

# Impact of omalizumab in children from a middle-income country with severe therapy-resistant asthma: A real-life study

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## Abstract

**Background:** Severe asthma in children is a global health problem. Severe therapy-resistant asthma (STRA) in children is a major clinical challenge due to persistent symptoms despite high doses of corticosteroids and results in high public health costs. Omalizumab (anti-IgE monoclonal antibody) has been described as an effective add-on therapy in these patients. The characteristics of children with STRA from low- and middle-income countries have scarcely been reported, and no real-life study has been published on the effects of omalizumab in this group of patients. The aim of our study is to report the first clinical real-life experiences with omalizumab in Brazilian children with STRA.

**Methods:** Children (6-18 years old) from a referral center who were diagnosed with STRA were included in this retrospective study based on our clinical databases. The included children had undergone at least 6 months of omalizumab treatment and fulfilled the following initial criteria: 1) >6 years old; 2) a positive skin-prick test for at least one aeroallergen; and 3) a serum total IgE level between 30 and 1500 IU/mL. Clinical and lung function variables were analyzed before and after treatment.

**Results:** Fourteen children (mean age: 11.9 years; percentage female: 72%) were included in this study. Omalizumab treatment significantly increased control of the disease according to a standardized questionnaire administered at every visit ( $P < 0.0001$ ), ceased hospitalizations in 70% ( $P = 0.02$ ) of patients, and allowed 8/9 (89%) patients to be weaned off oral steroids ( $P = 0.004$ ).

**Conclusions:** In this retrospective report, the use of omalizumab in Brazilian children with STRA significantly improved disease control, decreased hospitalizations, and allowed suspension of continuous oral corticosteroids.

## KEYWORDS

allergy, anti-IgE, atopy, monoclonal antibody, severe asthma

## 1 | INTRODUCTION

Asthma is the most common chronic disease in children, with a high prevalence and high morbidity in many populations. Asthma is a major public health concern, particularly in low- and middle-income

countries (LMICs), with significant direct and indirect costs to society.<sup>1</sup> Although severe asthma cases account for 5-10% of the patients in most populations, this end of the disease spectrum accounts for the largest burden of illness and highest healthcare costs.<sup>2</sup>

Severe asthma is a clinical challenge that requires a careful management protocol. After properly managing the basic characteristics of treatment (adherence to treatment, inhaler technique, and modifiable comorbidities and environmental factors), the diagnosis of true severe therapy-resistant asthma (STRA) is then made.<sup>2,3</sup> This particular group of patients usually requires Global Initiative for Asthma (GINA) step five therapy in which the preferred choice is omalizumab (anti-IgE monoclonal antibody).<sup>4</sup> The clinical responses and safety of omalizumab have been studied in children with severe asthma in clinical trials during the last decade, which have shown reductions in exacerbations, improvements in asthma control, and a steroid-sparing effect.<sup>5–7</sup> One real-life French multicenter study showed that omalizumab had a significant impact on exacerbations, hospitalizations, and asthma control in children with severe asthma.<sup>8,9</sup>

No published real-life study has shown the impact of omalizumab treatment in children with STRA from LMIC populations. The importance of such a study is that given the high cost of omalizumab, it is necessary to assess real-life clinical responses to treatment in countries with limited resources. Importantly, asthma is a major public health problem in Latin America, which includes countries with some of the highest prevalences of asthma among children worldwide.<sup>10,11</sup> In Brazil, a continental country, the prevalence of asthma in schoolchildren is between 11% and 29%, with a high proportion of severe cases (approximately 10%) and a large burden of disease.<sup>12–14</sup> We have recently reported the clinical characteristics of Brazilian children with STRA.<sup>15</sup> Omalizumab has been prescribed in clinical practice for children with STRA in Brazil in some referral centers but has not yet been approved and provided by the public health care system. Therefore, the aim of our study is to report the first real-life clinical experiences with omalizumab in children with STRA from a tertiary service.

