Real-world effectiveness and safety of vedolizumab induction therapy for ulcerative colitis: A prospective nationwide Polish observational study

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Abstract

Background. Vedolizumab is recommended as a first-line biological treatment, along with other biological drugs, in ulcerative colitis (UC) patients in whom conventional therapy failed and as a second-line biological treatment following a failure of a tumor necrosis factor alpha (TNF-α) antagonist.

Objectives. We aimed to assess the real-world effectiveness and safety of vedolizumab induction therapy in UC patients treated in the scope of the National Drug Program (NDP) in Poland.

Materials and methods. The endpoints were the proportions of patients who reached clinical response, clinical remission and mucosal healing at week 14. Partial Mayo scores, Mayo subscores and C-reactive protein (CRP) levels were also evaluated.

Results. Our study population consisted of 100 patients (55 biologic-naïve and 45 biologic-exposed). The median total Mayo score at baseline was 10 (interquartile range (IQR): 9–11), and 52 patients (52%) had extensive colitis. The clinical response at week 14 was achieved in 83 (83%) and clinical remission in 24 (24%) cases. Mucosal healing was observed in 56 (62%) patients at week 14. In patients with prior failure of biologic treatment (n = 25), 17 (68%) responded to vedolizumab treatment. A decrease in the median CRP level (from 3.7 mg/L to 2.6 mg/L) and the median total Mayo score (from 10 to 4) was observed. No new safety concerns were recorded and no patients discontinued the treatment due to adverse events (AEs).

Conclusions. Vedolizumab was effective and safe as induction therapy for UC in a Polish real-world population including patients with severely active UC and a low number of patients with prior biological treatment failures.

Key words: vedolizumab, ulcerative colitis, induction therapy, real-world evidence, National Drug Program

Conflict of interest

Edyta Zagórowicz received lecture fees from Janssen, Sandoz, Ferring, and Pfizer; consultancy fees from Pfizer, Janssen and Takeda; and other compensations from Takeda and Janssen. Piotr Eder received lecture fees and/or travel grants from Takeda, Ferring, Astellas, Pfizer, and Janssen. Kamila Stawczyk-Eder received travel grants and lecture fees from Janssen, Pfizer and Takeda. Aleksandra Kaczka received lecture fee(s)/travel/accommodation/meeting expenses from Takeda, Janssen-Cilag, Biogen, Astellas, and Alfa-Sigma. Ariel Liebert received payment for lectures from Janssen, Takeda, Egis, Abbvie, and Pharmabest, and travel/accommodation/meeting expenses from Janssen, Takeda, Egis, and Abbvie. Maria Kłopocka has received payment for lectures from Janssen, Takeda, Ferring, Alfa-Sigma, and Pharmabest, and travel/accommodation/meeting expenses from Ferring, Janssen, Takeda, Alfa-Sigma, and Pharmabest. Rafał Filip served as a speaker for Gramineer International AB, Egis, Ferring, Janssen, and Takeda; received investigational grants from Gramineer International AB and Egis; and received support for travelling and congress assistance from MSD, Abbvie, Alfa-Sigma, Egis, Takeda, and Ferring. Hubert Zatorski received lecture fees and travel grants from Takeda. Anna Solarska-Półchłopek received lecture fees and travel grants from Janssen. Renata Talar-Wojnarowska received lecture fees and/or travel grants from Abbvie, Alfasigma, Astellas, Ferring, Janssen, Pfizer, and Takeda. Krzysztof Wojciechowski and Szymon Drygała are permanent employees of Takeda Pharma sp. z o.o. Krzysztof Wojciechowski is now an employee of Independent Public Health Care Center in Tarczyn, Poland. The remaining authors disclose no conflicts of interest.

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Background

Ulcerative colitis (UC) is an idiopathic, relapsing disorder of the large bowel, usually characterized by abdominal pain, bloody diarrhea and fatigue.[1] Ulcerative colitis, if uncontrolled, leads to functional deterioration and impaired quality of life of affected individuals.[2] Hospitalization and surgical intervention may be required in patients with severe UC; moreover, chronic inflammation of the bowel increases colorectal cancer risk.[3]

Patients with UC usually need lifelong medical therapy, which typically includes aminosalicylates, corticosteroids, thiopurines, and biologics such as tumor necrosis factor alpha (TNF-α) antagonists.[4] Corticosteroids, thiopurines and TNF-α antagonists act as systemic immunosuppressants and are associated with an increased risk of serious infections. Disease management with agents representing a more selective mechanism of action is therefore highly preferable.

