

Systemic reaction rates with omalizumab, subcutaneous immunotherapy, and combination therapy in children with allergic asthma

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ABSTRACT

Background: For children with moderate-to-severe persistent allergic asthma, omalizumab is effective. However, it is expensive, and there are no current guidelines for discontinuation. Subcutaneous immunotherapy (SCIT) is the only approach that can provide persistent beneficial effects after treatment is discontinued. However, SCIT is contraindicated in poorly controlled asthma. Therefore, we performed, to our knowledge, the first U.S. study that exclusively compared the safety of omalizumab, SCIT, and combination (omalizumab and SCIT) therapy in children with allergic asthma.

Objective: We hypothesize that the systemic reaction (SR) rates in children who receive combination therapy are comparable with omalizumab alone.

Methods: We performed a retrospective study of children ages 6–18 years old with allergic asthma who, from July 2010 to June 2017, received SCIT, omalizumab, or combination therapy in our children's allergy clinic. Our primary end point was to determine the SR rate among each of these groups.

Results: We reviewed the records of 89 patients: 30 patients with SCIT (1550 injections), 30 patients with omalizumab (729 injections), and 29 patients with combination therapy (954 injections). In the SCIT group, 19 SRs (1.2% of injections) occurred in 10 patients (33%). In the omalizumab group, three SRs (0.4% of injections) occurred in three patients (10%). Similarly, in the combination group, three SRs (0.3% of injections) occurred in three patients (10%). Compared with the SR rate in the SCIT group, both omalizumab and combination groups had significantly lower SR rates ($p = 0.045$ and $p = 0.011$, respectively). The SR rates in children who received omalizumab and children who received combination therapy were not statistically different ($p = 0.73$).

Conclusion: Children with moderate-severe persistent allergic asthma who received omalizumab or combination therapy had significantly lower SR rates compared with children with allergic asthma who received SCIT alone. SCIT in children treated with omalizumab was safe and may serve both as an omalizumab-sparing treatment and as a bridge to safely administer SCIT.

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Asthma is one of the most common chronic diseases of childhood, with the latest estimated prevalence of ~10% in the United States.¹ Children with moderate-severe asthma often have exacerbations, which may be associated with the loss of lung function, limitation in activity, hospital admissions, and time lost from school.^{1–4} Fifty percent of patients with severe asthma have allergic asthma, which is characterized by elevated levels of immunoglobulin E (IgE).^{5,6} For children ≥ 6 years of age and with moderate-to-severe persistent allergic asthma, the National Asthma Education and Prevention Program (NAEPP) guide-

lines⁷ recommend adding omalizumab, which is a recombinant humanized anti-IgE antibody. Recent literature reviews of children with asthma demonstrated that omalizumab was not only well tolerated but also decreased inhaled corticosteroid use; decreased the use of rescue medication; improved the forced expiratory volume in the first second of expiration (FEV₁); and reduced health care resource utilization, including fewer hospitalizations, emergency department visits, and unscheduled medical visits.^{8,9} Although omalizumab is safe and effective, it is expensive, and there are no current guidelines for discontinuation.^{10,11}

Subcutaneous immunotherapy (SCIT) is an alternative therapy in those with allergic asthma and is associated with a reduction in symptom scores and medication requirements.^{12,13} It represents the only approach capable of modifying the immune system to provide beneficial effects that persist for years after treatment is discontinued.¹⁴ Most experts recommend stopping SCIT after 5 years of therapy. Because SCIT offers both the potential for immunomodulation and an end point in therapy, this modality is intriguing as

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an adjunct to omalizumab or as an approach to discontinue omalizumab. However, given the potential for severe reactions in individuals with symptomatic asthma, experts do not recommend starting SCIT in individuals with unstable or severe asthma. Therefore, it is important to establish the safety of omalizumab pretreatment, followed by SCIT for this patient population.

