Sublingual immunotherapy: A novel, albeit not so new, immunotherapy treatment modality

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ABSTRACT

Background: *Specific allergy immunotherapy traditionally has been thought of as subcutaneous injection immunotherapy (SCIT). There also are noninjection routes for the administration of immunotherapy. The best-known and studied of these noninjection routes is the sublingual route, usually known as sublingual immunotherapy (SLIT). SLIT has been in use for many decades; however, to this date, it is not well known to the majority of allergy practitioners in this country. The purpose of this study is to help change this perception so that SLIT eventually can be considered one more tool in the allergist's armamentarium.*

Methods: *A literature review was performed. It included articles from the early American clinicians and present publications that are mostly of European origin.*

Results: *It will become clear to the reader that the key features of SLIT are its efficacy, great safety, and simplicity of administration.*

Conclusion: *SLIT is a safe treatment modality that should be considered as a useful additional tool in the therapeutic armamentarium.*

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Key words: Allergic rhinitis, allergy drops, efficacy, immune modulation, immunotherapy, safety, SLIT, sublingual immunotherapy, therapy

There is a growing interest in the United States regarding the use of sublingual drops for immunotherapy administration. Although existing bibliography is mainly of European origin, oral immunotherapy was first developed in the United States. The first publication dates back to 1900.[1]

The reason for sublingual immunotherapy (SLIT) resurgence in Europe is related to a series of deaths after administration of SCIT in England (reported in 1986 by the British Committee for the Safety of Medicines). This event precipitated a serious decline in SCIT use that stimulated seeking alternative routes for immunotherapy administration. SLIT was rediscovered and quickly became well accepted in Europe.[2]

In 1998 a World Health Organization panel of experts concluded that SLIT was a viable alternative to the injection route, finding its use justified in clinical practice.[2] Soon after that the Allergic Rhinitis and Its Impact on Asthma workshop also supported SLIT use,[3] stating that immunotherapy could be administered not only by injection but also sublingually to both adults and children.[4] SLIT efficacy was based on category A evidence (derived from meta-analysis of results of randomized controlled trials).[3]

There is an abundance of evidence that this "not-so-new" treatment modality is as effective as injection immunotherapy, but in contrast to SCIT, SLIT is extremely safe. Although sublingual application of the antigen without swallowing (method known as sublingual spit) could present activity, scientific proof of activity is only available for the sublingual-swallow method of therapy that is called SLIT.[5]

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HISTORICAL PERSPECTIVE

The earliest publication on sublingual treatments dates back to 1900 when Curtis[1] first suggested an oral mode of immunotherapy, 11 years before Noon's classic publication on subcutaneous immunotherapy.[6] Several articles and books were published in the 1930s.[7,8] With Hansel, the otolaryngologic approach to allergy management developed[9] and in the 1940s SLIT was based on skin end point titration results.[10] Rinkel's concept of 1:5 dilutions was applied to SLIT[10] and a course called "Sublingual Therapy in Allergy" was offered at the American Academy of Otolaryngic Allergy (AAOA) from 1963 through the 1980s.[10] In those early days, SLIT was not only available as drops but also as rapidly dissolving tablets[11] (that only recently have been introduced in Europe).[12–14] The reason why SLIT did not remain a useful treatment modality in the United States is probably related to the anecdotal nature of the reports that lacked the rigor of scientific proof.[6]

A PUB MED search from 1980 to 2006 was done for the major ear, nose, and throat (ENT) journals, finding no references about SLIT. Five references were found in non-ENT US Journals (published by Morris DL); and hundreds of references were found in the European journals (mainly articles published after 1986). In the European literature SLIT is sometimes perceived as a new development.[15,16]

Recently, U.S. allergy institutions have published extensive literature reviews[17,18] and a task force has been formed to study SLIT, addressing the interest that U.S. allergists are exhibiting in this treatment modality.[18] When SLIT was rediscovered in Europe, the clinical trials generally used a much higher dosing regimen than was done previously in the United States. The efficacy and excellent safety record of SLIT were promptly established. It is now clear that a dose of antigen that is much higher than the optimal dose will elicit an immunologic change where the proallergic Th2 system, dominated by IL-5 and IL-13 with the eosinophil as the key effector cell and IgE as the responding antibody, shifts toward

a Th1 response characterized by an IgG response with absence of eosinophils.[19]

