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ORIGINAL ARTICLE

Perception and clinical decisions from inflammatory bowel diseases' specialists towards positioning of new therapies in Crohn's disease and ulcerative colitis: A national web-based survey from the Brazilian IBD study group (GEDIIB)

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Abstract
Background: In the last decade, new therapies with different mechanisms of action have been approved for the treatment of moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). Due to the lack of comparative head-to-head trials, the ideal positioning of agents as the most appropriate first- or second-line therapies remains to be defined.
Objective: This survey aimed to evaluate the perception and decisions of Brazilian Inflammatory Bowel Diseases (IBD) specialists in positioning of new therapies (vedolizumab [VEDO], ustekinumab [UST] and tofacitinib [TOFA]) in the management of IBD in different clinical scenarios.
Methodology: An anonymous national web-based questionnaire was used to determine the positioning of treatment options in different clinical scenarios (using Google Forms platform), which

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involved different age ranges, phenotypes, clinical situations and previous exposure to anti-TNF agents (14 scenarios for CD and 10 scenarios for UC). In CD, physicians could choose between UST or VEDO, whilst in UC, between UST, VEDO or TOFA. Six reasons for the specific choice were proposed, such as mechanism of action, safety, method of administration or onset of action. Statistical analysis was carried out with chi-square and *t*-tests.
Results: A total of 150 out of 672 GEDIIB IBD specialists (22.32%) responded to the survey. In CD scenarios, UST was the most dominant choice (11/14 scenarios), with VEDO dominating only 3 clinical situations. In UC scenarios, VEDO was the dominant choice (8/10), with UST being chosen for scenarios that included extraintestinal manifestations. Among the reasons for specific choices, the most commonly chosen were the higher efficacy due to the intrinsic mechanism of action and safety profile.
Conclusions: UST was the dominant choice as compared to VEDO in CD in most scenarios, especially due to its mechanism of action and safety. VEDO was the dominant choice as compared to UST and TOFA in UC scenarios, mainly for reasons also related to its mechanism of action and safety profile. Comparative studies including patient outcomes are needed to better define the positioning of new IBD therapeutic options in our country.

PALABRAS CLAVE
Enfermedad de Crohn;
Colitis ulcerosa;
Ustekinumab;
Integrinas;
Inhibidores de la Janus quinasa;
Productos biológicos

Percepción y decisiones clínicas de especialistas en enfermedades inflamatorias intestinales hacia el posicionamiento de nuevas terapias en la enfermedad de Crohn y la colitis ulcerosa: una encuesta web de práctica clínica nacional del Grupo de Estudios Brasileño de Enfermedades Inflamatorias (GEDIIB)

Resumen
Antecedentes: En la última década se han aprobado nuevas terapias con diferentes mecanismos de acción para el tratamiento de la enfermedad de Crohn (EC) y de la colitis ulcerosa (CU) de moderada a grave. Debido a la falta de ensayos comparativos cara a cara, aún no se ha definido el posicionamiento ideal de los agentes como terapias de primera o segunda línea más adecuadas.
Objetivo: El objetivo de esta encuesta fue evaluar la percepción y las decisiones de los especialistas brasileños en enfermedades inflamatorias intestinales (EII) en el posicionamiento de las nuevas terapias (vedolizumab [VEDO], ustekinumab [UST] y tofacitinib [TOFA]) en el manejo de la EII en diferentes escenarios clínicos.
Metodología: Se utilizó un cuestionario nacional anónimo basado en la web para determinar el posicionamiento de las opciones de tratamiento en diferentes escenarios clínicos (utilizando la plataforma Google Forms), que implicaban diferentes rangos de edad, fenotipos, situaciones clínicas y exposición previa a agentes anti-TNF (14 escenarios para la EC y 10 escenarios para la CU). En la EC, los médicos podían elegir entre UST o VEDO, mientras que, en la CU, entre UST, VEDO o TOFA. Se propusieron 6 razones para la elección específica, como el mecanismo de acción, la seguridad, el método de administración o el inicio de acción. El análisis estadístico se llevó a cabo con las pruebas de Chi-cuadrado y la t de Student.
Resultados: Un total de 150 de los 672 especialistas en EII del Grupo de Estudios Brasileño de Enfermedades Inflamatorias (GEDIIB) (22,32%) respondieron a la encuesta. En los escenarios de la EC, la UST fue la opción más dominante (11/14 escenarios), y la VEDO solo dominó 3 situaciones clínicas. En los escenarios de la CU, la VEDO fue la elección dominante (8/10), siendo la UST la elegida para los escenarios que incluían manifestaciones extraintestinales. Entre los motivos de elección específicos, los más elegidos fueron la mayor eficacia debido al mecanismo de acción intrínseco y el perfil de seguridad.
Conclusiones: La UST fue la elección dominante en comparación con la VEDO en la EC en la mayoría de los escenarios, especialmente debido a su mecanismo de acción y seguridad. La VEDO fue la opción dominante en comparación con UST y TOFA en escenarios de la CU, principalmente por razones también relacionadas con su mecanismo de acción y perfil de seguridad. Se necesitan estudios comparativos que incluyan los resultados de los pacientes para definir mejor el posicionamiento de las nuevas opciones terapéuticas para la EII en nuestro país.