Although there are a few European studies that have studied the safety of this combination in children with allergic asthma, SCIT in Europe is drastically different from SCIT in the United States. SCIT with regard to schedule, standardization of extracts, treatment formulation, extract type, and approach to patients who are polyallergic.^{15,16} There is no U.S. literature, to our knowledge, that compares adverse reactions of SCIT, omalizumab, and combination therapy in children with allergic asthma. We hoped to show that the rate of systemic reactions (SR) with omalizumab and SCIT combination (SCIT and omalizumab) is comparable with omalizumab alone. In addition to the cost benefits of discontinuing omalizumab, the findings in this study can help determine the role of SCIT in the treatment plan for children with persistent allergic asthma.

METHODS

Study Population and Statistical Analysis

An institutional review board of the University of Texas Southwestern Medical Center approved a retrospective chart review (STU 062017-088), which was conducted of children (ages 6–18 years) treated for allergic asthma between July 2010 and June 2017, in the allergy and immunology outpatient clinic at the University of Texas Southwestern Medical Center in Dallas, Texas. Children between 6 and 18 years old with allergic asthma and with complete electronic medical records were included and categorized into one of the following three groups based on their therapy: SCIT alone, omalizumab alone, or combination (SCIT and omalizumab) therapy. We matched the number of patients in the SCIT-alone and omalizumab-alone groups to the number in the combination group ($n = 29$), which had the least number of patients. We then excluded patients who received <10 immunotherapy (IT) injections in the SCIT alone group and combination group and <4 omalizumab injections in the omalizumab alone group and combination group.

All the children who received omalizumab met the criteria for omalizumab indication and received doses based on manufacturer's guidelines. Not all the children who received SCIT had asthma as their primary indication, but they all required control of their asthma before starting SCIT. Within the three groups, the primary objective was the rate of systemic reactions (SR) in each group. This was assessed by examining the

percentage of patients who had an SR and the percentage of the number of injections that were labeled as an SR. Secondary objectives included severity of SRs, organ involvement during SR, and management of the SR. The severity of SR was based on the World Allergy Organization (WAO) grading system.¹⁷ In brief, grade 1 SRs involve symptoms of one organ system, usually cutaneous or upper respiratory (rhinitis) or conjunctival. Grade 2 SRs involve symptoms of more than one organ system and can include the lower respiratory tract (wheezing) or gastrointestinal tract. Grade 3 SRs involve further progression of symptoms, such as laryngeal edema or asthma symptoms not responding to an inhaled bronchodilator. Grade 4 SRs include hypotension or respiratory failure, with or without loss of consciousness. Grade 5 SRs are defined by death. In our study, the grade was determined by the physician's clinical judgment. Organ involvement in this study was stratified by skin, pulmonary, gastrointestinal, or cardiac involvement. Also, patient baseline characteristics for age, gender, ethnicity, asthma severity, and initial FEV₁ were reviewed.

There were no significant changes within the practice with regard to the antigens used for IT, the extract manufacturer, the buildup dosing schedule, or the target maintenance dose for each antigen. All the patients who received IT were polysensitized and received conventional buildup for SCIT and did not receive a rush or cluster IT schedule. Descriptive statistics were used for analysis. Within the three aforementioned groups, the SR rate was calculated by dividing the number of reactions observed in patients or injections by the total number of patients or injections examined. The p value was calculated by using the χ^2 test for comparison of proportions for SR and analysis of variance of baseline characteristics and SR.

RESULTS

Eighty-nine patient charts were included in this study, with 30 patients (729 injections) in the omalizumab group, 29 (954 injections) in the combination group, and 30 (1550 injections) in the SCIT group. Baseline characteristics are outlined in Table 1. The majority of the patients were black boys, with a mean age of 10 years. All the patients in the omalizumab group and the combination group had moderate-to-severe persistent asthma with initial FEV₁ as low as 37% predicted. Significant differences in baseline characteristics were seen for race (black/Hispanic), asthma severity, and FEV₁. With regard to the details of the therapy, the mean duration of total IT in the SCIT group was 12 months, with 4 months for the buildup phase and 8 months of a maintenance phase. In the combination group, the mean duration of total injections was 9 months, with 4 months for the buildup