The pathogenesis of UC involves the disruption of the cytokine signaling network responsible for the maintenance of homeostasis between epithelial cells of the intestines and immune cells, which leads to the infiltration of lymphocytes from the systemic circulation to the colon.[5] This process is mediated by interactions between α4β7 integrins located on the lymphocyte cell surface and the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) present on intestinal endothelial cells.[6,7] Vedolizumab, a gut-selective, humanized IgG1 monoclonal antibody directed against the human lymphocyte integrin α4β7, has a well-established efficacy and safety profile in adult patients with inflammatory bowel disease based on extensive clinical trials and real-world data.[8] Due to its gut-selective manner, it does not induce systemic immunosuppression.[9]

In 2014, based on the results of the GEMINI-1 phase III study which confirmed the efficacy and safety of vedolizumab in patients with moderate-to-severe active UC,[10] vedolizumab was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of moderate-to-severe UC in adults. Vedolizumab is recommended as a first-line biological treatment, along with other biological drugs, in ulcerative colitis (UC) patients in whom conventional therapy failed and as a second-line biological treatment following a failure of a TNF-α antagonist.[11] The effectiveness and safety of vedolizumab for the treatment of UC patients have been confirmed in real-world studies.[12]

In Poland, vedolizumab and infliximab are the only reimbursed biologic treatments for UC within the scope of the National Drug Program (NDP).[13] Thus, the baseline characteristics of patients treated with vedolizumab in Poland depend on the criteria of the NDP. In the population enrolled in this study, 55% of patients treated with vedolizumab were biological-naïve (bio-naïve), and only 25% had previously failed anti-TNF-α therapy.[14] These characteristics are in contrast to cohorts from other real-world studies investigating the effectiveness and safety of vedolizumab for UC, where most patients failed 1 or 2 anti-TNF-α therapies and bio-naïve patients constituted less than 25% of the studied populations.[12] Failure of previous anti-TNF-α therapy possibly impacts the achieved treatment results.

Objectives

This study aimed to evaluate the real-world effectiveness and safety of vedolizumab induction therapy for UC patients treated within the scope of the NDP in Poland.

Materials and methods

Study design, setting and participants

The POLONEZ study is a multicenter, non-interventional, prospective study to evaluate the effectiveness and safety of vedolizumab for the treatment

of moderate-to-severe active UC in Poland. Consecutive patients who qualified for reimbursed treatment with vedolizumab within the scope of the NDP were recruited between February and November 2019 from 12 centers in Poland. The inclusion criteria, defined by the NDP, were: moderate-to-severe active UC (total Mayo score >6),[15] contraindications to treatment with ciclosporin, and inadequate response, intolerance or other contraindication to conventional therapy (including both corticosteroids and immunosuppressive drugs).[13]

The study protocol was approved by the Bioethics Committee of the Maria Sklodowska-Curie National Research Institute of Oncology (approval No. 79/2018). All patients gave written informed consent to participate in the study. The study was registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) clinical trial database.

Variables

The data regarding patient sex, age, body mass index (BMI), disease duration, smoking status, type of extraintestinal disease manifestations if present, previous and current concomitant medications (including the status of previous biologic treatment), and disease phenotype (according to the Montreal classification)[16] were collected. The total Mayo score[14] (range: 0–12, with higher scores indicating a more active disease) was used to assess disease activity at week 0 and to assess induction effectiveness at week 14. The partial Mayo score (total Mayo score without the endoscopic component, range: 0–9)[17] was used in subsequent follow-up visits. Clinical response was defined as a total Mayo score reduction by ≥3 points. Clinical remission was established as a Mayo score ≤2 and no subscore higher than 1. Mucosal healing was defined as an endoscopic Mayo score ≤1.

Vedolizumab was administered as induction therapy according to its label (300 mg intravenous (i.v.) at weeks 0, 2 and 6). Concomitant medications such as 5-aminosalicylic acid (5-ASA) derivatives (mesalazine or sulfasalazine), steroids (prednisone, methylprednisolone or budesonide) and immunomodulators (azathioprine or mercaptopurine) were recorded.

