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Crohn's Disease Treatment Expenditures over Fifteen Years of Follow-Up

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Abstract

Background: The increasing Crohn's Disease (CD) prevalence worldwide has contributed to CD related healthcare resource use increase and the disease treatment has a considerable economic burden, varying between countries. The aim of this study was to assess the direct medical cost of CD treatment over fifteen years of follow up in Brazil.

Methods: A total of 46,886 CD patients were included. Patients were identified from the Brazilian public health system databases between 2000 and 2014. The mean annual expenditure was calculated for each patient. Expenditures included the costs of all (CD-related or not) medications, diagnostics and monitoring exams, outpatient care and hospitalizations. Multivariate analyses were conducted to evaluate the relation between demographic and clinical variables in mean annual expenditure.

Results: The total expenditures were US$ 844.24 million over the entire study period (2000-2014) with annual mean [95% CI] of US$ 3,451.0 [3,399.2-3,502.7] per patient. Of the total expenditures, 90.3% were for CD medications with Tumor Necrosis Factor inhibitors being the primary cost driver, accounting for 76.0% of the total – medication cost in 2000 and 85.9% in 2014. Hospitalization cost accounted for 3.0% of the overall total expenditures. The multivariate analyses showed that gender, age, region of residence, and medication used at study entry can predict DC treatment costs.

Conclusion: In Brazil, the annual direct medical cost of CD treatment is substantial. Medication cost, in particular that of anti-TNF alpha agents is increasingly the most important cost driver.

Keywords: Crohn's disease; Health costs; Cost analysis

Introduction

Crohn's Disease (CD) is an inflammatory bowel disease (IBD) characterized by chronic inflammation of the gastrointestinal tract affecting most frequently the ileum and colon [1]. The etiology is not completely understood but typically involves the interaction of environmental, genetic, and immune factors [1-4]. Characteristic symptoms are chronic diarrhea (more than 6 weeks), abdominal pain, weight loss, blood and/or mucus in the stool. Extra-intestinal manifestations are frequent and can affect the joints, skin, eyes and the hepatobiliary tract [5].

As a relapsing disease, its natural history is characterized by periods of active disease with graded clinical severity usually classified as mild, moderate and severe, and periods of remission [6]. The treatment is based on drug or surgery induction of remission, followed by maintenance with medicines in combination with lifestyle changes [7]. Medical treatment increasingly includes the earlier use of immunomodulators and biologic agents such as the Tumor Necrosis Factor alpha inhibitors (anti-TNF alpha), especially in Western Countries, [8-12] although treatment with these medications varies between countries according to drug reimbursement policy and patient co-payment [3,13].

The incidence and prevalence of IBD is traditionally higher in developed countries especially in the United States (US), Canada and countries of Western Europe, but reports of increasing cases have also appeared in other regions such as Africa, Asia and Latin America [14]. In Europe, the highest reported incidence and prevalence of CD was 12.7 per 100,00 person-year and 322 per 100,000, respectively [15]. In the US annual incidence range from approximately 3 to 20 cases per 100,000 population [4,16], and it was estimated that up to 3 million Americans had IBD in 2015, representing 1.3% of the population [4]. In Brazil, epidemiological data about IBD are scarce and only a few local or regional studies have been conducted. Nonetheless, limited data point to an increase in CD prevalence over recent years [17-19].

CD onset is more common between the second and fifth decade of life, peaking between 20 and 30 years of age and then decreasing to peak again to a smaller extent after age 50 years [4]. CD is associated with high morbidity. Hence due to its early onset, it has a significant impact on the patient's quality of life and work productivity. CD-related long-term cost is substantial to the patient, health care system, and society [12,14,20].

Cost analysis studies conducted in various countries have agreed that the economic burden of CD is considerable, although their

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reported figures varied between countries [16,20,21]. For instance, recent studies have estimated the total costs of CD, including both direct and indirect costs, to be between US$10.9 billion and US$15.5 billion in the US, US$2.8 billion in Canada (for IBD including CD and ulcerative colitis), and between €2.1 billion and €16.7 billion in Europe [12,21]. Mean total CD-related costs per patient per year have also varied between Western Countries, ranging between US$18,962 to US$26,192 in the US [22] with higher costs for patients with fistulizing disease, to €18,525 in Germany [23], €15,521 in Italy [24] and €6,808 in Spain [25]. Costs per patient are currently lower in Eastern European countries where there is limited access to biological therapies that are only available with high patient co-payments [3].

