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Clinical evolution of a severe asthmatics group in the use of immunobiological therapy in a Brazilian Public Hospital

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SUMMARY

OBJECTIVE: A small portion of the asthmatic population (3.6%) has severe asthma (SA), presenting high morbimortality rates and demanding more financial resources than other asthmatic populations. The use of immunobiological therapy is an effective tool in controlling symptoms, decreasing the number of exacerbations, and reducing the use of systemic corticosteroids in these patients. In Brazil, epidemiological data regarding this asthmatic population using immunobiologicals and their evolution are scarce.

METHODS: This is an observational, analytical, cross-sectional, and retrospective study. The sample consisted of adult patients with SA in follow-up at the pulmonology service of the Complexo Hospital de Clínicas of the Federal University of Paraná, from January 2011 to August 2019. The analyzed variables were as follows: the number of exacerbations that required hospitalization in the previous year, forced expiratory volume in one second (FEV1), and asthma control test (ACT) scores before and after the start of immunobiological therapy.

RESULTS: We studied 20 patients with SA using omalizumab or mepolizumab. We observed an increase in the mean ACT score of 4.8 points, a nonsignificant reduction in the number of exacerbations that required hospitalization, and a slight improvement in the FEV1. Regarding the patients using chronic systemic corticosteroid therapy, 14.2% (n=1) of patients had the medication discontinued and 57% (n=4) of patients had the dose reduced by half.

CONCLUSION: The use of omalizumab and mepolizumab as additional therapy in SA provided a significant improvement in the ACT and allowed the dose reduction of systemic corticosteroids, without significant improvement in FEV1 and in the frequency of severe exacerbations.

KEYWORDS: Asthma. Omalizumab. Mepolizumab.

INTRODUCTION

Asthma is a highly prevalent chronic disease, currently affecting approximately 339 million people worldwide and 20 million Brazilians[1-3]. Of note, 3–10% of asthmatics have severe asthma (SA), consuming six times more resources than those who have mild and moderate asthma, accounting for 50–60% of the total costs of asthma treatment[4-6].

According to a Dutch population study, only 3.6% of asthmatics have SA[7], which, according to the criteria of the 2014 ATS/ERS document[4], is defined as asthma that remains symptomatic and with exacerbations even with high doses of inhaled corticosteroids, along with the association of one or more therapeutic classes after excluding the main noncontrol factors[6].

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SA imposes great suffering on these patients who remain symptomatic, exacerbating and losing lung function, even after diagnostic confirmation, treatment of associated comorbidities, adherence and drug compliance, correct technique for using inhaler devices, and the use of high glucocorticoid doses associated with other therapeutic options[6,8,9]. Moreover, these patients suffer from the side effects of medications, have a high mortality rate, and have profound negative consequences in their psychological, physical, and social dimensions[10].

New therapeutic options have emerged in recent years for this specific group of asthmatics, such as omalizumab, commercialized in Brazil since 2004, which is a recombinant humanized monoclonal antibody anti-immunoglobulin E (IgE) that acts in the inflammatory process of allergic asthma, improving the quality of life, decreasing the number of exacerbations, and reducing the need for using systemic corticosteroids[11,12].

In 2017, mepolizumab, which is a humanized monoclonal anti-interleukin 5 (anti-IL5) antibody that acts by reducing the number of systemic eosinophils in severe eosinophilic asthmatics, was approved for commercialization in our country[13]. The consequent decrease in the eosinophilic inflammation of the airways has a positive impact not only on increasing the quality of life and lung function but also on decreasing exacerbations and the use of oral corticosteroids[14].

Despite being already used for treating SA and suggested as a therapeutic option in step 5 of the asthma treatment in the Global Initiative for Asthma (GINA) document of 2019[2], studies that evaluate the effectiveness of these medications in "real life" are scarce and thus necessary.

Through an observational and retrospective study, we assessed 20 patients with SA who were treated with omalizumab and mepolizumab from January 2011 to August 2019 at the asthma outpatient clinic of the Complexo Hospital de Clínicas of the Federal University of Paraná (CHC-UFPR).

