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Original article

Vedolizumab does not increase risk of clostridium difficile infection in patients with inflammatory bowel disease using vedolizumab: A retrospective cohort study

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ABSTRACT

Introduction: Several studies have shown increased incidence, recurrence, and severity of Clostridium *difficile* infection (CDI) over the last decade. Patients with inflammatory bowel disease (IBD) who develop CDI are more prone to morbidity and mortality than CDI in patients without IBD. This study seeks to evaluate whether IBD patients who use vedolizumab are at increased risk of CDI compared to IBD patients using other therapies.

Methods: This was a retrospective cohort study, and 684 patients with confirmed IBD (228 on vedolizumab, 228 on anti-TNF, and 228 on 5- Aminosalicylates acid therapy) were enrolled from January 2009 to August 2019 at a tertiary referral IBD center at McMaster University Medical Centre (MUMC) in Hamilton, Ontario, Canada. The primary outcome was time to the development of CDI in IBD patients using different therapies. Secondary outcomes included rates of CDI and the association between baseline variables and risk of CDI. A Cox proportional hazards (PH) model was used to evaluate baseline factors and development of CDI.

Result: There was no difference in time to CDI between the three treatment groups (log rank p-value 0.37). CDI occurred in 16 patients (2.3%), specifically four patients (1.75%) in the vedolizumab group, four patients (1.75%) in the anti-TNF group, and eight patients (3.5%) in the 5-ASA group. The Cox PH model found current smoking, older age, and concomitant immunomodulator use as risk factors for CDI, after adjustment for other covariates. Vedolizumab was not associated with increased risk of CDI in the model.

Conclusion: Biologic *therapy* with vedolizumab or anti-TNF did not impact risk of CDI. Risk factors for CDI in IBD patients included smoking, older age at the onset of medication, and immunomodulator therapy. Clinicians should have high degree of suspicion for CDI in IBD patients presenting with diarrhea, particularly in those with risk factors identified in this study.

1. Introduction

Clostridium difficile infection (CDI) is considered a major cause of infectious diarrhea in hospitalized patients (Magill et al., 2014) and is the most common infectious cause of pseudomembranous colitis (Bartlett et al., 1978). Several studies have revealed an increase in severity, incidence, and recurrence of CDI over the last few years (Rodemann et al., 2007) In the United States, CDI leads to a higher rate of hospitalization comparing to infection with methicillin-resistant staphylococcus aureus (MRSA) and cost approximately $1.8 annually (Lessa et al., 2015; Miller et al., 2011; Zimlichman et al., 2013). These infections are associated with increased rate of hospitalizations time and increased mortality among hospitalized patients (Lessa et al., 2015). Most of the

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studies demonstrated that the most common risk factor for CDI is the use of antibiotics while the other factors include advanced age, severity of an underlying illness, prior hospitalization, use of feeding tubes, gastrointestinal surgery, and proton-pump inhibitors (PPI) (Bignardi, 1998).

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). The rate of morbidity and mortality is higher in IBD patient who is infected with CDI than in IBD patient without CDI (Ananthakrishnan et al., 2008; Khanna and Pardi, 2012). Common risk factors may not be found in many IBD patients, and clinical findings such as pseudomembranous are not commonly present (Rodemann et al., 2007). In contrast to epidemiological studies, CDI is being increasingly recognized as a cause of diarrhea in communities, especially in young age group and populations lacking classic risk factors (CDC, 2005; Khanna and Pardi, 2010; Khanna et al., 2012).