With the increasing prevalence of CD, and growing constraints on budgets, economic analysis are important to enhance health resource allocation, especially in countries striving to attain or retain universal access to healthcare for their patients.

In Brazil, the Unified Health System (Sistema Único de Saúde, SUS) provides high cost treatments free of charge for all patients with chronic diseases providing they meet national Clinical Protocols and Therapeutic Guidelines [26,27]. The biologicals (anti-TNF alpha), aminosalycilates and immunomodulators for CD are available through the Specialized Component of Pharmaceutical Services [28-30]. The indication associated with the dispensation of these medications is recorded in the SUS databases, which also records other health resource utilization such as outpatient procedures and hospitalizations.

Currently, there is a lack of data concerning the epidemiology and expenditure on CD in Brazil. The likely CD incidence and prevalence growth and impact on morbidity and mortality emphasize the need to assess its costs, particularly in a country that is trying to meet its economic challenges and optimize the use of its resources. The aim of this study was to assess the CD-related direct medical costs and changes over time from the perspective of the Brazilian public health system in a fifteen-year follow-up study.

Methods

A national population-based cohort of Crohn's Disease patient's ages 10-100 years from January 2000 to December 2014 was constructed by deterministic-probabilistic linkage of the following SUS administrative databases: Hospital Information System (SIH), Ambulatory Information System (SIA) and Mortality Information System (SIM) [31].

Patients were identified by the use of the following medications: mesalazine, sulfasalazine, azathioprine, cyclosporine, methotrexate, methylprednisolone, ciprofloxacin, infliximab and adalimumab in combination with CD diagnosis according to the International Classification of Diseases, 10th Revision (ICD-10) codes K50, K50.0, K50.1, K50.8, K50.9 and M074. Follow-up started at the first date of eligible medication recorded in the period and ended at the date of the last record on one of the databases, death, or December 31, 2014. Only patients with a minimal of 12 months follow-up were retained. Comorbidities developed during the follow-up were identified according to Elixhauser Comorbidity Indicators which is based on the diagnosis provide by ICD codes found in the administrative data [32,33]. Total medical costs were assessed from a public health (SUS) perspective. Costs of outpatient and hospital procedures were based on the values recorded in the SIH and SIA databases. The costs of medications, were determined using the government registered (acquisition) price during the period. All costs were converted to the US dollar adjusted by purchasing power parities (PPP) for each calendar year of the period [34].

Categorical variables were reported by frequency distribution. For continuous variables we calculated the mean and standard deviation (SD) and median (1st and 3rd quartiles) of expenditure per patient by time of follow-up (mean and median annual expenditure) stratified by demographic and clinical variables at study entry, including gender, age category, region of residence, diagnosis according to ICD-10 codes, medication used and respective therapeutic class, and calendar period; and by events that that occurred during the follow-up including medication switch, comorbidity and death. The mean expenditure per patient was also calculated for each year of follow-up by health resource category.

The distribution of the mean annual expenditure per patient was examined to assess normality using histograms and normal probability plots. Univariate and multivariate analyses were subsequently undertaken using a log-linear regression model to evaluate the relation between the demographic and clinical variables and the mean annual expenditure per patient. A threshold of $p<0.2$ was used to determine which variables would be incorporated into a multivariate regression analysis, with manual backwards elimination. Data analyses were performed using the software R Studio Version 1.0.143; $p<0.05$ indicated statistical significance. Subgroup analyses were also conducted dividing study patients in two groups, those who only used medications and those who used medications and other SUS health resources (hospitalizations, outpatient care). This study followed the ethics concepts and was approved by the Research Ethics Committee of the Federal University of Minas Gerais.

