Gastroenterologists' preference and risk perception on the use of immunomodulators and biological therapies in elderly patients with ulcerative colitis: an international survey

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Background and aims: Comorbidities, polypharmacy, malignancies, and infections complicate management of elderly patients with inflammatory bowel diseases (IBD). This study assessed gastroenterologists' preference in the prescription of medications or surgery to elderly patients with IBD, and the factors associated with their choices.

Methods An international case-based survey was conducted that presented three cases of steroid-dependent ulcerative colitis assessing young-age versus elderly-age patients, with and without comorbidity. Physician characteristics and practice demographics were collected. Factors associated with selection of different choices of therapy were determined by logistic regression analysis.

Results A total of 424 respondents from 41 countries were included. Vedolizumab (53.2%) and thiopurines (19.4%) were the top treatment preferences for moderate-to-severe ulcerative colitis ($P<0.0001$). Comorbidity and older age were independently associated with more frequent use of vedolizumab ($P<0.0001$), and less frequent use of immunomodulators and anti-tumour necrosis factor (TNF; $P<0.0001$). Comorbidity was the only independent predictor for selecting colectomy ($P<0.0001$). A history of lymphoma (94%) and opportunistic infection (78.3%) were the most frequent conditions precluding the use of thiopurine and anti-TNF in elderly patients with IBD. Only 6.1% of respondents considered patient age a limit for vedolizumab, while 37.9% considered age as a limiting factor in prescribing thiopurines ($P<0.001$). Geographical heterogeneity was identified with significantly more physicians from Oceania and North America favouring the use of vedolizumab.

Conclusion Vedolizumab was the preferred first-line agent in the treatment of elderly patients with IBD with steroid-dependent moderate-to-severe ulcerative colitis. Older age and presence of comorbidity influenced the selection of medication. Comorbidity was the main predictor of colectomy. Geographical heterogeneity in prescribing habits may relate to medication reimbursement in individual countries. Eur J Gastroenterol Hepatol XXX: 00–00

Introduction

Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, is a global disease with increasing incidence and prevalence [1]. The rising incidence has been reported across all age groups including the elderly population. Elderly patients with IBD include those diagnosed at a younger age who transition to an elderly age and those diagnosed after the age of 60 years (elderly-onset IBD) [2]. An estimated 10–30% of patients with IBD worldwide are aged >60 years [3], and recent studies have found that between 10 and 23% of patients are diagnosed with IBD after the age of 60 years [4,5]. As the global population ages, the prevalence of IBD in the elderly is also expected to rise, and peaks at 1061 per 100 000 in patients >85 years old [6].

Conventional IBD therapy consists of mesalazine, corticosteroids, and immunomodulators which include thiopurines (such as azathioprine and 6-mercaptopurine) and methotrexate. Anti-tumour necrosis factor (TNF)-α agents (infliximab, adalimumab, certolizumab pegol, and golimumab), as well as anti-integrin agents (vedolizumab) [7] have been approved for induction and maintenance therapy in both moderate-to-severe Crohn's disease and ulcerative colitis. More recently, the anti-IL 12/23 agent ustekinumab [8] and tofacitinib, a nonselective janus

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kinase inhibitor [9], have been approved. Expert consensus suggests that the principles of medical management of elderly-onset IBD are generally the same as in other age groups [2]. However, a recent meta-analysis and systematic review have reported that elderly-onset IBD patients use less conventional immunomodulators and biological therapy, but have comparable or even higher rates of IBD-related surgery than younger-onset patients [10]. Moreover, corticosteroids are often prescribed to the elderly IBD patients, with 32% of patients with IBD aged >65 years maintained on steroids for >6 months [11]. It is uncertain if the identified differences in the utilisation of immunosuppressive therapies and surgery between young-onset and elderly-onset IBD reflect a more aggressive disease course in elderly-onset IBD, or reluctance of physicians to prescribe immunomodulators and biological therapies because of concern of adverse events precipitated by concurrent comorbidities [12], polypharmacy and potential for drug interactions [13], or medication nonadherence issues [14] in elderly subjects. Both thiopurine and anti-TNF uses are associated with increased risk of lymphoma [15], and serious and opportunistic infections [16–18]. Moreover, thiopurine use is associated with nonmelanoma skin cancer [19,20]. Efficacy and safety data of biological agents in elderly patients with IBD are scarce, as most pivotal clinical trials excluded the recruitment of elderly subjects.

