (First Patient In) to 10 December 2021 (database lock). It was detected during an internal audit of the study database that the first name of patient [redacted] was mentioned in a SAE narrative field of the electronic case report form (eCRF). The necessary field of the eCRF was unlocked on 09 May 2022. The Investigator deleted the first name of patient [redacted] from the eCRF and resigned the eCRF, and the database was relocked on 18 May 2022. No other changes were made to the data.

A total of 5,208 patients were enrolled in the study (signed an informed consent): among them, 5,094 patients met the inclusion/exclusion criteria (eligible patients) and 5,008 were included in the full analysis set (FAS; enrolled patients who had non-missing informed consent date, received at least one dose of vedolizumab or other biologic agent, had UC or CD diagnosis, and had non-missing prior exposure to biologics).

Of the 5,008 patients in the FAS, 2,502 were included in the vedolizumab cohort (1,361 with UC and 1,141 with CD) and 2,506 were included in the other biologic cohort (766 with UC and 1,740 with CD).

Among the 86 eligible patients excluded from the FAS population, 52 patients had indeterminate colitis (28 patients in the vedolizumab cohort and 24 patients in the other biologic cohort), 13 patients were excluded because the Principal Investigator did not sign the eCRF, and 22 patients had an informed consent form issue.

In the FAS, the mean (standard deviation [SD]) study duration was 37.4 (14.1) months, (37.1 [14.3] months in the vedolizumab cohort and 37.8 [13.8] months in the other biologic cohort).

A total of 1,168 patients (23.3%) discontinued the study (25.4% in the vedolizumab cohort and 21.2% in the other biologic cohort): reasons for study discontinuation included withdrawal of consent (5.3%), enrolled in clinical trial (2.2%), administrative reasons (2.2%), physician determination (1.8%), death (1.1%), lost to follow-up (0.3%), and other (12.3%).

Baseline Characteristics

The percentage of female patients was comparable between treatment cohorts (52.4% in both cohorts). The mean (SD) age in years at baseline was greater in the vedolizumab cohort, 44.5 (16.3) years, than in the other biologic cohort, 40.4 (14.4) years. The mean (SD) body mass index was comparable in the vedolizumab cohort and in the other biologic cohort, 25.4 (5.3) kg/m² and 25.4 (5.4) kg/m², respectively.

On average (mean [SD]), patients treated with vedolizumab were older at inflammatory bowel disease (IBD) diagnosis than patients treated with other biologics (33.1 [15.9] years and 31.4 [13.7] years, respectively). The mean (SD) duration of IBD at baseline was 12.5 (10.9) years in the vedolizumab cohort and 10.4 (10.1) years in the other biologic cohort.

Among patients with non-missing age at IBD diagnosis, 57.3% of patients had CD (45.4% in the vedolizumab cohort and 69.1% in the other biologic cohort) and 42.3% had UC (54.3% in the vedolizumab cohort and 30.4% in the other biologic cohort).

The mean (SD) age at IBD diagnosis was 34.2 (15.1) years in UC patients and 30.7 (14.4) years in CD patients. In UC patients, 43.5% of patients had pancolitis, 39.1% had left-sided UC, 16.1% had ulcerative proctitis, and 7.3% had extensive UC. Extra-intestinal manifestations were reported in 19.0% of patients. In CD patients, the most frequent disease locations were the ileum (76.0%), the colon (60.0%), and the rectum (22.0%). Furthermore, 30.1% of patients had a history of fistula and 10.4% presented with an active fistula.

History of IBD surgery was reported in 24.8% in the vedolizumab cohort and 29.4% in the other biologic cohort (most frequently in CD patients in both cohorts). The mean (SD) time since most recent surgery was 86.0 (99.5) months in the vedolizumab cohort and 71.3 (91.5) in the other biologic cohort.

At baseline, 93.3% of patients in the vedolizumab cohort and 86.9% in the other biologic cohort received prior medications for IBD. In the vedolizumab cohort and in the other biologic cohort, prior biologic agents were reported in 65.3% and 35.4% of patients respectively, prior steroid medications in 61.4% and 54.9% of patients respectively, prior immunomodulators in 51.0% and 39.6% of patients respectively, and prior 5-ASA medications in 50.4% and 42.7% of patients respectively. The increased prior medications for IBD in the vedolizumab cohort compared to the other biologic cohort may reflect the greater average age and duration of IBD.