Results

In total, 46,886 patients fulfilled the inclusion criteria (had at least 12 months of follow-up and were 10 to 100 years of age at study entry). Among these, 27,252 (58.1%) were female, with a ratio of 1.4 women for each man. The majority of patients (63.0%) were between 26 and 55 years of age at study entry, with a mean age ± standard deviation of 40.5 ± 15.5 years. The most common diagnosis at study entry was Crohn's disease of the small intestine (K50.0), with 26,127 (55.7%) patients in this category. The Brazilian region with the largest number of patients was the Southeast with 29,437 (62.8%) of the population. The majority of patients (86.7%) received monotherapy. Aminosalicylates were the most frequently prescribed medicines at study entry (62.4%) and mesalazine was the initial medication in 43.4% of patients. Medication switch, that indicated the addition of a new medication and/or change for a new one, occurred in 22,223 (47.4%) of the study population. An appreciable number of patients in the databases, 21,378 (45.6%) started treatment between 2005 and 2009. Comorbidities developed during the follow-up were identified in 13,762 (29.4%) of the patients and the most frequent were rheumatoid arthritis/collagen vascular diseases affecting 9.3% of the patients, renal failure (4.5%), liver disease (2.9%) and solid tumor without metastasis (2.3%). About 5.8% of the patients died during follow-up. The most common cause of death was non-infectious colitis and enteritis (Table 1).

The mean of follow-up was 5.3 years. The mean annual expenditure per patient over the period was US$ 3451.0, 95% CI [3399.2 3502.7] and varied by the clinical and demographic categories described above. Considering gender and age categories at study entry, higher values were observed among males and ages 18 to 25 years, while among geographic regions and CD medications, those residing in the center-west and users of the anti-TNF alpha adalimumab at study entry

Variable	n (%)	Mean annual expenditure per patient US$ (SD)	Median annual expenditure per patient US$ (IQR)
Total patients	46886 (100.00)	3218.13 (321.58)	4462 (1402-18831)
Gender			
Female	27252 (58.12)	2867.92 (296.44)	4010 (1307-16123)
Male	19634 (41.88)	3704.44 (367.27)	5323 (1554-22892)
Age mean-years ± SD	40.50 ± 15.51	-	-
Female	42.05 ± 15.33	-	-
Male	38.35 ± 15.49	-	-
Age category (years)			
10-17	2418 (5.16)	4076.33 (415.55)	5785 (1373-35262)
18-25	6552 (13.97)	4262.70 (456.79)	6547 (1645 – 28162)
26-35	10149 (21.65)	3627.52 (534.84)	5280 (1484 – 23471)
36-45	10484 (22.36)	3211.41 (202.54)	4461 (1433-19101)
46-55	8921 (19.03)	2691.93 (381.92)	4027 (1399-15750)
56-65	5319 (11.34)	2029.21 (603.93)	3639 (1280-12311)
> 65	3043 (6.49)	1447.88 (552.30)	3639 (1027-7599)
Region of residence			
Southeast	29437 (62.78)	3571.82 (336.07)	5431 (1667-22240)
South	8281 (17.67)	2415.52 (410.93)	4289 (1457-14135)
Northeast	6484 (13.83)	2497.02 (498.09)	1850 (736-6728)
Midwest	2335 (4.98)	3800.57 (843.24)	8069 (1878-28036)
North	349 (0.74)	3135.14 (1505.20)	2447 (865-14159)
Primary diagnosis-ICD-10			
K50-Crohn's disease [regional enteritis]	7620 (16.25)	2759(786.87)	4361,51(1822-15858)
K50.0-Crohn's disease of small intestine	26127 (55.72)	2979.39 (462.48)	4047 (1243-17626)
K50.1-Crohn's disease of large intestine	5817 (12.41)	3650.39 (451.20)	5034 (1382-21145)
K50.8-Other Crohn's disease (both small and large intestine)	5126 (10.93)	3842.82 (475.69)	5107 (1332-22368)
K50.9-Crohn's disease unspecified	2142 (4.57)	3664.94 (632.11)	8448 (3088-29271)
M074-Arthropathy in Crohn disease (regional enteritis)	54 (0.12)	2190.29 (986.32)	3944 (1498-7307)
Pharmaceutical medication class			
DMARDs	29496 (62.91)	2553.18 (370.98)	3398 (1235-10202)
Immunomodulator	8601 (18.34)	3159.47 (582.46)	2461 (933-14210)
Anti-TNF alpha	3473 (7.41)	4325.13 (496.73)	7374 (23234-68135)
DMARDs+Immunomodulator	3407 (7.27)	9201.15 (4639.42)	40840 (2508-24292)
Anti-TNF alpha+Immunomodulator	741 (1.58)	8743.28 (4285.05)	32764 (20635-50592)
Anti-TNF alpha+DMARDs	381 (0.81)	8882.70 (4922.30)	39747 (21913-64786)
Other classes or assotiations	787 (1.68)	6172.84 (2510.19)	27478 (10383-58392)
Medication			
Mesalazine	20510 (43.74)	2471.55 (448.19)	3579 (1220-10530)
Azathioprine	8447 (18.02)	2406.08 (608.74)	2333 (1247-8901)
Sulfasalazine	8285 (17.67)	3125.00 (589.54)	3001 (905-13254)
Azathioprine+Mesalazine	2843 (6.06)	3524.05 (1336.00)	7714 (2592-23730)
Infliximab	2354 (5.02)	9541.15 (5051.53)	47218 (26075-79121)
Adalimumab	1051 (2.24)	9873.48 (5258.73)	31201 (19618-3267)
Other medications or association	3396 (7.24)	5274.17 (1803.27)	21464 (5671-46921)
Period of beginning of treatment			
2000 to 2004	8984 (19.16)	3023.45(580.69)	6117 (2234-20709)
2005 to 2009	21378 (45.60)	3023.81 (525.75)	3945 (1447-16385)
2010 to 2014	16524 (35.24)	4014.06 (1129.21)	4293 (1081-20546)
End of follow-up			
Loss of follow-up	44154 (94.17)	3202.70 (317.69)	4391 (1375-18927)
Death	2732 (5.83)	3520.69 (810.03)	5548 (1824-17530)
Medication switch			
Yes	22223 (47.40)	4512.64 (561.73)	12612 (3717 – 37307)
No	24663 (52.60)	1416.09 (458.53)	2089 (833 – 6123)
Comorbidities			
No	33124(60.6)	2839.27 (302.71)	3665 (1211-15286)

