Jornal de Assistência Farmacêutica e Farmacoeconomia
v.9, n.1, 2024.
Original Article

Post incorporation monitoring into the Brazilian Public Health System: an analysis of Infliximab, Vedolizumab and Tofacitinib for the treatment of ulcerative retocolitis

Monitoramento pós incorporação no Sistema Único de Saúde: uma análise de Infliximabe, Vedolizumabe e Tofacitinibe para o tratamento da Retocolite Ulcerativa

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How to cite this article:
Santos JBR, Lyrio AO, Ferré F, Mega TP, Lopes ACF, Bonan LFS. Post-incorporation monitoring in the Brazilian Unified Health System: an analysis of infliximab, vedolizumab, and tofacitinib for the treatment of ulcerative colitis. JAFF [Internet]. 2024;9(1):44–57. doi: 10.22563/2525-7323.2024.v9.n.1.p.44-57e

Received: Oct 20, 2023.

Accepted for publication: Jan 31, 2024.

ABSTRACT

Objective: to evaluate the implementation, use, cost of treatment per patient-year and the budgetary impact of infliximab, vedolizumab and tofacitinib for the treatment of moderate to severe ulcerative colitis in the SUS. **Methods:** A retrospective cohort study was carried out using the Open Health Intelligence Situation Room, which originates from the SUS Ambulatory Information System. All patients with primary ICD-10 ulcerative colitis and using infliximab, vedolizumab or tofacitinib were included. The analysis period was from May 2020 to December 2022. **Results:** After incorporation into the SUS, the time for medicines to become available ranged from 7 to 20 months. Infliximab was the most used (55%), but vedolizumab spread faster, with approximately 60 new patients per month, followed by infliximab and tofacitinib with approximately 35 and 18 patients, respectively. Unit prices for medicines were lower than those proposed in the incorporation, except for tofacitinib in the last acquisition. In 2021, the cost per patient-year was similar for infliximab and vedolizumab. In 2022, vedolizumab had the highest cost. The budgetary impact of infliximab and vedolizumab was similar in the first year of implementation and both had a lower budgetary impact than estimated at incorporation. In the second year of infliximab implementation, the budgetary impact almost doubled due to the greater dissemination of the drug. **Conclusion:** This analysis presents real-world data, verifying the importance of monitoring the technologies incorporated by the SUS.
Keywords: Infliximab, Monitoring, Ulcerative Colitis, Brazilian Public Health System, Tofacitinib, Vedolizumab

RESUMO

Objetivo: avaliar a implementação, a utilização, o custo do tratamento por paciente-ano e o impacto orçamentário de infliximabe, vedolizumabe e tofacitinibe para o tratamento da retocolite ulcerativa moderada a grave no SUS. **Métodos:** Foi realizado um estudo de coorte retrospectiva por meio da Sala Aberta de Situação de Inteligência em Saúde, que é originada do Sistema de Informações Ambulatoriais do SUS. Foram incluídos todos os pacientes com CID-10 primário da retocolite ulcerativa e em uso de infliximabe, vedolizumabe ou tofacitinibe. O período de análise foi de maio de 2020 a dezembro de 2022. **Resultados:** Após a incorporação no SUS, o tempo para o início da disponibilização dos medicamentos variou de 7 a 20 meses. Infliximabe foi o mais utilizado (55%), mas vedolizumabe apresentou difusão mais rápida, com aproximadamente 60 novos pacientes por mês, seguido por infliximabe e tofacitinibe com cerca de 35 e 18 pacientes, respectivamente. Os preços unitários dos medicamentos foram inferiores aos propostos na incorporação, exceto pelo tofacitinibe na última aquisição. Em 2021, o custo por paciente-ano foi similar para infliximabe e vedolizumabe. Em 2022 o vedolizumabe teve o maior custo. O impacto orçamentário do infliximabe e vedolizumabe foi similar no primeiro ano da implementação e ambos tiveram impacto orçamentário menor que o estimado na incorporação. No segundo ano de implementação do infliximabe, o impacto orçamentário quase duplicou devido à maior difusão do medicamento. **Conclusão:** Essa análise apresenta dados de mundo real, verificando-se a importância do monitoramento das tecnologias incorporadas pelo SUS.
Palavras-chave: Infliximabe, Monitoramento, Retocolite Ulcerativa, Sistema Único de Saúde, Tofacitinibe, Vedolizumabe

Introduction

Ulcerative colitis is a chronic immune-mediated inflammatory condition of the large intestine, frequently associated with inflammation of the rectum, but it often extends proximally to involve additional areas of the colon. The initial presentation of the disease is characterized by symptoms of rectal inflammation, such as bleeding, urgency, and tenesmus.[1]

The global prevalence of ulcerative colitis can range from 5 to 500 per 100,000 inhabitants.v In Brazil, in the state of Espírito Santo, a prevalence of 38.2 per 100,000 inhabitants was found.[4] The peak incidence of the disease occurs between 20 and 40 years of age, with a smaller peak in the fifth decade of life[3]. Furthermore, patients with active disease are more likely to experience anxiety and depression, as well as impaired social interactions or career progression.[5] Long-standing ulcerative colitis is also associated with an increased risk of colorectal cancer.[6]