METHODS

The asthma outpatient clinic at the Complexo Hospital de Clínicas of the Federal University of Paraná (CHC-UFPR) was created in 2002 and is a reference for the treatment of this disease in the State of Paraná, Brazil. A total of 1,071 patients diagnosed with asthma are accompanied at this outpatient clinic, and 32 of them have SA (Table 1); however, only 22 patients were eligible to use immunobiologicals (omalizumab or mepolizumab), according to the criteria shown in Tables 2 and 3.

Inclusion criteria were as follows: patients aged above 18 years; patients with a minimum follow-up period of 6 months; patients diagnosed with SA that remained uncontrolled in spite of the optimized therapy in steps 4 or 5 of the GINA; and patients who needed systemic corticosteroids for more than 50% of the days of the year[4].

Uncontrolled asthma criteria (Table 2) consisted of the asthma control test (ACT) score lower than 20 points, as well as one or more exacerbations of asthma in the previous year[4], in addition to fulfilling the necessary criteria for the use of omalizumab or mepolizumab (Tables 3 and 4)[15,16].

Two patients were excluded from this study: one for having started omalizumab in another service and the other for having less than 12 weeks of the use of mepolizumab.

We analyzed the pre-bronchodilator forced expiratory volume in one second (FEV1) percentage predicted, the scores in the ACT, the number of severe exacerbations that required hospitalization in the previous year, and the use of systemic corticosteroids before and 1 year after initiating omalizumab.

Since the use of mepolizumab is recently studied in our service, we took into consideration the period of 12 weeks of the use of this medication for the analysis of variables.

The results of quantitative variables were described as mean, standard deviation, median, and minimum and maximum values. Categorical variables were described by frequency and percentage.

Student's *t*-test for paired samples or the nonparametric Wilcoxon test were used to compare both assessments (before and after the use of the immunobiological) in relation to quantitative variables. The normality condition was analyzed by using the Kolmogorov-Smirnov test. p values <0.05 indicated statistical significance. The data were analyzed using the computer program Stata/SE v.14.1. StataCorpLP, USA.

This study was approved by the Research Ethics Committee of CHC-UFPR, approval number 03076918.0.0000.0096.

RESULTS

From all the 1,071 asthmatics, we evaluated 20 patients who had SA and who were using immunobiologicals in the period ranging from January 2011 to August 2019. The majority were females, consisting of 15 (75%) patients, and in 7 patients (35%), the onset of asthma occurred in their childhood. Only two patients (10%) had a history of low smoking load (≤5 pack-years) and more than 15 years of smoking cessation (Table 1).

Regarding comorbidities, 11 patients had (55%) allergic rhinitis and 9 (45%) patients had gastroesophageal reflux disease (GERD); the mean body mass index (BMI) was 29.8 (±5), and nine patients (45%) were obese (BMI≥30) (Table 1).

In addition to treating comorbidities, both the therapeutic adherence and the correct use of the inhaler device were also routinely checked when possible.

Table 1. Basic characteristics of patients.

Variable	Valid n	Classification	Result*
Age (years)	20		49.2±11.7 (29–72)
Body mass index (kg/m^2)	20		29.8±5.0 (21.2–39.7)
SpO_2	20		95.5±2.2 (91–99)
Eosinophils (number)	20		369±271 (0–1062)
Eosinophils (%)	20		4.2±2.6 (0–10)
Total immunoglobulin E	20		472±340 (50–1244)
Asthma in childhood	20	No	13 (65)
		Yes	7 (35)
Osteoporosis	20	No	17 (85)
		Yes	3 (15)
Diabetes	20	No	18 (90)
		Yes	2 (10)
High blood pressure	20	No	14 (70)
		Yes	6 (30)
Rhinitis	20	No	9 (45)
		Yes	11 (55)
Gastroesophageal reflux disease	20	No	11 (55)
		Yes	9 (45)
Smoking load (pack years)	20	0	18 (90)
		3	1 (50)
		5	1 (50)
Active smoker	20	No	20 (100)
		Yes	0 (0)
Cessation (years)	20	0	18 (90)
		17	1 (50)
		20	1 (50)
Use of long acting muscarinic antagonist	20	No	8 (40)
		Yes	12 (60)
Use of leukotriene inhibitor	20	No	16 (80)
		Yes	4 20)
Use of systemic corticosteroid before the use of immunobiological therapy	20	No	13 (65)
		Yes	7 (35)
Prednisone dose	7	5	1 (14.3)
		10	1 (14.3)
		20	1 (14.3)
		30	1 (14.3)
		40	2 (28.6)
		60	1 (14.3)
Use of systemic corticosteroid after the use of immunobiological therapy	20	No	14 (70)
		Yes	6 (30)
Prednisone dose	6	5	2 (33.3)
		10	2 (33.3)
		20	1 (16.7)
		60	1 (16.7)
Use of omalizumab	20	No	3 (15)
		Yes	17 (85)
Use of mepolizumab	20	No	17 (85)
		Yes	3 (15)