Yes	13762 (29.4)	3751.16 (510.87)	7140 (2131-31567)
ICD-10 Groups – Cause of deaths			
Noninfective enteritis and colitis	377 (13.80)	5426.79 (1729.74)	8487 (2989-29224)
Ischaemic heart diseases	174 (6.37)	3386.55 (2172.94)	4737 (1561-14403)
Malignant neoplasms of digestive organs	167 (6.11)	3681.27 (2296.73)	6761 (2905-17012)
Cerebrovascular diseases	128 (4.69)	2728.28 (825.28)	3372 (1531-9280)
Influenza and pneumonia	124 (4.54)	3154.38 (1094.00)	7154 (2726-22906)
Other heart diseases	111 (4.06)	2098.92 (1042.78)	3751 (1537-12461)
Other ICD-10 groups	1651 (60.43)	3304.57 (982.93)	5259 (1733-14978)

Table 1: Demographic and clinical characteristics of CD patients.

showed greater mean annual expenditure. Patients who experienced medication switch, those who developed comorbidities and those who died during follow-up also showed higher mean annual expenditure compared to those without these events, respectively. The highest average cost for patients were found in those who entered the cohort between 2010 and 2014.

The total expenditure between 2000 and 2014 was US$ 844.68 million, from which US$ 762.44 million (90.3%) were for CD medications, US$ 42.50 million (5.0%) for other medications, US$ 25.66 million (3.0%) for hospitalizations, US$ 10.12 million (1.2%) for outpatient care (excluding medications) and US$ 3.96 million (0.5%) for diagnostics and monitoring exams.

In the breakdown of expenditures by year of follow-up, medications were the major cost driver in all years, although the ratio of medication to other expenditures fluctuated slightly over the period. An increase in hospitalization expenditures was also apparent throughout the study period (Figure 1).

The evolution of mean annual expenditure per patient in by year of follow-up according to health resource category, showed that mean of CD medications expenditure was higher in the first year, US$ 3826.6/ patient, 95% IC [3732.7 3920.6], and dropped dramatically in the second year for US$ 3074.5/ patient, 95% IC 2998.1 3150.9], fluctuating slightly in the following years. Among patients that were hospitalized the mean of hospitalization costs were US$ 1143.0/patient, 95% IC [1042.5 1243.3], in the first year and fluctuated thereafter, rising considerably in the last two years reaching US$ 1937.0/patient, 95% IC [618.9 3254.4]. Other medication expenditures also fluctuated and were higher than those for hospitalizations until the eleventh year. Outpatient care, diagnostics and monitoring exams were less expensive and presented little fluctuations over the study period (Figure 2).