There were numerically greater percentages of patients in the vedolizumab cohort with prior opportunistic infections (0.7%), gastrointestinal infections (10.8%), upper respiratory tract infections (5.0%), lower respiratory tract infections (5.9%), and other infections (12.1%) than in the other biologic cohort (0.5%, 8.5%, 4.3%, 3.0%, and 9.6%, respectively). Histories of malignancy and infusion-related reactions were reported in the vedolizumab cohort as 8.4% and 6.6%, respectively, and in the other biologic cohort as 3.2% and 3.0%, respectively.

Study Treatments

Baseline

At baseline, 2,502 patients (50.0%) were treated with vedolizumab and 2,506 (50.0%) with another biologic agent (25.8% with infliximab, 14.6% with adalimumab, 7.8% with ustekinumab, 1.5% with golimumab, 0.3% with certolizumab pegol, and 1 patient [0.0%] with natalizumab).

Concomitant medications for IBD at baseline were reported in 72.9% of patients in the vedolizumab cohort and 70.2% in the other biologic cohort. Concomitant steroid and 5-ASA medications were more frequent in the vedolizumab cohort (46.3% and 36.2%, respectively) than in the other biologic cohort (38.7% and 26.2%, respectively). Conversely, concomitant immunomodulators were more frequent in the other biologic cohort (29.9%) than in the vedolizumab cohort (19.8%). Increased concomitant medications in the vedolizumab cohort compared to the other biologic cohort may also reflect the greater average age and duration of IBD. Differences in concomitant medications also reflect the imbalance in UC and CD between the vedolizumab and other biologics cohorts.

Follow-up

In the vedolizumab cohort, vedolizumab dose was modified in 3.4% of patients during follow-up and vedolizumab was discontinued in 39.7% of patients: 26.0% had a new agent administered (ustekinumab [12.8%], infliximab [7.3%], adalimumab [4.4%], golimumab [1.1%], and certolizumab pegol [0.1%]) and 13.7% had no new agent administered. The main reasons for discontinuation included lack of response (26.6%), loss of response (25.9%), patient choice (5.9%), surgery (5.9%), and intolerance/adverse event (6.6%).

In the other biologic cohort, the dose of the initial biologic agent was modified in 50.7% of patients during follow-up and the initial biologic agent was discontinued in 21.3% of patients: 15.1% had a new agent administered (vedolizumab [6.1%], adalimumab [3.7%], ustekinumab [3.7%], infliximab [1.1%], golimumab [0.4%], certolizumab pegol [0.1%]) and 6.2% had no new agent administered. The main reasons for discontinuation included lack of response (18.9%), intolerance/adverse event (18.5%), loss of response (17.0%), patient choice (4.5%), surgery (3.9%), and indication resolved or improved (3.9%). The percentage of discontinuation due to intolerance/adverse events was greater in the other biologic cohort compared to the vedolizumab cohort.

Overall, 2,876 patients (57.4% of patients in the FAS) were exposed to vedolizumab (2,502 patients in the vedolizumab cohort and 374 patients in the other biologic cohort [patients who switched to vedolizumab]): the mean duration of exposure was 22.9 (SD: 15.6) months. Additionally, 3,179 patients (63.5% of patients in the FAS) were exposed to at least one other biologic agent (2,506 patients in the other biologic cohort and 673 patients in the vedolizumab cohort [patients who switched to another biologic agent]): the mean duration of exposure to other biologic agents was 23.1 (SD: 15.3) months.

During follow-up, concomitant medications for IBD were reported in 84.7% of patients in the vedolizumab cohort and 81.8% in the other biologic cohort. Consistent with baseline results, concomitant steroid and 5-ASA medications were more frequent in the vedolizumab cohort (61.7% and 44.6%, respectively) than in the other biologic cohort (53.6% and 32.5%, respectively), and concomitant immunomodulators were more frequent in the other biologic cohort (42.0%) than in the vedolizumab cohort (33.4%). Similar to baseline, increased concomitant medications in the vedolizumab cohort compared to the other biologic cohort may reflect the greater average age and duration of IBD. Differences in concomitant medications also reflect the imbalance in UC and CD between the vedolizumab and other biologics cohorts.

Main Results

This analysis focused on the long-term safety of vedolizumab versus other biologic agents in patients with UC or CD.