*Described by mean±standard deviation (minimum–maximum) or by frequency (percentage).

Table 2. Criteria to define severe asthma (SA).

SA (use of >800 µg/day of inhaled budesonide or equivalent):
√ In regular use of long-acting beta-2-agonist
√ ACT <20 points
√ At least one exacerbation requiring hospitalization in the previous year or need for using systemic corticosteroid for more than 50% of the days of the year

Table 3. Eligibility criteria for the use of omalizumab.

√ Adults over 18 years old, with adherence to the treatment, with a follow-up period longer than one year, and diagnosed with SA
√ Allergic asthma, diagnosed by allergic skin test
√ Weight between 30 and 150 kg
√ Total serum IgE between 30 and 1,500 IU/mL

Table 4. Eligibility criteria for the use of mepolizumab.

√ Adults above 18 years old, with adherence to the treatment, with a follow-up period longer than 1 year, and diagnosed with SA
√ Serum eosinophil count ≥150 cells/mm^3 in the screening, or eosinophils ≥300 cells/mm^3 in previous 12 months

All patients were regularly using high-dose inhaled corticosteroids (>800 µg budesonide per day, or equivalent) and long-acting beta-2-agonist; 12 patients (60%) were on regular use of long-acting antimuscarinic, 16 (80%) patients were using a leukotriene inhibitor, and 7 (35%) patients were using systemic corticosteroids, of which 71.5% of patients were on 20 mg of prednisone/day or more (Table 1).

Seventeen patients (85%) were eligible for using omalizumab (Table 3); however, 3 (17%) of them had the drug discontinued after one year of follow-up due to therapeutic failure. The dose was prescribed according to the label indication in the medication package insert, taking into consideration the body weight and serum IgE at the beginning of the treatment. In case of more than 10% of the change in the patient's body weight, the dose was adjusted accordingly.

The analyzed data of two patients were incomplete, missing FEV1 for the first patient and ACT score for the second.

Three patients (15%) were eligible to use mepolizumab, according to the criteria described in Table 4. In this case, the variables were assessed at the beginning and after 12 weeks of using this medication.

The mean pre-bronchodilator FEV1 percentage predicted was 47.3% (27.3–129%), and the mean number of exacerbations requiring hospitalization in the previous year was 1.8 (0–5). The mean ACT before the intervention was 10.5 (4.2–17).

After the use of immunobiologicals, we observed a slight increase in the absolute FEV1 and in the percentage predicted, but without statistical significance (p=0.111).

The mean number of severe exacerbations requiring hospitalization dropped from 1.8 to 1.1, a decrease of 0.7, however, with p value=0.191.

The ACT score presented the most significant change among all the analyzed variables, with a mean increase of 4.8 points (5.8–18) and with the value of p=0.001, as shown in Figure 1. Initially, seven patients were chronically using systemic corticosteroids; for one patient, we were able to discontinue the use of prednisone, and for four others, the medication was half dosed (Table 5).

DISCUSSION

Studies regarding omalizumab and mepolizumab for the treatment of SA show, as outcomes, decrease in the number of exacerbations, as well as improvement in quality of life, decrease in symptoms, reduction in the dosage, or discontinuing of chronic use of systemic corticosteroids. The results regarding the improvement in lung function are still controversial, and there is no compelling evidence that the use of immunobiologicals results in a significant increase in lung function[13-16].

