Sublingual Immunotherapy and Asthma

by Diego Saporta, MD

Abstract

Asthma and allergic rhinitis (AR) often coexist in the same patients, as they are different manifestation of the same disease. Asthma is considered an allergic condition affecting the lower airways. It is a serious disease carrying a risk of mortality. Administration of specific immunotherapy (SIT) by injections is effective for the treatment of nasal allergies and asthma, but there are infrequent (though well-known) risks, including the possibility of irreversible bronchial obstruction. Sublingual immunotherapy (SLIT) is widely used in Europe as, while being effective, it is much safer than subcutaneous injection immunotherapy. According to the European literature, SLIT is successfully used for the management of the patient with nasal allergies and asthma. This experience is still lacking in the US.

The results of an observational study on 10 AR-asthmatic patients managed with SLIT are presented here. Treated patients exhibited a marked improvement in symptom scores, a decrease in medication use, and an improvement in objective respiratory parameters.

Introduction

Asthma is a complex, multifactorial disease in which allergic and nonallergic factors lead to bronchial obstruction and inflammation.[1] There has been a steady increase in asthma deaths from 1980 to 1996.[2] While mortality rates have decreased each year since 2000, there were still 4055 deaths in 2003 and 3884 (or 1.3 per 100,000) in 2005.[3]

There is a tendency to consider asthma and allergic rhinitis two separate entities, but there is strong evidence to the contrary. The term *rhinobronchitis* has been proposed to help recognize the concept of chronic inflammation throughout the entire airway in the patient with concurrent allergic rhinitis and asthma.[4] The upper and lower airways are considered a single entity influenced by a common inflammatory process.[1]

The evidence in support of the asthma–AR link includes:

- epidemiological studies which reveal that up to 19% or more of hay-fever sufferers develop asthma later in life[1–8];
- physiological studies which show that some AR patients with no perceived asthma develop bronchial hyperreactivity (BHR) during AR exacerbation, and these are apparently the patients at risk of developing asthma[4,9,10];
- anatomical and immuno-pathological studies and clinical studies that show that SIT may have a preventative effect on the development of further sensitizations, progression of AR into asthma, and worsening of asthma over time.[1,6,8,11–14]

In asthmatic patients SIT reduces asthma symptoms, reduces drug use, and decreases BHR.[15]

All these data support the concept that the upper and lower airways are a single entity modified by a common, evolving inflammatory process. Therefore, from the immunotherapeutic point of view, AR and asthma should be considered a single disease.[1]

Because it is clear that AR will frequently lead into asthma and because SIT will prevent such a progression, it is only logical to initiate SIT as soon as the allergic condition is diagnosed. But SIT administration by injections – subcutaneous injection immunotherapy (SCIT) – carries risks that, though infrequent, can be severe, even fatal.[1,8,11] Thus SIT is rarely started in children under age 5, as it is reported that it has a higher incidence of systemic reactions in young children and that the majority of the SIT-related deaths occur in asthmatic patients.[15–19]

These circumstances lead to a clinically contradictory situation: while SIT should be offered to children with AR and asthmatic patients as soon as possible, it is often not given for fear of a severe reaction. Therefore, the risks of SIT administration (when given by subcutaneous injections) often preclude its use in the patients who would most benefit from it: the asthmatic patient and the young child.

This is where the role of SLIT should be considered, as it has already been in use for many decades.[20] Its safety and efficacy for the management of patients with AR and asthma have

been extensively evaluated in Europe. Evidence has been collected from randomized controlled studies that meet the strictest criteria of evidence-based medicine, with indication of long-lasting effects after its discontinuation.[21–23] There are meta-analyses that establish significant effect of SLIT in AR, and efficacy in asthmatic patients and in children with asthma.[24–26] These reports show that asthmatic patients treated with SLIT exhibit a decrease in asthma symptoms, decrease in medication use, and improvement in respiratory function parameters. Therefore, it appears appropriate to use SLIT to treat asthmatic patients, including children, as these are the patients more at risk for a severe anaphylactic reaction if SCIT is used.