In the FAS population, the incidence rate for serious infections was comparable in patients exposed to vedolizumab (0.013 [95% CI: 0.010, 0.017] per patient year [PY]) and in patients exposed to other biologic agents (0.009 [95% CI: 0.007, 0.012] per PY). The unadjusted incidence rate ratio (IRR) (vedolizumab/other biologic agents) for serious infections was significantly greater than 1 (IRR: 1.457 [95 % CI: 1.020, 2.082]). However, results of the propensity-score adjusted Cox model showed that the risk for serious infections was not significantly different in patients exposed to vedolizumab and in patients exposed to other biologic agents (hazard ratio [HR]:1.038 [95% CI: 0.981, 1.098], p-value=0.19). The incidence rate for lower and upper respiratory tract infections was 0.092 (95% CI: 0.083, 0.101) per PY in

patients exposed to vedolizumab and 0.075 (95% CI: 0.068, 0.083) per PY in patients exposed to other biologic, and the IRR (vedolizumab/other biologic agents) was significantly greater than 1 (IRR: 1.220 [95% CI: 1.064, 1.398]), suggesting that the incidence rate for lower and upper respiratory tract infections was greater in patients exposed to vedolizumab than in patients exposed to other biologic agents. The incidence rates for gastrointestinal infections were comparable in patients exposed to vedolizumab and in patients exposed to the other biologic agents (0.036 [95% CI: 0.031, 0.041] per PY vs. 0.032 [95% CI: 0.028, 0.037] per PY, respectively; IRR: 1.109 [95% CI: 0.904, 1.361]).

In addition, incidence rates of the following safety outcomes were comparable between vedolizumab and other biologic agents: the incidence rates of malignancies from 6 months after cohort entry to end of follow-up were 0.012 per PY in patients exposed to vedolizumab and 0.010 per PY in patients exposed to other biologic agents (IRR: 1.239 [95% CI: 0.870, 1.765]). The highest incidence rates for infusion-related reactions were observed within the 2-day risk window: 2.207 per PY in patients exposed to vedolizumab and 2.784 per PY in patients exposed to other biologic agents (IRR: 0.793 ([95% CI: 0.403, 1.560]). Highest incidence rates for hepatic injury were observed within the 5-day risk window, 0.037 per PY in patients exposed to vedolizumab and 0.073 per PY in patients exposed to other biologic agents (IRR: 0.502 [95% CI: 0.046, 5.534]).

The incidence rates for all other SAEs were 0.117 per PY in patients exposed to vedolizumab and 0.110 per PY in patients exposed to other biologic agents (IRR: 1.067 [95% CI: 0.949, 1.199]). The incidence rate of vedolizumab adverse drug reactions (ADRs) was 0.089 per PY and the incidence rate for other biologic agents ADRs was 0.121 per PY (IRR: 0.739 [95% CI: 0.653, 0.836]).

In the FAS population, 273 pregnancies (227 female patients) were reported: 91 pregnancies were exposed to vedolizumab at conception and 89 during pregnancy. There were 100 pregnancies exposed to another biologic agent at conception and 137 during pregnancy. Pregnancy outcomes included 169 full-term live births (76 in the vedolizumab cohort and 93 in the other biologic cohort), 35 miscarriages (14 in the vedolizumab cohort and 21 in the other biologic cohort), 25 pre-term live births (12 in the vedolizumab cohort and 13 in the other biologic cohort), 10 induced abortions (5 in the vedolizumab cohort and 5 in the other biologic cohort), 1 stillbirth (in the other biologic cohort), and 33 cases, in which pregnancy outcome was unknown (12 in the vedolizumab cohort and 21 in the other biologic cohort).

Other Safety Results

Treatment-emergent adverse events (TEAEs) were reported in 61.3% of patients in the vedolizumab cohort and 59.5% of patients in the other biologic cohort. SAEs were reported in 27.5% of patients in the vedolizumab cohort and 25.7% of patients in the other biologic cohort.

In the vedolizumab cohort, non-serious and serious vedolizumab ADRs were reported in 13.9% and 3.2% of patients, respectively. In the other biologic cohort, non-serious and serious other biologic agents ADRs were reported in 19.2% and 4.7% of patients respectively. In both cohorts, the most frequently reported serious ADRs (SADRs) consisted of colitis ulcerative and Crohn's disease. Although patients in the vedolizumab cohort reported greater average age, duration of IBD, history of infection, history of malignancy, and increased concomitant medications compared to the other biologic cohort, they resulted in fewer non-serious and serious ADRs.

A total of 32 deaths were reported: 19 in the vedolizumab cohort including 1 patient with fatal outcome that the investigator assessed as related to vedolizumab (patient with pneumonia) and 13 in the other biologic cohort including 2 patients with fatal outcome that the investigator assessed as related to other biologic agents (one patient had septic shock and pneumonia, and one patient had non-small cell lung cancer).