Patients were evaluated during their visits at baseline and week 14. The primary endpoint of this study was clinical response and clinical remission, as defined above. The secondary endpoint was the drug's safety. There were also the following exploratory endpoints: mucosal healing, changes in the total and partial Mayo scores, Mayo subscale scores, C-reactive protein (CRP) concentrations, corticosteroid usage, and occurrence of extraintestinal symptoms.

Subgroup analyses included bio-naïve, biologic-exposed (bio-exposed) and biologic-failure (bio-failure) patients. Additionally, clinical response was evaluated separately in the following subgroups: I. patients who had mucosal appearance upon endoscopy indicative of severe disease (Mayo score on an endoscopic subscale = 3) at baseline; II. patients who had a high total Mayo score (>9) at baseline; III. patients who were hospitalized up to 12 months before the enrollment into the study.

Safety

The safety population consisted of all patients who received at least 1 dose of vedolizumab. All adverse events (AEs) which occurred between the visit at week 0 and the visit at week 14 were recorded. The results were expressed according to the Medical Dictionary of Regulatory Activities (MedDRA) 23.0 terminology.[18]

Statistical analyses

Continuous variables are shown as median and interquartile ranges (IQRs; 1st quartile–3rd quartile (Q1–Q3)). Boxplots represent median values and IQRs (boxes) while error bars represent the minimum and maximum values. Categorical variables are shown as the number of observations and percentages. To compare groups, the Mann–Whitney U test or paired Wilcoxon test was used for quantitative variables and the χ^2 test (or Fisher's test) for qualitative variables. All statistical analyses were done using R v. 3.5 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient flow and baseline characteristics

A total of 100 patients were recruited for the study and 91 completed the visit at week 14. Patient dispositions are shown in Fig. 1. A median of 3 vedolizumab doses were administered to each patient.

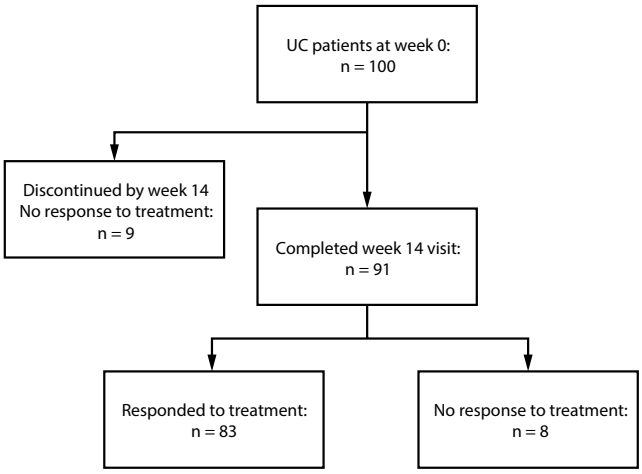

Fig. 1. Patient disposition

UC – ulcerative colitis.

Table 1. Baseline characteristics of the patients (baseline demographic and clinical characteristics of the study population were published elsewhere[14])

Characteristic		Value (n = 100)
Age [years]		35.0 (26.0–43.0)
Male sex, n (%)		51 (51)
BMI [kg/m^2]		23.4 (19.7–26.8)
Smoking status, n (%)	smoker	4 (4)
	ex-smoker	26 (26)
	nonsmoker	70 (70)
Time from diagnosis [years]		6 (3–11)
Total Mayo score		10.0 (9.0–11.0)
Partial Mayo score		7.0 (6.0–8.0)
Disease extent, n (%)	proctitis	6 (6)
	left-sided colitis	42 (42)
	pancolitis	52 (52)
Extraintestinal manifestations at enrollment, n (%)	arthralgia	12 (12)
	primary sclerosing cholangitis	1 (1)
Previous biologic treatment, n (%)	biologic-naïve	55 (55)
	biologic-exposed	45 (45)
	infliximab only	40 (40)
	adalimumab only	2 (2)
	infliximab and adalimumab	2 (2)
	golimumab and vedolizumab within clinical trials	1 (1)
Concomitant immunomodulator, n (%)		45 (45)
Concomitant systemic corticosteroids, n (%)		68 (68)

BMI – body mass index. Values are shown as medians (interquartile range (IQR)) unless stated otherwise.