Vedolizumab is a biologic used to treat IBD which specifically targets the gastrointestinal tract (GIT) (Wyant et al., 2016). Vedolizumab binds the α4β7 integrin that is expressed on activated gut-homing T lymphocytes and blocks the interaction of the α4β7 integrin and the mucosal addressing cell adhesion molecule 1 (MAdCAM-1) (Pijls and Gilissen, 2016). MAdCAM-1 is preferentially expressed on the endothelium of the blood vessels in the GIT. Blockade of the interaction between the α4β7 integrin and the MAdCAM-1 results in a gut-targeted therapy. This reduces the side effects often associated with systemic immunosuppression such as infections or malignancy. However, it is unclear if blockade of lymphocyte homing to the GIT can increase risk of enteric infections or result in serious sequalae in those who develop enteric infections.

Giving the risk of CDI and rate of morbidity and mortality is higher in CDI patients with IBD. Moreover, the burden of usage of biologic agents treating IBD increased in the last years, This study aimed to evaluate whether IBD patients who use vedolizumab are at higher risk of CDI compared to patients who use anti-TNF and *5-aminosalicylic acid* (5-ASA) therapies.

2. Methods

2.1. Study population and design

We conducted a retrospective cohort study using 684 patients with confirmed IBD from January 2009 to August 2019 at a tertiary referral IBD center at McMaster University Medical Centre (MUMC) in Hamilton, Ontario, Canada. We extracted the clinical data from the electronic medical records of patients. The inclusion criteria were: (a) an established diagnosis of IBD; (b) initiation of vedolizumab, anti-TNF therapy, or 5-ASA supervised by a gastroenterologist at MUMC; (c) at least two years of follow-up data from the time of drug initiation. We anticipated that the least number of patients who would meet the criteria would be those treated with vedolizumab and planned to include an identical number of patients in the comparison groups of anti-TNF and 5-ASA treated patients.

2.2. Ethics considerations

The Hamilton Integrated Research Ethics Board approved the study. The research protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and local regulations.

2.3. Variables

The demographic and clinical variables considered for the eligible patients included: age at commencement of therapy (vedolizumab, anti-TNF, and 5-ASA); gender; disease distribution, smoking status, previous and current medical therapies (including 5-ASA, corticosteroids, immunomodulator (thiopurines or methotrexate), and biologic therapy (tumor necrosis factor-alpha antagonists or anti-integrin therapy).

2.4. Outcomes

We considered the time to development of CDI from the initiation of drug therapy as our primary outcome. CDI had to be diagnosed at our health facility with a confirmed positive test for CDI and documented within the electronic health record. The details of CDI (including age at the time of diagnosis, months to the event, the therapy used for the treatment of CDI, and the success of treatment) were also collected.

2.5. Statistical analysis

The characteristics of the patients were described using proportions for categorical variables. Continuous data were presented as means with standard deviations for the parametric distributions and medians with interquartile ranges for the non-parametric distributions. A chi-square test was used to compare the categorical variables, and Kruskal-Wallis was used to compare the continuous variables between the patients treated with different therapies. Kaplan-Meier survival curve analysis was performed to compare time to the development of CDI in the patients on vedolizumab, anti-TNF, or 5-ASA therapy. Log-rank statistics were performed to compare these groups.

A Cox proportional hazards regression model with stepwise selection was used to account for potential confounding factors. The significance level for both entry and exit criteria were set at 0.05. The variables in the model were selected based on prior clinical knowledge. This included: drug treatment (variable of primary interest), gender, age at start of drug therapy, smoking status, IBD subtype, and concomitant medications used at time of drug initiation (corticosteroids or immunomodulators). Concomitant corticosteroids or immunomodulators, gender, and smoking status were treated as binary variables; age at the commencement of drug therapy was continuous, and the remaining variables were analyzed as categorical. The Supremum test was used to test the proportional hazards assumptions. The results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Statistical significance was chosen to be at a two-sided p-value < 0.05. The analysis was performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Demographics

The baseline characteristics of the 684 patients included are presented in Table 1. There was no significant difference in age, smoking status, or following concomitant steroids between the three groups. However, the prevalence of female gender was significantly the highest among the Vedolizumab group (53.9%), followed by 5-ASA (48.7%). Also, the type of disease was significantly different between the three groups: Crohn's disease was more prevalent in those using anti-TNF (73.2%) while ulcerative colitis and IBD-unclassified were more prevalent among those using 5-ASA with 73.7% and 2.6% respectively. Furthermore, there was significant difference of the use of concomitant immune modulator between vedolizumab, anti-TNF, and 5-ASA groups (6.6%, 30.7% and 15.4% respectively).