Effectiveness

Vedolizumab was found to be effective for the duration of the study. Results were comparable between the vedolizumab cohort and the cohort of patients receiving other biologics, based on disease activity, QoL assessments, and health resource utilization, including when analyzed by previous exposure to biologics.

Discussion

The post authorization safety study (PASS) MLN0002 401 was conducted to further characterize the potential risk of serious infections; specific infections including gastrointestinal, upper and lower respiratory infections, PML; malignancies, liver toxicity, and infusion-related reactions, including hypersensitivity reactions in patients treated with vedolizumab. The PASS MLN0002_401 also aimed to describe vedolizumab use in pregnant women and vedolizumab long-term safety.

Of the 5,008 patients in the FAS, 2,502 patients (50.0%) received vedolizumab and 2,506 patients (50.0%) received another biologic agent at baseline.

Patients in the vedolizumab cohort compared to the other biologic cohort reported greater average age, duration of IBD, history of infection, history of malignancy, and increased concomitant medications, which indicated patients with more advanced and clinically complex disease.

In total, 2,876 patients were exposed to vedolizumab (2,502 patients in the vedolizumab cohort and 374 patients who switched to vedolizumab in the other biologic cohort) and 3,179 patients were exposed to at least one other biologic agent (2,506 patients in the other biologic cohort and 673 patients who switched to another biologic agent in the vedolizumab cohort).

Vedolizumab, like other monoclonal antibodies, is associated with an increased risk for developing infections in light of the drug's antagonism of the lymphocyte receptor, α4β7 integrin. Incidence rates of serious infections in patients exposed to vedolizumab in the PASS MLN0002_401 was 0.013 per PY. The incidence rate of GI infections was 0.036 per PY and the incidence rate of upper and lower respiratory tract infections was 0.092 per PY. There were no cases of PML reported in the PASS MLN0002 401. Overall, incidence rates of infections in patients exposed to vedolizumab in the PASS MLN0002_401 were lower than rates observed in previous randomized clinical trials.

The incidence rate of infusion-related reactions was 2.207 per PY considering a 2-day risk window, and the incidence rate of hepatic injury was 0.037 per PY considering a 5-day risk window .

The incidence rate of malignancies was 0.012 per PY in patients exposed to vedolizumab considering a risk window from 6 months after cohort entry to the end of follow-up. These results suggest that there is no increased risk for malignancy.

The results of the PASS MLN0002 401 showed that the incidence rates of adverse events of special interest were generally comparable between vedolizumab and other biologic agents.

As mentioned above, the patients in the vedolizumab cohort had in general a more advanced and clinically complex disease than patients in the other biologic cohort. In spite of that, the frequency of SAEs was comparable between the vedolizumab cohort and the other biologic cohort (27.5% and 25.7% respectively). Additionally, ADRs and SADRs tended to be less frequent in the vedolizumab cohort (vedolizumab ADRs: 13.9%; vedolizumab SADRs: 3.2%) than in the other biologic cohort (other biologic agents ADRs: 19.2%; other biologic agents SADRs: 4.7%).

In addition to long-term safety data, PASS MLN0002 401 also provided pregnancy data. A total of 119 pregnancies were reported in 100 female patients in the vedolizumab cohort, 75 pregnancies being exposed to vedolizumab at conception and 74 during pregnancy. Of the 107 known pregnancy outcomes, there were 76 full-term live births, 14 miscarriages, and 12 pre-term live births. Five induced abortions were also reported. There were no confirmed safety concerns related to pregnancies (there was one case of congenital pulmonary airway malformation related to vedolizumab and mesalazine, but causality was confounded by concomitant use of mesalazine). Pregnancy data in the vedolizumab cohort were comparable to the other biologic cohort.

Overall, the vedolizumab cohort data was consistent with the known safety profile of vedolizumab. The results of the PASS MLN0002 401 suggest that there are no new safety concerns associated with vedolizumab treatment.

Conclusion

This final study report provides insights into the safety profile of vedolizumab in real-world clinical settings. There were no new trends or changes of clinical importance for infections (serious infections, GI infections, respiratory tract infections, other infections), malignancies, infusion-related reactions, hepatotoxicity, and pregnancies. No cases of PML were reported. Vedolizumab has an acceptable safety profile, which is consistent with previous data and now also includes long-term safety. No new safety concerns were identified.

Vedolizumab was found to be effective for the duration of the study. Results were comparable between the vedolizumab cohort and the cohort of patients receiving other biologics, based on disease activity, QoL assessments, and health resource utilization, including when analyzed by previous exposure to biologics.

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