The main goal of ulcerative colitis treatment is to achieve steroid-free clinical remission and maintain long-term remission, avoiding relapses.[7] Currently, the treatment recommended by the Brazilian Ministry of Health is outlined in the Clinical Protocol and Therapeutic Guidelines (PCDT), and is based on the severity, distribution (proctitis, left-sided colitis, or pancolitis), and pattern of the disease, including relapse frequency, disease course, response to previous medications, adverse drug reactions, and extraintestinal manifestations.[8]

According to the PCDT, patients with active disease classified as moderate to severe should initially be treated with oral corticosteroids and aminosalicylates. If the patient does not respond completely to corticosteroids or cannot taper the prednisone dose without disease recurrence, an immunosuppressant should be introduced. In cases of immunosuppressant failure, characterized by corticosteroid dependence despite an adequate dose of azathioprine for a minimum of 12 weeks, the use of infliximab, vedolizumab, or tofacitinib should be considered.[8]

Recently, the drugs infliximab, vedolizumab, and tofacitinib were incorporated into the Brazilian Unified Health System (SUS), the incorporation was recommended by the National Committee for Health Technology Incorporation (Conitec). Infliximab and vedolizumab were incorporated in October 2019, and tofacitinib in June 2021.[9,10] However, it is important to highlight that, despite the meticulous assessment conducted during the incorporation process, the results observed after implementation do not always reflect the expected clinical outcomes. This is partly due to the difficulty in using studies that faithfully represent the Brazilian reality and that of the SUS at the time of incorporation, as the initial evaluation is predominantly based on randomized clinical trials conducted under ideal and highly controlled conditions, or on observational studies which, in general, do not reflect the actual experience of SUS users.[11-14].

Another important post-incorporation consideration is the actual budget impact. Deviations from previous estimates may occur due to inaccuracies in determining the proportion of individuals eligible for therapy and the degree of adherence to this therapy after incorporation, in addition to projections based on the current costs and prices of the technologies.[15,16] Moreover, the time between the incorporation of a technology into the SUS and actual access by the population is also a relevant variable. Article 25 of Decree No. 7.646 of 2011 establishes a 180-day (6-month) deadline for effective availability in the SUS, counted from the date of publication of the health technology incorporation decision. However, this deadline may be exceeded due to various barriers to timely implementation.[17]

In this context, it is important to include in the incorporation process of new technologies a mechanism that anticipates or mandates the conduct of studies to evaluate the performance of technologies in the healthcare setting. The results of these studies will guide decision-making regarding the continuation or exclusion of the technology under the conditions established during the incorporation process.[16]

This study carried out a monitoring analysis of the drugs infliximab, vedolizumab, and tofacitinib for the treatment of moderate to severe ulcerative colitis, with the aim of tracking the utilization patterns of these drugs within the SUS.

Objective

To evaluate the implementation, utilization, and budgetary impact of the drugs infliximab, vedolizumab, and tofacitinib for the treatment of moderate to severe ulcerative colitis, aiming to monitor their implementation within the scope of the Brazilian Unified Health System (SUS).

Methods

An open cohort study was conducted using retrospective, real-world, administrative, and national dispensing data extracted from the Open Room of the Health Intelligence Situation (Sabeis).

Sabeis was developed within the Department of Health Technology Management and Incorporation of the Secretariat of Science, Technology, Innovation and the Health Complex of the Ministry of Health (Departamento de Gestão e Incorporação de Tecnologias em Saúde, da Secretaria de Ciência, Tecnologia, Inovação e Complexo da Saúde, do Ministério da Saúde – DGITSDGITS/SECTICS/MS), in order to meet the information needs for the assessment and monitoring of health technologies. This database is derived from the open data of the SUS Outpatient Information System (Sistema de Informações Ambulatoriais do Sistema Único de Saúde - SIA/SUS), bringing together all available subsystems to obtain individualized and anonymized data of procedures recorded in the Authorization of Outpatient Procedures (Autorização de Procedimentos Ambulatoriais - Apac). [18]

The study period covered May 2020 — the date of the first dispensing of this treatment line for moderate to severe ulcerative colitis within SUS — through December 2022. For this analysis, the data updated in March 2023 was used.

All patients registered in the SIA with ulcerative colitis, according to the primary International Statistical Classification of Diseases and Related Health Problems (ICD-10), and who were using the medications infliximab 10 mg/mL, tofacitinib 5 mg, and vedolizumab 300 mg, were included in the cohort. To this end, the ICD-10 codes related to ulcerative colitis were identified in Sabeis, as per the Clinical Protocol and Therapeutic Guidelines (PCDT): K51.0; K51.2; K51.3; K51.5; and K51.8. Additionally, the medication codes were verified in the SUS Procedure, Medication, and Orthotics/Prosthetics and Special Materials Table Management System (SIGTAP): 06.04.38.005-4; 06.04.38.011-9; 06.04.32.016-7; and 06.04.32.015-9.

The time required for the implementation of the technologies was quantified and included the evaluation of the interval between the publication of the incorporation ordinance and the publication of the Clinical Protocol and Therapeutic Guidelines (PCDT), the creation or update of the procedure for dispensing, and the first record in the SIA (SUS Outpatient Information System) referring to the use of the medicines. The date of incorporation into SUS refers to the date of the Ministry of Health's incorporation ordinance published in the *Diário Oficial da União* (DOU). The date of inclusion in the PCDT refers to the publication date in the DOU of the ordinance from the Ministry of Health regarding the update of the PCDT including the drugs. The date of inclusion in SIGTAP refers to the publication date in the DOU of the ordinance that includes the drug in SIGTAP. The date of first dispensing refers to the first dispensing record identified in Sabeis.