## 2 | METHODS

We selected children aged 6–12 years who were referred to our center with a diagnosis of problematic asthma. Children with a confirmed diagnosis of STRA were considered for omalizumab treatment. All of these children underwent our clinical protocol for the diagnosis of this condition based on the ERS/ATS criteria.<sup>2</sup> Briefly, cases of asthma that required GINA step 4–5 medications (inhaled corticosteroids (ICS) with long-acting beta-2 agonists associated with a leukotriene modifier or daily oral corticosteroid (OCS)) to prevent the disease from becoming uncontrolled or cases that remained uncontrolled despite this therapy were selected. Lack of disease control was defined as the presence of poor symptom control (according to the GINA criteria for control of disease),<sup>4</sup> >2 severe/serious exacerbations in the previous year (with use of an OCS or hospitalization), or persistent airflow limitation (post-bronchodilator  $FEV_1 < 80\%$ ). Children with modifiable factors that could be addressed during clinical follow-up

(eg, nonadherence to treatment, inadequate inhalation technique, relevant environmental factors, or treatable comorbidities) or who had other chronic diseases (eg, cystic fibrosis, congenital cardiac diseases, neurological disorders or immunodeficiencies) were excluded. At every clinic visit, inhaler technique was assessed, and adherence to treatment was checked by dose counting from metered dose inhalers or dry powders that were being used by the patients. Omalizumab was then prescribed for children with 1) a diagnosis of STRA; 2) a positive skin-prick test for at least one allergen; and 3) a total serum IgE level between 30 and 1500 UI/mL. All subjects were followed in our center for at least 6 months before the first omalizumab prescription, unless they were referred by another tertiary center with an adequate previous diagnostic workup in which case this period could be shortened to 3 months.

All data were retrospectively collected from standardized patient files that were recorded in a database at each clinic visit. The variables assessed included clinical history, medications, assessment of disease control during clinic visits, hospitalizations, and spirometry results. The history of exacerbations was not included in the analysis because many episodes between clinical visits were reported by parents, which may lead to a lack of precision in diagnoses based on this type of retrospective report. Basal (at the first visit to the referral center) and post-omalizumab (approximately 6 months after the first administration) spirometry measurements were performed (Koko equipment; Ferraris Respiratory, Louisville, CO) according to the ERS/ATS criteria,<sup>2</sup> and the  $FEV_1$ ,  $FEV_1/FVC$  ratio, FVC and  $FEF_{25–75\%}$ , pre- and post-bronchodilator (400 µg of salbutamol) were analyzed. The bronchodilator response was considered positive when the post-bronchodilator  $FEV_1$  increased by more than 12%.<sup>16</sup> Reference values for lung function were based on the Global Lung Function Initiative (GLI 2012) and were presented as Z-scores.<sup>17</sup> Sensitization to allergens was assessed by skin-prick tests to the following aeroallergens: *D. pteronyssinus*, *D. farinae*, *B. tropicalis*, cockroach, mold, cat and dog dander, grass and *A. fumigatus* (ALK-Abelló, Denmark). A positive test was defined by a wheal  $\geq 3$  mm in the absence of a positive reaction to the negative control for at least one of the allergens tested. Obesity and overweight status were classified according to the Centers for Disease Control and Prevention (CDC) criteria through body mass index (BMI) Z-scores and were adjusted for both gender and age.<sup>18</sup> Corticosteroid responsiveness was evaluated by assessing improvement in disease control with the GINA criteria (from uncontrolled or partially controlled disease to controlled disease) after a complete course of prednisolone (1 mg/kg/day) for 14 days. The use of an OCS for the assessment of a steroid response was justified because intramuscular triamcinolone acetonide is not provided by the public health care system in Brazil. After corticosteroid responsiveness was assessed, doses of medications were clinically optimized, and only those patients who were not responsive to corticosteroids or who required daily OCSs for clinical control were candidates for omalizumab treatment. Induced sputum and forced

exhaled nitric oxide (FeNO) measurements were performed in some patients but did not follow a strict protocol in our center during the studied period; therefore, these measurements were not included in the final analysis.

Our primary outcome for assessing the omalizumab response was asthma hospitalization. Secondary outcomes included control of the disease (assessed with GINA criteria, defined during clinic visits),<sup>4</sup> dose of ICS standardized as fluticasone propionate equivalent-dose per day, OCS cessation, and lung function measurements. Before omalizumab treatment, disease control was assessed for at least three visits. Asthma control was assessed at every clinical visit in our referral center using the four asthma symptom control questions of the GINA report.<sup>4</sup> After the first omalizumab prescription, all subjects were followed for at least 12 months.

