



Economic burden of chronic urticaria in Brazil: a 1 year real life study

Carga econômica da urticária crônica no Brasil: um estudo de vida real no período de 1 ano

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ABSTRACT

Background: The costs of chronic urticaria (CU) are unknown in Brazil. The objective of this study was to describe the costs associated with the treatment of CU. **Methods:** This longitudinal, descriptive study recruited patients with chronic spontaneous urticaria and/or chronic inducible urticaria, who attended at least 4 visits to a specialized outpatient clinic within a 12-month period. Patients with other skin diseases and those who discontinued treatment were excluded. Patients underwent a provocation test and an objective evaluation, before receiving treatment according to the most recent guidelines. Data on direct and indirect costs of treatment were collected at each visit, and analyzed using Chi-square tests, the Mann-Whitney test, analysis of variance (ANOVA), paired *t*-tests, Tukey post-hoc tests and Wilcoxon tests. A *p*-value of 5% was considered significant. **Results:** From November 2016 to December 2018, 55 out of 68 enrolled patients completed the protocol. The cost of absenteeism was US\$ 21,125.84 and that of transportation was US\$ 3,755.69. The total indirect cost of CU was US\$ 24,881.53 (US\$ 452.39 per patient-year; SD, 461.11). The cost of medical appointments was US\$ 3,838.17, and that of laboratory tests, US\$ 6,607.39. The total cost of medications was US\$ 174,697.58, of which US\$ 141,582.91 was associated with the use of omalizumab in 12 patients. The total direct cost of CU was US\$ 185,143.14 (US\$ 3,366.23 per patient-year; SD, 6,446.58), resulting in an overall annual cost of US\$ 210,024.67 (US\$ 3,818.63 per patient-year). The higher the household income, the higher the costs of CU treatment. **Conclusion:** CU had a significant cost to the study population. The total estimated mean cost of illness was US\$ 3,818.63 patient-year. The cost of medication was significantly increased by the use of omalizumab, an effective option for patients with CU refractory to high-dose antihistamine therapy, but a major contributor to the economic burden of patients with CU.

Keywords: Cost analysis, quality-of-life, therapeutics, urticaria.

RESUMO

Introdução: Os custos da urticária crônica (UC) são desconhecidos no Brasil. O objetivo deste estudo é descrever os custos relacionados ao seu tratamento. **Métodos:** Estudo longitudinal descritivo de pacientes com urticária crônica espontânea e/ou urticária crônica induzível, que compareceram a pelo menos quatro consultas em um ambulatório especializado em um período de 12 meses. Foram excluídos aqueles com outras doenças de pele e que interromperam o tratamento. Os pacientes foram submetidos a testes de provocação, avaliação objetiva e tratamento de acordo com as diretrizes mais recentes. Dados sobre custos diretos e indiretos do tratamento foram coletados em cada visita. Foram utilizados os testes qui-quadrado, Mann-Whitney, Anova, *t*-pareado, post-hoc Tukey, e Wilcoxon's. Foi considerado significativo $p < 0,05$. **Resultados:** De novembro de 2016 a dezembro de 2018, 55 pacientes dos 68 inscritos completaram o protocolo. O custo do absenteísmo foi de US\$ 21.125,84, e o transporte, de US\$ 3.755,69. O custo indireto total foi de US\$ 24.881,53 (US\$ 452,39 paciente-ano; DP \pm 61,11). As despesas com consultas foram de US\$ 3.838,17, e o custo total de exames laboratoriais foi de US\$ 6.607,39. O custo total com medicamentos foi de US\$ 174.697,58, dos quais US\$ 141.582,91 relacionados ao uso de omalizumabe em 12 pacientes. O custo direto total foi de US\$ 185.143,12 (US\$ 3.366,23 por paciente-ano, DP \pm 6.446,58), resultando em um custo anual global relacionado à doença de US\$ 210.024,67 (US\$ 3.818,63 paciente-ano). Quanto maior a renda familiar, maiores os custos com a urticária crônica. **Conclusão:** A UC tem um custo significativo para a população do estudo. O custo médio total estimado foi de US\$ 3.818,63 paciente-ano. Os altos custos com medicamentos, aumentados pelo uso do omalizumabe, que é uma opção eficaz em pacientes com altas doses de anti-histamínicos, resultam na maior carga econômica entre os pacientes com UC.