Among the CD medications, the anti-TNF alpha drugs represented 79.1% of the total medication expenditure overall years, and were also the major cost drivers for all the follow-up years. The evolution of expenditures with anti-TNF alpha during the period showed that the mean annual expenditure per patient was higher in the first year of follow-up and dropped dramatically and consistently until the final years. DMARDs were the second therapeutic class in expenditure followed by immunomodulators. Whilst DMARDs showed a decrease in expenditure by year of follow-up, from 21.8 to 8.7% of the total expenditures on medications by year, the immunomodulators expenditures rose from 2.1% to 5.4% (Figure 3). Ciprofloxacin and methylprednisolone together represented less than 0.5% of total medication expenditure.

On multivariate analyses, the log-linear model showed that the variables associated with the annual mean total CD-related health expenditures were gender, age category, region of residence, CD medication used and calendar period at study entry and explained 29.0% of expenditure (Table 2). Men had an increase of 15.0% in mean annual expenditure compared to women. All ages category had an increase compared to patients older than 65 years and the higher increase was in ages 18 to 25 years. About the region of residence, reside in North and Northeast at study entry represented a decrease about 36.0% in mean annual expenditure whilst reside in Southeast and Mid-west represented an increase of 17.0% and 26.0%, respectively. Among medications used at study entry, compared to sulfasalazine, all medications represented increase in expenditures and it was more significant for the anti-TNF alpha agents, with adalimumab and infliximab representing an increase of 14.80 and 16.15 times the expenditure of patients that used sulfasalazine at study entry. Patients that entered in the study between 2005 and 2009 had 13% of decrease in expenditures, compared to patients who entered between 2000 and 2004. The subgroup analyses showed that variables associated with mean annual expenditure were the same of the total population model in both groups.

Discussion

The CD population in Brazil was on average 40.44 ± 15.56 years of age at study entry and most of them were female. These findings are concordant with other epidemiological data reported by Lowe, et al [35] that showed slight female predominance among Canadian CD patients and an average age at diagnosis of 38.7 years. Another study conducted by Benedini et al. in Italy included CD patients with mean age at diagnosis of 43 years [24] and although men were a minority in that study, they showed a mean annual expenditure higher than that of women as found in our study.

The majority of CD patients in our study were diagnosed as having CD of the small intestine (ICD-10 K50.1). Although the unadjusted annual mean expenditures seemed higher for those diagnosed as other CD (K50.8) that affected both the small and large intestine, adjusted analyses showed a non-significant result. Studies have reported that Ileocolonic disease localization is associated with a complicated course of disease and may explain higher expenditure among patients with both small and large intestine disease [36]. However, this finding could not be examined in our data because the ICD-10 classification for CD is limited in terms of information on disease location that is provided only in a general way. Although disease behavior (structuring or penetrating) and extension of anatomical involvement are relevant to predict CD outcomes [37], they could not be assessed in our study.

The comparison between patients who had a medication switch, comorbidity and death and those without the event showed that mean annual expenditure was higher in patients that subsequently died and in those with comorbidities who may represent a group of patients with