Table 1 Baseline characteristics of patients

	Omalizumab (n = 30)	Combination: SCIT + Omalizumab (n = 29)	SCIT (n = 30)
Age, mean (range), y	10 (6–16)	10 (6–15)	11 (7–15)
Sex, no. (%)			
Boys	20 (67)	19 (65)	16 (53)
Girls	10 (33)	10 (35)	14 (47)
Race, no. (%)			
White	2 (7)	5 (17)	2 (7)
Black*	24 (80)	15 (52)	12 (40)
Hispanic*	3 (10)	9 (31)	14 (47)
Other	1 (3)	0 (0)	2 (7)
Asthma severity, no. (%)			
Intermittent: SABA as needed	0	0	5 (17)
Mild persistent: low-dose ICS*	0	0	14 (47)
Moderate-severe persistent: ICS + LABA*	30 (100)	29 (100)	11 (37)
Initial FEV ₁ , mean (range), % predicted*	79 (37–124)	88 (43–119)	96 (63–135)

SCIT = Subcutaneous immunotherapy; SABA = short-acting β -agonist; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; FEV₁ = forced expiratory volume in the first second of expiration.

* $p = <0.05$.

phase and 5 months of the maintenance phase. Furthermore, 25 of the 30 patients in the SCIT group (86%) were on a buildup IT dose similar to 26 of the 29 patients in the combination group (87%) at the time of the study. In the combination group, omalizumab preceded initiation of SCIT in 90% of the patients (27/30), with an average duration of 6 months before starting SCIT. The average duration of omalizumab and SCIT combined was 9 months. Four of 30 patients had omalizumab stopped temporarily while on SCIT, whereas all the other patients (26/30) continued with combination of omalizumab and SCIT.

SRs were observed in 10% (3/30), 10% (3/29), and 33% (10/30) of the patients in the omalizumab, combination, and SCIT groups, respectively (Fig. 1). There was no significant difference in SRs between the omalizumab and combination groups ($p = ns$). More importantly, both omalizumab and combination groups had significantly lower SR rates ($p = 0.032$ and $p = 0.034$, respectively) compared with the SCIT group. When stratifying by the number of injections, SRs were observed in 0.4% (3/729), 0.3% (3/954), and 1.2% (19/1550) of total injections within omalizumab, combination, and SCIT groups (Fig. 2). Once again, there was no statistically significant difference between the omalizumab and combination groups ($p = 0.73$), but there was a statistically significant lower SR rate in the omalizumab group and the combination group compared with the SCIT group ($p = 0.045$ and $p = 0.011$, respectively). In other words, the relative risk of developing an SR during SCIT without omalizumab was 3.9 times the risk of those on the combination therapy

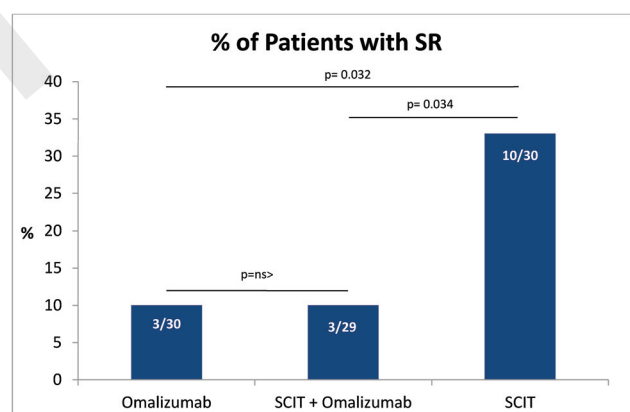


Figure 1. Percentage of patients with systemic reactions in each group ns = not significant.

(95% confidence interval, 1.2–13.1). Further examination of IT reactions showed that two of the three reactions (66%) in combination group occurred during the buildup phase compared with 16 of the 19 reactions (84%) in the SCIT group.

With regard to SR grading, the majority of SRs were WAO grade 1 or 2, with several WAO grade 3 reactions only in the SCIT group (Table 2). No grade 4 or 5 SRs were observed. All of the SRs involved the respiratory or skin organ systems, with the majority of these patients being treated with oral antihistamines or β -agonists (Table 3). There were three patients in the SCIT group who received intramuscular epinephrine compared with one patient in the combination group who received intramuscular epinephrine for shortness of breath, throat pain, and itchy eyes.

