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ORIGINAL ARTICLE

The significance of individual patient characteristics in a cohort of patients with inflammatory bowel disease treated with vedolizumab

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ABSTRACT

Aim Care for the inflammatory bowel disease (IBD) patients presents unique challenges as decisions regarding therapy must consider numerous distinct characteristics of each patient. The aim of the study was to recognize patients' characteristics as predictors of success in vedolizumab treatment.
Methods In a retrospective observational study, data regarding age, gender, body mass index (BMI), length of disease, previous exposure to anti-tumour necrosis factor (TNF), drugs, and smoking status were extracted from the routine clinical practice. Patients were assessed for clinical remission and steroid-free remission after the 26-week treatment with vedolizumab.
Results The study included 76 patients with UC and 63 with CD. A total of 63 (out of 76; 82.9%) (Cl: 72.5-90.6%) of UC and 54 (out of 63; 85.7%) (Cl: 74.6-93.3%) CD patients achieved clinical remission in the 26-week vedolizumab treatment. Over five years, illness was noticed in 32 (53.1%) CD patients. Clinical remission was not achieved in six (out of 13; 46.1%) UC patients aged 40-49 years and six (out of nine; 66.6%) CD patients aged 30-49 years. Among CD patients, remission was achieved in 22 (85.7%) females and 23 (63.6%) males. Remission rates were generally higher in patients with a BMI of 18.6-25 and 25.1-30. Previous exposure to anti TNF drugs and smoking status did not influence treatment outcomes.
Conclusion The efficacy of vedolizumab is a viable treatment option for both ulcerative colitis and Crohn's disease. The exploration of individual patient characteristics holds promise in predicting a treatment outcome.

Keywords: biologic treatment, individual disease control, predicting treatment success

INTRODUCTION

Inflammatory bowel disease (IBD) encompasses two main conditions: Crohn's disease (CD) and ulcerative colitis (UC). IBD presents a significant therapeutic challenge in clinical practice. The management of IBD aims at inducing and maintaining remission, improving quality of life and preventing complications (1). Conventional therapies, such as corticosteroids and immunomodulators, have been the mainstay of the treatment. However, their long-term use is often limited by side effects and decreasing efficacy over time (2).

Biological therapy has revolutionized the management of IBD, particularly for patients who have not responded well to conventional treatments (3). Initially, the therapeutic landscape for IBD was primarily dominated by anti-tumour necrosis factor (anti-TNF) agents. However, a notable proportion of patients either do not respond adequately to anti-TNF therapies, lose response over time, or discontinue the treatment due to adverse effects (1,3).

Biological therapy has significantly improved the management of IBD, offering many patients the opportunity for a better disease control and improved quality of life. However, the decision to initiate biological therapy should be individualized based on factors such as disease severity, treatment history, comorbidities and patient preferences. Biological drugs used in IBD are anti- tumour necrosis factor (TNF) drugs, anti-integrin drugs and anti-interleukin drugs (4).

One of the standard therapy options for the treatment of both CD and UC is the anti-α4β7 integrin antibody vedolizumab. Its efficacy and safety were shown in large phase III trials in 2013 and have been confirmed in multiple real-world reports since then (5). Vedolizumab has been shown to prevent the so-called gut homing process of α4β7-expressing immune cells, i.e. their extravasation from blood to the intestinal tissue (6). Probably due to this impact on circulating and not on resident immune cells, the onset of the effect is somewhat delayed in a considerable portion of the responding patients (7). Therefore, vedolizumab is seen as a rather "slow-acting" antibody, further emphasizing the importance of a high a priori likelihood of success to avoid long ineffective treatment periods before the

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response or non-response can be reliably assessed (8).

IBD can affect individuals of any age, but it is most diagnosed between the age of 20 and 40 (9). Vedolizumab can be an effective and well-tolerated treatment option across a wide range of ages, but careful assessment and monitoring are essential to ensure optimal outcomes, particularly in paediatric and elderly populations (7,10). Both males and females are affected by IBD, but some studies suggest a slightly higher prevalence in women, particularly for Crohn's disease (11).