Descritores: Análise de custo, qualidade de vida, terapêutica, urticária.

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Background

Chronic urticaria (CU) is a heterogeneous group of diseases characterized by the appearance of fleeting wheals of various shapes and sizes, with or without angioedema, for a period of at least 6 weeks. CU can be classified as chronic spontaneous urticaria (CSU) or chronic induced urticaria (CIndU). CIndU can be triggered by physical stimuli such as cold, heat, sunlight, vibration, pressure, as well as other factors such as contact with water or increased body temperature. In a significant portion of cases, CSU has unknown cause or is related to autoimmune mechanisms. In a minority of cases, CSU can be caused by medications such as opioids, antihypertensives and nonsteroidal anti-inflammatory drugs (NSAIDs), infections, parasitic infestations and autoimmune diseases such as diabetes mellitus, vitiligo and hypo/hyperthyroidism.¹⁻²

The prevalence of CU in the general population is estimated to be between 0.5 and 1%, with women affected more often than men. Although the peak incidence of CU occurs between the ages of 24 to 44 years, the disease may emerge at any age. The mean duration of symptoms is between 2 and 5 years, though it may be even longer in 20% of patients.¹⁻⁴

The diagnosis of CU is predominantly clinical, and is usually diagnosed based on a detailed medical history, since extensive diagnostic testing often fails to reveal the cause of the condition.

According to current guidelines, non-sedating antihistamines are the first line of treatment for CU. If symptom control is not achieved, the second-line treatment is up-titration to a maximum of 4 times the licensed dose.

CU adversely affects the quality of life of patients, especially those of working age. Additionally, CU has a considerable economic impact on patients, families and society, with an estimated mean cost of over US\$ 2,000 per patient-year in the United States (US).⁵ To date, there are no published studies on the costs of CU in Brazil.

The aim of this study was to estimate the economic costs associated with the treatment of CU in patients of a specialized outpatient clinic at a teaching institution that treats patients in the Brazilian Unified Health System (SUS).

Methods

This longitudinal study recruited patients with a diagnosis of CSU and/or CIndU who attended at

least 4 visits to the Chronic Urticaria and Angioedema Outpatient Clinic of the Allergy and Immunology Service at Policlínica Piquet Carneiro – Universidade do Estado do Rio de Janeiro (PPC-UERJ) in a 12-month period.

Patients with other chronic skin diseases and those who discontinued treatment were excluded from this study. Patients who missed any scheduled appointments were contacted and encouraged to return for a visit in order to reduce the dropout rate. Data collection began in the first patient visit, with questions regarding socioeconomic and demographic characteristics, pre-existing comorbidities, time of illness onset, and outpatient follow-up.

During each visit, clinical data were collected using several instruments. Quality of life was assessed using the Chronic Urticaria Quality of Life Questionnaire - CU2QoL (lowest impact: 23; greatest impact: 115). Disease severity was evaluated using the Urticaria Activity Score (UAS) (no activity: 0; greatest activity: 6) and the UAS7 (no activity: 0; greatest activity: 42),⁶ both of which evaluate the number of wheals and the severity of pruritus in the 7 days prior to the assessment. Lastly, disease control was assessed using two versions of the Urticaria Control Test (UCT): the short version, containing 4 items, and the long version, with 8 items.^{6,7}

Information on the financial costs (expenditures) of planned and unplanned medical visits was collected directly from patients or their parents. This included the costs of emergency room visits and/or admissions, complementary testing, medication, and transportation. Additional expenses included medical consultations, complementary laboratory testing, or absences from work or school by the patients and/or their caregivers. Data were collected for the 3-month period prior to each visit. Medical appointments, medications and laboratory tests were considered direct costs, whereas transportation and absenteeism were seen as indirect costs. Consultations and medications were divided by primary payer: SUS, health insurance or self-paid (out-of-pocket).