The study was approved by the Research Ethics Committee (#1.309.540) of our institution, and all parents signed an informed consent form authorizing the use of clinical data for the study.

## 2.1 | Statistical analysis

Categorical data, including the descriptive data, are presented as absolute and relative frequencies. Continuous variables are shown as the mean and standard deviation (SD) or the median and interquartile range. Comparisons between pre- and post-treatment time points were analyzed using a McNemar *t*-test or paired *t*-test. A *P*-value <0.05 was considered significant. All analyses were performed and graphs were generated using Prism 6.0 (GraphPad Software, Inc., La Jolla, CA).

## 3 | RESULTS

Fourteen children were included (mean age:  $9.2 \pm 1.8$  years, four males). The mean length of omalizumab treatment was  $27 \pm 16$  months. All patients were followed for more than 12 months. Nine (64%) patients were steroid-responsive and required long-term OCS treatment until the first omalizumab administration. All children had normal or mild airway obstruction during the basal lung function tests. House dust mite was the most common positive allergen detected, and *A. fumigatus* testing was negative for all subjects. The clinical characteristics of the patients are presented in Table 1.

Most children (10/14, 72%) had been hospitalized with STRA in the year prior to initiation of omalizumab therapy. Hospital admissions were significantly reduced after omalizumab treatment (reduced by 70%; *P* = 0.016). The percentage of time with the disease controlled during clinical follow-up also improved more than 90% after treatment with omalizumab (*P* < 0.0001) (Figure 1). OCSs were discontinued in 8/9 (89%; *P* = 0.008) patients. Patients who were under daily OCS therapy received 5–10 mg/day of prednisolone. The eight patients using this therapy were weaned off of continuous OCSs before 6 weeks of omalizumab therapy was initiated. However, the mean daily

**TABLE 1** Characteristics of the children included with severe therapy-resistant asthma

| <i>n</i> = 14                                     |                        |
|---------------------------------------------------|------------------------|
| Age, years                                        | 9.2 ± 1.8              |
| Gender, female                                    | 10 (72.6)              |
| Allergic diseases                                 |                        |
| Rhinitis                                          | 14 (100)               |
| Dermatitis                                        | 2 (14)                 |
| Serum total IgE (UI/mL)                           | 529 (316–1206)         |
| Medications                                       |                        |
| Inhaled corticosteroid dose <sup>a</sup> (μg/day) | 500 (400–500)          |
| LABA                                              | 14 (100)               |
| Oral corticosteroid                               | 9 (64)                 |
| Montelukast                                       | 7 (50)                 |
| Skin-prick test                                   |                        |
| <i>D. pteronyssinus</i>                           | 11 (78)                |
| <i>D. farinae</i>                                 | 11 (78)                |
| <i>B. tropicalis</i>                              | 8 (57)                 |
| Grass                                             | 2 (14)                 |
| Mold                                              | 1 (7)                  |
| Cockroach                                         | 1 (7)                  |
| Cat                                               | 1 (7)                  |
| Dog                                               | 0 (0)                  |
| Overweight/Obesity                                | 6 (42)                 |
| History of hospitalization                        | 10 (71)                |
| Baseline lung function <sup>b</sup>               |                        |
| FEV <sub>1</sub>                                  | −0.72 (−1.79–0.64)     |
| FVC                                               | 0.32 (−1.34–1.25)      |
| FEV <sub>1</sub> /FVC ratio                       | −1.16 (−1.67 to −0.61) |
| FEF <sub>25–75%</sub>                             | −1.23 (−2.22–0.17)     |
| Bronchodilator response (FEV <sub>1</sub> > 12%)  | 6/10 (60)              |

LABA, long-acting beta-2 agonist; FEV<sub>1</sub>, forced expiratory volume in the first second; FVC, forced vital capacity; FEF, forced expiratory flow.

Variables expressed by mean and standard deviation or absolute number and percentage.

<sup>a</sup>Fluticasone equivalent dose.

<sup>b</sup>Reference values of lung function are based on the Global Lung Function Initiative (GLI 2012; *n* = 10).<sup>17</sup>

dose of ICS was not significantly reduced after omalizumab treatment (pre: 492.8 μg/day; post: 407.1 μg/day) (Figure 2). Finally, lung function was not significantly changed by omalizumab treatment for all variables analyzed (FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, FVC, and FEF<sub>25–75%</sub>). We excluded four subjects from the lung function analysis because basal spirometry showed either inadequate or non-reproducible flow-volume curves. Only one patient, after an initial good clinical response to omalizumab, presented with severe uncontrolled disease again after 9 months of treatment. After a complete clinical reassessment, omalizumab was discontinued in this patient by the medical team.