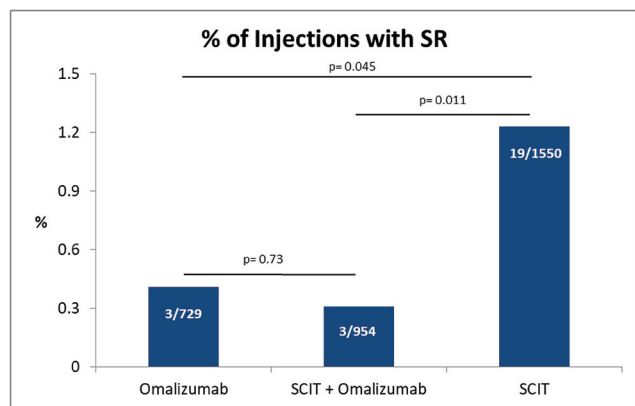


Figure 2. Percentage of injections with systemic reactions in each group.

Table 2 No. of systemic reactions per WAO category

WAO Grade	Systemic Reactions, no.			<i>p</i>
	Omalizumab	Combination: SCIT + Omalizumab	SCIT	
1	1	1	11	0.01
2	2	2	6	ns
3	0	0	2	ns
4 or 5	0	0	0	ns

WAO = World Allergy Organization; SCIT = subcutaneous immunotherapy; ns = not significant.

DISCUSSION

Uncontrolled asthma is challenging to manage and can significantly impact both the patients and their family. To our knowledge, this study was the first U.S. study that analyzed the SRs of omalizumab, SCIT, and combination therapy in children with allergic asthma. Here, we demonstrated that combining SCIT and omalizumab did not significantly increase the rate of SR compared with the patients who received omalizumab alone. More importantly, of all the injections received in each group, the combination group developed one-third fewer SRs compared with the SCIT group (0.4 versus 1.2%, respectively) ($p = 0.011$). There were no deaths in this study, and only one patient in the combination group had an SR that required epinephrine. Similar to a larger randomized U.S. study that evaluated SRs for allergic rhinitis and allergic asthma in adults, the majority of SRs were pulmonary related.¹⁸

Our SR rate in the SCIT group (1.2%) was higher than the rate reported in other studies (0.1 to 0.51%).^{19–24} One of the largest surveillance studies (23.3 million injection visits) from the American Academy of Allergy, Asthma & Immunology, and American College of Allergy,

Asthma, and Immunology (2008–2012) reported reaction rates of 0.1%.²⁵ Our rates were higher for multiple reasons. First, our population cohort was frequently nonadherent with injection visits. Therefore, the buildup phase was significantly longer for many patients, which led to a higher probability of SRs because this phase has been associated with a higher SR rate.^{20,21} Concordant with this, analysis of our data revealed that 86% of SRs occurred during the buildup phase. Besides nonadherence with visits, nonadherence to controller therapy likely contributed to overlabeling respiratory symptoms as SRs, when instead, the symptom may have been a manifestation of underlying uncontrolled asthma.

Second, all of our patients had allergic asthma, which is another statistically significant risk factor for increasing SR rates and may have been excluded from other IT studies.²¹ Third, a recent study demonstrated that grade 1 and grade 2 reactions are more likely to occur in children than in adults, even after accounting for factors such as asthma, gender, and buildup.¹⁹ Therefore, given that our cohort was exclusively children and that 89% of SRs were grades 1 and 2, it was not surprising that our SR rate may be higher than that of other, larger, studies that included adults. Fourth, because providers in the clinic respond differently to more subjective reactions (such as itching), there may have been variability in what was documented and considered an SR. Some of these reactions were likely not IgE mediated, given the delayed nature or atypical presentation (redness). Regardless of these points, our SR rate of patients on the combination therapy was statistically similar to those who received omalizumab therapy.

There are three randomized controlled trials that studied an omalizumab and SCIT combination in children, but all of these were performed in Europe and only one clearly enrolled subjects with asthma.^{15,26,27} Since then, one French study demonstrated tolerability of omalizumab pretreatment for dust-mite rush IT in six children with allergic asthma.²⁸ Another, Polish study, reported that five children with severe asthma and who previously did not tolerate SCIT, were now able to tolerate SCIT after 6 months of omalizumab pretreatment.¹⁶ As mentioned earlier, these studies may not be applicable to the SCIT in the United States due to significant differences in SCIT schedule, standardization of extracts, treatment formulation, extract type (e.g., allergoids or depot extracts), and approach to a patient who is polyallergic.