Transportation was categorized as public, private or provided by social assistance. Absenteeism from school and/or work was recorded for both patients and caregivers. All values were initially obtained in Brazilian reais (BRL) and converted to US Dollars (US\$) according to the most recent estimates of purchasing power parity, published by the World Bank in 2018⁸ (Table 1).

Following confirmation of the CU diagnosis, patients were submitted to CInDU provocation tests according to their clinical history. Autologous serum skin tests (ASST) were performed in patients who did not respond to treatment with standard doses of anti-H1, or tolerated the discontinuation of these drugs for 7 days prior to testing.⁴ Each participant was

examined and treated according to the most recent clinical guidelines.¹

Continuous variables were compared using analysis of variance (ANOVA) or Wilcoxon tests, for normally and non-normally distributed data, respectively. The Mann-Whitney test was used to compare costs between patients receiving

Table 1

Rating of economic components

Medical, nursing and psychologist visits, urgent care, hospitalizations, and complementary diagnostic tests	
Unified Health System (SUS)	Internet SUS ambulatory and hospital information systems – SIA and SIH/SIGTAP/DATASUS ⁹
Supplementary Healthcare System	Brazilian classification table of hierarchical medical procedures (CBHPM) – version 2016, which value of 1 medical consultation was R\$ 91.65 (equivalent to US\$ 40.05) ¹⁰
Private Healthcare	Value informed by patients/parents (out-of-pocket expenses)
Medications	
Provided by SUS	Table of medications for public purchasing from the Executive Secretariat of the Medication Regulation Board (ANVISA/Health Ministry), updated in December, 2018 ¹¹
Funded by patients	Value informed by patients/parents (out-of-pocket expenses) ¹¹
Transportation	
Public transportation (bus, train, subway) or taxi paid by patients	Value informed by patients/parents
Private vehicle and public social assistance vehicles (from SUS)	Distances obtained from the internet. ¹² Costs calculated assuming 10 kilometers per liter of gasoline (round trip), and considering the average price of gasoline as of March 2018 according to the National Petroleum Agency ¹³
Absenteeism	
At school	Number of absence days (not valued)
At work (for patients and parents or caregivers of patients < 15 days)	Number of absence days: value of each day = personal monthly income / 21 days (average number of working days per month). Absence cost = value of each day x number of days
By social security benefits (SSB) due to urticaria (> 15 days)	Number of months: value of each month = monthly salary. Lost value = monthly salary x number of months of SSB

omalizumab and the remainder of the sample. Categorical data were compared using chi-square tests (χ^2) or Fischer's exact test when the frequencies were below the expected values. Group comparisons were performed using Tukey Tests.

The total costs of CU were then submitted to multivariate analysis by linear regression with logarithmic transformation. Statistical analyses were performed using SPSS, version 20.0 (SPSS, Chicago, IL, USA), with results significant at $p < 0.05$.

Sensitivity analyses were conducted using a Tornado diagram of the standard deviation and mean value of each expenditure (appointments, laboratory tests, medications, absenteeism and transportation) to calculate the impact of each item on the total cost of illness.

This project was submitted to and approved by the local ethics committee. All procedures were conducted according to National Health Council Resolution 196/96. All adult participants and parents/guardians of underage participants signed an informed consent form before data collection.

Results

In the period from November 2016 to December 2018, a total of 68 patients were enrolled in the study. Eleven (17%) participants were subsequently excluded due to interruptions in the supply of omalizumab or a lack of resources for transportation and/or treatment. Only two patients were discharged during the study period.

The final study population comprised 55 patients, most of whom were adults (82%), female (80%), white (69%), lived in the city of Rio de Janeiro (78%), and had at least an elementary education (51%). Most participants had full-time employment (36%), and only 4% were unemployed at the time of the study. The categorization by type of urticaria revealed that 44% of the sample presented with CSU, 38% with CSU plus CIndU, 18% with CIndU and 43% with associated angioedema. Among patients with CIndU, 1 had only chronic cold-induced urticaria; 1 had delayed-pressure urticaria plus dermatographism; 1 had heat-induced urticaria plus dermatographism; and 51% had dermatographism only.