Table 1
Baseline characteristics of the patients included in the study.

Variable	Vedolizumab n = 228	Anti-TNF n = 228	5-ASA n = 228	P-value
Age in years (median, IQR)	35 (22)	35 (23.5)	35.5 (22)	0.92
Females	123(53.9%)	95(41.7%)	111(48.7%)	0.02
Medical history				
Type of disease				<0.001
Crohn's disease	124 (54.3%)	167 (73.2%)	52 (22.8%)	
Ulcerative colitis	96 (42.1%)	59 (25.8%)	168 (73.7%)	
IBD-unclassified	4 (1.8%)	0 (0%)	6 (2.6%)	
Active smoker	11 (4.8%)	13 (5.7%)	9 (3.9%)	0.68
Treatment regimen				
Concomitant immune modulator	15(6.6%)	70(30.7%)	35(15.4%)	<0.001
Concomitant steroids	10(4.4%)	20(8.8%)	21(9.2%)	0.10

5-ASA, 5-aminosalicylic acid; IBD, inflammatory bowel disease.

3.2. Drug therapy and risk of CDI

Use of those using anti-TNF did not impact the time to CDI (log rank p = 0.37) (Fig. 1). The median time to CDI was 7 months (IQR 3–14 months) in those using vedolizumab, 3 months (IQR 1–20 months) in those using anti-TNF, and 12 months (IQR 6–14 months) in those using 5-ASA.

3.3. Outcomes of patients with CDI

Table 2 summarizes the outcomes of the patients who had CDI. CDI occurred in 16 patients (2.3%), specifically four in 228 patients (1.75%) in the vedolizumab group, four in 228 patients (1.75%) in the Anti-TNF group, and eight in 228 patients (3.5%) in the 5-ASA group. There were no significant differences between the three groups in median age, drug therapy used to treat CDI, or success of initial treatment.

3.4. Predictors of CDI in IBD patients

The results of the Cox PH model evaluating other variables which impacted risk of CDI are summarized in Table 3. Advanced age (HR = 1.08, 95% CI = [1.05;1.12], p < 0.001), active smoking status(HR = 13.06, 95% CI = [3.84;44.45], p < 0.001), and concomitant immunomodulator use (HR = 2.91, 95% CI = [1.04; 8.20], p = 0.0045) were all significantly associated with increased risk for CDI. Treatment with biologics or 5-ASA was not found to be associated with risk of CDI in the model.