The attending physicians' knowledge and risk perception towards the use of immunomodulators and biological agents in the elderly may influence prescription practice. Medication class preferences may differ worldwide due to different pharmaceutical or health insurance reimbursement schemes. Avoidance of medication cost or medication unavailability might drive the selection of colectomy over medical therapy. We, therefore, conducted an international survey to determine the preferences of gastroenterologists on prescribing medical treatment versus colectomy in elderly patients with steroid-dependent ulcerative colitis and to determine whether age alone, presence of comorbidities or both, may drive treatment preference. Secondary aims were to identify factors associated with treatment preference, identify conditions that preclude gastroenterologists from prescribing immunomodulators and biological agents, and determine whether patient age is considered a limitation to prescribing the various medication classes.

Materials and methods

Survey design

This investigator-initiated study was conducted in collaboration with two operational boards of the European Crohn's and Colitis Organisation (ECCO): Young-ECCO (Y-ECCO) and the clinical committee of ECCO (ClinCom). The decision to support this proposal was made by these committees through an independent review board following an international call to submit projects. The first version of the survey was designed by V.K., S.K. and R.L., and reviewed by Y-ECCO, ClinCom and the members of the ECCO governing board. After two rounds of modifications, the final version of the survey was approved by consensus. The survey consisted of 17 questions and was divided into four categories. First, demographic information, including medical position, continent and country of practice, years in gastroenterology practice, number of patients with IBD reviewed per week, and practice type was collected for each gastroenterologist. Second, we presented the clinical cases of three patients, both young and elderly, either with or without comorbidity, who had steroid-dependent ulcerative colitis. Third, we assessed the conditions that precluded gastroenterologists from prescribing the immunomodulators and biological agents. Fourth, the age limits of ordering such medications were recorded. The estimated time to complete the survey was 5 min. (Supplement 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A538*). As this was a general survey and not developed as a quantitative tool, it was validated for semantics and understandability by testing on three gastroenterologists.

Study population

The inclusion criteria were adult gastroenterologists who completed >50% of the questionnaire. In the absence of a universal definition of an 'IBD subspecialist' and in accord with previous studies [21], we pragmatically defined gastroenterologists as IBD subspecialists if they looked after >100 patients with IBD per year. The survey was distributed in hard copy format and through an online platform (SurveyMonkey) to gastroenterologist attendees at conferences and online mailing lists.

The case scenarios

Three case scenarios were designed to assess the impact of age, comorbidity, and the combination of both, on the choice of treatment modalities for ulcerative colitis. The first case scenario was a 76-year-old female with steroid-dependent ulcerative colitis, despite adherence to oral mesalazine 4 g daily. She required three courses of oral corticosteroids over a 9-month period (Supplement 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A538*). Her colonoscopy revealed extensive colitis consistent with the Mayo endoscopic subscore of 3. The patient had no other comorbidity (hereinafter referred to as 'elderly ulcerative colitis without comorbidity'). Scenario 2 was similar to the first one but the patient had comorbidities including type 2 diabetes mellitus with diabetic nephropathy and ductal adenocarcinoma of the left breast in remission ('elderly ulcerative colitis with comorbidity'). Scenario 3 was identical to scenario 2 but the patient was now 28 years old ('young ulcerative colitis with comorbidity').

All three case scenarios included five treatment options including prescribing immunomodulators, high-dose maintenance corticosteroids, mono- or combination therapy with anti-TNF, mono- or combination therapy with vedolizumab, and colectomy. The participants were asked to rank their choices of treatment, with one being the most preferred to five the least preferred.