The most prevalent comorbidities in the sample were obesity (36%), arterial hypertension (32%), rhinitis (20%), psychiatric disorders (15%), asthma (13%) and hypothyroidism (13%) (Table 2). Three

patients reported a worsening of depression/anxiety disorders after the onset of CU.

ASST was performed in 32 patients, and positive findings were observed in 62.5% of cases. Most patients ($n = 41/75\%$) had one or more pre-existing comorbidities.

The mean duration of disease, time until diagnosis and length of follow-up at the outpatient clinic were 66 (SD, 37), 24 (SD, 23) and 18 (SD, 12) months, respectively.

Mean UAS was 0.96 (SD, 1.33; range: 0-4) in the first visit and 0.71 (SD, 1.18; range: 0-4) in the last. The mean UAS7 on the last visit was 4.56 (SD, 8.67; range: 0-37). The mean UCT score in the last visit was 11.29 (SD, 4.80; range: 2-16) for the short version and 23.33 (SD, 7.92; range: 6-32) for the long version. The mean CUQ2oL score at the first visit was 48 (SD, 18.67; range: 23-89) and on the last visit, 41 (SD, 18.05; range: 23-91), suggesting a negative impact of CU on patients' quality of life.

Non-sedating antihistamines were prescribed to all patients as the first line of treatment. The use of current, standard H1-antihistamines at normally prescribed doses was effective at resolving symptoms in 47% of patients. The most frequently prescribed antihistamine was cetirizine (mean annual cost per patient = US\$ 343.34; SD, 404.72), followed by loratadine (mean annual cost per patient = US\$ 69.30; SD, 172.06) and hydroxyzine (mean annual cost per patient = US\$ 16.37; SD, 61.58). In 12 cases where patients did not respond to antihistamines at 4 times the standard dose, omalizumab was prescribed and led to improvements in UAS. A leukotriene receptor antagonist (montelukast) was prescribed to six patients (mean annual cost per patient = US\$ 17.46; SD, 83.02) and nine patients required short courses of oral corticosteroids (mean annual cost per patient = US\$ 15.02; SD, 81.59). Only 1 patient experienced side effects associated with long-term corticosteroid use (psychiatric disturbances, skin thinning and bruising, weight gain and fat redistribution).

Patients who received omalizumab did not differ from their peers with regards to skin color, occupation, city of residence, type of urticaria, angioedema and pre-existing comorbidities. The two groups differed, however, with regard to education level ($p = 0.01$) and psychiatric illnesses ($p = 0.03$).

During the follow-up period, 42% of participants required 1 or more additional medical appointments

and 9% required urgent consultation. Additionally, 11% of participants received psychological follow-up. No patients were hospitalized during the study. The total cost of CU treatment for the year was US\$ 210,024.67, with a mean of US\$ 3,818.63 (SD, 7,101.74) per patient-year. The highest indirect costs

were associated with absenteeism (US\$ 21,125.84, US\$ 384.10 patient-year; SD, 2,127.01). One patient missed work for a period of 90 days, which led to a decrease in quality of life, but was able to return to work after starting treatment with omalizumab. No patients received sick pay during the study. The