Patients who have previously used and failed other medications for IBD may respond differently to vedolizumab (12). Understanding a patient's treatment history can help healthcare providers tailor therapy and manage expectations regarding response.

Early intervention and treatment initiation are associated with better outcomes in IBD, the efficacy of the treatment can be influenced by the duration of the disease (12,13). Patients with longer disease duration may have a more complex disease course, reduced treatment responsiveness, and a higher likelihood of requiring surgical interventions or experiencing treatment-related complications (14). However, individual responses to the treatment vary, and a personalized approach to IBD management, considering disease duration, severity, comorbidities, and patient preferences, is essential for optimizing outcomes and improving the overall care of patients with IBD (15).

The prevalence of IBD is increasing in parallel with overweight and obesity (16). Obesity and IBD can interact in complex ways, with obesity potentially influencing the risk, course, and management of IBD, and vice versa (17). Understanding and addressing the interplay between these two conditions are crucial for optimizing outcomes and improving the overall health of individuals living with both obesity and IBD.

Smoking significantly increases the chances of developing and worsening CD but provides some protection against the development and severity of ulcerative colitis. However, it is not entirely clear how smoking affects the effectiveness of treatments for IBD. There are likely many lifestyle and psychosocial factors that play a role in the connection between smoking and IBD, but these factors may not be fully recognized (18).

Each patient is unique, with their own characteristics like age, overall health and any risks they may face. Understanding these individual traits is key to tailoring vedolizumab treatment effectively for IBD (19). By considering aspects such as the type and severity of the disease, past treatments, other medications used, any complications, what the patient prefers, and how often they need to be monitored, healthcare providers can improve outcomes and make patients happier and healthier (20).

The treatment of advanced IBD with drugs such as vedolizumab is new, so research on predictors of response to therapy is not modest. None has been conducted in our country.
The aim of the study is to identify the characteristics of IBD patients that may have an impact on the efficacy of treatment with vedolizumab.

PATIENTS AND METHODS

Patients and study design

A retrospective study with data from routine clinical practice was conducted. The study included patients who received vedolizumab between June 2014 and May 2020 in IBD centres (Sarajevo, Banjaluka, Tuzla and Mostar) in Bosnia and Herzegovina. Individual patient data were collected from electronic patient records (anonymously).

The Ethics Committee of the University Clinical Centre Sarajevo approved the research.

Patients aged 18 years or older were considered for analysis if they met the following conditions: a confirmed diagnosis of CD or UC supported by clinical evidence and either endoscopic or radiographic findings, and experienced active symptoms of CD or UC prior to initiating the vedolizumab treatment. Exclusion criteria encompassed cases of microscopic colitis and undefined IBD. Extensive medical documentation was reviewed for each patient to extract relevant data related to patient characteristics (age, gender, BMI, smoking status), and disease characteristics (duration, activity, exposure to anti-TNF drugs, and details of treatment with vedolizumab).

Methods

The disease activity was assessed at the start of the vedolizumab treatment and regular intervals in 26th week using standardized clinical indices: Crohn's disease activity index (CDAI) (21) for patients with CD and the Mayo score (22) for patients with UC. Endoscopic evaluations, radiologic imaging findings and histopathology reports, if performed as part of routine clinical care, were also reviewed to confirm clinical assessments of the disease activity.

The following basic parameters were collected: age at the disease onset, disease duration, clinical disease activity as assessed by the 9-point partial Mayo score (PMS) (23) and Harvey–Bradshaw index (HBI) (24) for UC and CD, previous exposure anti-TNF-α to assess the efficacy of vedolizumab in this patient population. All data were anonymized to ensure patient confidentiality.

Data were compiled regarding clinical remission outcomes after 26 weeks. Furthermore, an assessment was conducted to ascertain the potential impact of patient characteristics and disease attributes on the efficacy of the vedolizumab treatment.