Statistical analysis

Descriptive statistics of demographic data and overall responses for each question were documented. Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as medians

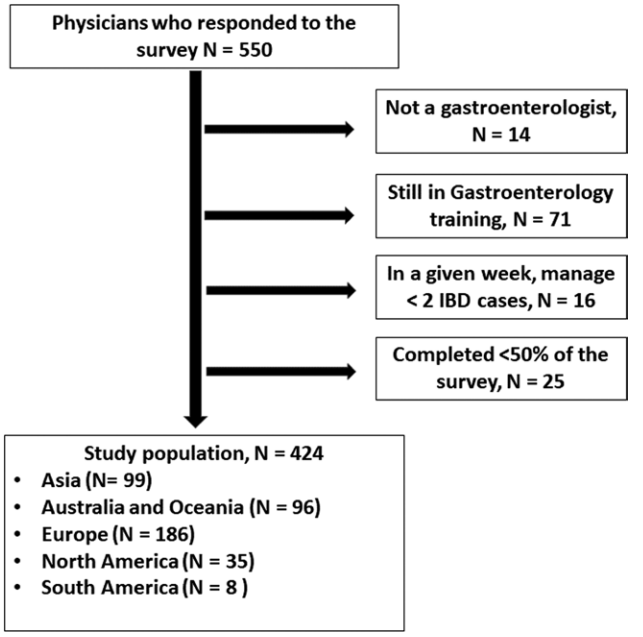


Fig. 1. Flow diagram showing the recruitment of gastroenterologists globally.

and interquartile range (IQR). Comparison of responses between groups was by chi-square test for categorical variables, Kruskal–Wallis test for nonparametrically distributed scales, and the ANOVA *t*-test for parametrically distributed scales, as appropriate. Univariate and multivariate binary logistic regression was used to determine variables associated with each treatment choice. Variables with a *P*-value of <0.05 in univariate analysis were included in multivariate analysis. Results were expressed as odds ratios (OR) and their 95% confidence intervals (95% CI). Statistical analyses were conducted using SPSS [IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, New York, USA)].

Ethics

The anonymous survey was approved by the Centralised Institutional Review Board (CIRB) of SingHealth Research (CIRB Reference number: 2019/2056) and completion and return of the survey were deemed informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (sixth revision, 2008) as reflected in a priori approval by the institution's human research committee.

Results

Study cohort

The questionnaire was distributed in 41 countries covering five continents. The written survey had a response rate of 55%. The online survey encouraged distribution amongst gastroenterology colleagues to increase the sample size. The exact response rate, therefore, was undefined. About 950 email invitations were sent. A total of 550 gastroenterologists responded to the survey, of whom 424 met the inclusion criteria (Fig. 1). Characteristics of the gastroenterologists included are depicted in Table 1 (and Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A538*). Of those surveyed, 43.9% (*n*=186) were from Europe, 23.3% (*n*=99) from Asia, and 22.6% (*n*=96) from Oceania. The median duration of gastroenterology experience was 12.0 years (IQR: 5.0–20.75) with 69% working in public hospitals and 68% of respondents treating >10 patients with IBD per week.

Table 1. Gastroenterologists' demographic and clinical characteristics

Gastroenterologists' characteristics	*N*=424 (%)
Continents	
Asia	Total=99 (23.3%)
Australia and Oceania	Total=96 (22.6%)
Europe	Total=186 (43.9%)
North America	Total=35 (8.3%)
South America	Total=8 (1.9%)
Years in practice	
Mean [years (SD)]	13.9 (9.7)
<5 years	98 (23.1)
6–10 years	77 (18.2)
11–15 years	60 (14.2)
>15 years	152 (35.8)
Missing	37 (8.7)
Number of patients with IBD seen per week	
2–5 patients	78 (18.6)
6–10 patients	59 (13.9)
>10 patients	286 (67.5)
Practice setting	
Public	291 (68.6)
Private	56 (13.2)
Mixed (public + private)	76 (17.9)
Missing	1 (0.2)

IBD, inflammatory bowel diseases.

Response to case scenarios

Vedolizumab was the most preferred treatment choice in all three cases, with 43.9, 64.9, and 50.9% of gastroenterologists selecting it as the first choice for cases 1, 2, and 3, respectively (Table 2). In the 'elderly ulcerative colitis without comorbidity' (case 1) and 'young ulcerative colitis with comorbidity' (case 3), the second preferred option was immunomodulators (28.5 and 18.7%, respectively), followed by anti-TNF (23.8 and 18.3%, respectively). In the 'elderly ulcerative colitis with comorbidity' (case 2), colectomy was the second most preferred choice (13.3%), followed by immunomodulators (10.9%). Increasing the dose of prednisolone was the least preferred option among all 3 scenarios (Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/EJGH/A538*).