Introduction

Inflammatory bowel diseases (IBD), which comprise ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the gastrointestinal tract characterized by alternating periods of remission and disease activity. The geographical prevalence of IBD varies considerably. Higher prevalence is traditionally reported in Northern America and Europe with rates reaching 249 and 505 per 100,000 habitants, respectively.[1] The precise prevalence, incidence and mortality rates in Brazil are still unknown, although regional reports describe an increase in the incidence of CD and UC, likely resulting in a high burden of IBD in the country.[2]

Over the past two decades, there has been a revolution in the treatment of IBD as a consequence of the introduction of biological agents (monoclonal antibodies).[3,4] The first group of biologicals consisted of anti-tumor necrosis factor (TNF) agents. In the last five years, emerging therapies with different mechanisms of action including targeted monoclonal antibodies (vedolizumab [VEDO] and ustekinumab [UST]) and small molecules (Tofacitinib [TOFA]) have been incorporated into treatment algorithms.[5–8] In addition, the development of different treatment strategies (such as early intervention and the treat-to-target approach) has also contributed to better outcomes for patients.[9–11]

The increased availability of new treatment options with varying profiles of efficacy and safety has been challenging clinicians in regard to the appropriate positioning of different agents as first- (in biologic naïve patients) and second-line (in patients with previous exposure to anti-TNF agents) therapies. Even though there are several algorithms to assist decision-making, a single approach is not entirely practical for patients with different clinical characteristics or comorbidities.[12] Recently, the first head-to-head trial (VARSITY) comparing biologics in IBD conducted by Sands et al.[13] demonstrated that VEDO was superior to adalimumab regarding clinical remission and endoscopic improvement in UC. However, there is a lack of other direct comparative studies on different drugs, and decisions about treatment choices in different settings rely on the physician's experience, opinion-based treatment algorithms, patient preference, cost of treatment and other specific issues. As expected, there is considerable variability in clinical practice concerning the ideal choice of biologics and small molecules.

In this scenario, this survey aimed to evaluate the perception and clinical decisions of Brazilian IBD specialists in the positioning of new therapies in the management of IBD patients in different clinical settings, excluding anti-TNFs agents. The preference was compared between VEDO and UST for the treatment of CD and between VEDO, UST or TOFA for the treatment of UC.

Methods

The questionnaire

The questionnaire was developed by the Brazilian IBD Study Group (GEDIIB) in collaboration with IBD experts in the field in order to assess the positioning of IBD treatments (new biologics in CD, new biologics or small molecule in UC) in different situations. It consisted of 24 multiple-choice questions addressing 14 hypothetical clinical scenarios for CD (Table 1) and 10 for UC (Table 2), in which patients had an indication for the use of new agents, with no access restrictions (e.g., private practice).