Statistical analysis

Baseline characteristics of the patients, including demographic data, disease characteristics, and previous treatments, were summarized using descriptive statistics. Continuous variables such as age and duration of the disease were presented as means and standard deviation (SD) if normally distributed, or as medians in case of non-normal distribution. Categorical variables (gender, smoking status, exposure to anti-TNF drugs) were expressed as frequencies and percentages. The effectiveness of vedolizumab was assessed by comparing clinical outcome at the time point of 26 weeks. The primary outcome measures were compared using the χ^2 test or Fisher's exact test for categorical variables. For continuous variables changes over time were analysed using paired t-tests or Wilcoxon signed-rank tests, depending on the distribution of the data. Subgroup analyses were conducted to explore differences in treatment response between various patient groups. Differences between the analysed variables were considered significant if $p<0.05$. All statistical tests were two-sided, with calculation of 95% confidence interval (CI), where appropriate.

RESULTS

The study involved 139 patients with IBD, of which 76 UC and 63 with CD. The efficacy of vedolizumab was assessed at the conclusion of a 26-week treatment period.

The results showed that 54 (out of 63; 85.7%) of CD patients (CI: 74.6-93.3%) and 63 (out of 76; 82.9%) of UC patients (CI: 72.5-90.6%) achieved clinical remission without the need for steroid therapy (Table 1).

The median age of patients with UC was 42 (range 28-54) years (p=0.822), while for CD patients, 39 (range 29-48) years (p=0.582). The age did not significantly impact clinical outcomes in any of the disease groups (Table 1).

In the UC group, 47.4% were female, and 52.6% were male (p=0.735) and in the CD group 46.1% were female, and 53.9% male (p=1.0). Gender did not significantly affect clinical outcome in any of the groups (Table 1).

A higher proportion of CD patients (65.1%) (p=0.375) had been exposed to anti-TNF therapy compared to UC patients (51.3%) (p=1.0). TNF exposition had no significant effect (Table 1).

The duration of the disease as well as smoking status did not significantly affect a clinical outcome in UC (p=0.423 and p=0.175, respectively) nor in the CD (p=0644) group; data for CD patients were not available for comparison of groups (Table 1).

In the UC group, remission rates were significantly higher in patients aged 20-29, 40-49, and 50-59 (p=0.00088, p=0.00098, and p=0.0117, respectively) comparing to other groups. For CD patients, the highest remission rates were seen in the 20-29 age group (p = 0.00088) (Table 2).

Regarding Body Mass Index (BMI), remission rates were generally higher in patients with a BMI of 18.6-25 and 25.1-30 (p=0.00088 in both UC and CD groups). The p-value for the 16-18.5 BMI group was 0.25, indicating no significant difference in remission rates, while in the BMI group over 30 BMI in UC patients a significant difference was found (p=0.03) (Table 2).

An analysis of the disease duration revealed that patients with a disease duration of 0-5 and 6-10 years had significantly higher remission rates in both UC and CD groups (p=0.0008 and p=0.0012, respectively). The group >21 years of the disease duration had a significant difference (p=0.01), particularly in UC, suggesting that prolonged disease duration might still allow for high remission rates in some cases (Table 2).

A total of 41 (out of 76; 53.9%) UC patients had a prior treatment with anti-TNF drugs, of which 11 (out of 41; 26.8%) failing to achieve remission without corticosteroids. Among those not treated with TNF drugs, eight (23.0%) did not achieve remission. For CD patients, 42 (out of 63; 65.6%) were previously treated with TNF medication, of which 11 (26.4%) achieved remission, while eight (out of 22; 36.4%) patients who had not been previously treated with TNF drugs achieved remission (Table 3).

DISCUSSION

In a retrospective clinical study, a cohort of 139 patients with inflammatory bowel disease (IBD) was analysed, comprising 76 with ulcerative colitis (UC) and 63 with Crohn's disease (CD). The efficacy of vedolizumab treatment was evaluated at the end of a 26-week period and demonstrated it to be a highly effective therapeutic option for IBD patients. However, UC patients aged 30 to 49, as well as CD patients, had the lowest success rates in achieving remission; both female and males are affected by IBD. Some studies suggest a slightly higher female prevalence, particularly for Crohn's disease (23). Although European and American females are affected approximately twice as often as males by Crohn's disease, in Asia males are more frequently affected than females. In UC, there is no difference in gender prevalence, nor between continents (24,25). Our study showed no gender difference of the treatment efficacy at 26 weeks among the patients with UC and CD patients. Whether gender alone is a potential risk factor for greater disease activity and a more complicated disease course has been scarcely studied and the results are contradictory (25,26). A German study found that females with Crohn's disease showed an increased disease activity as compared with males (27). In the inception cohort study CREST-CD, male gender was significantly associated with the presence of perianal lesions (28). Predictors of response to a particular therapy have been repeatedly investigated; a systematic review of a total of 11 studies with 995 included CD patients treated with adalimumab identified male gender as an independent risk factor for loss of response and the need for dose escalation (29).

