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Letter to the Editor

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Vedolizumab Is Safe in Elderly Veteran Patients With Inflammatory Bowel Disease

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Lay Summary

Many medications used to treat inflammatory bowel disease (IBD) can increase the risk of infection and cancer, particularly in elderly patients. This study found that vedolizumab, a targeted therapy, was effective and safe in elderly patients with IBD.

To the Editor,

Treating elderly patients (defined as over the age of 65 years old) with a diagnosis of inflammatory bowel disease (IBD) is challenging because of their increased risk of infection and malignancy.[1,2] Presumably in efforts to minimize potential harm, elderly patients are more likely to receive potentially less effective medications such as aminosalicylates, more likely to be on chronic corticosteroids, and less likely to receive biologics.[3,4]

Vedolizumab (VDZ) is an anti-integrin agent that inhibits alpha-4, beta-7 lymphocyte homing of Th17 and Th9 cells as well as regulatory T cells to the intestine.[5] The gut-specific nature of VDZ holds potential for achieving and maintaining remission in IBD without increasing the risk of severe infection or malignancy. However, there is a paucity of data regarding its safety in the elderly population. In phase 3 VDZ trials, only 46 patients were over age 65.[5] We conducted a retrospective study to better define the safety profile of VDZ in a cohort of elderly veterans.

This retrospective study included 17 elderly male veterans with IBD who received VDZ at the Veterans Affairs Loma Linda Healthcare System. Patients were eligible for inclusion if they met the following criteria: (1) established diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) and (2) initiated VDZ at age 65 years or older. Patients were excluded if VDZ was initiated prior to age 65 years. Patients were identified and data were collected using the Computerized Patient Record System. Relevant covariates examined included age at diagnosis of IBD, duration of disease, prior treatment history, disease location and behavior, polypharmacy, drug–drug interactions (DDIs), and the Charlson comorbidity index. The primary outcome was adverse events, including infusion reaction, infection, IBD-related hospitalization, IBD-related surgery, and malignancy while receiving VDZ. Serious infections were defined as any infection requiring hospitalization, interruption, or discontinuation of VDZ. The secondary outcome was clinical efficacy.

Patients' demographics and disease characteristics are outlined in Table 1. The median age was 71 (range, 66–83). The median Charlson comorbidity index was 4 (range, 3–7). All patients had previous anti-TNF exposure. The median duration of VDZ therapy was 24 months (range 1–48). The average number of total medications used by patients was 10 (range 2–22). One, 6, and 10 patients had mild, moderate, and severe polypharmacy, respectively. Further, there were a total of 12 (10%), 94 (78%), and 15 (12%) minor, moderate, and major DDIs, respectively. However, VDZ was not associated with any DDI. Data on disease status were available on 14 patients at 6 months of follow-up: 3 (27.3%) had active disease, 11 (78.6%) were in clinical remission. Two patients remain in histologic remission at their 4-year follow-up. Data for other follow-up time periods are summarized in Table 2.

Six patients eventually failed VDZ and required a change in therapy. No patients discontinued VDZ due to infections or other adverse events. None had septic complications or intensive care unit admissions. There were no IBD-related hospitalizations. One patient was hospitalized for elective therapy for previously diagnosed renal cell carcinoma and another following a motor vehicle accident. One patient was evaluated in the Emergency Department (ED) for uncomplicated diverticulitis but was discharged from the ED within 24 hours. Overall, 2 patients developed *Clostridium difficile* infections (CDI), 1 developed bronchitis, and 1 developed diverticulitis. One case of CDI recurred, resulting in withholding of 1 dose of VDZ and treatment with fecal microbiota transplant, after which the infection resolved and VDZ therapy was resumed. All other infections resolved with standard antibiotic use without VDZ interruption.

Table 1. Patients' demographic and disease characteristics.

Age (years), median (range)	71 (66–83)
Male, *n* (%)	17 (100)
Charlson comorbidity index, median (range)	4 (3–7)
Total medications, median (range)	10 (7–22)
History of malignancy, *n* (%)	
Renal cell carcinoma	1 (6)
Melanoma	1 (6)
Bladder cancer	1 (6)
Hepatocellular carcinoma	1 (6)
Updated influenza vaccination (yes), *n* (%)	8 (47)
Updated pneumonia vaccination (yes), *n* (%)	12 (71)
PCP clinic visits, median (range)	2 (1–9)
IBD clinic visits, median (range)	9 (1–25)
IBD phenotype	
Crohn's disease, *n* (%)	10 (59)
Ulcerative colitis, *n* (%)	7 (41)
Age at diagnosis (years), median (range)	63 (35–73)
Disease duration (years), median (range)	14 (4–37)
Location (ulcerative colitis), *n* (%)	
Left sided (E2)	4 (57)
Extensive colitis (E3)	3 (43)
Location (Crohn's disease), *n* (%)	
Colonic (L2)	3 (30)
Ileocolonic (L3)	7 (70)
Natalizumab exposure, *n* (%)	0
Anti-TNF exposure, *n* (%)	
Infliximab	9 (53)
Adalimumab	11 (65)
Certolizumab	1 (6)
Golimumab	1 (6)
Anti IL12/23 exposure, *n* (%)	0
Thiopurine exposure, *n* (%)	12 (71)
Methotrexate exposure, *n* (%)	0
Concomitant immunomodulator therapy, *n* (%)	3 (18)