Factors associated with treatment choices

On multivariate analysis, comorbidity and older age were independent factors associated with less frequent use of immunomodulators. Compared with 'elderly ulcerative colitis with comorbidity' (case 2), immunomodulators were more frequently used in 'elderly ulcerative colitis without comorbidity' (case 1; OR, 4.06; 95% CI, 2.26–6.29; $P<0.0001$) and 'young ulcerative colitis with comorbidity' (case 3; OR, 2.28; 95% CI, 1.45–3.58; $P<0.0001$; Table 4). Other factors associated with less frequent prescription of immunomodulators included practicing in Europe (OR, 0.51; 95% CI, 0.34–0.79; $P=0.002$) and North America (OR, 0.03; 95% CI, 0.004–0.22; $P=0.001$) compared to Asia; having a perceived maximum age limit to prescribing thiopurines (OR, 0.46; 95% CI,

Table 2. First choices of treatment based on case scenarios

First choice of treatment	Case scenarios: Elderly ulcerative colitis without comorbidity (case 1)	Elderly ulcerative colitis with comorbidity (case 2)	Young ulcerative colitis with comorbidity (case 3)	Overall (%)	*P* value
Prescribe immunomodulators	28.5% (113/397)	10.9% (43/394)	18.7% (73/390)	19.4	*P*<0.0001
Increase dose of prednisolone and continue on that dose for maintenance	1.8% (7/397)	3.0% (12/395)	2.1% (8/389)	2.7	*P*=0.622
Prescribe anti-TNF	23.8% (95/400)	8.8% (35/396)	18.3% (72/394)	17.0	*P*<0.0001
Prescribe vedolizumab	43.9% (175/399)	64.9% (259/399)	50.9% (200/393)	53.2	*P*<0.0001
Recommend colectomy	2.8% (11/397)	13.3% (53/399)	11.5% (45/393)	9.2	*P*<0.0001

TNF, tumour necrosis factor.

Table 3. Conditions precluding the use of immunomodulators and biological agents in elderly patients with inflammatory bowel diseases

Conditions	Preclude commencing medications (% from respondents within the drug): Missing input (% of total)	Immuno-modulator	Anti-TNF	Vedolizumab	*P* value
History of lymphoma	16	94.0	69.0	30.4	<0.0001
History of solid organ cancer	5.7	65.1	57.4	20.0	<0.0001
Melanoma skin cancer	16.3	44.7	61.0	20.6	<0.0001
Nonmelanoma skin cancer	14.3	53.2	29.2	13.6	<0.0001
Congestive heart failure	16.1	5.3	76.6	12.1	<0.0001
Demyelination	14.2	7.8	61.8	19.5	<0.0001
Osteoporosis	16.3	1.5	1.0	0.7	0.627
Hepatotoxicity	5.8	69.1	22.2	19.1	<0.0001
Opportunistic infection	16.2	72.6	78.3	57.4	<0.0001
Drug to drug interaction	14.5	52.3	31.4	38.2	<0.0001

TNF, tumour necrosis factor.

0.29–0.68; *P*<0.001), steroids (OR, 0.32; 95% CI, 0.13–0.79; *P*=0.014) and combination therapy (OR, 0.64; 95% CI, 0.43–0.96; *P*=0.029). In contrast, working in private practice (OR 1.69; 95% CI, 1.05–2.73; *P*=0.03); and having a perceived age limit to prescribing an anti-TNF (OR, 1.73; 95% CI, 1.04–2.88; *P*=0.036), and vedolizumab (OR, 3.45; 95% CI, 1.76–6.76; *P*<0.0001) were associated with more frequent use of immunomodulators.

Similarly, the presence of comorbidity and older age were independently associated with less frequent use of anti-TNF. Compared with 'elderly ulcerative colitis with comorbidity' (case 2), anti-TNF was more frequently prescribed in 'elderly ulcerative colitis without comorbidity' (case 1) (OR, 3.57; 95% CI, 2.21–5.77; *P*<0.0001) and 'young ulcerative colitis with comorbidity' (case 3) (OR, 2.50; 95% CI, 1.53–4.10; *P*<0.0001) (Table 4). Other factors associated with more frequent prescription of anti-TNF was practicing in South America (OR, 4.29; 95% CI, 1.45–12.69; *P*=0.009) compared to Asia, and having a perceived age limit in prescribing corticosteroids (OR, 1.95; 95% CI, 1.01–3.78; *P*=0.048). Increased years practicing in gastroenterology and seeing >10 patients with IBD per week, were associated with less frequent use of anti-TNF (OR, 0.80; 95% CI, 0.70–0.93; *P*=0.003, and OR, 0.52; 95% CI, 0.32–0.82; *P*=0.005, respectively).