The questionnaire initially included demographic data from physicians, such as time in clinical practice, specialty, number of IBD patients treated per month, practice profile (public, private or academic), among others. Subsequently, the following treatment options were offered as possible alternatives in each different clinical scenario: TOFA/VEDO/UST for treatment of UC and VEDO/UST for treatment of CD. All cases were simulated in private practice, as these new therapeutic options are not available in the public health system. The 14 simulated clinical scenarios of CD (Table 1) involved patients with ileal or colon/rectal disease, with or without perianal involvement, older or younger than 70 years of age, with or without previous exposure to anti-TNFs, with or without extraintestinal manifestations. The 10 cases of UC (Table 2) involved patients with proctitis, proctocolitis or extensive colitis, older or younger than 70 years of age, with or without previous exposure to anti-TNFs, with or without extraintestinal manifestations.

After the therapeutic options were chosen in each scenario, the following reasons were offered as justifications: efficacy related to the mechanism of action, better access, safety, physician's experience, scientific evidence, convenience in mode of administration and onset of action (Table 3).

Ethical considerations

This research project was approved by the Ethics Committee of GEDIIB and the Ethics Committee of Sao Paulo State University (UNESP, Botucatu) under reference number CAAE 49333621.7.0000.5411 at the national ministry of health central website. This study was conducted in compliance with regulations stated in the 1975 Declaration of Helsinki. The survey offered self-selective recruitment, so the consent form was waived. In addition, data were de-identified and individual participant data were not published, which maintained confidentiality in all steps of study analysis.

Statistical analysis

Data were collected and stored in a Microsoft Excel spreadsheet. Ten identified duplicate responses were excluded. Data analysis was performed by a statistician, with the support of the software SPSS v.22.0 (UNICOM Global, Mission Hills, United States). Quantitative variables (as age) were expressed as means and standard deviations (SD) while qualitative variables were expressed by frequencies and percentages and were analyzed using the Pearson chi-square test. Student's t test was used for quantitative variables in comparisons. Statistically, a significant difference was considered when $p < 0.05$.

Table 1 summary of CD clinical scenarios.

1. A 45-year-old patient from private practice, with active Crohn's colitis, with previous failure to 2 anti-TNFs in combination with immunosuppressants.
2. A 70-year-old patient from private practice, with active Crohn's colitis, who had previously failed to 2 anti-TNFs.
3. A 45-year-old patient from private practice, with active Crohn's colitis, naïve to biologics, refractory to optimized conventional treatment. Patient does not accept to use anti-TNFs.
4. A 70-year-old patient from private practice, with active Crohn's colitis, naïve to biologics, refractory to optimized conventional treatment. Patient does not accept to use anti-TNFs.
5. A 45-year-old patient from private practice, with active luminal Crohn's disease, who had previously failed to 2 anti-TNFs in combination with immunosuppressants.
6. A 70-year-old patient from private practice, with an active terminal ileum luminal Crohn's disease, who had previously failed to 2 anti-TNFs.
7. A 45-year-old patient from private practice, with active luminal Crohn's disease, naïve to biologics, refractory to optimized conventional treatment. Patient does not accept to use anti-TNFs.
8. A 70-year-old patient from private practice, with active luminal Crohn's disease, naïve to biologics, refractory to optimized conventional treatment. Patient does not accept to use anti-TNFs.
9. A 45-year-old patient from private practice, with luminal Crohn's located in sigmoid colon and rectum with active fistulizing perianal disease, with previous failure to 2 anti-TNFs.
10. A 70-year-old patient from private practice, with luminal Crohn's located in sigmoid colon and rectum with active fistulizing perianal disease, with previous failure to 2 anti-TNFs.
11. A 45-year-old patient from private practice, with luminal Crohn's located in sigmoid colon and rectum with active fistulizing perianal disease, naïve to biologics, refractory to optimized conventional treatment. Patient has contraindication to the use of anti-TNF (for example, heart failure grade III or IV).
12. A 70-year-old patient from private practice, with luminal Crohn's located in sigmoid colon and rectum with active fistulizing perianal disease, naïve to biologics, refractory to conventional optimized treatment. Patient has contraindication to the use of anti-TNF (for example, heart failure grade III or IV).
13. A 45-year-old patient from private practice, with active luminal Crohn's disease, naïve to biologics, refractory to optimized conventional treatment. Patient has contraindication to the use of anti-TNF (for example, heart failure grade III or IV). Patient with erythema nodosum and type 1 arthritis (parallel to the disease activity) as extraintestinal manifestations.
14. A 70-year-old patient from private practice, with an active terminal ileum luminal Crohn's disease, naïve to biologics, refractory to optimized conventional treatment. Patient has contraindication to the use of anti-TNF (for example, heart failure grade III or IV). Patient with erythema nodosum and type 1 arthritis (parallel to the disease activity) as extraintestinal manifestations.