The baseline characteristics of the patients are given in Table 1. Approximately half of the patients had extensive mucosal involvement (pancolitis). More than half of the patients had not been previously exposed to biological drugs (i.e., they were bio-naïve). Among bio-exposed patients, 44 (98%) received anti-TNF-α treatment (infliximab and/or adalimumab). Failure of anti-TNF-α treatment was reported in 25 individuals (57% of patients treated with anti-TNF-α). At baseline, almost half of the patients received concomitant immunosuppressants, and 2 in 3 received corticosteroids. Detailed baseline demographics and the clinical profile of the study group were described previously.[14]

Effectiveness outcomes

Overall, 83 (83%) patients responded to vedolizumab at week 14. The percentage of responding patients was slightly higher in bio-naïve patients and lower in bio-exposed patients. In patients who had previously failed to respond to anti-TNF-α treatment, approx. 2/3 responded to induction treatment with vedolizumab (Fig. 2A). Twenty-four percent of all patients (27% of bio-naïve patients and 20% of bio-exposed patients) were in clinical remission at week 14 (Fig. 2B). Mucosal healing was achieved in 56 patients (62% of patients reaching week 14, 68% of responders; Fig. 2C, Fig. 3A).

The median total Mayo score decreased from 10 at week 0 to 4 at week 14 (Fig. 2D). The magnitude of change in the total Mayo score was similar across subgroups (Fig. 2D). In the subgroup of responders, the decrease in the median total Mayo score was more pronounced, from 10 at week 0 to 3 at week 14 (Fig. 3B). In the overall study group, a decrease in the median CRP concentration from 3.7 mg/L at baseline to 2.6 mg/L at week 14 was reported (Fig. 2E). The decrease in CRP from baseline to week 14 reached statistical significance only in the bio-naïve patients. In the bio-exposed and bio-failure subgroups, CRP median values increased throughout the study (Fig. 2E). For the subgroup of responders, CRP levels and partial Mayo score at weeks 0 and 14 as well as clinical remission results are presented in Supplementary Fig. 1.

Improvements were reported in all Mayo subscales from baseline to week 14 in the overall study group ($p < 0.001$ for each subscale, Table 2). A quarter of patients had normal stool frequency (compared to 0% at baseline) and almost half of the patients had 1–2 stools more than normal at week 14 (compared to 3.3% at baseline). At week 14, 2/3 of patients reported no rectal bleeding. Approximately 1 in 5 patients had a mucosal appearance graded as normal or corresponding to inactive disease, and had disease activity rated by the physician as normal at week 14. The results for the bio-naïve, bio-exposed and bio-failure subgroups are shown in Supplementary Table 1.

No major change in extraintestinal symptoms throughout the induction therapy with vedolizumab was observed. At baseline, 11 (12%) patients reported extraintestinal symptoms, mostly arthralgia (n = 10, 11%). At week 14, among the 91 evaluated patients, extraintestinal symptoms were present in 12 (13%) individuals and arthralgia in 11 (12%).

Concomitant treatment with corticosteroids

In the overall study group, the percentage of patients treated with corticosteroids dropped by 45% from week 0 to week 14 (Supplementary Fig. 2A). The decrease was most pronounced in the bio-naïve patients (53.1%). In the bio-exposed and bio-failure groups, the number of individuals on corticosteroids decreased by 35.7% and 21.7%, respectively. At week 14, 1 in 8 patients in the bio-naïve subgroup and more than half of the patients in the bio-failure subgroup were on corticosteroids (Supplementary Fig. 2B).

