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Real-world effectiveness and safety of ustekinumab and vedolizumab in elderly patients with Crohn's disease

Rajat Garg[1], **Manik Aggarwal**[2], **Abdul Mohammed**[2], **Jean Paul Achkar**[1], **Bret Lashner**[1], **Jessica Philpott**[1], **Benjamin Cohen**[1], **Taha Qazi**[1], **Florian Rieder**[1], **Miguel Regueiro**[1], **Benjamin Click**[1]

[1] Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA

[2] Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, USA

Abstract

Studies report favorable efficacy and safety profiles of ustekinumab (UST) and vedolizumab (VDZ) in Crohn's disease (CD), but effectiveness and safety data in elderly patients with CD is lacking. We retrospectively analyzed 78 elderly patients (39 each UST and VDZ) and found that patients on UST and VDZ experienced similar rates of clinical response, remission and mucosal healing despite high proportion of prior biologic exposure. Both UST and VDZ appear to be effective and safe in this at-risk CD population. Further large studies are needed to validate our findings.

Keywords

Biologics; Crohn's disease; Elderly; Inflammatory bowel diseases; Ustekinumab; Vedolizumab

✉ Rajat Garg drgargrajat@gmail.com.

Conflict of interest RG, MA, AM, JPA, BL, JP, BC, TQ, FR, MR and BC have no conflict of interest.

Ethics statement The study was performed conforming to the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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Introduction

Clinical trials of ustekinumab (UST) and vedolizumab (VDZ) in Crohn's disease (CD) report favorable efficacy and safety profiles [1, 2]. Ongoing data from long-term extension arms of the clinical trial programs in both CD have suggested favorable safety profiles for UST and VDZ comparable to placebo-treated participants [1, 3]. Recently, several real-world studies have confirmed effectiveness and adverse events ranging from 40% to 60% and 6% to 12%, respectively, of UST and VDZ for the treatment of CD, but a few studies include or examine elderly cohorts [4–6]. Unfortunately, elderly patients are often underrepresented in clinical trials and efficacy evaluations by age is challenging due to limited sample size. Thus, targeted real-world comparative effectiveness studies of this underrepresented population represent a critical knowledge gap.

Elderly inflammatory bowel disease (IBD) patients are often considered a challenging IBD sub-population due to the higher prevalence of comorbidities, polypharmacy, malnutrition, frailty, hospitalization and infection risk with immune modulation [7]. Consequently, there is an underutilization of biologic agents and steroid-sparing agents in elderly patients [5, 8, 9]. Real-world comparative effectiveness studies are needed to assess the safety concerns in elderly IBD patients, particularly as new agents come to market. Thus, we aimed to assess the real-world effectiveness and safety of UST and VDZ in elderly patients with CD.

Methods

Study design

We retrospectively identified elderly patients (≥ 65 years) in the Cleveland Clinic health system, who received UST or VDZ for the treatment of CD from September 2016 to December 2020. The decision to start UST or VDZ was individualized based on physician and patient's preference based on clinical status of the patient either as first or second-line biologic agents. Patients were included if they had prior confirmed diagnosis of CD, received at least one infusion of UST or VDZ and had at least one follow-up (either clinical or endoscopic) after first infusion. We excluded any patient with diagnosis of ulcerative colitis, indeterminate colitis, a non-IBD primary indication for UST or missing follow-up data. In line with prior literature designations, we used age 65 to define the elderly cohort [9].

Outcomes

Our study's aim was to assess real-world effectiveness and safety of UST and VDZ in elderly CD patients. For effectiveness, the outcomes of interest were proportion of patients achieving clinical response or remission, steroid-free response or remission and mucosal healing. Clinical response or remission was classified based on physician global assessment (PGA). We used objective scale Harvey Bradshaw Index or Crohn's Disease Activity Index, if available. Additionally, it is standard practice at our center to routinely record variables to be used for Patient-Reported Outcome-2 calculation such as number of bowel movements. These could then be compared with the data prior to drug initiation for response/remission. If on the rare occasion, no such data was included, we interpreted the clinical documentation