Table 2
Sample characteristics

Variable	Total sample (n)	(%)	Patients with omalizumab (n)	(%)	Patients without omalizumab (n)	%	p ^a
Gender							
Female	44	80	10	83	34	79	0.74
Male	11	20	2	17	9	21	
Age							
Adults (≥ 18 years)	45	82	12	100	33	77	0.03
Children/adolescents (< 18 years)	10	18	0	0	10	23	
Ethnicity/skin color							
White	38	69	9	75	29	67	0.61
Black/brown	17	31	3	25	14	33	
Educational level							
Elementary school	28	51	3	25	25	58	0.01
High school	13	24	2	17	11	26	
Higher education	14	25	7	58	7	16	
Place of residence							
Rio de Janeiro city	43	78	11	92	32	74	0.20
Other cities	12	22	1	8	11	26	
Occupation							
Employee	20	36	8	67	12	28	0.15
Student	14	25	1	8	13	30	
Housekeeper	12	22	2	17	11	26	
Retired	07	13	1	8	5	12	
Unemployed	02	04	0	0	2	4	
Type of urticaria							
CSU	24	44	7	58	17	40	0.43
CSU plus CIndU	21	38	4	33	17	40	
CIndU	10	18	1	8	9	20	
Associated angioedema	24	43	8	67	16	37	0.06
Comorbidities							
Obesity	20	36	3	25	17	40	0.35
Arterial hypertension	18	32	6	50	12	28	0.14
Rhinitis	11	20	2	17	9	20	0.74
Psychiatric disorders	8	15	4	33	4	10	0.03
Asthma	7	13	1	8	6	14	0.60
Hypothyroidism	7	13	3	25	4	9	0.14

^a Chi-square test.

CSU = chronic spontaneous urticaria, CIndU = chronic inducible urticaria.

highest direct costs of CU were associated with medication expenses, especially for patients receiving omalizumab, which accounted for 45% of the total cost of medication (US\$ 141,582.91, US\$ 2,574.23 patient-year; SD, 5,925.58) (Table 3).

A complete blood count (CBC) was performed for all patients, as were measurements of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. A skin biopsy was only performed for 5% of patients.

The comparison of patients treated with omalizumab and those who received other treatments revealed significant differences in transportation types, absenteeism, appointments, exams and medications between groups. There were also significant differences in family income: patients who used omalizumab had an average monthly income of US\$ 2,954.27 (SD, 2,784.03) while the group who received other treatments had an average monthly income of US\$ 1,007.26 (SD, 547.14)

Bivariate analysis revealed significant differences in total cost between education levels, income brackets and UAS7 at the last visit (Table 4). However, only

the differences between income brackets remained significant in the multivariate analysis (Table 5).

The Tornado diagram (Figure 1) shows the variations in total cost associated with changes in different cost categories. These results demonstrate the potential impact of cost variations associated with medications, especially omalizumab, on the overall cost of the disease.

Discussion

Most participants in the present study were 25 to 45 years old, living and working in Rio de Janeiro, the second largest city in Brazil. The mean duration of illness was 5 years, and data collected in the initial appointments revealed that CU had a negative impact on quality of life across the entire sample. Dias et al. obtained similar findings in a study conducted in another teaching hospital in the same city: participants in that study were mostly (85.7%) female, with a mean age of 46 years, median disease duration of 10 years and mean scores of 36 on the CUQ2oL with dimension I (sleep/mental/status/eating) emerging as the most affected by the illness.¹⁴ In the study in question,

Table 3
Economic burden of chronic urticaria

Type of cost	Total (US\$)	Mean	SD	OMA	Mean	SD	No OMA	Mean	SD	p ^a
Indirect										
Transportation	3,755.69	68.28	77.00	1,525.56	127.13	104.92	2,230.13	51.86	58.95	0.007
Absenteeism	21,125.84	384.10	2,127.01	15,508.56	1,292.30	2,351.69	5,617.28	130.63	209.05	0.013
Subtotal	24,881.53	452.39	461.11	17,034.12	1,418.51	2,456.61	7,847.41	182.50	268.00	0.002
Direct										
Appointments	3,838.17	69.79	112.09	1,163.64	96.97	69.67	2,674.53	62.19	120.88	<0.00
Laboratory tests	6,607.39	120.13	63.81	1,974.00	164.50	59.53	4,633.39	107.75	58.65	0.005
Medications	174,697.58	3,176.31	6,271.71	156,367.68	13,030.64	7,546.96	18,329.90	426.27	407.19	<0.00
Omalizumab	141,582.91	2,574.23	5,925.58	141,582.91	11,798.57	7,324.10	0	0	0	
Subtotal	185,143.14	3,366.23	6,446.58	159,505.32	13,292.10	7,595.80	25,637.82	596.23	459.12	<0.00
Total	210,024.67	3,818.63	7,101.74	176,539.44	14,711.62	9,979.28	33,485.23	778.72	605.26	<0.00

^a Mann-Whitney U test compared costs between patients treated with and without omalizumab.