MECHANISM OF ACTION

Hansel correctly hypothesized that the sublingual mucosa has immunologic properties.[11] Currently, we know that the mechanism of action of sublingually administered antigen is very complex and does not involve submucosal absorption.[20] Sublingually administered antigen will be retained in the submucosa without direct absorption. Even a short contact of the allergen with the oral mucosa is enough to determine its persistence in the mouth for hours, which may be consistent with the hypothesis of mucosal immunity in the mechanism of action of local immunotherapy.[20] This also supports the finding by Morris that holding the antigen sublingually for only 20–30 seconds is sufficient to attain clinical results.[21]

The antigen (or its by-products) will be absorbed only after swallowing.[20] However, swallowed molecules will not necessarily be destroyed by the digestion process because there is evidence of absorption of macromolecules in immunologically active forms, which is more likely in the atopic individual.[5] Nevertheless, there is some digestion of the molecules; therefore, large doses will be needed to produce a serological or clinical response. This could explain the need to administer dosages that are many times greater than the dose required by the subcutaneous route.[22] There is evidence of efficacy of oral capsules (resistant to gastric pH) used for the treatment of allergy symptoms.[14]

The oral mucosa is rich in dendritic cells that can act as antigen processing cells. Dendritic cells produce IL-12, which favors the shift of a Th2-weighted immunologic response toward a Th1 response. On the other hand, the oral mucosa lacks mast cells, eosinophils, and basophils that likely help in the role of the oral mucosa to acquire immunologic tolerance.[16] Early effects of SLIT administration are likely to be associated with cell desensitization and are dose dependent; long-term effects are associated with a switch of Th2 cells into Th1 and the occurrence of regulatory T cells (T reg cells).[23] There is clear evidence that T reg cells are required for specific allergy suppression. Specific immunotherapy stimulates production of T reg cells, suppresses production of IgE, and stimulates production of IgG4 and IgA (*via* production of IL-10).[24]

SLIT has been found to reduce T-cell proliferation by generating T reg cells capable of inducing tolerance to the involved allergen and elicit production of IL-10 that reduces production of proallergic cytokines.[25] Local production of IgA and specific T suppressor cells may play a role in local immunotherapy.[5]

CURRENT CONCEPTS IN TREATMENT

At this time there is a lack of consensus regarding treatment protocols. Although there is controversy about dosing regimens, the most convincing evidence supports using a high-dose regimen with ranges of 5–100 times the dosage of a standard course of SCIT; and prolonged courses of therapy appear to be more effective than short doses.[4,15,22] Attempting to compare results is difficult because of the different protocols for dose advancement, preseasonal or coseasonal nature of the treatment, difference in the units considered, amount of antigen administered, number of dosages per week, total cumulative dose, maintenance dose, and amount of time that the patient is treated.[5] Different authors have used any number of drops from 1 to 15 or more per day. Despite these differences, there usually is an escalation phase and a maintenance period. During escalation drops are usually given daily. During maintenance there are more discrepancies, and drops can be given daily, twice, or even three times a week. Most of the authors use a 1:10 dilution system.[14,15,26–28]

We developed a sublingual treatment protocol following the same thought process ENT allergists use to treat patients by SCIT.[29] The AAOA also has proposed a treatment protocol.[30]

SAFETY AND EFFICACY

From our country's early literature it is already inferred that SLIT is efficacious, there is no risk of developing life-threatening reactions,[10] and when adverse events (AEs) occurred they were deemed insignificant.[31] In the European literature there are countless reports of its efficacy and great safety, with many double-blind, placebo-controlled (DBPC) studies. Efficacy and safety data usually are reported together.