The data on drug utilization included the absolute frequency of patients by year, sex, age group, and drug. In addition, the relative frequency of patients by Brazilian region was assessed. The market share was evaluated by the proportion of patients using infliximab, vedolizumab, or tofacitinib. For the time series analysis of the number of patients using each medication, a generalized Prais-Winsten linear regression was performed. This regression model is one of the most commonly used to assess trends in time series, as it accounts for serial autocorrelation—that is, the relationship of a series of values of a given measure over previous time periods.[19] Trends were considered increasing when the regression coefficient was positive with $p < 0.05$, decreasing when the coefficient was negative with $p < 0.05$, and stationary when $p > 0.05$.

The budget impact was assessed from the SUS perspective. For this analysis, the unit cost of medications was retrieved from the database of the Integrated System for General Services Administration (SIASG), through the Health Price Database (*Banco*

de Preços em Saúde – BPS). It is noteworthy that the medications are part of Group 1A of the Specialized Component of Pharmaceutical Assistance (Ceaf); therefore, their funding and procurement are the responsibility of the Ministry of Health.

The eligibility criteria for price inclusion comprised purchases made by the Department of Health Logistics of the Ministry of Health between the years 2019 and 2022. Among the returned data, records with a quantity of less than 100 units purchased were excluded, as they could be associated with litigation and therefore not reflect the administrative purchase price for SUS. The query to the Health Price Database (Banco de Preços em Saúde – BPS) was conducted on March 29, 2023.[20]The unit price of infliximab acquired through Productive Development Partnerships (PDPs) was retrieved from the Ministry of Health's official website. Infliximab has been acquired through PDPs since November 2014.[21]

Subsequently, the budget impact was calculated for each year based on the quantity dispensed of each drug and its unit monthly price. The annual budget impact for tofacitinib was not presented, as this medication had been implemented in SUS for less than one year at the time of analysis.

Additionally, the annual cost of treatment per patient for each drug was calculated for both the first year (induction dose + maintenance dose) and the second year (maintenance dose) of implementation, using the drug regimens specified in the PCDT for ulcerative colitis and the most recent unit acquisition prices.

The database modeling was performed using PostgreSQL 4.2, and statistical analyses were conducted in Stata 16.1, serial number 301606218030.

Results

Implementation History of Infliximab, Vedolizumab, and Tofacitinib for Ulcerative Colitis in the SUS

Table 1 presents the dates and elapsed time for the key milestones required for the implementation and effective availability of the drugs in the Brazilian Unified Health System (SUS). After the incorporation of infliximab, vedolizumab, and tofacitinib into SUS, the elapsed time for the publication of the updated Clinical Protocol and Therapeutic Guidelines (PCDT) was six months. However, the time to first utilization of these medications ranged from **7 to 20 months** (Table 1).

Utilization Profile of Infliximab, Vedolizumab, and Tofacitinib for Ulcerative Colitis in the SUS

The demographic and clinical characteristics are presented in Table 2. A total of 5,485 patients were included in the cohort between May 2020 and December 2022. The majority of patients were female (n = 3,222; 58.8%), aged between 20 and 59 years (n = 4,152; 75.7%), and resided in the Southeast and South regions (n = 4,258; 77.6%).

Table 1. Dates and time elapsed for the implementation of infliximab, vedolizumab, and tofacitinib for the treatment of ulcerative colitis in the Brazilian Unified Health System (SUS).

Medication	Date of incorporation into SUS	Date of inclusion in the PCDT	Date of inclusion in SIGTAP	Date of first [a] dispensing	Time between incorporation and inclusion in the PCDT	Time between incorporation and inclusion in SIGTAP	Time until implementation [a]
Infliximab	October 2019	April 2020	April 2020	May 2020	6 months	6 months	7 months
Vedolizumab	October 2019	April 2020	April 2021	June 2021	6 months	18 months	20 months
Tofacitinib	June 2021	December 2021	February 2022	April 2022	6 months	8 months	10 months

[a]Time elapsed between the publication of the incorporation ordinance and the first dispensing.
Source: Prepared by the authors.

Table 2. Demographic and clinical baseline characteristics of patients using infliximab, vedolizumab, and tofacitinib for the treatment of ulcerative colitis (n = 5,485).