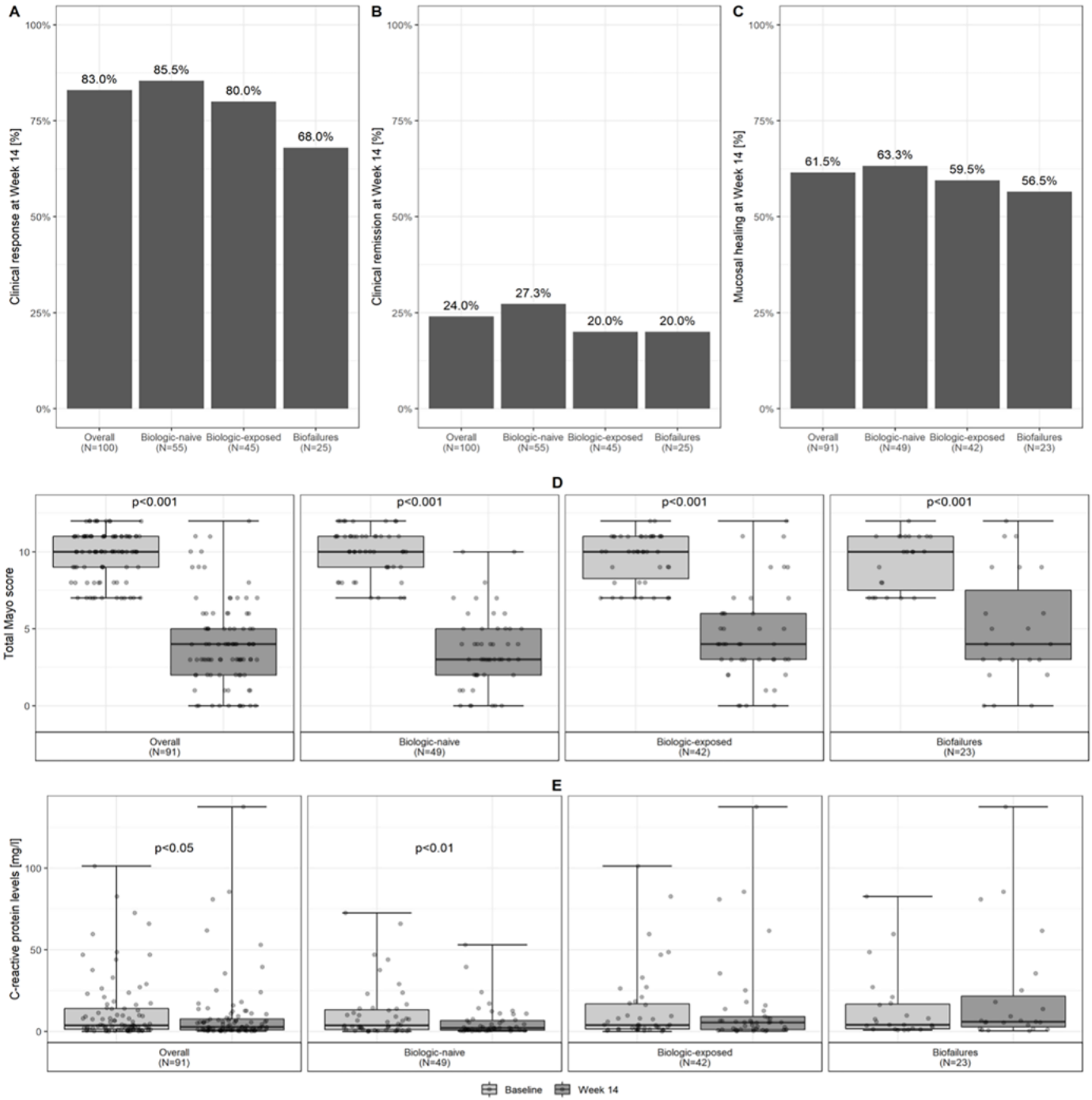

Fig. 2. Clinical effectiveness of vedolizumab in induction therapy for ulcerative colitis in the overall study population. A. Clinical response at week 14; B. Clinical remission at week 14; C. Mucosal healing at week 14; D. Total Mayo score at weeks 0 and 14; E. C-reactive protein (CRP) levels at weeks 0 and 14. Boxes correspond to median values and interquartile ranges (IQRs), and error bars represent minimums and maximums

The median daily dose of prednisolone equivalent decreased in the general study population (from 10 mg at week 0 to 0 mg at week 14) and in each subgroup (Supplementary Fig. 2C), similarly to the subgroup of responders (Supplementary Fig. 2D). Taking into consideration only patients treated with corticosteroids, the median (range) dose of prednisolone equivalent changed from 20 mg (5–60 mg) at week 0 to 15 mg (2.5–40 mg) at week 14 (Supplementary Fig. 2E).