describing patient's subjective response using superlative language such as *most, many, some* or something similar to indicate response. In contrast, the complete resolution of CD-related symptoms denoted clinical remission. Steroid-free response or remission was only assessed in patients using corticosteroids at the time of UST or VDZ initiation. Steroid-free remission was achieved if steroids were completely tapered off in conjunction with meeting criteria for clinical remission and as steroid-free response if steroids were being tapered below baseline dose and patient achieved clinical response. Mucosal healing was defined based on clinically indicated endoscopic assessment as the absence of ulcers or erosions as reported in VICTORY consortium [4] and the fact that endoscopic scores are always not available in endoscopic reports. These outcomes and definitions were similar to those utilized in other real-world comparative effectiveness studies of newer biologic agents [4, 6, 10, 11]. Dose escalation was performed as clinically indicated and was defined as any increase in frequency of UST or VDZ from standard every eight weeks dosing or reinduction. Patients were followed until drug discontinuation or last observed follow-up clinic visit or endoscopy.

Safety outcomes assessed included infusion or injection site reactions, infections or serious adverse events. Infusion or injection reactions were further categorized into mild, if patients were able to continue UST or VDZ, or serious, if the reaction resulted in stopping therapy. Infections were further classified if they required antibiotics, hospitalization or resulted in death.

Categorical variables are presented as proportions and compared by age group via Pearson Chi-square test. Continuous variables were presented as mean and standard deviation and compared with independent Sample 't'-test. Cleveland Clinic Institutional Review Board (Study number 19–1271) approved this study.

Results

Total 78 (39 UST, 39 VDZ) patients were included in our study. The UST group had significantly more colonic (28.2% vs. 17.9%), ileo-colonic (66.7% vs. 56.4%), penetrating disease (43.6% vs. 7.7%) as compared to VDZ group ($p < 0.05$ for all). The UST group had significantly more prior biologic use (94.9% vs. 65.8%, $p < 0.001$), including anti-tumor necrosis factor (TNF) inhibitors, but no difference in concurrent steroid use (51.3% vs. 43.6%, $p = 0.49$) or history of malignancy (Table 1). No patients received prior VDZ or UST in either group.

The mean overall follow-up was 16.1 ± 17.4 and 25.5 ± 18.1 months in UST and VDZ group, respectively. Clinical response and remission were achieved in 64.1% and 28.2% on UST as compared to 38.5% and 46.2% on VDZ, respectively. Steroid-free response and remission assessed only in patients on corticosteroids at the time of initiation was achieved in 50% and 30% in UST group and 17.6% and 35.6% in VDZ group, respectively. There was no difference in time to clinical response or steroid-free response between both groups. Mucosal healing was assessed in 69.2% (27/39) UST and 79.5% (31/39) VDZ and achieved in 25.9% patients in UST and 41.9% in VDZ group. There were no differences between UST and VDZ groups in dose escalation (17.9% vs. 10%), infusion

or injection reactions (2.6% vs. 2.6%) (Table 2). Two patients in UST group (recurrent cystitis and *Mycobacterium avium-intracellulare* infection) and one patient in VDZ group (recurrent upper respiratory infections) developed infectious complications (5.2% vs. 2.6%). The *p*-values are provided in supplementary Table 1.

Discussion

In this first real-world population of elderly patients with CD receiving UST or VDZ, a substantial and equivocal portion experienced clinical response, remission and mucosal healing despite high proportion of prior biologic exposure and baseline disease differences. UST and VDZ had similarly low rates of adverse events suggesting that both agents are safe in this at-risk population.

Both UST and VDZ are commonly utilized in elderly CD due to perceived favorable safety profiles; however, effectiveness and safety data specific to these two agents and this population is very limited. VDZ has been shown to be equally effective in elderly and non-elderly CD patients [12, 13]. UST has demonstrated higher rates of steroid-free remission as compared to VDZ in anti-TNF refractory CD in non-elderly populations, but no direct comparisons in elderly patients exist [14, 15]. Our data builds on prior findings and suggests similar safety profile of UST and VDZ in elderly CD patients.