Results

Initially 160 replies were identified, and 10 duplicates were removed. A total of 150 respondents (50.7% males, mean age 48 years, SD $\pm$ 10.94) out of 672 GEDIIB members (22.32%) replied to the survey (convenience sample, not specifically powered for pre-determined outcomes). The baseline characteristics of the respondents are detailed in Table 4. Fifty-six percent of respondents were gastroenterologists, while 40% were colorectal surgeons. Regarding the time in clinical practice, 50.7% had less than 20 years and 49.3% had more than 20 years. Most prescribers (54.7%) worked in private clinics and public hospitals. Eighty percent of the participants already needed litigation to ensure access to a new biological to their patients and 75.3% worked with a multidisciplinary team.

Responses regarding CD scenarios are detailed in Table 5. As noted, the most commonly chosen agent among the 14 scenarios was UST. VEDO was the most voted drug in only three scenarios: a 70-year-old patient with Crohn's colitis refractory to two anti-TNF drugs, a 45-year-old patient with Crohn's colitis refractory to conventional treatment, but who does not accept the use of anti-TNF and a 70-year-old patient with Crohn's colitis refractory to conventional treatment, but who does not accept the use of anti-TNF. Among the reasons for the therapeutic options, the most chosen were the better efficacy due to the mechanism of action in this type of disease and better safety profile.

The replies for UC scenarios are detailed in Table 6. As observed, the most commonly chosen agent was VEDO. UST was the dominant choice in the only two scenarios which involved proctocolitis and extraintestinal manifestations. Similarly to CD, among the reasons, the most chosen were better efficacy due to the intrinsic mechanism of action in this type of disease and better safety profile. There was no scenario in which tofacitinib was the most prevalent chosen option.

After induction with intravenous UST in biologic naïve patients, most prescribers preferred the 8-week interval regimen for subcutaneous maintenance of the agent, both in CD (76.5%) and in UC (70.7%).

In a sub-analysis which compared the responses of gastroenterologists in comparison with colorectal surgeons, it was observed that gastroenterologists see a greater number of patients per month ($p = 0.035$). Regarding the choice of drugs in CD, there was a significant difference only in scenarios 6 ($p = 0.041$) and 11 ($p = 0.029$), with gastroenterologists prescribing more UST than colorectal surgeons (data

Table 2 Summary of UC clinical scenarios.