Characteristic	N	%
Age (years)		
0–9	48	0.9
10–19	356	6.5
20–29	953	17.4
30–39	1,189	21.7
40–49	1,079	19.7
50–59	931	17.0
60–69	648	11.8
70–79	241	4.4
>79	39	0.7
Sex		
Female	3,222	58.8
Male	2,262	41.2
Region of residence		
Southeast	2,993	54.6
South	1,265	23.1
Northeast	716	13.1
Midwest	337	6.1
North	113	2.1
Not reported	60	1.1
ICD-10 code		
K51.0 Ulcerative enterocolitis	3,725	67.9
K51.8 Other ulcerative colitis	1,028	18.7
K51.3 Ulcerative rectosigmoiditis	519	9.5
K51.2 Ulcerative proctitis	143	2.6
K51.5 Left-sided colitis	70	1.3

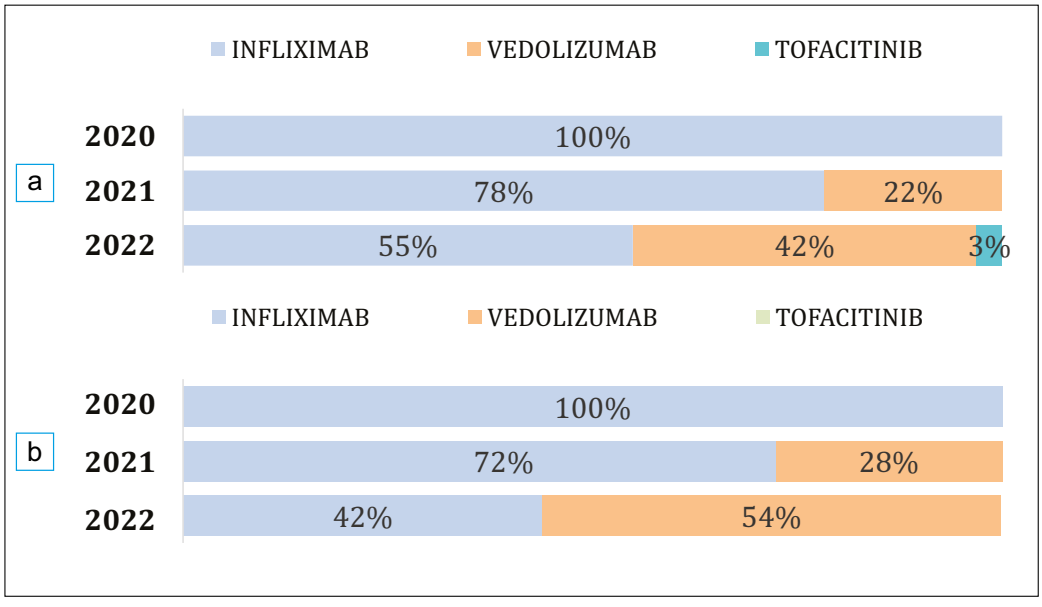
Source: Prepared by the authors.

Regarding the market share of the medications, it was found that the most widely used drug was infliximab. However, it was observed that this medication decreased its market share when vedolizumab and tofacitinib were incorporated into SUS, with usage starting in 2021 and 2022, respectively (Figure 1a).

In addition, it was verified that most patients began treatment with infliximab in 2021. However, vedolizumab became the most used medication among new patients in 2022 (Figure 1b).

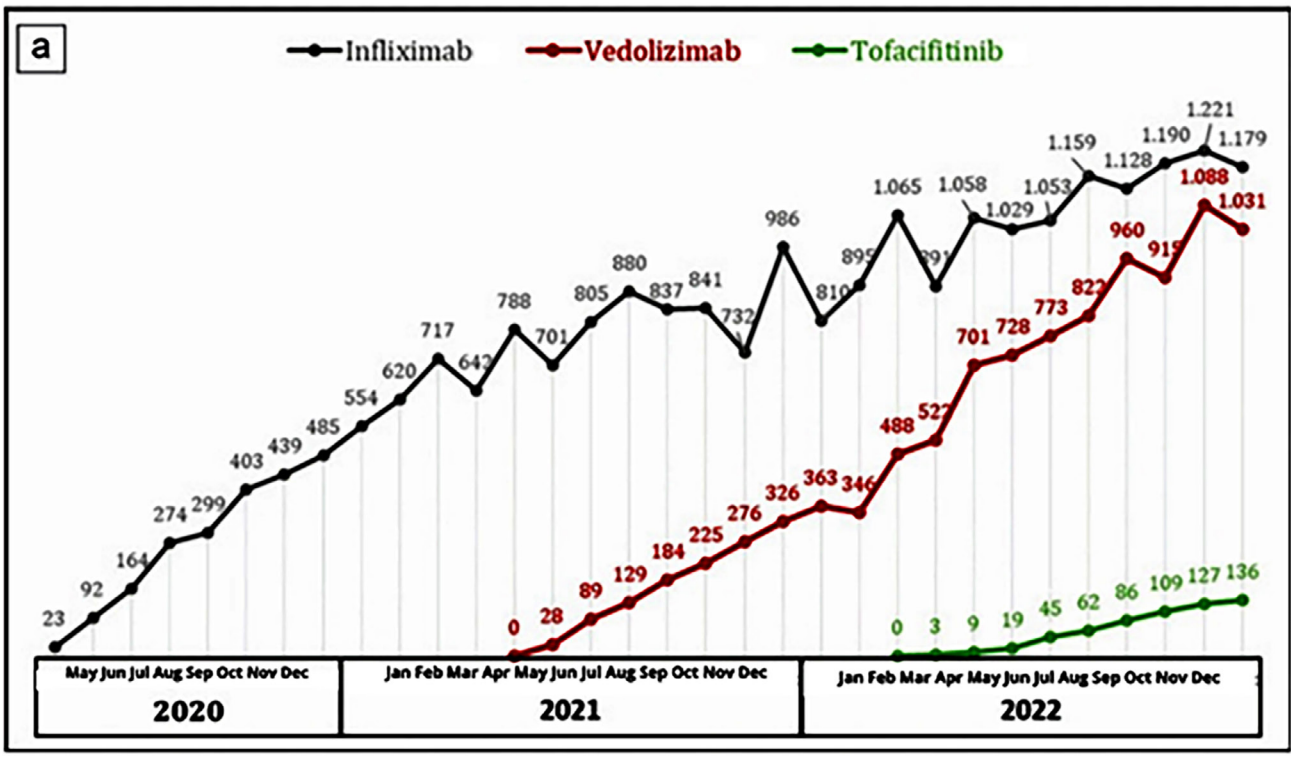
A trend of growth was observed in the number of patients using infliximab, vedolizumab, and tofacitinib after the incorporation of these medications over the months ($p<0.001$). The medication that presented the highest growth trend was vedolizumab, with an increase of approximately 60 patients per month, followed by infliximab and tofacitinib, with around 35 and 18 patients per month, respectively. However, it was observed that the growth trend of infliximab decreased after the availability of vedolizumab. Before the implementation of vedolizumab, the growth trend in the number of infliximab patients was approximately 61 patients per month and, after the implementation of vedolizumab, this growth trend decreased by 35 patients, reducing to 26 patients per month (Figure 2a; Table 3).