The results of this study showed that the median BMI was higher in UC patients compared to CD patients. Prevalence of

Table 1. Clinical characteristics of patients with ulcerative colitis (UC) and Crohn disease (CD)

Variable	UC (N=76)		CD (N=63)	
	Value	p	Value	p
Median age (range) (years)	42 (28-54)	0.822	39 (29-48)	0.582
Gender (No; %)		0.735		1.0
Female	36 (47.4)		29 (46.1%)	
Male	40 (52.6)		34 (53.9%)	
BMI (kg/m²)	24.4	0.0057	23.0	0.065
Previous anti TNF exposition (No; %)	39 (51.3)	1.0	41 (65.1%)	0.375
Duration of disease (years)	8	0.423	9	0.644
Smoking status YES (No; %)	16 (25.3)	0.175		
Clinical remission in 26th week (No; %) (CI%)	63/76 (82.9) (72.5-90.6)		54/63 (85.7) (74.6-93.3)	

BMI, body mass index; TNF, anti-tumour necrosis factor; CI, confidence interval;

Table 2. Clinical remission in the 26th week according to patients' age, body mass index (BMI) and disease duration

Variable	**Ulcerative colitis** (N=76)	**Crohn disease** (N=63)	p
Clinical remission in 26th week (No; %)	63 (82.9)	54 (85.7)	
	No (%) of patients in remission (% in the group)		
Age group (years)			
<20	2 (3.2) (100.0)	0	0.25
20-29	18 (28.6) (85.7)	16 (29.6) (94.1)	0.00088
30-39	9 (14.3) (69.2)	14 (25.9) (82.4)	0.09
40-49	10 (15.9) (100.0)	14 (25.9) 82.4)	0.00098
50-59	15 (23.8) (75.0)	5 (9.2) (83.3)	0.0117
60-69	8 (12.7) (100.0)	5 (9.2) (83.3)	0.0078
70-79	1 (1.6) (50.0)	0	0.75
BMI (kg/m^2)			
16-18.5	2 (3.2) (100.0)	4 (7.4) (57.1)	0.25
18.6-25	38 (60.3) (77.6)	33 (61.1) (91.4)	0.00088
25.1-30	17 (27.0) (94.4)	14 (25.9) (92.86)	0.11
>30	6 (9.5) (75.0)	3 (5.6) (100.0)	0.03
Disease duration (years)			
0-5	19 (30.2) (76.0)	16 (29.6) (88.9)	0.0008
6-10	26 (41.3) (86.7)	15 (27.8) (78.9)	0.0012
11-15	12 (19.0) 92.3)	13 (24.1) (86.7)	0.09
16-20	3 (4.8) (60.0)	3 (5.6) (75.0)	0.19
>21	3 (4.8) (100.0)	7 (13.0) (100.0)	0.01

Table 3. Clinical remission in the 26th week according to previous tumour necrosis factor (TNF) exposition

No (%) of patients in the group			
UC (N=76)		**CD (N=63)**	
YES	**NO**	**YES**	**NO**
Previous exposition TNF			
41 (53.9)	35 (46.0)	42 (65.6)	21 (33.3)
Clinical remission			
11 (26.8)	8 (23.0)	11 (26.4)	13 (61.9)

UC, ulcerative colitis; CD, Crohn disease, TNF anti-tumour necrosis factor

IBD is increasing in parallel with overweight and obesity. How obesity actually impacts the medical management of IBD remains unclear. Two commonly implicated factors by which obesity may impact response to biological therapy in particular include the mode of drug administration (subcutaneous vs intravenous) and the issue of weight-based vs fixed-dose regimens (30). The dysfunction of mesenteric fat worsens the inflammatory course of Crohn's disease and may induce a formation of strictures or fistulas (16). Furthermore, obesity may affect the disease course or treatment response of IBD (17). Given the increasing data supporting the pathophysiologic and epidemiologic relationship between obesity and IBD, obesity control is being suggested as a novel management for IBD (30).