Adverse events

A total of 5 patients experienced AEs during vedolizumab induction therapy (Supplementary Table 3). All recorded AEs were classified as serious AEs (SAEs). In 1 patient, the AE was deemed to be associated with treatment by the treating physician. Two AEs belonged to the MedDRA system organ class (SOC) of infections

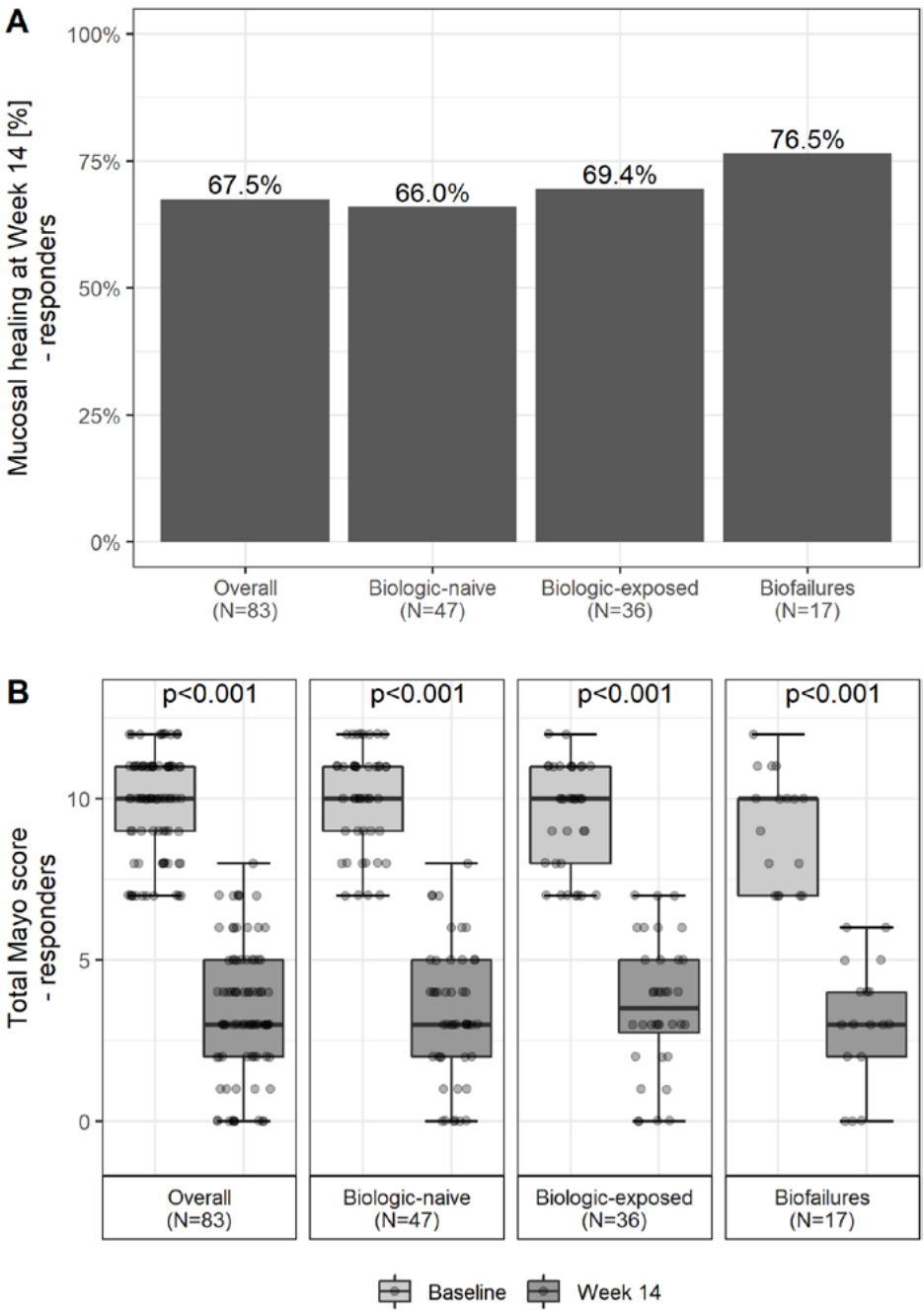

Fig. 3. Clinical effectiveness of vedolizumab in induction therapy for ulcerative colitis in the subgroup of responders. A. Mucosal healing at week 14; B. Total Mayo score at weeks 0 and 14. Boxes correspond to median values and interquartile ranges (IQRs), and error bars represent minimums and maximums

and infestations. None of the patients discontinued vedolizumab treatment due to AEs.