1. A 45-year-old patient from private practice, with UC with phenotype of proctitis, refractory to conventional treatment, with moderate to severe active disease, with previous failure to 2 anti-TNFs.
2. A 70-year-old patient from private practice, with UC with phenotype of proctitis refractory to conventional treatment, with moderate to severe active disease, with previous failure to 2 anti-TNFs.
3. A 45-year-old patient from private practice, with UC with phenotype of proctitis refractory to optimized conventional treatment, with moderate to severe active disease, naïve to biologics.
4. A 70-year-old patient from private practice, with UC with phenotype of proctitis refractory to optimized conventional treatment, with moderate to severe active disease, naïve to biologics.
5. A 45-year-old patient from private practice, with UC with a phenotype of pancolitis (extensive or universal colitis) refractory to conventional treatment, with moderate to severe active disease, with previous failure to 2 anti-TNFs.
6. A 70-year-old patient from private practice, with UC with a phenotype of pancolitis (extensive or universal colitis) refractory to conventional treatment, with moderate to severe active disease, with previous failure to 2 anti-TNFs.
7. A 45-year-old patient from private practice, with UC with a phenotype of pancolitis (extensive or universal colitis), refractory to optimized conventional treatment, with moderate to severe active disease, naïve to biologics.
8. A 70-year-old patient from private practice, with UC with a phenotype of pancolitis (extensive or universal colitis), refractory to optimized conventional treatment, with moderate to severe active disease, naïve to biologics.
9. A 45-year-old patient from private practice, with UC with a phenotype of left side colitis refractory to optimized conventional treatment, with moderate to severe active disease, näive to biologics. Patient has contraindication to the use of anti-TNF (for example, heart failure grade III or IV). Patient with erythema nodosum and type 1 arthritis (parallel to the disease activity) as extraintestinal manifestations.
10. A 70-year-old patient from private practice, with UC with a phenotype of left side colitis refractory to optimized conventional treatment, with moderate to severe active disease, näive to biologics. Patient has contraindication to the use of anti-TNF (for example, heart failure grade III or IV). Patient with erythema nodosum and type 1 arthritis (parallel to the disease activity) as extraintestinal manifestations.

Table 3 reasons for specific choices (replies) clinical scenarios.

What is the main reason for your choice?
a) I believe in better efficacy due to the mechanism of action in this type of disease
b) Easier access
c) Better safety profile
d) I have better personal experience with the drug
e) Supported by better scientific evidence
f) Posology and administration mode
g) Rapid onset of action

not shown). For UC, there was no significant difference in the choice of drugs between specialties.

When comparing the responses from prescribers who only work in the private setting with the others (private + public and only public), there was a significant statistical difference in scenarios 11 ($p = 0.039$), 12 ($p = 0.025$) and 13 ($p = 0.035$) from CD, in which it was observed that the others prescribe proportionally more UST compared to the prescribers who work only in the private setting (data not shown). For UC, there was no significant difference between the groups.

Regarding the time in practice (more than 20 years versus less than 20 years), there was a significant difference in scenario 8 ($p = 0.012$) of CD, where those who have more than 20 years of practice prescribed more UST. In scenario 10 of CD, those with less than 20 years of practice prescribed more UST ($p = 0.040$). For UC, there was a significant difference

Table 4 Demographic data from the sample of respondents.

Gender	*N. (%)*
Female	74 (49.3%)
Male	76 (50.7%)
Age	
Mean (SD)	48 (±10.94)
Specialty	
Gastroenterology	86 (57.3%)
Colorectal Surgeon	60 (40%)
Gastropediatric	2 (1.3%)
Gastroenterology Surgeon	2 (1.3%)
Time in practice	
<5 years	15 (10%)
5–10 years	19 (12.7%)
10–20 years	42 (28%)
>20 years	74 (49.3%)
Main practice	
Public and private	83 (55.3%)
Private	45 (30%)
Academic/University	22 (14.7%)
Number of IBD patients assisted per month	
<20	31 (20.7%)
20–50	56 (37.3%)
50–100	40 (26.7%)
>100	23 (15.3%)

Table 5 Crohn's disease scenarios, with included reasons.