In the US, there is still little published on experiences with SLIT, and in particular with SLIT related to asthma.[27] Presented here is an observational study pertaining to treatment results in a group of 10 patients from the author's practice who exhibited symptoms of AR and asthma and were treated with SLIT using a previously published protocol.[28] To the best of our knowledge, this is the first report in this country on treatment of asthmatic patients with SLIT using multiple allergens. (A PubMed search was done for treatment of asthma with sublingual immunotherapy in the US; no articles were found).

Material and Methods

Patients

All our immunotherapy patients are properly counseled about risks and benefits of this therapy, and symptoms are routinely scored pretreatment and periodically during treatment. Patients are always trained in the use of an adrenaline autoinjector. When SLIT is considered, patients are clearly advised that it constitutes an off-label use of immunotherapy extracts, not approved by the FDA and not reimbursable by most insurance carriers. Data presented here were obtained by chart review in the author's practice; all patients were aware that their charts were reviewed for this purpose. All pertinent personal information has been removed from the material for analysis to protect patient confidentiality. Inclusion criteria for the study were: (a) completion of symptom questionnaires and collection of objective data at least twice during the period of the study, and (b) having been treated for more than 6 months. Ten patient charts satisfied such criteria and are presented here for analysis.

To the best of our knowledge, this is the first report in this country on treatment of asthmatic patients with SLIT using multiple allergens.

Symptom and Medication Scoring, and Evaluation of Objective Parameters

Symptom scoring (for patients both on SCIT and SLIT) is done using a scoring sheet with a numerical analog on a scale of 0–3.[29]

Scoring for symptoms is: 0 = symptom not present; 1 = mild symptom; 2 = moderate symptom; 3 = severe symptom.

Scoring for medication use is: 0 = medication not used; 1 = medication used once per week or less; 2 = medication used 2–3 times per week; 4 = medication used 4 or more times per week.

Objective parameters in our office include peak flow meter (PFM) and/or spirometry parameters. Measured values were used for analysis.

Asthma symptoms for this study included cough, shortness of breath (SOB), and wheezing, as well as provocation of such symptoms by exercise or waking up during the night because of symptoms. Only the use of specific asthma medications – short-acting bronchoagonists (SABA) and inhaled corticosteroids (ICS) – were evaluated. Asthma patients being treated with SCIT get their peak-flows evaluated each time they receive an injection. For SLIT patients, we attempt to do this when the patient picks up the SLIT bottle, but this is not always possible. Spirometries are not always obtained, as sometimes patients are very young and/or not cooperative.

Allergy Treatment Plan

Allergy treatment was planned after obtaining an intradermal test with progressive dilutions according to AAOA (American Academy of Otolaryngic Allergy) guidelines.[30] Standardized antigens were used for testing and treatment whenever these were available; otherwise weight/volume antigen extracts were used.[31]

Asthma Diagnosis

Asthma diagnosis was based on history (asthma symptoms: recurrent cough, tight chest, SOB, or wheezing) and/or abnormal spirometry results (obstruction and/or improvement of respiratory parameters after administration of bronchodilators) and/or symptom-response to bronchodilators.[32]

Results Analysis

The numerical value of symptoms at presentation (pretreatment) and at the time of chart review was recorded. An average was obtained for pretreatment values and values at the time of data collection. A percentage of change was calculated for symptoms and medication use. The value of PFM or pulmonary function parameters on presentation and at the time of chart review was recorded. An average was obtained for pretreatment values and at the time of data collection. A percentage of change was calculated.

Results

The total number of patients was 10. Sex distribution was: male: 2; female: 8. Age range was 5–63 years with a mean age of 29 years. There were 3 patients younger than 12,

➤

➤

with a mean child age of 7 years. The length of treatment was from 7 to 21 months with a mean duration of 13.8 months.

Symptom, Medication and Objective Parameters Analysis

In Table 1, the results of the symptom "cough" are analyzed. Eight patients reported this symptom before treatment. At the time of data collection, 5 patients reported having the symptom. Six out of the 8 patients exhibited a reduction of 2 or more grades. Overall, the symptom had an improvement of 74%.

In Table 2, the results of the PFM determinations are shown. Nine patients had PFM determinations. All of them exhibit some improvement, and 7 out of the 9 had an improvement of 20% or more. Overall the measurements improved 28.0%.