Discussion

In this study, vedolizumab was effective and safe as induction therapy for UC in a Polish real-world study population. Approximately 8 in 10 patients responded to treatment and more than 60% of patients achieved endoscopic remission at week 14. To our knowledge, this is the first report on vedolizumab's real-world effectiveness in UC treatment not only for Poland but also for the Central and Eastern Europe regions.

The clinical response rate observed in our study was higher than in the randomized clinical trials. In a pivotal trial reported by Feagan et al.,[10] 47.1% of patients responded to treatment at week 6, and in a more recent study conducted by Sands et al.,[19] the response rate at week 14 was 67.1%. Across multiple European real-world studies, the clinical response rate at week 14 varied between 43.2% and 67%.[20–24] In our study, a response rate of 68% was reported for patients with a prior failure to biologic treatment. However, our definition of response was generally less stringent than those applied in corresponding studies, as it included only the criterion of a decrease in the Mayo score by at least 3 points. Additionally, our study population included a higher percentage of bio-naïve patients.

Table 2. Changes in Mayo subscales from week 0 to week 14 of induction therapy with vedolizumab (n = 91)

Mayo score on a subscale		Week 0, n (%)	Week 14, n (%)	p-value*
Stool frequency	normal (0)	0 (0.0)	23 (25.3)	<0.001
	1–2 stools/day more than normal (1)	3 (3.3)	43 (47.3)	
	3–4 stools/day more than normal (2)	19 (20.9)	15 (16.5)	
	>4 stools/day more than normal (3)	69 (75.8)	10 (11.0)	
Rectal bleeding	none (0)	3 (3.3)	60 (65.9)	<0.001
	visible blood with stool less than half of the time (1)	19 (20.9)	23 (25.3)	
	visible blood with stool half of the time or more (2)	56 (61.5)	7 (7.7)	
	passing blood alone (3)	13 (14.3)	1 (1.1)	
Mucosal appearance at endoscopy	normal or inactive disease (0)	0 (0.0)	17 (18.7)	<0.001
	mild disease (1)	3 (3.3)	39 (42.9)	
	moderate disease (2)	25 (27.5)	22 (24.2)	
	severe disease (3)	63 (69.2)	13 (14.3)	
Physician rating of disease activity	normal (0)	0 (0.0)	15 (16.5)	<0.001
	mild (1)	0 (0.0)	55 (60.4)	
	moderate (2)	36 (39.6)	17 (18.7)	
	severe (3)	55 (60.4)	4 (4.4)	

* paired Wilcoxon test.

In a study reported by Kopylov et al. on a cohort of bio-naïve patients, the response rate of 79.1% at week 14 was more similar to our findings.[25] Furthermore, a reported mucosal healing rate of 58.5% at week 14 was also similar to the rate reported in our study (61.5%). However, in the aforementioned study, clinical remission was found in almost 40% of patients at week 14, which was a higher percentage than in our patient population (overall: 24%, bio-naïve: 27.3%). Similarly, in a recent observational study including only bio-naïve patients with UC and Crohn's disease, a clinical response after 14 weeks of vedolizumab treatment was reported in 67.9% of UC patients and steroid-free remission – in almost half of them (46.4%).[26]

In line with the observed reduced effectiveness of 2nd and 3rd anti-TNF-α treatments in patients with UC in whom anti-TNF-α therapy failed before,[27,28] vedolizumab was shown to be less effective in anti-TNF-α-experienced individuals. A recent randomized trial by Sands et al. reported that 34.2% of bio-naïve patients achieved clinical remission at week 52, compared with 20.3% of those who were previously treated with anti-TNF-α drugs.[19] These findings were confirmed in real-world populations. In studies reported by Narula et al. and Plevris et al., patients treated with vedolizumab with prior exposure to anti-TNF-α therapy had a reduced probability of achieving clinical remission and mucosal healing than those with no history of anti-TNF-α treatment.[29,30] The greater effectiveness of vedolizumab in bio-naïve patients was also highlighted in a meta-analysis of real-world studies by Schreiber et al.[31] Our study is consistent with these reports – both clinical response and endoscopic remission rates were observed more frequently in bio-naïve compared to bio-failure patients.