Scenario	Agents		Reasons						
	VEDO *N.* (%)	UST *N.* (%)	Efficacy (A) *N.* (%)	Access (B) *N.* (%)	Safety (C) *N.* (%)	Personal experience (D) *N.* (%)	Scientific evidence (E) *N.* (%)	Mode of administration (F) *N.* (%)	Rapid onset (G) *N.* (%)
1	42 (28%)	**108 (72%)**	**55 (36.7%)**	14 (9.3%)	10 (6.7%)	13 (8.7%)	33 (22%)	5 (3.3%)	20 (13.3%)
2	**89 (59.3%)**	61 (40.7%)	23 (15.3%)	5 (3.3%)	**89 (59.3%)**	7 (4.7%)	20 (13.3%)	0 (0%)	6 (4%)
3	**77 (51.3%)**	73 (48.7%)	48 (32%)	14 (9.3%)	28 (18.7%)	12 (8%)	26 (17.3%)	9 (6%)	13 (8.7)
4	**104 (69.3%)**	46 (30.7%)	23 (15.3%)	5 (3.3%)	**91 (60.7%)**	8 (5.3%)	19 (12.7%)	1 (0.7%)	3 (2%)
5	20 (13.3%)	**130 (86.7%)**	**69 (46%)**	5 (3.3%)	7 (4.7%)	10 (6.7%)	47 (31.3%)	4 (2.7%)	8 (5.3%)
6	49 (32.7%)	**101 (67.3%)**	**54 (36%)**	6 (4%)	49 (32.7%)	6 (4%)	28 (18.7%)	0 (0%)	7 (4.7%)
7	38 (25.3%)	**112 (74.7%)**	**59 (39.3%)**	10 (6.7%)	13 (8.7%)	10 (6.7%)	43 (28.7%)	7 (4.7%)	8 (5.3%)
8	67 (44.7%)	**83 (55.3%)**	38 (25.3%)	5 (3.3%)	**65 (43.3%)**	3 (2%)	30 (20%)	4 (2.7%)	5 (3.3%)
9	18 (12%)	**132 (88%)**	**84 (56%)**	2 (1.3%)	7 (4.7%)	9 (6%)	39 (26%)	2 (1.3%)	7 (4.7%)
10	36 (24%)	**114 (76%)**	**76 (50.7%)**	2 (1.3%)	26 (17.3%)	7 (4.7%)	32 (21.3%)	0 (0%)	7 (4.7%)
11	34 (22.7%)	**116 (77.3%)**	**78 (52%)**	4 (2.7%)	25 (16.7%)	3 (2%)	29 (19.3%)	3 (2%)	8 (5.3%)
12	49 (32.7%)	**101 (67.3%)**	**68 (45.3%)**	4 (2.7%)	43 (28.7%)	3 (2%)	27 (18%)	1 (0.7%)	4 (2.7%)
13	24 (16%)	**126 (84%)**	**86 (57.3%)**	4 (2.7%)	13 (8.7%)	5 (3.3%)	33 (22%)	3 (2%)	6 (4%)
14	26 (24%)	**114 (76%)**	**82 (54.7%)**	2 (1.3%)	30 (20%)	2 (1.3%)	26 (17.3%)	0 (0%)	8 (5.3%)

VEDO (vedolizumab); UST (ustekinumab). Reasons: A (efficacy); B (access); C (safety); D (personal experience); E (scientific evidence); F (administration); G (rapid onset).
Bold values represent more frequent options of agents and reasons.

Table 6 Ulcerative Colitis scenarios, with included reasons.

Scenario	Agents			Reasons						
	VEDO *N.* (%)	UST *N.* (%)	TOFA *N.* (%)	Efficacy (A) *N.* (%)	Access (B) *N.* (%)	Safety (C) *N.* (%)	Personal experience (D) *N.* (%)	Scientific evidence (E) *N.* (%)	Mode of administration (F) *N.* (%)	Rapid onset (G) *N.* (%)
1	**91 (60.7%)**	15 (10%)	44 (29.3%)	**62 (41.3%)**	8 (5.3)	16 (10.7%)	12 (8%)	28 (18.7%)	9 (6%)	15 (10)
2	**120 (80%)**	19 (12.7%)	11 (7.3%)	47 (31.3%)	6 (4%)	**56 (37.3%)**	9 (6%)	27 (18%)	2 (1.3%)	3 (2%)
3	**103 (68.7%)**	17 (11.3%)	30 (20%)	**65 (43.3%)**	10 (6.7%)	16 (10.7%)	10 (6.7%)	30 (20%)	9 (6%)	10 (6.7%)
4	**131 (87.3%)**	11 (7.3%)	8 (5.3%)	48 (32%)	6 (4%)	**60 (40%)**	8 (5.3%)	20 (13.3%)	4 (2.7%)	4 (2.7%)
5	**72 (48%)**	37 (24.7%)	41 (27.3%)	**58 (38.7%)**	5 (3.3%)	10 (6.7%)	15 (10%)	34 (22.7%)	8 (5.3%)	20 (13.3%)
6	**100 (66.7%)**	41 (27.3%)	9 (6%)	43 (28.7%)	5 (3.3%)	**52 (34.7%)**	7 (4.7%)	25 (16.7%)	3 (2%)	15 (10%)
7	**98 (65.3%)**	27 (18%)	25 (16.7%)	**60 (40%)**	9 (6%)	13 (8.7%)	12 (8%)	31 (20.7%)	9 (6%)	16 (10.7%)
8	**120 (80%)**	20 (13.3%)	10 (6.7%)	43 (28.7%)	9 (6%)	**50 (33.3%)**	8 (5.3%)	30 (20%)	2 (1.3%)	8 (5.3%)
9	50 (33.3%)	**84 (56%)**	16 (10.7%)	**82 (54.7%)**	6 (4%)	20 (13.3%)	5 (3.3%)	31 (20.7%)	3 (2%)	3 (2%)
10	59 (39.3%)	**83 (55.3%)**	8 (5.3%)	**73 (48.7%)**	5 (3.3%)	42 (28%)	1 (0.7%)	27 (18%)	1 (0.7%)	1 (0.7%)