Tables 1 and 2 are examples of how data were tabulated. In Table 3, a summary of all the results is shown, with the number of patients who had the reported symptom, medication use, or objective parameter determination, with the average value for each parameter pretreatment and at the time of data collection, the percentage of change, and the number of subjects that exhibited the improvement.

Symptoms

(a) Cough was present in 8 patients at the beginning of the treatment. It had an average value of 2.38. With treatment, 3 patients had a complete symptom resolution. Seven out of the 8 patients exhibited some improvement, and 6 out of 8 patients (75%) had an improvement of 2 or more grades. The average value at the time of data collection decreased from 2.38 to 0.63 for a 73.5% overall improvement.

(b) SOB was present in 5 patients at the beginning of the treatment with an average value of 2.40. It resolved in all patients for an improvement of 100%.

(c) Wheezing was present in 5 patients at the beginning of the treatment with an average value of 2.80 and it resolved in all patients for an improvement of 100%.

(d) Cough elicited by exercise was present in 4 patients, with an average value of 2.50. With treatment it resolved in 2 patients and decreased in a third patient. The fourth patient exhibited no changes. The average value at the time of data collection was 0.50 for an overall improvement of 80%.

(e) SOB elicited by exercise was present in 7 patients, with an average value of 1.86. With treatment it resolved in 4 patients, decreased in 2 patients and had no changes in 1 patient, for a total of 6 out of 7 patients improved. The average value at the time of data collection decreased from 1.86 to 0.50 for an overall improvement of 76.9%.

(f) Waking up at night because of asthma symptoms occurred in 3 patients with a pretreatment value of 1.34. It resolved in all 3 patients for an improvement of 100%.

Medication use

(a) SABA medications were used by 6 patients before the treatment. According to frequency of use, the average was 2.00. No patient was using SABA at the time of data collection for an improvement of 100%.

(b) ICS medications were used by 4 patients before the treatment. According to frequency of use, the average was 2.50. No patient was using this medication at the time of data collection for an improvement of 100%.

Respiratory parameters

(a) PFM measurements were available in 9 patients. The average value for the 9 patients before treatment was 319. The average at the time of data collection was 409. This amounts to an average improvement of 28.0%. The smallest improvement

Table 1: Symptom Scoring Example.

Cough (present in 8 of 10 patients). Pretreatment symptom value and value at the time of data collection are shown in a scoring system of 0–3 (0 = no symptom; 1 = mild; 2 = moderate; 3 = severe). In parentheses, the percentage of improvement.

Cough Scoring: 0–3	Pretreatment	Posttreatment	Moderate–severe (grades 2 or 3) pretreatment	Moderate–severe (grades 2 or 3) posttreatment	Significant Improvement (reduction of 2 or more grades)
Patient #1	3	0	Yes	No	Yes
Patient #2	2	0	Yes	No	Yes
Patient #3	2	1	Yes	No	No
Patient #4	1	1	No	No	No
Patient #5	3	1	Yes	No	Yes
Patient #7	3	1	Yes	No	Yes
Patient #8	2	0	Yes	No	Yes
Patient #9	3	1	Yes	No	Yes
Moderate–severe			7/8	0/8 (100%)	
Average	2.38	0.63 (74%)			6/8 (75%)

was 8%. The largest improvement was 109%. All patients exhibited some improvement in PFM values. Seven out of 9 patients had an improvement of at least 20%.

(b) Spirometric measurements were available in 4 patients.
- FEV1 increased in 3 patients and decreased in 1 patient at the time of data collection, with an average increase of 6.2%.
- FVC increased in 2 patients and decreased in 2 patients at the time of data collection for an average improvement of 6.9%.

Conclusion

SLIT is an effective and safe treatment modality for the management of patients with nasal allergies and asthma. With this treatment, patients exhibited a decrease in symptom scores, a reduction in medication use, and an improvement in the respiratory parameters.

Discussion

In our experience, it is common to see patients seeking consultation for AR symptoms who also have a history of cough or exercise-induced or nocturnal symptoms – with or without spirometric abnormalities – that often respond to the administration of short acting bronchoagonists. It is also common to find abnormal spirometries in patients that deny history of asthma. All these patients are likely to have bronchial hyperreactivity. If they were to have a reaction to the administration of SCIT, it could potentially be more severe. Using SLIT according to a previously published technique, we have never encountered a case of a severe reaction in any patient, child or adult.[27,28] Therefore we even more strongly recommend SLIT to treat the

➤

Table 2: PFM (peak flow meter) recording (obtained in 9 of 10 patients). Values before treatment and at the time of data collection and the percentage of change are shown.