On multivariate analysis, comorbidity and old age were independently associated with more frequent use of vedolizumab. Vedolizumab was less frequently used in 'elderly ulcerative colitis without comorbidity' (case 1) (OR, 0.37; 95% CI, 0.27–0.51; *P*<0.0001) and 'young ulcerative colitis with comorbidity' (case 3) (OR, 0.51; 95% CI, 0.37–0.69; *P*<0.0001) compared against 'elderly ulcerative colitis with comorbidity' (case 2; Table 4). Other factors associated with more frequent prescription of vedolizumab included practicing in Oceania and North America (OR, 1.47; 95% CI, 1.02–2.13; *P*=0.04 and OR, 5.58; 95% CI, 2.96–10.51; *P*<0.0001, respectively) compared to Asia; seeing >10 patients with IBD per week (OR, 1.92; 95% CI, 1.36–2.71; *P*<0.0001), and having a perceived age limit in prescribing thiopurines (OR, 1.54; 95% CI, 1.17–2.03; *P*=0.002).

The presence of comorbidity was the only independent predictor for selecting colectomy. Compared with 'elderly ulcerative colitis with comorbidity' (case 2), surgery was less frequently recommended in 'elderly ulcerative colitis without comorbidity' (case 1) (OR, 0.18; 95% CI, 0.09–0.36; *P*<0.0001). There was no statistically significant difference in recommending colectomy between 'elderly ulcerative colitis with comorbidity' and 'young ulcerative colitis with comorbidity' (OR, 0.81; 95% CI, 0.52–1.26; *P*=0.34). Corticosteroid use was not associated with age or comorbidity (Supplementary Table 4, Supplemental digital content 1, *http://links.lww.com/EJGH/A538*).

Conditions precluding immunomodulators and biological agents in elderly patients with inflammatory bowel diseases

A history of lymphoma (94.0%) and opportunistic infection (78.3%) were the commonest reported events precluding the use of thiopurines and anti-TNF in elderly patients with IBD (Table 3). Opportunistic infection (57.4%) was the commonest condition considered as contraindications to vedolizumab in elderly patients with IBD.

Age limit for prescribing immunomodulators and biological therapy

Vedolizumab and corticosteroids were prescribed without age as a limiting factor by 93.9 and 93.7% of respondents, respectively. However, 37.9% of gastroenterologists

Table 4. Multivariate logistic regression analysis of variables associated with the selection of first line treatment