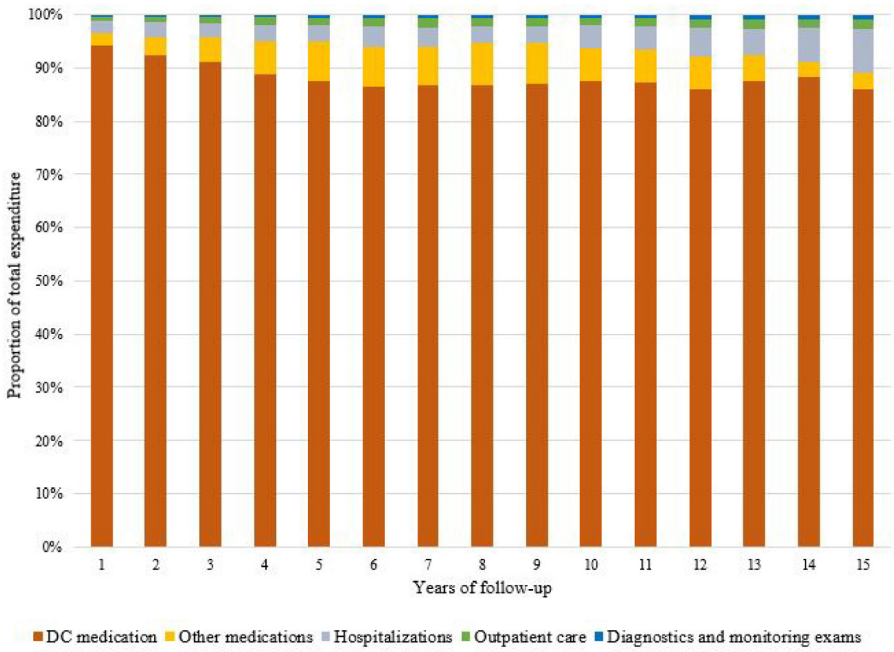

Figure 1: Distribution of total expenditure by health category resource and year of follow-up.

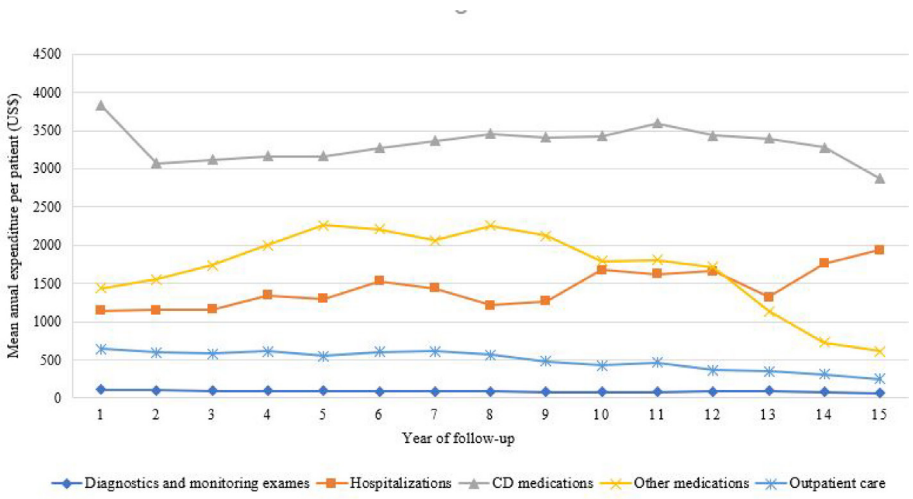

Figure 2: Mean annual expenditure per patient by health resource and year of follow-up.

more severe disease and more complications resulting in more health resource utilization. Higher expenditures also occurred in the group of patients with medication switch and can be explained by the fact that in general CD patients start the treatment with not so expensive medications like aminosalicylates following to the high cost medications anti-TNF alpha agents. Besides that, medication switch is indicative of therapeutic failure and/or increase of disease severity, which demand more intensive care. Although the occurrence of these events suggests a higher expenditure, a specific and more robust analysis would be required to evaluate their relation with the expenditure.

Mesalazine was the most prescribed medication at treatment onset, confirming its traditional use as a first line therapy in patients with mild to moderate CD disease [38]. Although a lower proportion of patients started with anti-TNF alpha medication, these represented the highest annual mean expenditure as was expected since the anti-TNF alpha are the most costly medications in the management of CD. The introduction of adalimumab in 2010 may explain a higher annual average expenditure for patients who started treatment between 2010 and 2014.

The higher mean expenditure per patient for CD medication in the first year can be associated to high doses medication utilization in patients that are using medications to induce remission and the need of switch medication in case of failure of the first line treatment. Bernstein and colleagues found that costs of CD treatment were greater in the first year of diagnosis and decreased in the following years [39] as showed for CD medications in our study. The exception in our study was for hospitalization outlay, which increased during this period. A prospective study of CD patients with fifteen years follow-up [40]