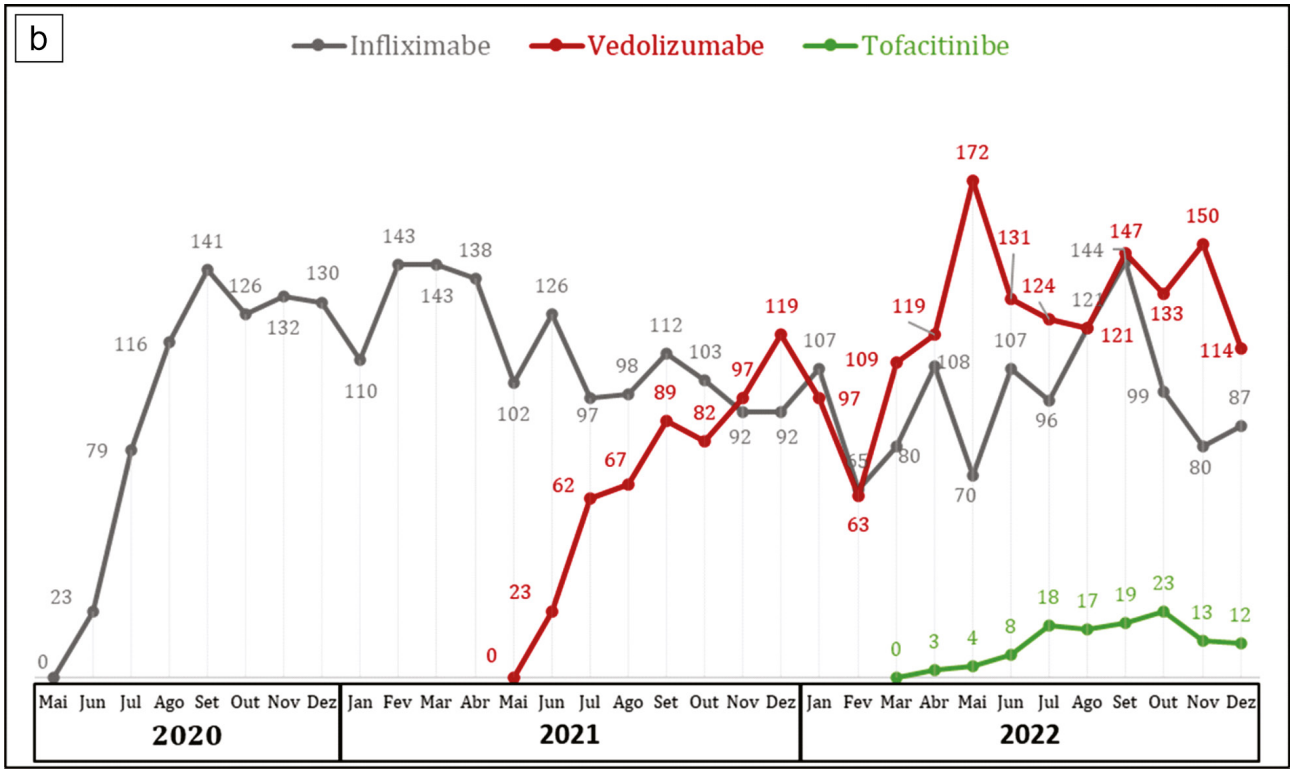
Figure 1. Percentage of total patients (A) and new patients (B) using infliximab, vedolizumab, and tofacitinib for the treatment of ulcerative colitis between 2020 and 2022.



Prepared by the authors.

Figure 2. Monthly number of total patients (A) and new patients (B) using infliximab, vedolizumab, and tofacitinib for the treatment of ulcerative colitis between 2020 and 2022.





Prepared by the authors.

Table 3. Trend and monthly variation in the number of total and new patients using infliximab, vedolizumab, and tofacitinib for the treatment of ulcerative colitis.