Abbreviations: IBD, inflammatory bowel disease; PCP, primary care provider.

Table 2. Disease status at different follow-up time points.

	Active disease	Clinical remission	Histologic remission	Not available
3 months	5	9	0	3
6 months	3	11	0	3
12 months	2	7	3	5
24 months	1	3	4	9
36 months	1	0	3	13
48 months	0	0	2	15

Data represent the number of patients at each follow-up time point. Not available includes patients who are deceased or no longer on vedolizumab.

Two patients, one of which had thiopurine exposure, developed cutaneous squamous cell carcinoma. One patient with chronic urticaria developed a rash after receiving the first dose of VDZ but tolerated subsequent doses without complications or drug interruption. Three deaths occurred for reasons not attributed to VDZ usage. Other outcomes are outlined in Table 3.

Table 3. Outcomes in IBD patients 65 years and older on vedolizumab.

IBD-related surgery, *n* (%)	0
IBD-related hospitalization, *n* (%)	0
All-cause hospitalization, *n* (%)	2 (12)
Infection, *n* (%)	
Nasopharyngitis	0
Upper respiratory tract infection	0
Bronchitis	1 (6)
Pneumonia	0
Urinary tract infection	0
Clostridium difficile	2 (12)
Diverticulitis	1 (6)
Serious infection, *n* (%)	1 (6)
Noninfectious adverse events, *n* (%)	
Infusion reaction	0
Arthralgia	1 (6)
Nausea	1 (6)
Anemia	6 (35)
Rash	1 (6)
Headache	0
Fatigue	0
Cough	0
Venous thromboembolism	0
Myocardial infarction	0
Stroke	0
Fall/fracture	0
Serious noninfectious adverse events, *n* (%)	0
Cancer, *n* (%)	
Cutaneous squamous cell carcinoma	2 (12)
Deaths, *n* (%)	3 (18)
Antibiotic use, *n* (%)	4 (24)
Steroid use, *n* (%)	3 (18)

Abbreviation: IBD, inflammatory bowel disease. Serious infection is defined as any infection requiring hospitalization, interruption, or discontinuation of vedolizumab.

The elderly IBD population is comprised of individuals with longstanding disease initially diagnosed at a younger age as well as those with newly diagnosed disease.[6] Irrespective of the age at diagnosis, epidemiological studies have estimated that about 25%–35% of patients with IBD are >60 years of age.[7] Nevertheless, the elderly account for about 25% of IBD-related hospitalizations and experience comparably higher in-hospital morbidity and mortality, even after adjusting for comorbidities.[8] A "start low, go slow" approach has previously been advocated for the elderly, calling for starting lower potency therapy with careful monitoring for medication intolerance while maintaining an openness to more advanced therapies, namely biologics.[7] Frailty, rather than specific age, has also been suggested as an indicator of fitness for advanced therapies.[9] However, an examination of prescribing patterns has revealed a higher proportion of aminosalicylates and chronic steroid therapy, and lower proportion of biologics among the elderly, indicating that in clinical practice, therapy may not be escalated frequently enough, resulting in undertreatment.[3,4]

Unique challenges associated with treating IBD in the elderly include, but are not limited to: polypharmacy, medication-related adverse effects, underlying comorbidities, susceptibility to infection, and risk of malignancy.[2] Older IBD patients with CD and UC take an average of 10 and 9 medications, respectively.[10] Yet, medication nonadherence greatly increases with number of drugs, with a rate of 35% when 4 or more drugs are included.[11] Topical therapies can pose challenges in the elderly due to decreased dexterity and fecal incontinence.[6] Adverse effects and underlying comorbidities can also limit the use of specific IBD therapies. Thiopurines in older individuals have been associated with higher rates of lymphomoproliferative disorders, hepatoxicity, myelosuppression, and digestive intolerance.[6,12] Anti-TNF therapy is contraindicated in moderate to severe New York Heart Association class 3 or 4 heart failure.[6] A previous meta-analysis also revealed that older biologic users (excluding VDZ) had a 3-fold increase in the risk of infection compared to older nonbiologic users.[13] Indeed, many older individuals ultimately fail anti-TNF therapy due to the development of serious infections or lack of efficacy.[14] For the clinician caring for an elderly patient with IBD, these age-specific challenges substantially increase the difficulty of properly positioning therapies, particularly biologics.