Several predictors of response to vedolizumab in UC were described in previous real-world studies. Prior anti-TNF-α exposure is the most recognized negative predictive factor for vedolizumab treatment response and our report seems to confirm those results.[32–35] Also, elevated CRP levels at baseline were associated with a lower chance of achieving response[34,36] or steroid-free remission,[21] which is in line with our findings. Recently, colonic eosinophilia was described as a promising biomarker for response to vedolizumab.[36] Our study, in contrast to other reports,[22,23,32,37] showed no relationship between clinical activity at baseline and treatment outcome.

The number of AEs reported in our study was generally lower than in other real-world studies. In France, SAEs were detected in 8.2% of patients in a 14-week induction trial in inflammatory bowel disease, and in 5.1% of individuals, vedolizumab was discontinued due to the SAEs.[22] Kopylov et al. reported AEs in 14.2% of patients receiving vedolizumab as induction therapy for inflammatory bowel disease in Israel.[23] In a multinational cohort of bio-naïve patients, AEs occurred in 11% of patients during induction therapy with vedolizumab, leading to treatment discontinuation in 3.3% of individuals.[25] However, in a 2018 meta-analysis by Schreiber et al. summarizing safety data from 46 real-world studies on vedolizumab for inflammatory bowel disease, the overall AE rates were reported to range between 0% and 67% (for SAEs, 0–13%).[31] In our study, infections and infestations were the most frequent category of AEs. *Clostridioides difficile* and cytomegalovirus infections were reported in 2.5% of patients from the Israeli cohort,[23] which is in line with our findings. No new safety concerns were identified in our study. Importantly, no patient discontinued the treatment due to AEs.

Limitations

Although the group of 100 consecutive patients with UC represents one of the largest real-world cohorts studied prospectively for vedolizumab,[12,32] the study limitations include a relatively small sample size. For this reason, we could not analyze treatment response in the subgroups of patients co-treated with corticosteroids and/or immunosuppressants. The low number of non-responders to vedolizumab induction therapy impacted the approach to perform statistical analysis for predictors of treatment response and could have also affected the results. Additionally, as this was a multicenter real-world study, certain differences in clinical practice patterns and medical procedures cannot be excluded. Nevertheless, all patients included in our study were treated with vedolizumab in the scope of the NDP, and its requirements allowed for the clinical data to be fully and systematically collected. Furthermore, data for an important therapeutic monitoring biomarker, fecal calprotectin, were not assessed in our study.

Conclusions

In summary, our study showed that vedolizumab is effective as induction therapy for UC, with 8 in 10 patients responding to treatment in a Polish real-world study population characterized by a high severity of UC and a low number of patients with prior anti-TNF-α therapy failure. The observed favorable safety profile of vedolizumab was consistent with the results of randomized clinical trials and other real-world studies.

Supplementary data

The supplementary materials are available at https://doi.org/10.5281/zenodo.7773901. The package contains the following files:

Supplementary Table 1. Changes in Mayo subscales from week 0 to week 14 of induction therapy with vedolizumab in bio-naïve, bio-exposed and bio-failure patients with UC.

Supplementary Table 2. Adverse events in patients with UC treated with vedolizumab using MedDRA 23.0 terminology.

Supplementary Fig. 1. Clinical effectiveness of vedolizumab in induction therapy for UC in the group of responders. A. Clinical remission at week 14; B. Partial Mayo scores at weeks 0 and 14; C. C-reactive protein levels at weeks 0 and 14. Boxes correspond to median values and IQRs, error bars represent minimums and maximums.

Supplementary Fig. 2. Percentage of patients receiving concomitant corticosteroids at weeks 0 and 14 in the overall study population (A) and in the subgroup of responders (B); Doses of prednisolone equivalent (without budesonide) at weeks 0 and 14 in the overall study population (C), in the subgroup of responders (D), and only in patients currently treated with corticosteroids (E). Boxes correspond to median values and IQRs, error bars represent minimums and maximums.

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