In our study, we observed significant improvement in asthma control with the use of immunobiologicals, with a mean increase of 4.8 points in the ACT score (Figure 1). There was a nonsignificant reduction in the number of severe exacerbations

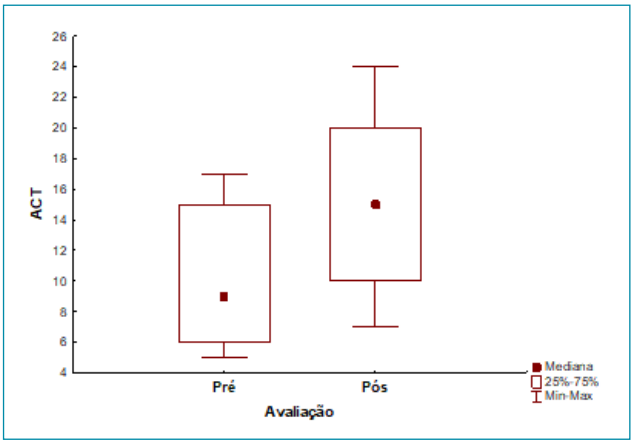

Figure 1. Evolution of the asthma control test before and after the use of immunobiological therapy.

Table 5. Evaluation of variables: number of severe exacerbations in the previous year, forced expiratory volume in one second, and asthma control test score before and after the use of immunobiological therapy.

Variable	Evaluation	n	Mean	Standard deviation	Median	Minimum	Maximum	p*
Number of severe exacerbations in the previous year (requiring hospitalization)	Before	20	1.8	1.7	1	0	5	0.191
	After	20	1.1	1.4	0.5	0	5	
	Difference	20	-0.7	2.2	-0.5	-5	3	
FEV1 (N°)	Before	19	1.3	1.3	0.4	0.6	2.5	0.093
	After	19	1.5	1.3	0.5	0.8	3.8	
	Difference	19	0.2	0	-0.5	0.5	1.8	
FEV1 (%)	Before	19	47.3	46	15	16.4	88	0.111
	After	19	54.6	46	16	27.3	129	
	Difference	19	7.3	1	-14	19	62	
ACT	Before	19	10.5	9	5	4.2	17	0.001
	After	19	15.3	15	7	5.5	24	
	Difference	19	4.8	3	-2	5.8	18	

*Student's *t*-test for paired samples or nonparametric Wilcoxon test, p<0.05. FEV1: forced expiratory volume in one second; ACT: asthma control test.

(requiring hospitalization) and a reduction in the total dose of systemic corticosteroids. We did not observe a significant increase in FEV1. These findings have already been shown in other Brazilian studies that used omalizumab to treat SA, whose main results were the improvement of symptoms and of quality of life[17,18].

It is worth noting that, although small, the group of patients with SA in this study share similar characteristics (Table 1) with the large cohorts of severe asthmatics (TENOR II and U BIOPRED), having a predominance of females, high BMI scores, and low FEV1[10,19].

The unavailability of endotype biomarkers[20], such as FeNo[21], periostin[22], and sputum eosinophils[23], for patients with SA in this study may have influenced our results regarding therapeutic effectiveness, since a better understanding of the inflammatory pathway of asthma influences the decision of using not only the immunobiologicals but also its choice.

Due to the high cost of immunobiologicals, creating a regional database for longitudinal studies regarding this small group of asthmatics is necessary in order to provide more evidence of cost-effectiveness and long-term safety[24].

CONCLUSION

With an adequate indication, the use of omalizumab and mepolizumab in the study population provided a significant improvement in asthma control, as measured by the ACT; however, there was no significant change in the frequency of exacerbations with the need for hospitalization, as well as no significant change in FEV1.

AUTHORS' CONTRIBUTIONS

LMR: Conceptualization, Data curation, Formal analysis, Investigation Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RSMS:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **DD:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **JS:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **GLL:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **MFRQF:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **FMC:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Visualization, Writing – original draft, Writing – review & editing.

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