In 2000, Andre *et al.*[13] reviewed 8 DBPC studies that included 347 active patients and 343 placebo patients. The patients were adults and children with either rhinitis or mild to moderate asthma. This review clearly confirms the good safety record for SLIT when used in both adults and children. The adverse reactions were all minor and occurred at the same rate in adults and children. They mainly involved the oral cavity and gastrointestinal (GI) tract. Urticaria and exacerbation of rhinoconjunctivitis had the same incidence in the active and in the placebo groups. Asthma attacks were significantly lower in the active group.[13]

In 2003 Canonica and Passalacqua[2] reviewed the literature finding 22 properly done DBPC studies (with 567 active patients). Nineteen of these 22 studies confirmed the efficacy of SLIT, not only for rhinitis but also for asthma. When SLIT was compared with SCIT, it was found that both had a similar effectiveness, but SLIT was found to be safer and more easily tolerated. AEs were reported infrequently. The most common AE was oral itching after taking the dose, which was always described as mild and self-resolving. No severe systemic reaction was ever reported in the literature over the 15 years reviewed by these authors.[2] In no case did the treatment needed to be interrupted. By contrast, the authors compare this situation with SCIT where severe, sometimes near-fatal, reactions occur in 0.5–6% of patients.[2]

In 2005, Wilson *et al.* performed a meta-analysis of 22 DBPC studies,[19] finding a significant decrease in symptom scores and medication use after SLIT. These effects persisted for at least 3 years after discontinuation of therapy. Increasing treatment duration beyond 12 months appeared to increase effectiveness. None of the studies reported any significant side effects during SLIT. Two studies reported similar efficacy for SLIT and SCIT.[19]

Efficacy

Individual publications have reported complete symptom remission in 80% of the patients,[26] significant decrease of

symptom and medication scores (with $p = 0.0001$),[27] or improvement in 96% of the patients with either asthma or rhinitis,[32] with protective effect lasting 5 years after discontinuation of therapy.[15] SLIT also appears to be effective over a wide range of different dosing regimens.[33–35]In patients with nasal allergies and asthma, a long-lasting effect is attained after 2–4 years of SLIT, finding an elevation of IL-12 and an increase in IgG4/IgE ratios.[36] SLIT could show a long-lasting effect after discontinuation of therapy,[15] similar to the effect attained after SCIT.[37,38] Patients with rhinitis who were treated with SLIT did not develop asthma.[38]

Safety and AEs

The most common AEs include itching (oral, sublingual, nasal, facial, and rarely diffuse), rhinorrhea, GI side effects (nausea, vomiting, abdominal pain, and diarrhea), urticaria rash, dizziness or lightheadedness, and headaches. There is a consensus in the European literature that no serious AEs occur from SLIT administration and that a fatal reaction has never been reported.[2,13,19]Except for AEs involving the buccal cavity and the GI tract (that occur more frequently in the active group)[2,13] the reported incidence for AEs usually is the same in the active and placebo groups.[14,39,40]

The AEs usually resolve spontaneously and do not require discontinuation of therapy.[2,13,15,27] Intervention is limited to dose adjustment or occasional antihistaminic administration but rescue medications such as adrenaline or other parenteral medication has never been reported.[2] Asthma episodes were more frequent in the placebo group, a fact that usually is cited as proof of SLIT efficacy.[13]

Combining efficacy with the simple mode of administration, SLIT appears uniquely positioned to be used as a "home-based immunotherapy." Even though home-based immunotherapy with SCIT was found to be very safe,[41] major reactions did occur at home. Even if these reactions occur infrequently, the concept of home-based injection immunotherapy will remain, at best, controversial.[42]

We also found that high-dose SLIT is effective and very safe[29] but when administering immunotherapy caution is always warranted. Symptoms can be provoked sublingually.[43] Supporting this statement are two recent case reports of anaphylaxis related to SLIT administration.[44,45]

ADVANTAGES TO SLIT USE

Given the safety record of SLIT it appears that it can be used as home-based immunotherapy.[46] It also can be used to treat patients that at this time are not considered good candidates for SCIT such as young children or high-risk patients.[47]

Other advantages include no local arm reactions that often interfere with dose advancement in SCIT. Patients save significant time and transportation-related costs by doing treatment at home.[48] This can potentially contribute to patient compliance because apparently treatment adherence (despite being a home-based treatment) is excellent.[49] Sublingual drops, if diluted in glycerin, do not need refrigeration because glycerin is an excellent preservative that maintains potency for a long time.[11,48]