With regard to the U.S. studies, Massanari *et al.*¹⁸ conducted randomized a controlled trial that demonstrated that adults who received 16 weeks of omalizumab pretreatment followed by a 4-week cluster SCIT regimen experienced significantly fewer SR during IT than those who received IT alone (13.5 versus 26.2%) ($p = 0.006$). However, this study only enrolled adults

Table 3 No. of organ systemic involved per systemic reactions

	Systemic Reactions, no.			<i>p</i>
	Omalizumab	Combination: SCIT + Omalizumab	SCIT	
Organ system				
Skin	1	2	9	0.02
Pulmonary	3	3	12	0.01
Gastrointestinal	0	0	0	ns
Cardiac	0	0	0	ns
Rescue medication				
Antihistamine	1	2	13	0.004
β -Agonist	3	2	10	0.02
Systemic steroid	0	0	2	ns
Epinephrine	0	1	3	ns

SCIT = Subcutaneous immunotherapy; ns = not significant.

(mean age, 38.2 years) and only administered only cluster IT, which may not be generalizable to many allergy practices. Casale *et al.*²⁹ showed a similar favorable safety profile when using 9 weeks of omalizumab pretreatment before rush IT but excluded children and adults with asthma.

Our study had several limitations. The retrospective nature of this investigation lent itself to inherent recall and selection biases. In addition, as mentioned previously, nonadherence to medications and to visits was a significant issue. As a result, this could potentially account for higher SR rates compared with other published studies. Nonadherence also complicated our ability to accurately assess the duration of omalizumab pretreatment required before starting SCIT. Although 16 weeks of omalizumab pretreatment seems to be the most frequently studied, studies thus far range from 2 weeks to at least 8 months.^{15,16,28} There was a limitation in the selection of the groups. The number of patients for each group was limited by the number of patients who received combination therapy in our allergy clinic. Due to the small sample size, we did not match the SCIT and combination groups based on patient baseline characteristics nor therapy duration and/or phase of IT treatment.

However, the differences in asthma severity and FEV₁ were inherent to the patients being treated with omalizumab who have moderate-severe persistent asthma for drug approval. In addition, postselection analysis showed similar total duration of therapy and duration in the buildup phase in these two groups. Importantly, this study demonstrated real-life treatment scenarios and SRs in these population. Furthermore, aside from pulmonary function test data, there was a lack of consistent documentation with regard to the number of emergency department visits and the number of patients who were adherent to chronic oral

steroid use before starting omalizumab therapy. Therefore, more objective data regarding asthma severity was not included. Also, as stated earlier, the providers may have judged SRs differently, which led to variability in what was considered an SR. In going forward, although compliance may be difficult to enforce (but could be generalizable to other populations), larger multicenter prospective trials with predetermined omalizumab pretreatment schedules and consistent grading of SRs would be more ideal.

CONCLUSION

In children with moderate-severe persistent asthma, omalizumab pretreatment, followed by SCIT had comparable safety rates compared with omalizumab therapy alone. More importantly, omalizumab pretreatment was associated with one-third of the risk of SR compared with the SCIT group. Therefore, SCIT in children treated with omalizumab seemed to be safe and in line with previous U.S. studies in adults.¹⁸ Starting omalizumab in children with inadequately controlled asthma can reduce the burden on health care systems, improve quality of life, and decrease use of medications with adverse effects. Because the optimum duration of omalizumab treatment is still unknown, additional SCIT may serve as an end point to omalizumab therapy, with potentially long-lasting immune modulating benefits. Larger randomized prospective U.S. studies are warranted to confirm the results of this pilot study. In addition to safety data, further research with regard to the efficacy and cost-effectiveness of this management strategy, the optimal duration of omalizumab pretreatment, and the optimal time to wean omalizumab is clearly needed in managing these children with this difficult-to-control disease.

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