Medication	Estimate (B^1)	95% CI	p-value	R^2
Total patients				
Infliximab	34.77	29.49–40.05	<0.001	0.83
Before*	61.31	55.85–66.76	<0.001	0.98
After**	26.37	22.15–30.59	<0.001	0.94
Vedolizumab	59.79	54.67–64.91	<0.001	0.97
Tofacitinib	18.08	15.62–20.54	<0.001	0.97
New patients				
Infliximab	0.61	-1.49–2.70	0.560	NA
Vedolizumab	5.86	3.20–8.53	<0.001	0.44
Tofacitinib	1.60	-0.44–3.64	0.108	NA

* Before vedolizumab implementation. ** After vedolizumab implementation. NA: not applicale.

With regard to new patients, a trend of growth was observed in the number of patients using vedolizumab after the incorporation of this medication over the months ($p<0.001$). There was an increase of approximately six patients per month for vedolizumab. The trend was stationary for the number of new patients using infliximab and tofacitinib. Vedolizumab surpassed the number of new patients using infliximab starting in November 2021, except for the months of January, February, and August 2022 (Figure 2b; Table 3).

Unit prices of the medications

Over the years, a reduction in the unit purchase price of infliximab was observed, except for the most recent acquisition of this medication. Infliximab, vedolizumab, and tofacitinib showed an increase of 5.8%, 2.7%, and 6.5%, respectively, in the unit price of the latest acquisition compared to the previous one (Supplementary Table 1).

All medications incorporated by Conitec showed a reduction in their unit price when compared to the value proposed in the incorporation report, with the exception of tofacitinib in the latest acquisition. Vedolizumab, infliximab, and tofacitinib presented a reduction in their unit price of 32.3%, 29.1%, and 1.0%, respectively, in relation to the minimum purchase price by the Ministry of Health during the study period. On the other hand, there was a reduction of 30.5% for vedolizumab and 1.87% for infliximab, and an increase of 5.4% for tofacitinib when comparing the maximum purchase price to the price proposed in the incorporation report (Table 4).

Expected Annual Treatment Cost per Patient in 2022

Table 5 presents the annual cost per patient in 2022. The medication with the highest treatment cost per patient-year was vedolizumab (R$ 25,802.16 for the first year and R$ 19,351.62 for the second year of treatment). Infliximab and tofacitinib showed treatment costs approximately 20% and 50% lower than vedolizumab, respectively, for the first and second year of implementation.

Vedolizumab and infliximab presented a significant reduction in their cost per patient-year of 70.6% and 25.0%, respectively, when compared to the values reported in the incorporation report for the first and second year of implementation. On the other hand, tofacitinib showed an increase of 2.2% in the cost per patient-year.

Table 4. Unit price proposed in the recommendation report and minimum purchase price of infliximab, vedolizumab, and tofacitinib for the treatment of ulcerative colitis (2019–2022).

Medication	Proposed unit price for incorporation	Maximum purchase unit price	Minimum purchase unit price
Infliximab 100 mg vial	R$ 846.84*	R$ 830.97	R$ 600.00
Vedolizumab 300 mg vial	R$ 4,754.11**	R$ 3,305.26	R$ 3,218.00
Tofacitinib 5 mg tablets	R$ 13.61***	R$ 14.34	R$ 13.47

* Public procurement price via SIASG, according to incorporation report no. 480 (Oct 2019).
** Price proposed by manufacturer for Crohn's disease incorporation, report no. 480 (Oct 2019).
*** Price paid under Ministry of Health contract no. 183 (June 2020).
Source: SIASG, technical reports no. 480/2019 and 631/2021. Prepared by the authors.

Table 5. Expected cost per patient using infliximab, vedolizumab, and tofacitinib for ulcerative colitis in the first year and after the first year (2021–2022).

Use	Annual units per patient	Average unit price 2021 (R$)	Average unit price 2022 (R$)	Estimated cost per patient 2021 (R$)	Estimated cost per patient 2022 (R$)	Treatment cost per patient in recommendation report (R$)
First year (induction + maintenance)						
Infliximab	32	805.60	634.79	25,779.20	20,313.28	27,098.88
Vedolizumab	8	3,218.00	3,225.27	25,744.00	25,802.16	87,691.68*
Tofacitinib	840	13.47	13.91	11,314.80	11,684.40	11,432.40
After first year (maintenance only)						
Infliximab	24	805.60	634.79	19,334.40	15,234.96	20,324.16
Vedolizumab	6	3,218.00	3,225.27	19,308.00	19,351.62	65,768.76*
Tofacitinib	730	13.47	13.91	9,833.10	10,154.30	9,935.30

Source: Integrated System for General Services Administration (SIASG), Technical Report No. 480 (October 2019) and Technical Report No. 631 (June 2021).
Infliximab: 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter, considering an average body weight of 70 kg.
Vedolizumab: 300 mg at weeks 0, 2, and 6, then every 8 weeks thereafter.
Tofacitinib: 10 mg twice daily for 8 weeks, followed by 5 mg administered twice daily for maintenance.
* The unit price used to calculate the treatment cost for vedolizumab was that from SIASG (R$10,961.46) and differs from the price proposed at incorporation (R$4,754.11).

It is noteworthy that **Conitec recommended** the incorporation of vedolizumab conditional upon it being limited to the **treatment cost of infliximab**[22]. In 2021, the year vedolizumab was implemented, the annual treatment costs for both medications were very similar. However, in 2022, the cost of treatment with vedolizumab was higher than that of infliximab due to a reduction in the purchase price of the latter.