	Immunomodulators		Anti-TNF		Vedolizumab		Surgery	
Covariant considered in univariate analysis	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Scenario								
Scenario 2 (reference)	1		1		1		1	
Scenario 1 (vs. 2)	4.06 (2.26–6.29)	**<0.0001**	3.57 (2.21–5.77)	**<0.0001**	0.37 (0.27–0.51)	**<0.0001**	0.18 (0.09–0.36)	**<0.0001**
Scenario 3 (vs. 2)	2.28 (1.45–3.58)	**<0.0001**	2.50 (1.53–4.10)	**<0.0001**	0.51 (0.37–0.69)	**<0.0001**	0.81 (0.52–1.26)	0.34
Continents								
Asia	1		1		1		1	
Oceania	1.12 (0.71–1.76)	0.55	0.72 (0.41–1.26)	0.26	1.47 (1.02–2.13)	**0.04**	0.53 (0.25–1.10)	0.09
Europe	0.51 (0.34–0.79)	**0.002**	1.51 (0.95–2.39)	0.08	1.22 (0.89–1.68)	0.22	1.43 (0.86–2.34)	0.17
North America	0.03 (0.004–0.022)	**0.001**	0.68 (0.29–1.57)	0.36	5.58 (2.96–10.51)	**<0.0001**	0.56 (0.21–1.54)	0.26
South America	0.26 (0.03–2.02)	0.20	4.29 (1.45–12.69)	**0.009**	0.56 (0.20–1.55)	0.27	0.41 (0.05–3.48)	0.41
Years as gastroenterologist (years)	*		0.80 (0.70–0.93)	**0.003**	*		*	
Number of IBD patients reviewed per week	*						*	
2–5			1		1			
6–10			0.77 (0.43–1.39)	0.38	1.08 (0.69–1.67)	0.74		
>10			0.52 (0.32–0.82)	**0.005**	1.92 (1.36–2.71)	**<0.0001**		
Place of practice			*		*			
Public	1						1	
Private	1.69 (1.05–2.73)	**0.03**					0.46 (0.20–1.07)	0.07
Mixed	1.25 (0.81–1.04)	0.30					0.51 (0.26–1.01)	0.052
Age limit for thiopurines	0.46 (0.29–0.68)	**<0.0001**	*		1.54 (1.17–2.03)	**0.002**	*	
Age limit for vedolizumab	3.45 (1.76–6.76)	**<0.0001**	*		0.23 (0.11–0.48)	**<0.0001**	2.95 (1.38–6.34)	**0.001**
Age limit for anti-TNF	1.73 (1.04–2.88)	**0.036**	*		0.71 (0.49–1.03)	0.074	1.65 (0.98–2.78)	0.06
Age limit for steroids	0.32 (0.13–0.79)	**0.014**	1.95 (1.01–3.78)	**0.048**	*	*	*	
Age limit for combination therapy	0.64 (0.43–0.96)	**0.029**	*		*		*	

Scenario 1: elderly ulcerative colitis only. Scenario 2: elderly ulcerative colitis with comorbidity. Scenario 3: young ulcerative colitis with comorbidity.
TNF, tumour necrosis factor; IBD, inflammatory bowel diseases.
*Factors not statistically significant on univariate analysis.

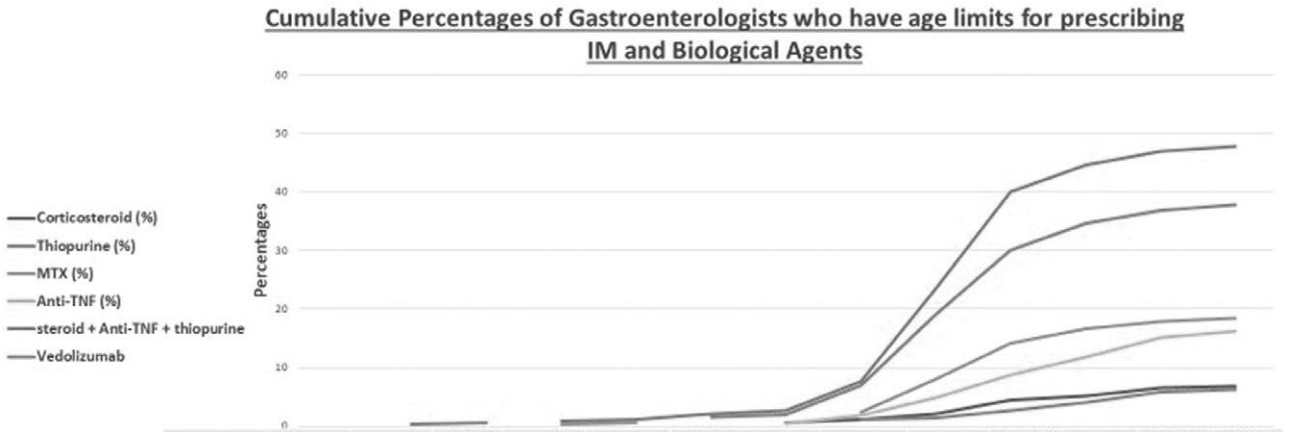
considered age as a limiting factor in prescribing thiopurines (Fig. 2).

Discussion

This study identified gastroenterologists preference and risk-perception with respect to prescribing various medication classes versus colectomy in elderly patients with steroid-dependent ulcerative colitis. First, vedolizumab was the most preferred treatment option for elderly patients with steroid-dependent ulcerative colitis. Second, both older age and the presence of comorbidity were independently associated with selection of vedolizumab and avoidance of immunomodulators and anti-TNF. In contrast, the presence of comorbidity rather than age-alone was the most important factor in recommending colectomy for steroid-dependent ulcerative colitis. Third, geographical heterogeneity was identified in the selection of treatment.