Goals of treatment in elderly IBD patients should involve managing symptoms, escalating treatments when indicated, reducing hospitalizations and surgeries, and minimizing adverse effects of medications. Given the preponderance of chronic corticosteroid usage, transitioning older patients to steroid-sparing therapies, namely biologics, would simultaneously help achieve and maintain remission while preventing exacerbation and complications of underlying conditions like congestive heart failure, diabetes, and osteoporosis.[6] Overall, IBD patients across all ages demonstrate high levels of openness to biologics.[15] While infusion therapy may be perceived as being less favorable among patients, providers may underestimate patients' openness to it.[16,17] While overall preference for subcutaneous versus intravenous therapy has had mixed results, older individuals tend to prefer intravenous treatment.[16,17] The impression of infusion therapy also favorably increases after the start of infusions.[17] Therefore, providers should not avoid biologics in the elderly either out of concern about willingness to start biologic therapy or the burden of administration.

VDZ is an appealing first line or alternative therapy. VDZ is effective across all ages, with an overall 52-week clinical remission rate of 39% and 38% for UC and CD, respectively.[18] It is also effective for fistulizing disease, with a closure rate of 41%.[19] In the recent first head-to-head trial of biologics for UC, there were reported higher rates of clinical, endoscopic, and histologic remission with VDZ compared to adalimumab.[20] There are no major contraindications with underlying medical conditions.[5] Opportunistic infections are rare with VDZ and most were nonserious in an analysis of VDZ's phase 3 clinical trials and post marketing analyses.[21]

The ongoing coronavirus disease 2019 (COVID-19) pandemic further highlights the importance of infection risk in all IBD patients, but particularly among the older population. Notably, the American Gastroenterology Association panel of experts recently recommended holding anti-TNF therapy and ustekinumab in cases of confirmed COVID-19, while holding VDZ was of uncertain necessity.[22] In the SECURE-IBD database, an international adult and pediatric database for reporting and monitoring COVID-19 cases occurring in IBD patients, there is a reported 3% mortality rate among patients on VDZ.[23] While not adjusted for age or other comorbidities, the overall low fatality rate is reassuring. In line with this, our cohort has also continued therapy through the current pandemic without any observed occurrences of COVID-19 infections.

Two previous studies of 29 patients over age 60 in the United States and 74 patients over age 60 in the United Kingdom receiving VDZ for IBD have reported low rates of adverse events.[24,25] Another retrospective study comparing patients starting anti-TNF or VDZ therapy at or above 60 years of age found no difference in overall risk of infection.[26] However, in the analysis of the multicenter VARSITY consortium, there were lower incidence rates of infections and serious infections with VDZ compared to adalimumab.[20] While additional studies comparing infection risk between VDZ and anti-TNF agents would be beneficial, it appears that VDZ is overall well tolerated, has fewer restrictions, and is at least as safe as anti-TNF therapy.

Our study offers additional long-term clinical outcomes in a cohort of elderly veterans with IBD. Our cohort is composed of individuals with significant comorbidities including heart failure, chronic obstructive pulmonary disease, and cirrhosis. Polypharmacy was pervasive. In addition, all of our patients are anti-TNF experienced, unlike groups represented in previous studies, which portends a worse response rate to VDZ and potentially more complex disease.[24–26] Despite this, we report favorable long-term efficacy rates. Interestingly, none of our patients went on to require IBD-related surgeries up to a follow-up period of 4 years. This is in contrast to the experience of Navaneethan et al and Ibraheim et al, who reported rates of surgery at 12 months of 10% and 17%, respectively.[24,25] Overall, VDZ appeared to be efficacious, well-tolerated, and safe in this elderly veteran group.

In conclusion, biologics are underutilized in the elderly IBD population. Our study of elderly male veterans over age 65 demonstrates that VDZ is an effective and safe long-term biologic therapy, with no increased incidence of severe infection, malignancy, or other adverse effects up to 48 months. The adverse effects observed are not more frequent than would be expected in the general IBD or geriatric population. Although larger studies are needed, clinicians should not be dissuaded from considering VDZ in the management of IBD in elderly patients.

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Conflicts of Interest

None declared.

Data Availability

Data not publicly available.