Budget Impact

In the first year of implementation, the number of patients estimated in the incorporation report was similar to the number actually observed for both infliximab and vedolizumab. On the other hand, the recommendation report underestimated the diffusion of infliximab in the second year of implementation. Regarding unit price, there was a greater reduction for vedolizumab compared to infliximab (Supplementary Table 2).

The budget impact in the first year of vedolizumab implementation was similar to that of infliximab's first year. In addition, an increase in the budget impact of infliximab was observed in the second year of implementation when compared to the first year, since the number of patients using infliximab almost doubled compared to the first year (Table 6).

Table 6. Observed budget impact of infliximab and vedolizumab for the treatment of ulcerative colitis in SUS

Medication and period	Average unit price	Approved quantity	Budget impact
Infliximab 1st year (May 2020–Apr 2021)	R$ 820.40	21,33	R$ 17,499,132.00
Infliximab 2nd year (May 2021–Apr 2022)	R$ 772.11	43,354	R$ 33,474,056.94
Vedolizumab 1st year (Jun 2021–May 2022)	R$ 3,218.00	4,742	R$ 15,259,756.00

Source: SIASG and Open Health Intelligence Situation Room (Sabeis). Prepared by the authors.

In the incorporation report, two scenarios were considered for the budget impact: the first did not take into account the patients who would discontinue the medication due to treatment failure, and the second considered therapeutic failure for each medication. In this context, it was observed that the actual budget impact was lower than the estimated impact in the incorporation report for infliximab and vedolizumab in most scenarios. Only the scenario that considered therapeutic failure for infliximab in the second year of implementation showed a lower impact when compared to the observed data (Supplementary Table 3). It is important to highlight that the incorporation report assumed that vedolizumab and infliximab would be used in equal proportions by the population. Therefore, the individual budget impact values were divided by two, since both medications were incorporated into SUS.

Discussion

This study evaluated real-world data on the use of infliximab, vedolizumab, and tofacitinib for the treatment of ulcerative colitis. After the incorporation of infliximab, vedolizumab, and tofacitinib into the Brazilian Unified Health System (SUS), the time required to update the Clinical Protocol and Therapeutic Guidelines (PCDT) was six months; however, the time to the first dispensing record of these medications ranged from 7 to 20 months (210 to 600 days) after incorporation. This finding is consistent with a study conducted between January 2017 and April 2020, which examined the incorporation and availability of 44 health technologies through the Specialized Component of Pharmaceutical Assistance (Ceaf), identifying a median time of 302 days (interquartile range: 180.8 – 421.8)[23].

According to Law No. 12.401/2011 and Decree No. 7.646, once incorporated, a medication must be made available within 180 days. However, this deadline is often exceeded, revealing challenges that must be addressed to ensure access to medications within the legally established period.[24,17] One such challenge that may impact the timeline for the availability of an incorporated technology is the agreement on responsibilities within the Tripartite Intermanagerial Commission (CIT). Nevertheless, the stages of the implementation process of the incorporated technology are not properly documented or communicated in an accessible way to health professionals, the general public, or even SUS managers. This gap hinders the effective realization of the constitutional principle of social participation in public health policies in Brazil.[23,24] Other challenges that may arise include difficulties in negotiating with the pharmaceutical company, bureaucracy in the procurement process, delivery delays, among others.[25,26] Therefore, studies that evaluate each implementation step and identify the main barriers are necessary.

A total of 5,485 patients were included in the cohort, with the majority being female (58.8%) and aged between 20 and 59 years (75.7%). This finding is consistent with some studies conducted in individuals with ulcerative colitis who were using these medications.[27-29] However, the gender distribution may vary depending on the study,[27,28] which may be explained by the higher tendency of women to seek health services.[30] Additionally, most individuals resided in the Southeast and South regions (77.6%), reflecting the inequality in access to healthcare across Brazil's regions.[31]

Infliximab was the most widely used medication. However, vedolizumab has been increasing its market share, surpassing infliximab for the treatment of new

patients in the year 2022. These findings are similar to those of other international studies. A study conducted in Germany identified a higher proportion of individuals using adalimumab (n = 230), followed by infliximab (n = 172), vedolizumab (n = 113), golimumab (n = 56), and tofacitinib (n = 3).[32] On the other hand, a study conducted in Belgium observed a greater proportion of individuals using vedolizumab compared to infliximab and tofacitinib (38 adalimumab, 14 golimumab, 54 infliximab, 9 ustekinumab, 99 vedolizumab, 9 tofacitinib). [33]

All incorporated medications showed a reduction in their unit price when compared to the value proposed in the incorporation report, except for tofacitinib in the most recent acquisition. This fact reinforces the importance of price negotiation after the incorporation of medications, especially those centrally procured by the Ministry of Health.[34,35] In addition, a reduction in the unit price of infliximab was observed, which began to be developed domestically as a result of a Productive Development Partnership (PDP). In this context, the importance of the PDP policy is evident for ensuring access to medications, with the aim of protecting the interests of public administration and the population by seeking cost-effectiveness and overall advantage, based on the following criteria: price, quality, technology, and social benefits.[36]

Infliximab, vedolizumab, and tofacitinib showed an increase in unit price ranging from 2.7% to 6.5% between the years 2021 and 2022. This price adjustment is in accordance with the maximum defined by CMED, which was 10.89% in 2022.[37]