PFM values (L/min)	Pretreatment	During Treatment	% change
Patient #1	250	390	56
Patient #2	360	490	37
Patient #3	360	390	9
Patient #4	320	460	44
Patient #5	110	230	109
Patient #6	380	410	8
Patient #7	470	560	20
Patient #9	320	390	22
Patient #10	300	390	30
Some improvement			9/9 (100%)
Improved 20 % or more			7/9 (78%)
Average	319	412	28.0

Table 3: Symptom and Medication Scores Summary

Symptom (0–3)	# patients	PreRX average	W/RX average	% improvement	# improved
Cough	8	2.38	0.63	73.5%	7 /8
SOB	5	2.40	0.00	100.0%	5/5
Wheezing	5	2.80	0.00	100.0%	5/5
Cough–ex	4	2.50	0.50	80.0%	3/4
SOB–ex	7	1.86	0.43	76.9%	6/7
Wake @ night	3	1.34	0.00	100.0%	3/3
SABA use (0–3)	6	2.00	0.00	100.0%	6/6
ICS use	4	2.50	0.00	100.0%	4/4
PFM (L/min)	9	319	409	28.0%	9/9
FEV1 (L/sec)	4	2.59	2.75	6.2%	3/4
FVC (L)	4	3.04	3.25	6.9%	2/4

 # patients: Number of patients who have the symptom, use the medication, or have the objective evaluations.
PreRX: pretreatment measurements average.
W/RX: average at the time of data collection, during treatment.
% improvement: Percentage of change for symptom or medication use, or change in value of objective respiratory parameters.
 # improved: Number of patients who showed an improvement in symptom scores, a reduction in medication use, or improvement in respiratory parameters.
SOB: Shortness of breath.
SOB–ex: Shortness of breath elicited by exercise.
Cough–ex: cough elicited by exercise.
SABA use: Short-acting bronchodilator use.
ICS use: Inhaled corticosteroid use.
PFM: Peak flow meter.
FEV1: Forced expiratory volume in 1 second.
FVC: Forced vital capacity.

➤

patient with bronchial hyperreactivity if this patient is a child.

This is an observational study based on a small sample, but results are encouraging. Ideally this study should be followed by a DBPC study. The value of this study is that the findings are in agreement with those reported in the European literature, and we believe that these findings are suggestive enough to encourage further studies using multiple antigens to treat patients with AR and asthma. With this particular SLIT technique, it appears that the clinical results are excellent, as medication use decreases markedly, respiratory parameters improve, and patients appear to tolerate treatment well.