References

1. Khan N, Vallarino C, Lissoos T, et al. Risk of infection and types of infection among elderly patients with inflammatory bowel

disease: a retrospective database analysis. *Inflamm Bowel Dis*. 2020;26(3):462–468.
2. Ha CY, Katz S. Clinical implications of ageing for the management of IBD. *Nat Rev Gastroenterol Hepatol*. 2014;11(2):128–138.
3. Barnes E, Hanson J, Reguerio M, et al. DOP25 Medication use and comorbidities among elderly when compared with younger patients with inflammatory bowel disease in the TARGET-IBD cohort. *J Crohns Colitis*. 2020;14(supp 1):S063–S066.
4. Juneja M, Baidoo L, Schwartz MB, et al. Geriatric inflammatory bowel disease: phenotypic presentation, treatment patterns, nutritional status, outcomes, and comorbidity. *Dig Dis Sci*. 2012;57(9):2408–2415.
5. *Entyvio (vedolizumab) [package insert]*. Deerfield, IL: Takeda Pharmaceuticals America; 2020.
6. Taleban S, Colombel JF, Mohler MJ, Fain MJ. Inflammatory bowel disease and the elderly: a review. *J Crohns Colitis*. 2015;9(6):507–515.
7. Katz S, Feldstein R. Inflammatory bowel disease of the elderly: a wake-up call. *Gastroenterol Hepatol (N Y)*. 2008;4(5):337–347.
8. Ananthakrishnan AN, McGinley EL, Binion DG. Inflammatory bowel disease in the elderly is associated with worse outcomes: a national study of hospitalizations. *Inflamm Bowel Dis*. 2009;15(2):182–189.
9. Sturm A, Maaser C, Mendall M, et al. European Crohn's and colitis organisation topical review on IBD in the elderly. *J Crohns Colitis*. 2017;11(3):263–273.
10. Parian A, Ha CY. Older age and steroid use are associated with increasing polypharmacy and potential medication interactions among patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21(6):1392–1400.
11. Rollason V, Vogt N. Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. *Drugs Aging*. 2003;20(11):817–832.
12. Calafat M, Mañosa M, Cañete F, et al. Increased risk of thiopurine-related adverse events in elderly patients with IBD. *Aliment Pharmacol Ther*. 2019;50(7):780–788.
13. Borren NZ, Ananthakrishnan AN. Safety of biologic therapy in older patients with immune-mediated diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2019;17(9):1736–1743.e4.
14. de Jong ME, Smits LJT, van Ruijven B, et al. Increased discontinuation rates of anti-TNF therapy in elderly inflammatory bowel disease patients. *J Crohns Colitis*. 2020;14(7):888–895.
15. Kariburyo MF, Xie L, Teeple A, et al. Predicting pre-emptive discussions of biologic treatment: results from an openness and preference survey of inflammatory bowel disease patients and their prescribers. *Adv Ther*. 2017;34(6):1398–1410.
16. Grisanti L, Kwiatkowski A, Dyrda P, et al. Patient perspectives on intravenous biologics for rheumatologic disease. *Arthritis Care Res (Hoboken)*. 2019;71(9):1234–1242.
17. Santus P, Ferrando M, Baiardini I, et al. Patients beliefs on intravenous and subcutaneous routes of administration of biologics for severe asthma treatment: a cross-sectional observational survey study. *World Allergy Organ J*. 2019;12(4):100030.
18. Engel T, Ungar B, Yung DE, et al. Vedolizumab in IBD-lessons from real-world experience; a systematic review and pooled analysis. *J Crohns Colitis*. 2018;12(2):245–257.
19. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711–721.
20. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019;381(13):1215–1226.
21. Ng SC, Hilmi IN, Blake A, et al. Low frequency of opportunistic infections in patients receiving vedolizumab in clinical trials and post-marketing setting. *Inflamm Bowel Dis*. 2018;24(11):2431–2441.
22. Rubin DT, Feuerstein JD, Wang AY, Cohen RD. AGA clinical practice update on management of inflammatory bowel disease during the COVID-19 pandemic: expert commentary. *Gastroenterology*. 2020;159(1):350–357.
23. Brenner EJ, Ungaro RC, Colombel JF, Kappelman MD. SECURE-IBD Database Public Data Update. Accessed May 29, 2020. covidibd.org
24. Navaneethan U, Edminister T, Zhu X, et al. Vedolizumab is safe and effective in elderly patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2017;23(4):E17.
25. Ibraheim H, Samaan MA, Srinivasan A, et al. Effectiveness and safety of vedolizumab in inflammatory bowel disease patients aged 60 and over: an observational multicenter UK experience. *Ann Gastroenterol*. 2020;33(2):170–177.
26. Adar T, Faleck D, Sasidharan S, et al. Comparative safety and effectiveness of tumor necrosis factor α antagonists and vedolizumab in elderly IBD patients: a multicentre study. *Aliment Pharmacol Ther*. 2019;49(7):873–879.