VEDO (vedolizumab); UST (ustekinumab); TOFA (tofacitinib). Reasons: A (efficacy); B (access); C (safety); D (personal experience); E (scientific evidence); F (administration); G (rapid onset).
Bold values represent more frequent options of agents and reasons.

in scenario 1 ($p = 0.041$), with UST being more prescribed by those with more than 20 years of practice (data not shown).

Discussion

The present study was carried out through a survey with prescribing physicians specialized in the treatment of IBD in Brazil. In scenarios involving CD, UST was the dominant agent among prescribers in most scenarios. For UC, VEDO was the most chosen medication. Among the reasons for the aforementioned choices, the most reported were the best efficacy due to the intrinsic mechanism of action and aspects related to better safety profile from the agents.

In total, 150 IBD specialists replied to the survey, most of them gastroenterologists and colorectal surgeons, which corresponded to 22.32% of GEDIIB members. There was a balance between the gender and the mean age of the

prescribers was 48 years. As opposed to what is observed in most countries, in Brazil, IBD clinical management is not an exclusive practice of gastroenterologists and it is common for some colorectal surgeons to treat IBD patients clinically, and consequently to prescribe biologics and small molecules. This uncommon trend was also seen in our sample, which included 60 colorectal surgeons (40% of specialists). In Brazil, there are different health systems (public and private), and it is common for physicians to work in both settings. The present sample is probably the closest illustration of the practice of most IBD physicians in the country, with the minority being involved in the academic field. Most respondents assist between 20 and 50 IBD patients per month and have access to a multidisciplinary team, which suggests expertise of these prescribers in the IBD care in the country.

UST was the most frequently chosen drug among CD scenarios, probably due to the available scientific evidence supporting the safety and efficacy of this drug. Despite the lack of head-to-head trials in the literature, a recent network meta-analysis conducted by Singh *et al*. and the retrospective comparative study between UST and VEDO by Alric *et al*. indirectly indicate the superiority of UST over VEDO in the context of previous anti-TNF failure.[14,15] Accordingly, most respondents reported the best efficacy by its mechanism of action of the medication as the reason for the choice of the drug. VEDO was most voted in two scenarios with elderly patients with Crohn's colitis, possibly due to its recognized safety profile.[5,6,13] In addition, it was also the drug of choice in the setting of a 45-year-old patient with Crohn's colitis naïve to biologics, as there is evidence of better efficacy in patients with this profile compared to those who have failed to anti-TNFs, according to the literature.[16–18]