SD = standard deviation, OMA = costs of patients treated with omalizumab, No OMA = costs of patients treated without omalizumab.

48.2% of the sample had CSU, 22.3% had CIndU, 28.5% had chronic autoimmune urticaria (CAU), and 23.2% had CIndU alone.¹⁴ In our sample, 18% had CIndU alone and 20 (62.5%) out of 32 patients who underwent ASST tested positive for CAU.

Approximately 70% of our sample had pre-existing comorbidities, with the most prevalent being obesity and hypertension, followed by rhinitis and psychiatric disorders. Similarly, Costa and colleagues showed that 75% of patients with urticaria reported comorbidities,

Table 4
Bivariate analysis of total costs

Variable	Mean (US\$)	± SD	p ^a	Post-hoc p ^b
Gender				
Female	3,420.00	6,130.15	0.41	
Male	5,410.00	10,227.13		
Age				
0-19 years	796.48	721.00	0.21	
20-60 years	4,855.77	7,689.94		
> 60 years	4,379.89	993.46		
Skin color				
White	4,720.00	7,377.00	0.48	
Brown	1,810.00	2,981.40		
Black	4,486.93	8,088.94		
Educational level				
1) Elementary school	2,170.85	5,515.57	0.02	1 and 3; p = 0.02
2) High school	2,540.20	3,888.94		2 and 1; p = 0.98
3) Higher education	8,312.06	10,160.80		3 and 2; p = 0.76
Occupation				
Student	857.28	729.14	0.10	
Employee	6,881.40	9,073.86		
Retired	4,280.40	10,267.83		
Housekeeper	2,139.19	3,578.39		
Unemployed	1,018.00	301.50		
Family income				
1) Up to 3 minimum wages	2,378.89	4,704.00	0.00	1 and 4; p = 0.00
2) 3-5 minimum wages	1,332.16	763.81		2 and 4; p = 0.00
3) 5-10 minimum wages	7,664.00	9,418.00		3 and 2; p = 0.00
4) > 10 minimum wages	23,468.00	9,693.46		4 and 3; p = 0.01
Angioedema				
No	2,506.03	5,963.81	0.12	
Yes	5,513.06	8,166.33		
UAS7 score at last appointment (0-42)				
1) 0	1,733.11	4,048.12	0.01	1 and 5; p = 0.00
2) 1-6	3,552.28	7,312.07		2 and 5; p = 0.01
3) 7-15	2,204.38	3,319.86		3 and 5; p = 0.00
4) 16-27	4,359.66	7,255.66		4 and 3; p = 0.96
5) 28-42	17,109.02	11,711.70		4 and 5; p = 0.04

^a One-way analysis of variance, ^b Tukey test.

UAS7 = Urticaria Activity Score in the past 7 days.

with the most frequent being cardiometabolic disease (52.6%) and depression (40.4%), followed by anxiety and allergic rhinitis, each observed in 35.1% of the sample.¹⁵

All patients had pre-existing illnesses before the onset of CU. We also observed a statistically significant difference in the prevalence of psychiatric illnesses

between groups with and without omalizumab use. It is possible that severe CU may aggravate psychiatric conditions leading to higher health costs, as reported by 3 patients in our study.