In 2022, the medication with the highest treatment cost per patient-year was vedolizumab. Infliximab and tofacitinib had treatment costs approximately 20% and 50% lower than vedolizumab, respectively, for the first and second year of implementation. These findings are similar to those of a study conducted in Mexico, which observed a higher cost for vedolizumab compared to infliximab.[38]

The budgetary impact of infliximab and vedolizumab was similar in the first year, as vedolizumab was incorporated with the recommendation that the costs of treatment with this biologic be equal to or lower than the annual treatment cost with infliximab (R$ 27,098.88 in the first year).[22] However, in the second year of incorporation, the unit price of infliximab decreased, which did not occur with vedolizumab. Despite the recommendation, there are challenges in maintaining this agreement in acquisitions beyond the first, and currently, there are no mechanisms to address this situation.

Finally, the importance of monitoring technologies incorporated by SUS was confirmed, as changes in prior estimates may occur due to inaccuracies in the proportion of patients eligible for treatment, the diffusion of treatment after incorporation, and the current prices of the technologies. Differences were observed between the number of patients estimated in the incorporation report and the number actually observed in the second year of infliximab implementation. Additionally, the unit price and the observed budget impact were lower than estimated in most scenarios.

This study presents strengths and limitations. One of the limitations is the accuracy of the generation of administrative data. However, it should be noted that the data were validated through Tabnet and VinculaSUS, with little to no differences observed regarding the approved quantity and the number of users, respectively.[18] Additionally, it was not possible to assess the budget impact in the first year for tofacitinib, nor in the second year for tofacitinib and vedolizumab, due to the short implementation period. Another limitation concerns the identification of the unit price of the medications, as procurement and dispensing may occur in different periods, which could affect the calculation of the budget impact. Nevertheless, it is believed that this impact is minimal due to the small price variation between periods, with the exception of infliximab.

On the other hand, the study has several strengths. It used national open-access data, providing representativeness and transparency in the analyses. Furthermore, this study is important for identifying progress and challenges to be addressed. It is observed that with Sabeis it will be possible to evaluate the time required for the implementation of medications, understand their utilization profile, and compare the budget impact estimated in the incorporation report with that observed in the real world.

Conclusion

After incorporation into the SUS, the evaluated medications were made available within a period ranging from 7 to 20 months. Infliximab was the most used drug (55%), but vedolizumab showed faster diffusion, with approximately 60 new patients per month, followed by infliximab and tofacitinib, with around 35 and 18 patients per month, respectively.

The budget impact of infliximab (R$ 15,259,756.00) and vedolizumab (R$ 17,499,132.00) was similar in the first year, and both had a lower budget impact than what was estimated at the time of incorporation. In the second year of infliximab implementation, the budget impact almost doubled (R$ 33,474,056.94) due to the greater diffusion of the medication.

The main impact of this analysis is to support decision-making within the SUS by providing performance data on infliximab, vedolizumab, and tofacitinib for the treatment of ulcerative colitis following the incorporation of these drugs by the SUS.

However, there are challenges to be overcome, including delays in the effective availability of the medications to the population, inequality in access between regions of Brazil, and difficulties in implementing incorporation recommendations linked to price reductions for acquisitions following the first.

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Supplementary Tables (Annex)

Supplementary Table 1. Acquisition date, manufacturer, procurement modality, and unit price of infliximab, vedolizumab, and tofacitinib (2019–2022).

Date	Unit Price
Infliximab	
24/12/2019	R$830,97
23/12/2020	R$805,60
17/12/2021	R$808,71
21/03/2022	R$600,00
13/12/2022	R$635,00

Date	Unit Price
Vedolizumab	
16/03/2021	R$ 3.218,00
27/12/2022	R$ 3.305,26
Tofacitinib	
15/07/2021	R$13,47
13/07/2022	R$14,34

Prepared by the authors..

Supplementary Table 2. Number of patients and unit price of infliximab and vedolizumab observed in Sabeis and proposed in the recommendation report for ulcerative colitis.

Medication / period	Observed number of patients	Estimated number of patients[1]	Observed average unit price	Proposed unit price[1]
Infliximab 1st year	1,383*	1,551	R$ 820.40*	R$ 846.84
Infliximab 2nd year	2,371**	1,657	R$ 772.11**	R$ 846.84
Vedolizumab 1st year	1,208***	1,551	R$ 3,218.00***	R$ 4,754.11

[1]Report no. 480 (October 2019).
* Observed: May 2020–Apr 2021.
** Observed: May 2021–Apr 2022.
*** Observed: Jun 2021–May 2022.
Prepared by the authors.

Supplementary Table 3. Observed and estimated budget impact (with and without therapeutic failure) of infliximab and vedolizumab for ulcerative colitis.

Medication / period	Observed impact	Estimated impact (no failure)	Estimated impact (with failure)
Infliximab 1st year	R$ 17,499,132.00	R$ 42,025,593.48	R$ 34,360,544.13
Infliximab 2nd year	R$ 33,474,056.94	R$ 34,402,954.94	R$ 23,847,578.01
Vedolizumab 1st year	R$ 15,259,756.00	R$ 58,982,303.10	R$ 45,922,752.22

Source: Technical report no. 480 (October 2019).