Notes

1. Bousquet J, Demoly P, Michel FB. Specific immunotherapy in rhinitis and asthma. *Ann Allergy Asthma Immunol*. 2001;87:38–42.
2. Mannino DM, Homa DM, Akinbami LJ, et al. Surveillance for asthma – United States, 1980–1999. *Morb Mortal Wkly Rep*. 2002;51(SS-1):1–14
3. US Centers for Disease Control. Asthma [Web document]. www.cdc.gov/nchs/fastats/asthma.htm.
4. Simmons FER. Allergic rhinobronchitis: the asthma-allergic rhinitis link. *JACI*. 1999;104(3–1):534–540.
5. Settipane RJ, Hagy GW. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc*. 1994 Jan–Feb;15(1):21–25.
6. Pederson PA, Weeke ER. Asthma and allergic rhinitis in the same patients. *Allergy*. 1983;38(1):25–29.
7. Linna O, Kokkonen J, Lukin M. A 10-year prognosis for childhood allergic rhinitis. *Act Paediatr*. 1992; 81:100–102.
8. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children – A 14-year study. *Pediatrics*. 1968; 42(5):793–801
9. Madonini E, Briatico-Vangosa G, Pappacoda A, et al. Seasonal increase of bronchial reactivity in allergic rhinitis. *J Allergy Clin Immunol*. 1987;79(2):358–363.
10. Braman, SS, Barrows AA, DeCotiis BA, et al. Airway hyperresponsiveness in allergic rhinitis. A risk factor for asthma. *Chest*. 1997;91(5):671–674.
11. Des Roches A, Paradis L, Menardo JL et al. Immunotherapy with a standardized Dermatophagoides Pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol*. 1997; 99(4):450–453.
12. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-Study). *J Allergy Clin Immunol*. 2002;109:251–256.
13. Rak S, Lowhagen O, Venge P. The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. *J Allergy Clin Immunol*. 1988;(82)3:470–480.
14. Jacobsen L, Nuchel Petersen B, Wihl JA, et al. Immunotherapy with partially purified and standardized tree pollen extracts. IV. Results from long-term (6-year) follow-up. *Allergy*. 1997; 52:914–920.
15. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2003;4:CD001186.doi: 10.
16. Ostergaard PA, Kaad PH, Kristensen T. A prospective study on the safety of immunotherapy in children with severe asthma. *Allergy*. 1986;41:588–593.
17. Allergy immunotherapy: a practice parameter. American Academy of Allergy Asthma and Immunology. *Ann Allergy Asthma Immunol*. 2003;90(1 suppl 1):1–40.
18. Heejjaoui A, Dhivert H, Michel FB, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. IV. Systemic reactions according to the immunotherapy schedule. *J Allergy Clin Immunol*. 1990 Feb;85(2):473–479.
19. Nelson HD. Allergen immunotherapy: Where is it now? *J Allergy Clin Immunol*. 2007;118(4):769–777.
20. Saporta D. Sublingual immunotherapy. A novel, albeit not so new, immunotherapy treatment modality. *Am J Rhinol*. 2008;22(3):253–257.
21. Andre C, Vatrinet C, Galvain S, et al. Safety of Sublingual-swallow immunotherapy in children and adults. *Int Arch All Imm*. 2000;121:229–234.
22. Pajno GB, Morabito L, Barberio G, et al. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo controlled study. *Allergy*. 2000;55:842–849.
23. Di Rienzo V, Marcucci F, Puccinelli P, et al. Long-lasting effect of immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy*. 2003;33:206–210.
24. Wilson DR, Torres Lima R, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy*. 2005;60:4–12.
25. Calamita Z, Saconato H, Pelá AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy*. 2006 Oct;61(10):1162–1172.
26. Penagos M, Passalacqua G, Compalati E, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest*. 2008 Mar;133(3):599–609. Epub 2007 Oct 20.
27. Cox LS, Linnemann DL, Nolte H, et al. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol*. 2006;117:1021–1035.
28. Saporta D, McDaniel AB. Safety and efficacy comparison of multiple-antigen subcutaneous immunotherapy with multiple-antigen sublingual immunotherapy. *Ear Nose Throat J*. 2007; 86(8):493–497.
29. Fell RF, Mabry RL, Mabry CS. Quality of life analysis of patients undergoing immunotherapy for allergic rhinitis. *Ear Nose Throat J*. 1997;528–536.
30. Fornadley JA. Skin testing in the diagnosis of inhalant allergy. In: Krouse JH, Chadwick SJ, Gordon BR, Derebery MJ, eds. *Allergy and Immunology: An Otolaryngic Approach*. Philadelphia: Lippincott Williams & Wilkins; 2002:114–123.
31. Alk-Abello Inc. 1700 Royston Lane, Round Rock, TX 78664, USA.
32. Novembre E, Galli E, Landi F, et al. Co-seasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis *J Allergy Clin Immunol*. 2004;114(4):851–857.

Diego Saporta, MD
drsaporta@allergydropsnj.com

Dr. Saporta completed his training in 1990 at Columbia Presbyterian Hospital in New York City. He is board certified in otolaryngology and has been a Fellow of the American Academy of Otolaryngic Allergy (AAOA) since 2001. His private practice in Elizabeth, New Jersey, is heavily oriented to the management of allergic conditions. Interested in the use of oral vaccines since early in his practice, Dr. Saporta presented a protocol for sublingual immunotherapy at the 64th annual meeting of the AAOA that since then has been successfully used for the management of allergic rhinitis with or without asthma.