In a study by Costa and colleagues, 76% of patients underwent a CBC and measurements of ESR and CRP levels, while 10.2% of patients

Table 5
Multivariate analysis

Variable	OR	95% CI		p
Educational level				
Elementary school	3.65	-14,030.3	177.58	0.05
High school	1.41	-12,431.7	3,038.24	0.23
Higher education	Reference			
UAS7 score at last appointment				
0	0.35	-12,297.7	23,236.05	0.54
1-6	0.30	-11,679.5	20,810.05	0.58
7-15	0.24	-13,046.4	21,872.13	0.62
16-27	0.53	-11,100.9	24,235.62	0.46
28-42	Reference			
Family income				
Up to 3 minimum wages	25.34	-57,995.9	-25,489.99	<0.001
3-5 minimum wages	26.41	-65,195.2	-29,200.08	<0.001
5-10 minimum wages	18.80	-51,734.5	-19,528.61	<0.001
>10 minimum wages	Reference			

OR = odds ratio, CI = confidence interval, UAS7 = Urticaria Activity Score in the past 7 days.

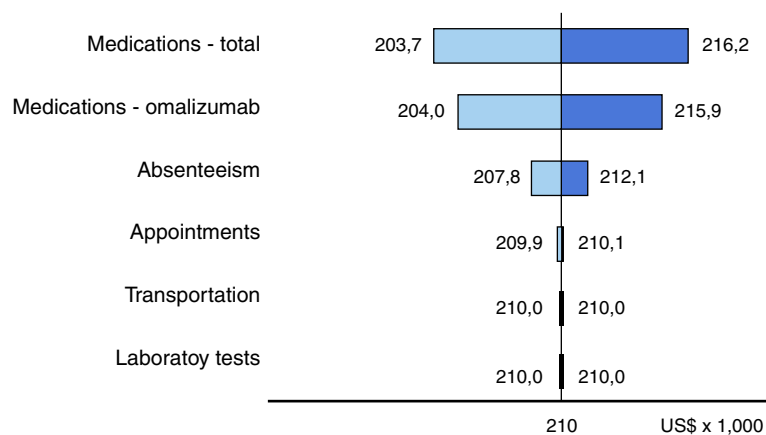


Figure 1
Sensitivity analysis: Tornado diagram

underwent skin biopsies.¹⁵ Yet in our study, all patients underwent a CBC, ESR and CRP testing as part of routine treatment. However, skin biopsies were only performed in 5% of participants, since this procedure is only indicated in atypical cases.

Antihistamines were prescribed to every patient, with second-generation drugs being the most commonly used. Cetirizine was the most frequently prescribed, followed by loratadine. Standard care with antihistamines at licensed doses was effective in 47% of patients, corroborating previous findings described in the literature, which notes that 50% of patients with CSU/CIndU achieve symptom control using standard doses.¹⁶

Short courses of oral corticosteroids (OC) over a multi-day period are recommended for patients with CIndU/CSU only if quadrupled up-titrated doses of antihistamines are ineffective.^{17,18} In the present study, 14.5% of patients received OC for short periods of time and only 1 did so for a longer period.

Direct costs were responsible for the highest share of expenses, with medication, especially omalizumab, representing the greatest expense. Due to its efficacy and safety, omalizumab is associated with a significant improvement in quality of life and reductions in absenteeism and presenteeism, though the latter was not measured in this study. From a pharmacoeconomic-societal perspective, the incremental cost-effectiveness ratio of omalizumab per quality-adjusted life years is reduced to an acceptable value.¹⁹

Maurer et al. performed a multicenter study with a 2-year evaluation period, in which 39.6% of European patients and 29.3% Central American patients sought emergency services. In our study, no patients were hospitalized during the follow-up period, although 9 were sought emergency services for symptom control, and received oral and/or injectable corticosteroids.²⁰ Costa et al. demonstrated that prior to the observational period of the study, 5.3% of patients had been hospitalized, and 50% had attended at least 1 primary care consultation.¹⁵ DeLong and colleagues found that only 1 out of 50 patients had a CIU-related hospitalization and the mean initial laboratory workup represented only 0.8% of the annual cost of illness.²¹ In our sample, the laboratory workup represented only 3.3% of total annual costs.

Indirect costs were heavily impacted by absenteeism, mainly due to visits to health care services. One patient with severe CU and angioedema

experienced a significant decrease in quality of life as a result of missed workdays, but after starting treatment with omalizumab, the symptoms were controlled and no more working days were missed.