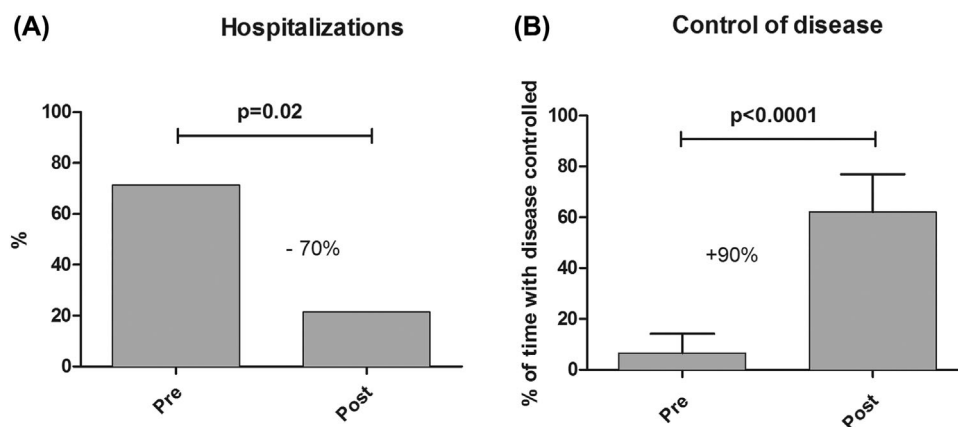


**FIGURE 1** Impact of omalizumab on hospital admissions and disease control in children with severe therapy-resistant asthma ( $n = 14$ ). Disease control was assessed according to the GINA questionnaire at every clinical visit.<sup>4</sup>

## 4 | DISCUSSION

This is the first real-life retrospective report on the impact of omalizumab in 14 children with STRA from a LMIC population. We have shown that omalizumab significantly decreased the number of hospitalizations, lowered the use of continuous OCSs and improved control of the disease in these children. Brazil is the largest country in Latin America and has a high prevalence of pediatric asthma and severe disease, particularly in large urban centers.<sup>12–14</sup> We have recently shown that the burden of asthma in Brazilian children is large, with a high prevalence of the disease (20%), and nearly half of the patients present with uncontrolled disease and a high number of hospitalizations (7.5% of subjects studied in the previous year).<sup>14</sup>

Children with STRA are at the end of the disease severity spectrum and are a major clinical challenge for tertiary services. These children are poorly responsive to high-dose ICSs even when they are given with other controller medications. Although the subjects were predominantly female in this small sample report of patients using omalizumab, our patients are predominantly schoolchildren with atopic severe asthma, are poorly responsive to steroids, and present with heterogeneous airway inflammatory patterns and mild airflow

obstruction or nearly normal lung function.<sup>15</sup> The clinical phenotypes of our patients with severe asthma are similar to those of patients from developed countries.<sup>15,19,20</sup>

Omalizumab has been shown to be an effective add-on therapy for children with atopic STRA.<sup>5–7</sup> More recently, one real-life French multicenter report has shown a greater positive impact on exacerbations and hospital admissions in children with STRA followed for 1 to 2 years.<sup>8,9</sup> Our real-life results in Brazilian children with STRA show that the impact on hospitalizations, disease control and reliance on oral steroids is quite significant, and these findings are similar to those observed in the published French study. Omalizumab reduced hospital admissions by 70% compared with the 88.5% reduction found in the French study (1-year follow-up). Only one patient from our study was maintained on regular OCSs despite omalizumab treatment, and control of the disease was significantly increased (by 90%). Overall, omalizumab was effective in 13/14 (92.8%) of our patients.