The ECCO consensus guidelines [22] recommended that steroid-dependent patients with moderate-to-severe ulcerative colitis be treated with a thiopurine, anti-TNF (preferably in combination with a thiopurine), or vedolizumab. Our survey identified that vedolizumab ranked first among these options. Older age, comorbidity, practicing in North America and Oceania, greater experience in managing IBD, and having a perceived age limit to prescribing thiopurines, were independent factors that were significantly associated with selecting vedolizumab as the preferred treatment. In clinical trials for infliximab [23] and golimumab [24], no upper age limit was set. For certolizumab [25], adalimumab [26], and vedolizumab [7], the upper age limits were 65, 75, and 80 years, respectively. Commencing thiopurines or anti-TNF agents in elderly patients is a challenge for physicians because of safety concerns for these medications. In a recent meta-analysis, the absolute risk of lymphoma in IBD patients treated with thiopurines was highest in patients >50 years old (1.35 cases per patient-year, with a relative risk of 4.78) [27]. A nationwide cohort study from France [17] provided evidence that patients exposed to anti-TNF monotherapy, thiopurine monotherapy, or combination therapy, had increased risks of serious infections compared with patients unexposed to either drug. In particular, the absolute risks were 2-fold to 3-fold greater in patients >65 years compared with younger patients [17]. Another retrospective, multicenter study [28] found that initiation of thiopurine therapy >60 years was associated with a higher risk of thiopurine-related adverse events. The efficacy and safety of vedolizumab are established in younger patients [29] and in the elderly [30]. A recent retrospective study [31] that compared the safety and efficacy of anti-TNF and vedolizumab in patients with IBD >60 years of age showed that both biological agents were similarly effective and well tolerated in this group of patients. There are limited data on the safety of vedolizumab in subjects with comorbidity. However, through its targeted, gut selective mechanism of action, vedolizumab is a well tolerated alternative to systemic immunosuppression and as such should be an attractive option in the elderly and for patients with comorbidities.

In addition to older age, patient comorbidity was another independent factor associated with less frequent use of immunomodulators and anti-TNF. Few data are available on the effect of comorbidity on the use of immunomodulators in elderly IBD. A systematic review and meta-analysis [10] along with cohort studies [5,32] reported lower utilization of conventional immunomodulators and biological therapies in elderly-onset IBD compared with young-onset IBD. It is uncertain if



	<13 years old	<14 years old	<15 years old	<18 years old	<40 years old	>50 years old	>55 years old	>60 years old	>65 years old	>70 years old	>75 years old	>80 years old	>85 years old
Corticosteroid (%)			0.3				0.6	1.1	2.1	4.4	5.2	6.5	6.8
Thiopurine (%)		0.3	0.6			1.6	1.9	7	19.1	30.1	34.6	36.9	37.9
MTX (%)				0.3	0.6			2.4	8	14.1	16.6	17.9	18.4
Anti-TNF (%)				0.2			0.4	1.8	4.9	8.7	11.8	15.1	16.3
steroid + Anti-TNF + thiopurine	0.3			0.8	1.1	2.1	2.6	7.7	23.6	40.1	44.7	47	47.8
Vedolizumab		0.3		0.6				1.1	1.4	2.7	4	5.8	6.3

Fig. 2. Cumulative percentages of gastroenterologists who have age limits for prescribing immunomodulators and biological agents.

the underutilization of such therapies reflects the disease course of IBD [5,10,32], physicians' preference, or both. Kariyawasam *et al*. [33] previously reported in a comparative study of elderly-onset and young-onset IBD patients, that the Charlson's Comorbidity Index was shown to delay immunomodulator introduction in both Crohn's disease (hazard ratios: 0.86; 95% CI, 0.79–0.95) and ulcerative colitis (hazard ratios: 0.81; 95% CI, 0.71–0.92) [33]. Lymphoma was regarded as the major contraindication to thiopurines in elderly patients. Following the diagnosis of a solid organ cancer, as many as 2–3 times more gastroenterologists would stop thiopurines (65.1%) or anti-TNF agents (57.4%) than vedolizumab (20%, $P \leq 0.0001$). There was a surprisingly high proportion of respondents to this survey that did not avoid using anti-TNF in the presence of demyelination, recent melanoma, or congestive heart failure.