The mean annual cost of CU in our sample was US\$ 3,818.63 per patient-year, with indirect costs accounting for 10% of this value. In 2005, DeLong et al. estimated that the total annual cost of CU in the USA was US\$ 2,047 per patient, with indirect costs accounting for 15.7% of this figure,²¹ which is a higher proportion than observed in our study. Lacour et al. found the mean total direct cost of CSU to be € 2,397 per patient-year, where the greatest expenses were treatment (€ 1,435) and inpatient costs (€ 859). The indirect costs during the 4-week period analyzed were mainly due to presenteeism (€ 421) and loss of work productivity (€ 420).²²

The financial costs of CU without the use of omalizumab were also analyzed in a study conducted in a private Latin American health organization in Buenos Aires, Argentina. The mean annual direct cost per patient was lower than that observed in this study, at US\$ 1,015 ± US\$ 752 (95% confidence interval [CI], 803-2,003).²³

In 2019, Carrilo-Martin et al. demonstrated that higher spending on complementary laboratory tests (mean of US\$ 569 ± 414) did not interfere with the diagnosis and management of CU. This finding suggests that requesting only the necessary exams for each case may be a promising cost-saving approach. Indeed, in our study in Brazil, the mean cost of examinations was much lower.²⁴

A similar study conducted in our institution estimated the mean total annual cost of asthma/rhinitis and respiratory infections at US\$ 1,276.72 per patient, with asthma alone incurring a mean annual cost of US\$ 1,140.94 per patient.²⁵ In this study, none of the patients with asthma were treated with omalizumab.

Recently, an economic analysis conducted in Brazil showed that the addition of omalizumab to standard treatment for uncontrolled severe allergic asthma and to refractory CU is cost-effective at a national level, and could feasibly be incorporated into the private healthcare system.^{26,27} The variables with the greatest impact on total cost of illness were medications (mainly omalizumab) and absenteeism.

Patients with more severe disease often require 4 times the standard dose of antihistamines, or added treatment with omalizumab, which greatly increased the cost of illness. It is important to emphasize that

approximately 60% of “good responders” discontinue antihistamine therapy. Therefore, in complete responders, omalizumab could be considered a single-drug therapy.^{28,29}

When comparing patients treated with omalizumab to the rest of the sample, we observed a significant difference in the costs of transportation, absenteeism, consultations, laboratory tests and medications. This is an important finding, as it suggests that the higher costs observed in patients treated with omalizumab are not only attributed to the drug itself, but also to indirect costs associated with a more severe disease profile, which leads to higher spending on transport, medical consultations, and laboratory testing, as well as greater absenteeism.

Although patients with higher family income have better access to education, only family income remained significantly associated with cost of illness on multivariate analysis. This may be explained by the fact that patients with a higher family income have access to newer and more expensive medications, and are not limited to the antihistamines available in the Brazilian Unified Health System (SUS), such as loratadine and cetirizine. In our study, we also found significant differences in mean family income between patients treated with omalizumab and the remainder of the sample.

On a similar note, a study performed in the United Kingdom revealed that the use of omalizumab as an adjunctive therapy to OC in patients who do not respond to the standard treatment may be a more cost-effective alternative for the National Health Service as compared to continued standard treatment alone.³⁰

Our study had some limitations, such as having been performed in a tertiary care hospital that is also a center of excellence in CU; this may have led to the recruitment of patients with more severe illnesses, whose treatment costs may not reflect that of other health care centers and regions of the country. The assessment of costs related to comorbidities and presenteeism were beyond the scope of this study, but the absence of these variables likely caused our results to underestimate the costs of CU.

Conclusion

CU resulted in significant expenses to the study population. The total estimated mean cost of the illness was US\$ 3,818.63 per patient-year. Higher

household incomes were associated with higher treatment costs. The high medication costs, especially for patients treated with omalizumab, accounted for the greatest share of the economic burden, although this treatment has been shown to be cost-effective for patients with CU refractory to high-dose antihistamine therapy.

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