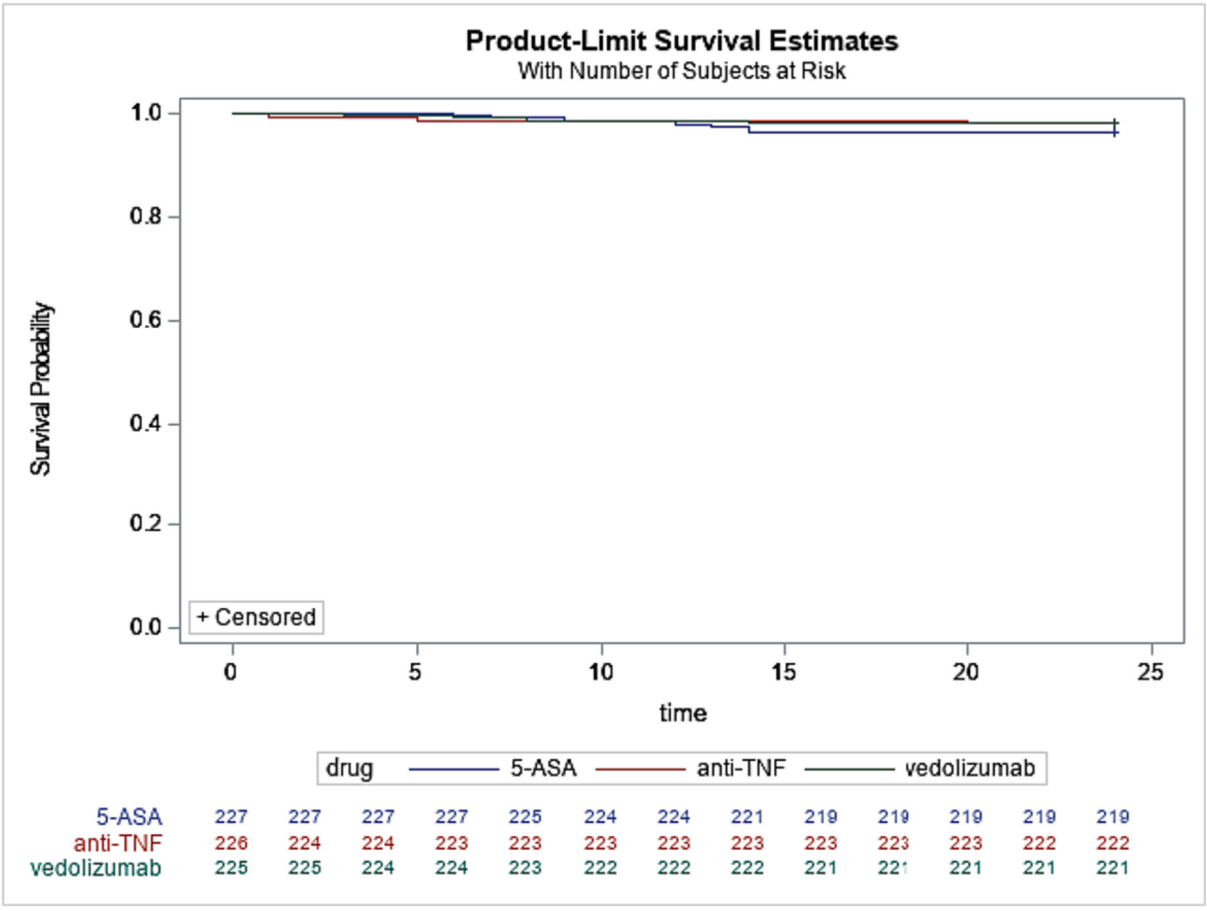

Fig. 1. Kaplan-Meier survival curves comparing time to relapse between the different treatment groups. 5-ASA: 5-aminosalicylic acid.

Table 2
Clostridium difficile (CDI) outcomes.

	Vedolizumab n = 4	Anti-TNF n = 4	5-ASA n = 8	P-value
Age at time of CDI, (median, IQR)	58 (53–63)	58.5 (52.5–66.5)	52.5 (46–60.5)	0.37
C. difficile initial treatment				0.48
Metronidazole	0	1 (25%)	2 (25%)	
Vancomycin	1 (25%)	0	3 (37.5%)	
Combination of metronidazole/vancomycin	3 (75%)	3 (75%)	3 (37.5%)	
Success of initial treatment	2 (50%)	4 (100%)	7 (87.5%)	0.16

5-ASA, 5-aminosalicylic acid; CDI, Clostridium difficile.

Table 3
Adjusted hazard ratio for impact of drug therapy on development of CDI.

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		P-value
Anti-TNF*	0.66	0.16	2.74	0.6809
5-ASA*	1.81	0.53	6.11	0.8319
Current smoker	13.06	3.84	44.45	<0.001
Age at drug start	1.08	1.05	1.12	<0.001
Concomitant immunomodulator	2.91	1.04	8.20	0.0045

*: Vedolizumab is the reference drug. ASA, aminosalicylic acid.