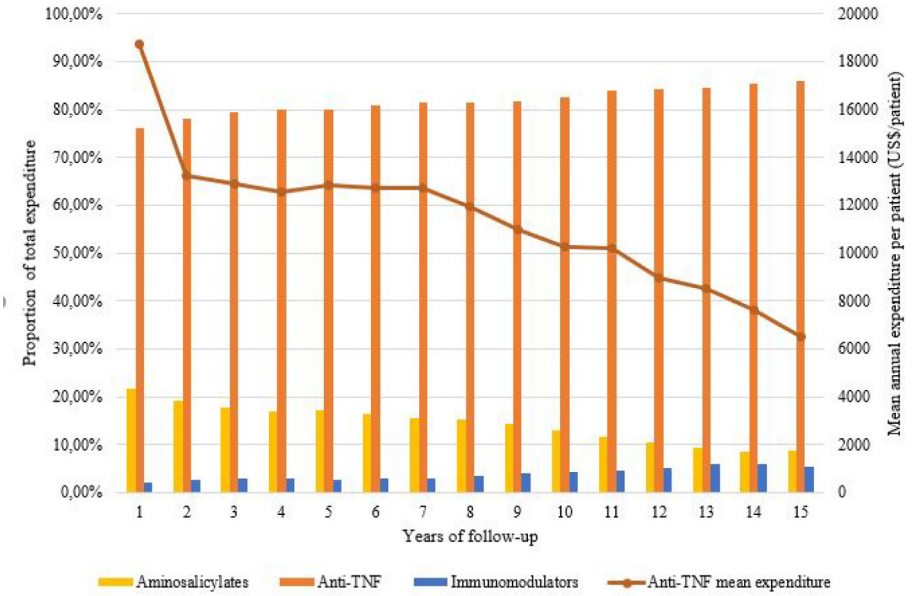

Figure 3: Distribution of CD medications expenditures by therapeutic class according to each year of follow-up and mean annual expenditure per patient of anti-TNF alpha medications.

Variable	Beta coefficient	Exp (Coefficient)	Standard error	t value	Pr (>|t|)
Intercept	6.190390	488.04	0.030923	200.184	<0.001
Male	0.139731	1.15	0.012409	11.261	<0.001
2005 to 2009/2000 to 2004	-0.138133	0.87	0.012479	-11.069	<0.001
10 to 17 years/>65 years	0.369707	1.45	0.036052	10.255	<0.001
18 to 25 years/>65 years	0.484038	1.62	0.029014	16.683	<0.001
26 to 35 years/>65 years	0.383023	1.47	0.027278	14.041	<0.001
36 to 45 years/>65 years	0.264105	1.30	0.027132	9.734	<0.001
46 to 55 years/>65 years	0.232816	1.26	0.027613	8.431	<0.001
56 to 65 years/>65 years	0.133650	1.14	0.029862	4.476	<0.001
North/South	-0.449768	0.64	0.071863	-6.259	<0.001
Northeast/South	-0.451238	0.64	0.021865	-20.637	<0.001
Southeast/South	0.159956	1.17	0.016396	9.756	<0.001
Midwest/South	0.230715	1.26	0.030897	7.467	<0.001
Mesalazine/Sulfasalazine	0.267712	1.31	0.017088	15.667	<0.001
Azathioprine/Sulfasalazine	0.008098	1.01	0.020401	0.397	0.691
Azathioprine+Mesalazine/Sulfasalazine	1.016734	2.76	0.028642	35.498	<0.001
Infliximab/Sulfasalazine	2.785832	16.21	0.030768	90.542	<0.001
Adalimumab/Sulfasalazine	2.698644	14.86	0.043517	62.014	<0.001
Other medications or associations/Sulfasalazine	1.618767	5.05	0.026809	60.382	<0.001
*exp: Exponnetiated					

Table 2: Multivariate analysis result.

showed that hospitalizations were required for only few patients, and this was most common in the early years, in contrast with our findings. However, the same study compared the mild and moderate to severe CD and it was observed that for patients with severe disease, disease activity and hospitalizations in subsequent years were more frequent than in those with mild and moderate CD. These findings may help to explain the increase of hospitalizations in the last years of our study follow-up, since part of the patients with more time of follow-up might have severe disease and needed of hospitalization.

The breakdown of expenditures showed that CD medications accounted for the highest proportion of health expenditure for these patients, followed by other medications and hospitalizations. Analyzing the proportion by year of follow-up, medications also represented the majority of expenditures over time, and in the final follow-up years hospitalization was the second cost driver. Anti-TNF alpha agents represented 71.4% of the total health resource expenditures and 79.1% of total expenditures on CD medications being the most cost driver in all years of follow-up. Among medications, the proportion on the expenditures on anti-TNF alpha increased over time from 76.0% to 85.9%.