Within our study population consisting of individuals diagnosed with UC, it was noted that 25.3% reported history of smoking. Among this subgroup, 15% failed to achieve corticosteroid-free remission (CSFR) after the 26-week treatment period. Smoking significantly increases the risk of developing and worsens Crohn's disease (CD) yet protects against the development and reduces the severity of ulcerative colitis (19). It is less clear whether smoking impacts the efficacy of therapeutics in inflammatory bowel disease (IBD. The outcome of anti-tumour necrosis factor therapy in active smokers appears neutral with data lacking for newer biologics (20). Multiple lifestyle and psychosocial confounders are likely under-recognized cofactors in the association between smoking and IBD (18). Smoking status has significant implications for the risk, course, treatment, and outcomes of IBD, particularly Crohn's disease (19). Understanding the relationship between smoking and IBD is crucial for optimizing patient care, treatment decisions, and long-term outcomes in individuals living with these conditions (20).

Patients with longer disease duration may have a more complex disease course, reduced treatment responsiveness, and higher likelihood of requiring surgical interventions or experiencing treatment-related complications (31). Patients with CD, but not UC, of shorter duration have higher rate of response to tumour necrosis factor antagonists than patients with longer disease duration, but little is known about the association between disease duration and response to other biological agents (32). Patients with CD for 2 years or less are significantly more likely to achieve a complete response, CSFR, or endoscopic response to vedolizumab than patients with longer disease duration (33). In this investigation among UC patients, no discernible discrepancy emerged concerning the attainment of CSFR by the 26th week, regardless of the duration of illness. Conversely, within the subset of CD patients whose condition persisted for over five years, a notable finding emerged, 30% did not achieve disease remission. Similar to our finding, Faleck et al. found that within 6 months from the initiation of the treatment with vedolizumab, a significantly higher proportion of patients with early-stage CD vs later-stage CD achieved clinical remission, CSFR, and endoscopic remission. After adjusting for disease-related factors including previous exposure to TNF antagonists, patients with early-stage CD were significantly more likely to achieve clinical remission than patients with later-stage CD. In contrast, the disease duration was not a significant predictor of response among patients with UC (33).

Our findings did not reveal any big difference between CD patients who had been treated with TNF therapy and those who had not. About 26% of those who had not received TNF drugs previously got better, while 36% of those who had been treated with TNF drugs achieved remission. Patients who have previously tried and failed other medications for IBD may respond differently to vedolizumab. Research suggests that the effectiveness of vedolizumab may not be significantly influenced by

prior TNF inhibitor use. However, individual responses can vary, and factors such as disease severity, duration of prior treatment, and specific patient characteristics may impact the outcome (31,34).

It is essential for healthcare providers to carefully assess each patient's medical history, including previous treatment and response, before initiating vedolizumab therapy. Monitoring of the disease activity and response to the treatment should be conducted regularly to optimize outcomes and ensure patients' well-being. Overall, while previous treatment with TNF inhibitors may influence the decision to start vedolizumab, it does not necessarily preclude its use, and vedolizumab can offer effective disease management for many patients with IBD (31).

In conclusion, the findings of our study highlight the importance of age, BMI and disease duration that significantly influence clinical remission in UC and CD patients emphsizing these variables in managing UC and CD patients, with implications for treatment strategies and patient counselling.

AUTHOR CONTRIBUTIONS

Conceptualization, N.Z. and M.B-D.; methodology, E.B.; software, E.B.; validation, T.B., A.S. and N.Č.; formal analysis, N.Č.; investigation, N.Z.; resources, M.B-D.; data curation, N.Č.; writing—original draft preparation, N.Z.; writing—review and editing, N.Z.; visualization, A.S.; supervision, T.B.; project administration, E.B.; funding acquisition, E.B. All authors have read and agreed to the published version of the manuscript.

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