4. Discussion

This current study analyzed a large retrospective cohort of patients with confirmed IBD to evaluate if use of vedolizumab was associated with higher risk for CDI. CDI occurred in 16 patients (2.3%), specifically four patients (1.75%) in the vedolizumab group, four patients (1.75%) in the anti-TNF group, and eight patients (3.5%) in the 5-ASA group. Biologic therapy with vedolizumab or anti-TNF did not impact the risk of developing CDI. Risk factors for CDI in IBD patients included smoking, older age at initiation of medication, and immunomodulator therapy.

Our results showed 2.3% of the patients with IBD experienced CDI. This was concordant with a previous study; nonetheless, the rate of incidence reported in this study is lower than those reported in previous epidemiological studies (Meyer et al., 2004; Mylonaki et al., 2004; Nguyen et al., 2008; Rodemann et al., 2007). This is likely due to differences in the follow-up period between patients in this study and some of the prior studies. This study did not find any difference in the incidence of CDI in IBD patients who were receiving vedolizumab compared to those receiving anti-TNF and 5-ASA therapies. A number of previous studies have shown that administering steroid or biologic therapy also did not increase the risk of CDI in IBD patients (Li et al., 2013; Masclee et al., 2013; Regnault et al., 2014).

Our study also found some other risk factors for CDI. Increasing age was identified as a risk factor in the Cox PH model, and advanced age is a well-recognized risk factor for CDI; however, some reports showed that IBD patients are also susceptible to CDI at a younger age. This may due to high rates of hospitalization, treatment and use of antibiotics, and immunosuppression in IBD patients (Gillespie et al., 2017). Our study demonstrated that the use of concomitant immunomodulators also is associated with increased risk of CDI. Previous studies have also suggested an association between immunomodulator therapy and the risk of CDI in IBD patients. In a large retrospective cohort study including 999 IBD patients, the risk of CDI in those using immunomodulators was increased (OR = 2.56, P = 0.008) (Issa et al., 2007). The last risk factor identified in the present study is active smoking. No previous study has reported this risk factor. This finding may be due to respiratory comorbidities that are generally observed in smokers. These comorbidities have been reported as risk factors for CDI in previous studies (D'Aoust et al., 2017; Maharshak et al., 2018). The main pharmacological risk factor for CDI in the general population is use of antibiotics; our study design did not permit us to evaluate this as a risk factor within this study (Goodhand et al., 2011). Study design also did not permit evaluation of other known risk factors for CDI including administration of proton pump inhibitors (PPIs) and previous/prolonged hospitalizations of IBD (Maharshak et al., 2018).

This study has some notable limitations. The study was retrospective which limits the temporality of the associations found. In addition, the study cohort comprised only IBD patients treated at a single tertiary academic center; therefore, it may not be as generalizable to IBD patients treated in the community or in other countries. There is also a possibility that IBD patients in our study had CDI infections outside of our health care institution, that were not reported to their gastroenterologist, which could underestimate the incidence of CDI reported in our study.

5. Conclusion

Our study did not find biologic therapy with vedolizumab or anti-TNF impacts the risk of CDI. However, advanced age, active smoking, and concomitant immunomodulator use were associated with increased risk of CDI. Clinicians should always consider CDI in the differential diagnosis when IBD patients present with diarrhea, and in particular should exercise high caution in those with risk factors identified in this study.

6. Specific author contributions

Abdulaziz Alshahrani, MD- acquisition and compilation of data; data interpretation; drafting of the manuscript; Danah Mohammad, MD– data interpretation; drafting of the manuscript; Mohammad attieh Alzahrani, MD– data interpretation; drafting of the manuscript; Neeraj Narula, MD - study concept and design; acquisition and compilation of data; statistical analysis; data interpretation; drafting of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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