A large European cohort, with ten years of follow-up that ended in 2004 showed different proportions on expenditures, with medical and

surgery hospitalizations being the most expensive resource representing 63% of total expenditures with medications being responsible for 30% [41]. Similarly, in a six-month retrospective follow-up of 172 patients in UK, from June to December 2000, medical and surgical hospitalization contributed to 60% of total costs and less than 20% was attributed to medications [2]. Differences between these earlier studies and ours may be explained by the limited availability of the anti-TNF alpha medications during the earlier study periods.

A study by Kappelman et al., conducted in the US based on data from 87 health plans covering 33 states, between 2003 and 2004, found that 31% of the costs were attributable to hospitalization, 33% to outpatient care, and 35% to pharmaceutical claims, with mean annual costs of US$8265 [42]. Another population-based study conducted in Manitoba, Canada using health services administrative databases between 2005 and 2006, showed that 5% of the costs were on outpatient care, 39% on hospital inpatient, 12% on physician office visits and 44% on medications [39]. Data from a prospective longitudinal study of 24 months, between 2010 and 2011, in the Netherlands, showed that the proportion of anti-TNF alpha therapy-related costs increased from 64.0% to 72.0% whilst hospitalization costs decreased from 19.0% to 13.0% [43]. As in our study, these reports reveal that biologic treatments account for the majority of the CD cost, while hospitalization that used to be the most expensive CD treatment, are now responsible for a small proportion of that cost.

In the breakdown of expenditures among CD medications by year of follow-up, the decrease in the proportion of aminosalicylates followed by an increase in the proportion of immunomodulators can be explained by the fact that aminosalicylates are more indicated in mild to moderate disease and are more effective to induce remission than for maintenance therapy while immunomodulators, apart from anti-TNF alpha, are effective in remission and maintenance therapy, being more used in the subsequent years of treatment. The increase of the proportion of anti-TNF alpha agents followed the disease course, and their increasing use is probably due to more active or severe disease that didn't response to aminosalicylates or initial immunomodulators, reflecting their growing role in the treatment of patients with CD. The decrease in mean annual expenditure per patient of anti-TNF alpha during the period is a result of using higher doses in the first weeks of treatment to induce remission, what contribute for a greater expenditure in first year of treatment, but is followed by a decrease during the maintenance therapy.

In our study, multivariate analyses showed an increase in mean annual expenditure for men what can be attributed to higher health resource utilization in this group than among the women in our study. The higher increase in expenditure in younger patients About the age category, some studies have reported that increasing age of diagnosis was associated with less complicated disease [44,45], what can be associated with less costs in treatment and can explain the greater increase on expenditure for patients that were younger at study entry. The increase in expenditures for Southeast and Midwest regions residents can be justified by the fact they are more developed regions [46] and have a greater access to health services [47] as well as a higher relation of gastroenterologists *per capita* [48] compared to North and Northeast, which result in more health resource utilization and more prescription medications, increasing the costs of treatment. The higher increase in expenditure for those patients, who used anti-TNF alpha agents adalimumab or infliximab at study entry, showed the great impact of their use on CD treatment costs, attributed mainly to their high unitary value, and highlighted the contribution of these medications in CD costs.

We believe the strength of this study is the population size and the inclusion of nationwide CD patients. Limitations included the utilization of information from administrative database that contains records of utilization and payment of procedures and does not provide clinical data about the disease. This did not allow evaluation of expenditures according to disease severity or activity. Other limitations include the fact that in Brazil 25.0% of the population have private health care insurance [49] and hospitalizations that are paid for privately could not be included in our study. This though has no to little impact on medication expenditures since high-cost drugs are more available and accessible in SUS. Besides that, moderate to severe CD patients are heavy health resource users and are more likely to use public resources. Therefore, our study is more likely to have missed some mild CD patients.

Overall, we believe our findings are robust and provide guidance to national and regional health authorities in Brazil regarding current expenditures on patients with CD, and their component parts. Medication costs may start to decrease with greater availability and use of biosimilars worldwide, with up to 60% discounts reported in some countries [50].

Conclusion

CD medications represented the greatest proportion of expenditure in managing CD patients, with anti-TNF alpha agents being the greatest cost driver and total outlay. Trends with the increasing use of biologics in the management of CD patients worldwide show the need and relevance of cost-effectiveness analyses. These data of real life drug utilization can be useful to enhance future cost-effectiveness studies in CD, as well as provide benchmark figures for health authority personnel in Brazil and wider.

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