We found that VDZ and UST had similar and high rates of response and remission in high-risk elderly population despite many of them having prior biologic exposure. In addition, both agents have similar safety profile. The likely reasons of these findings are different mechanism of action from anti-TNF and their improved safety profile. Though treatment with adalimumab and other subcutaneously anti-TNF formulations may have lowered the overall response rate of patients treated with anti-TNF, a significant proportion of patients achieved response in both groups. Another study examining the comparative safety and effectiveness of VDZ as compared to anti-TNF in elderly patients reported low rates of infection (20% for anti-TNF at one year vs. 17% for VDZ) and similar rates of clinical remission at six months [16]. One study also reported similar rates of clinical response and adverse events in patients receiving UST in elderly CD patients as compared to younger population [6]. It is also interesting to note that time to response in our study was eight to 10 months in both groups. It is a standard of practice to assess response after three to six months of drug initiation, but some patients might not have desired follow-up. In addition, we also assess the reason of inadequate response and dose escalate, if suboptimal response is noted at first follow-up before foregoing the current biologic agent.

The study of elderly patients with IBD is complex—there are clear phenotypic differences noted in elderly onset IBD and elderly patients with IBD have several decades of disease activity, that may make controlling their disease more challenging [17]. Comorbid conditions may make providers less likely to prescribe immunomodulator therapy and certain biologics such as anti-TNF agents. Rates of steroid use have been shown to be higher in this population with worse patient-reported outcomes [18]. None of the guidelines from the American College of Gastroenterology, American Gastroenterological Association and European Crohn’s and Colitis Organization specifically address the elderly

population, special attention is needed to ensure that like younger patients, medical therapy is appropriately escalated in the face of ongoing inflammation in elderly patients [19–21]. It is imperative to obtain more data regarding the safety and efficacy of these newer biologic agents in the elderly population.

Tertiary care center population, retrospective study design, limited sample size, confounding by indication, clinically oriented outcome measures using PGA and differential prior biologic exposure are the main limitations of our study. In addition, we did not assess outcomes and safety in elderly-onset CD. We also did not collect data on comorbidities, steroid rescues and did not do multi-variate analysis due to no significant differences detected on univariate analysis. Nevertheless, this is the first study to report comparative effectiveness and safety of UST and VDZ in elderly CD patients.

In conclusion, UST and VDZ demonstrated similar real-world clinical effectiveness and safety in elderly patients with CD. Confirmatory studies are needed. With an increasing elderly population, such comparative effectiveness studies are vital to informing biologic positioning in this unique patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Bullet points of the study highlights

What is already known?

- Real-world studies of ustekinumab (UST) and vedolizumab (VDZ) in Crohn's disease (CD) report favorable efficacy and safety profiles.
- Data comparing effectiveness and safety of UST to VDZ in elderly patients is lacking.

What is new in this study?

- We compared effectiveness and safety of UST to VDZ in elderly patients with Crohn's disease.
- Elderly patients with CD on UST and VDZ experienced similar rates of clinical response, remission and mucosal healing despite high proportion of prior biologic exposure.

What are the future clinical and research implications of the study findings?

- Both UST and VDZ appear to be effective and safe in elderly patients with Crohn's disease. Further large studies are needed to validate our findings.

Table 1

Baseline demographics and disease characteristics of Vedolizumab and Ustekinumab for elderly patients with Crohn's disease