Given the high cost of biologic therapies, our results support the choice of a GINA step 5 approach with the use of omalizumab, showing for the first time the large clinical effect in this group of patients from a LMIC setting. It is important to note that some of our patients, prior to omalizumab treatment, had a history of >5 hospitalizations per year,

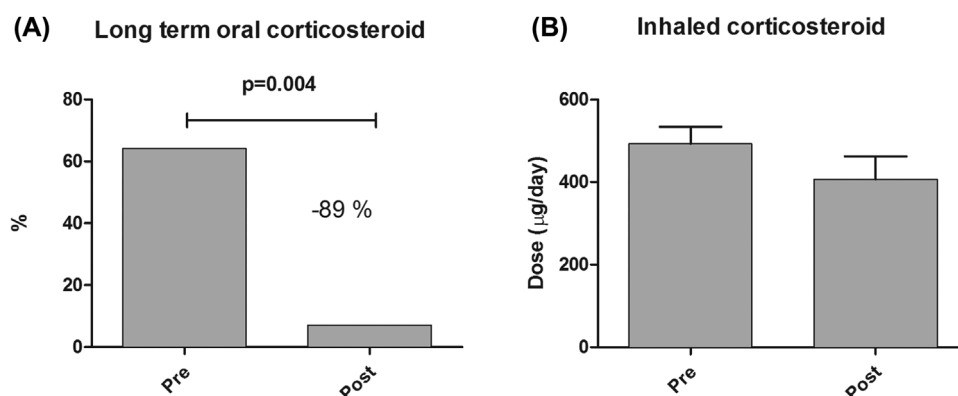


**FIGURE 2** Discontinuation of long-term oral steroids ( $n = 9$ ) and changes to inhaled corticosteroid doses after treatment with omalizumab in children with severe therapy-resistant asthma ( $n = 14$ )

and most patients exhibited uncontrolled disease even between exacerbations (data not shown). Most of our patients were sedentary, experienced high school absenteeism, and had frequent exacerbations.<sup>14,15</sup> Therefore, omalizumab is currently the best therapeutic alternative that positively influences the quality of life of children with atopic STRA. Even though we did not aim to assess cost-effectiveness issues in the population we studied, the results are so clinically impressive that we hope that this report can help change the reality for these patients in this region.

Other secondary outcomes analyzed were not significantly changed by omalizumab treatment. ICS doses remained unaltered after omalizumab treatment. Although all subjects underwent a step-down approach trial every three months in our center, this finding might be explained by the short follow-up period of the study. The influence of subjective clinical decisions to reduce the dose of ICS by the medical team may have also played some role. Thus, we believe that although omalizumab was effective for OCS cessation, most subjects continued to receive a stable medium ICS dose after treatment. Lung function was also not significantly changed by omalizumab treatment. Previous studies have shown that lung function in children with asthma is not a good marker of severity of disease and is less compromised than in adult patients.<sup>21,22</sup> Importantly, the basal lung function values of our patients were also not markedly reduced;<sup>15</sup> therefore, we believe that lung function in children with STRA is not an outcome that can be improved with omalizumab or other novel add-on therapies.

Our study has some limitations. First, our data were retrospectively collected. This may affect the quality of some recorded variables. We did not have a standardized number of clinical visits for assessment of disease control. However, this was not used as our primary outcome. Additionally, hospital admissions, our primary outcome, are easy to collect retrospectively from clinical charts and are not dependent on parental recall. Second, our sample size is not large. Given that children with STRA are not common and that only some of these patients receive omalizumab, these types of real-life findings should be considered valuable evidence that needs to be reported. In addition, a control group would have more precisely addressed our main objective, but this would not reflect an ideal real-life clinical setting, and ethical issues would be raised for not prescribing omalizumab to children with STRA. Finally, steroid responses and adherence to treatment were not assessed with intramuscular corticosteroid and electronic monitoring, respectively. Including these assessments would be ideal, but this is not practically feasible in many settings, especially in LMICs. Given that intramuscular triamcinolone is not available in our public health care pharmacy and that electronic inhalers for monitoring adherence to treatment are still expensive and not widely available, a careful "real-life" clinical evaluation is the most ideal practical approach.

In conclusion, we show that in a real-life clinical setting, omalizumab is a key treatment modality for children with STRA in our LMIC population. It significantly reduced the burden of disease and exerted a substantial impact in a short period after initiation of therapy by

decreasing hospital admissions, increasing disease control, and decreasing reliance on oral steroids. Finally, further studies are required to evaluate the real-life cost-effectiveness of omalizumab in children with STRA from LMIC populations.

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