The presence of comorbidity was the single most important factor in influencing the decision in recommending colectomy. Colectomy is generally viewed as being a curative option in ulcerative colitis, resulting in the cessation of all immunomodulator and biological drugs. However, this decision must be balanced against the increased rate of postoperative morbidity and mortality in operative subjects aged over 60 years with comorbidities [34]. Recent population-based studies demonstrated higher surgical rates in elderly-onset ulcerative colitis compared to young-onset ulcerative colitis patients [5,35,36]. The increased surgical rate was associated with very low frequency of immunomodulator use. Therefore, the decision to perform colectomy might have been driven by the treating physician's decision to select colectomy to avoid medical therapy, rather than the greater severity of ulcerative colitis.

Geographical heterogeneity was identified in the selection of immunomodulators and biological therapies. Physicians from Oceania and North America used vedolizumab significantly more frequently than other regions. European and North American gastroenterologists used immunomodulators less frequently compared with Asian countries. International variation in the treatment of patients with IBD is well-described [37]. Different healthcare systems, policies for medication reimbursement, and universal health insurance may influence the choice of medication prescription. For example, the Australian Pharmaceutical Benefits Scheme allows access to vedolizumab in the treatment of moderate-to-severe Crohn's disease and ulcerative colitis, even as the first-line biological agent, after failure of corticosteroids, mesalazine and an immunomodulator [38]. In Canada, vedolizumab is funded through public provincial drug plans for the treatment of IBD since 2017. Gastroenterologists from these countries, therefore, might select the newer biological agents that might be safer in the elderly. Gastroenterologists from South America, on the other hand, used anti-TNF more frequently due to the cost-benefit of infliximab biosimilar which has been available since 2015.

The strength of this study was the recruitment of hundreds of gastroenterologists from various countries across the world to reflect the global practice pattern. It demonstrates that vedolizumab has gained widespread acceptance worldwide as the first-line therapy in moderate to severe ulcerative colitis in the elderly. This study has limitations. First, despite the large sample size of respondents, the absolute numbers of gastroenterologists from some individual countries were small. Therefore, we analysed practice across regions based on similar healthcare systems and patient demographics. This increased statistical power and the ability to identify geographical heterogeneity in medication prescribing practice. Second, there was no possible calculation of the response rate to the survey as the exact number of invitations was unknown. Third, selection bias was possible in respondents who are familiar with vedolizumab. However, some respondents responded with limited use of vedolizumab suggesting a wide cross-section of physicians who responded to the survey. We also controlled for expertise in IBD based on the average number of IBD patients that the respondents saw per week. Very few differences were identified based on high volume IBD practices versus low volume practices. Fourth, we focused

on moderate-to-severe steroid-dependent ulcerative colitis in this survey. The pattern of use of therapies in paediatric subjects with IBD, and those with luminal Crohn's disease or perianal Crohn's disease will be the subject of future surveys. These data will likely differ from our current results. Last, we did not explore newer treatment options such as ustekinumab [8] and tofacitinib [9]. However, at the time of the survey, these agents were not yet available in most parts of the world and few respondents would have had ready access to these agents.

In conclusion, vedolizumab is the preferred first-line agent in the treatment of elderly IBD patients with steroid-dependent moderate-to-severe ulcerative colitis worldwide. Both old age and presence of comorbidity are the main factors that physicians consider when choosing between immunomodulators, anti-TNF, vedolizumab, and surgery. In elderly IBD patients, the presence of opportunistic infection and lymphoma were the main barriers in prescribing biological therapies and thiopurines, respectively. More data on the efficacy and safety of vedolizumab in the elderly IBD is needed to endorse it as the preferred first-line therapy in this group of patients.

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Conflicts of interest

There are no conflicts of interest.

W.C.: Guarantor of the article. W.C. and V.C.K. contributed equally to study design, data acquisition, analysis, and wrote and revised the manuscript. S.K. and H.H.S. contributed to data acquisition and manuscript revision. A.P., S.P., F.H.M., N.D., M.F., and R.W.L. contributed to study design, manuscript revision, and intellectual content. All authors approved the final version of the manuscript.

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