Factor	Vedolizumab		Ustekinumab		*p*-value
	n	*n* (%) or mean ± SD	*n*	*n* (%) or mean ± SD	
Age at the time of biologic		69.9 ± 5.26		69.5 ± 3.5	0.68
Female	39	19 (48.7%)	39	17 (43.6%)	0.65
Current smoker		2 (5.1%)		0 (0%)	0.29
Hospitalization within 1 year	39	18 (46.2%)	39	14 (35.9%)	0.25
Age of diagnosis	39		39		0.1
< 16 year		0 (0%)		3 (7.7%)	
17–40 year		17 (43.6%)		11 (28.2%)	
> 40 year		22 (56.4%)		25 (64.1%)	
Location	39		39		**0.04**
Ileal		10 (25.6%)		2 (5.1%)	
Colonic		7 (17.9%)		11 (28.2%)	
Ileo-colonic		22 (56.4%)		26 (66.7%)	
Behavior, Montreal	39		39		**0.001**
Non-stricturing, non-penetrating		10 (25.6%)		5 (12.8%)	
Stricturing		26 (66.7%)		17 (43.6%)	
Penetrating		3 (7.7%)		17 (43.6%)	
Perianal involvement	39	5 (12.8%)	39	4 (10.3%)	0.99
Disease severity per PGA	39		39		**0.001**
Mild		0 (0%)		0 (0%)	
Moderate		28 (71.8%)		34 (87.2%)	
Severe		11 (28.2%)		5 (12.8%)	
Endoscopic severity	28		29		0.53
Mild		4 (14.3%)		4 (13.8%)	
Moderate		18 (54.3%)		15 (51.7%)	
Severe		6 (21.4%)		10 (34.5%)	
Prior IBD related surgery	39	33 (84.6%)	38	28 (73.7%)	0.56
Type of surgery	33		28		0.34

Factor	Vedolizumab		Ustekinumab		*p*-value
	n	***n* (%) or mean ± SD**	***n***	***n* (%) or mean ± SD**	
Colectomy		8 (24.2%)		6 (21.4%)	
Ileo-colonic resection		14 (42.4%)		8 (28.6%)	
Segment small bowel resect		1 (3.0%)		4 (14.3%)	
Abscess drain		0 (0%)		0 (0%)	
Multiple		10 (30.3%)		10 (35.7%)	
Baseline steroids	39	17 (43.6%)	39	20 (51.3%)	0.49
Current thiopurine use	39	2 (5.1%)	39	2 (5.1%)	0.51
Prior biologic use	38	25 (65.8%)	39	37 (94.9%)	< **0.001**
Prior anti-TNF use	39	23 (59%)	39	36 (92.3%)	**0.001**
Biologic type					
Infliximab		7 (17.9%)		15 (38.5%)	**0.04**
Adalimumab		20 (51.3%)		25 (64.1%)	0.25
Golimumab		1 (2.6%)		26 (66.7%)	< **0.001**
Certolizumab		7 (17.9%)		6 (15.4%)	0.76
History of malignancy	39	12 (30.8%)	39	8 (20.5%)	0.3
Mean follow-up after drug initiation (months)	39	25.5 ± 18.1	39	16.1 ± 17.4	0.2

Bold indicates significant *p*-value < 0.05

SD standard deviation, *IBD* inflammatory bowel disease, *PGA* Physician Global Assessment, *TNF* tumor necrosis factor

Table 2

Outcomes of vedolizumab and ustekinumab for elderly patients with Crohn's disease

Factor	Vedolizumab		Ustekinumab	
Overall PGA response	39		39	
No response		6 (15.4%)		3 (7.7%)
Clinical response		15 (15.4%)		25 (64.1%)
Complete response/remission		18 (46.2%)		11 (28.2%)
Time to response (months)	32	9.81 ± 7.5	39	7.56 ± 6.9
Steroid-free response	17		20	
No response		8 (47.1%)		4 (20%)
Steroid-free response		3 (17.6%)		10 (50%)
Steroid-free remission		6 (35.3%)		6 (30%)
Time to steroid-free state (months) (based on baseline steroid use)	8	10.1 ± 16.8	16	6.1 ± 6.7
Dose escalation	30	3 (10%)	39	7 (17.9%)
Mucosal healing	31	13 (41.9%)	27	7 (25.9%)
Adverse infusion reaction	39		39	
Yes—continue infusion		1 (2.6%)		1 (2.6%)
Stop infusion/therapy		0		0
Adverse infection	38		39	
Yes-antibiotic		1 (2.6%)		1 (2.6%)
Yes-need hospitalization		0 (0%)		1 (2.6%)

PGA Physician Global Assessment