The choice of VEDO was more prevalent in cases of UC, clearly because it is a drug with better scientific evidence in these scenarios, as demonstrated by a prospective direct head-to-head comparison in the VARSITY study.[13] Furthermore, it is possibly speculated that VEDO is more effective in the large intestine as compared with the small bowel, which would justify a possibly greater efficacy in UC than in CD.[18] In scenarios that included extraintestinal manifestations, UST was the most chosen agent due to its systemic action, a natural option due to systemic mechanism of action. There are controversies about the impact of VEDO in extraintestinal manifestations.[19,20] It is important to note that UST was only recently approved for UC in Brazil (end of 2019), therefore, the experience of Brazilian physicians with the drug is lower in UC as compared to VEDO, which was approved for more than 5 years. TOFA was not the drug of choice in any of the proposed scenarios, despite it was preferred over UST by some physicians in 3 scenarios which VEDO was the first choice for the majority of respondents. A possible reason for these findings is the lack of experience of most physicians with the drug, due to difficult access from healthcare payors and recent approval. Possible safety issues may also have impacted the results. Experience with TOFA in our country is increasing over the years, and physicians definitely will include this small molecule as first option in certain cases in clinical practice.

Regarding the subcutaneous maintenance dosage of the UST, most respondents used the 8-week interval. However, approximately a quarter of respondents still use the 12-week dosage, possibly based on pivotal studies or influenced by companies' marketing aiming at cost reduction, thus facilitating access to medication by healthcare payors.

As expected, gastroenterologists reported to assist a greater number of IBD patients per month as compared with colorectal surgeons, which is justified by the fact that most colorectal surgeons in the country assist more surgical IBD patients. There were few differences in responses between specialties, with UST being more prescribed by gastroenterologists only on two occasions. No explanation was speculated for this finding, which may only be a matter of coincidence in a sample of a limited number of respondents.

When comparing the responses between physicians working exclusively in the private system with the others (private + public or just public), there were 3 situations in which VEDO was preferred to UST in CD by prescribing physicians who work exclusively in private practice, with statistically significant difference (scenarios 11, 12 and 13). This finding may be the result of a broader panel of physicians visited by the marketing teams of the pharmaceutical company which promotes and manufactures VEDO and by the longer time from the drug's approval. The differences observed in the time in clinical practice in the treatment of IBD (more or less than 20 years) presented results that are difficult to interpret, and perhaps a greater number of respondents could lead to better understanding of such observations.

The present study is associated with important limitations, which need to be taken into account for the proper analysis of the results. First, the use of an anonymous, non-validated questionnaire with a limited number of participants may not represent the full positioning reality of a continental country as Brazil. In addition, responses may possibly be induced by the order of options for medications and reasons. Self-reported surveys also have limitations with measurement possibilities, as the minority of specialists replied to the questionnaire. The subjectivity of these replies is also a matter of debate. Specific data on the numbers of patients seen by respondents with each drug could not be captured. Despite these limitations, our study represents the first experience of drug positioning in the treatment of IBD in Brazil, which demonstrates the profile of drug choice in various scenarios of clinical practice. These results may illustrate the clinical practice regarding agents with different mechanisms of action in our country and may be applicable in countries with a similar reality in medical care, mostly in Latin America.

In summary, UST was the preferred option when compared to VEDO for the treatment of CD in most clinical scenarios, especially due to its mechanism of action. On the other hand, VEDO was the dominant choice in comparison to UST and TOFA in UC scenarios, mainly for reasons related to its mechanism of action and safety profile. Comparative studies including patient outcomes are needed to better define the positioning of new IBD therapeutic options in our country.

Authors' contributions

Romero RK and Kotze PG designed the study. Romero RK, Kotze PG, Queiroz NSF, Damião AOMC, Magro DO did data

collection. Magro DO did the statistical analysis. Romero RK, Queiroz NSF and Kotze PG wrote the manuscript. All authors participated in data analyses, gave intellectual contribution and approved the final version of the manuscript.

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Conflicts of interest

NFSQ: Abbvie, Janssen and Takeda. AOMCD: Abbvie, Janssen, Pfizer and Takeda. FVT: Abbvie, Janssen, Pfizer and Takeda. LYS: Takeda, Nestle, Janssen, Abbvie and UCB. RSH: Pfizer, Janssen, Abbvie and Takeda. PGK: Abbvie, Janssen, Pfizer, Takeda, Novartis. RKR, DOM and RBN have no conflicts of interest.

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