SPECIAL SITUATIONS

SLIT and Asthma

Asthma frequently is associated with allergic rhinitis. Epidemiological studies have consistently shown that asthma and rhinitis often coexist in the same patients and that rhinitis often precedes the development of asthma.[50] Bronchial hyperreactivity, a consistent finding in asthma, is a frequent finding in patients with allergies, and when present there are more chances that the patient will become asthmatic.[51] Currently, we are witnessing a substantial increase in asthma cases and asthma mortality.[52] It is known that patients with nasal allergies, if left untreated, have up to a 19% chance of developing asthma.[53] Inhalant sensitivities tend to persist with time, especially perennials such as house-dust mites. Early administration of specific immunotherapy will prevent the development of new sensitivities, will improve asthma that may be present at the time of treatment initiation, and will prevent the development of asthma in the future.[50,54,55]

Opinions conflict as to the efficacy of SLIT[59] but review of the literature frequently shows that SLIT leads to an improvement of not only nasal allergy symptoms but also asthma symptoms: SLIT decreases asthma symptoms,[27,28,39] increases respiratory parameters,[15,39] and decreases medication use.[15,27,39] These positive effects can be seen even 5 years after the discontinuation of therapy.[15]

It appears that specific immunotherapy should be offered to children[55] starting early in the disease process, as soon as allergy has been diagnosed.[50] Given the safety profile, the simplicity of its administration and the evidence of efficacy presented here, it appears that SLIT could then be considered to treat children with asthma.

SLIT and the Very Young Patient

Obvious difficulties for injection administration are encountered in the very young child, often involving the parents as well. In this situation SLIT actually might be considered the first line of therapy.

FUTURE DIRECTIONS

SLIT and the Patient on β-Blockers

A significant percentage of the general population is on β-blockers. These patients generally are considered at higher risk for immunotherapy administration. They require both special considerations and careful informed consent before treatment is started.[56] The actual risk produced by β-blockade is unknown but may be of the same magnitude as the risk posed by asthma.[57] These patients could potentially be successfully treated with SLIT. A PUB MED search from 1980 to present day failed to reveal any reference addressing this issue, which hopefully will be addressed in future studies.

CONTROVERSIES

SLIT is not approved by the Food and Drug Administration remaining an off-label use of allergenic extracts. The Joint Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology[18] concluded that there is evidence that SLIT is an effective treatment. Still, many questions remain unan-

swered including effective dose, treatment schedule, and overall duration of treatment. Until these have been determined an assessment of the cost benefit ratio of this treatment modality cannot be made.[18]

Contrary to SCIT in which its effectiveness is not in question (there are DBPC studies dating back to the 1960s[58]), SLIT effectiveness is strongly suggested but not firmly established.[59] Until SLIT becomes an accepted treatment modality insurance companies likely will not reimburse for its use. At this time there is no specific CPT code for SLIT.

Despite the massive amount of literature suggesting SLIT safety, caution is always warranted (as with any type of immunotherapy treatment). Recently, two reports were published regarding anaphylaxis related to SLIT. One report was related to the administration of rush SLIT for latex desensitization[45] and the other was related to the use of SLIT for inhalant allergies.[44] There is no report of mortality related to the use of SLIT for the treatment of inhalant allergies.

SUMMARY

The purpose of this article is to bring SLIT to the attention of the allergy practitioner (and practitioners in related fields) presenting SLIT as an effective and extremely safe treatment modality. This treatment has been used in the United States for >100 years and is being used in Europe with increased frequency for the last 20 years. It is of simple implementation and offers the possibility of safe in-home administration.

SLIT should be considered for the management of patients with asthma as it appears uniquely positioned to treat them with a minimal risk. These higher-risk patients are, on the other hand, the ones that would benefit the most from immunotherapy.

SLIT dose should always start low and progress to high. In our opinion, this progression should be slow, so that the potential development of an AE could be the warning sign to decrease the dose without need for treatment interruption, maintaining efficacy and keeping the treatment safe. It is still not clear that one can safely use any treatment regimen with the same safety. Certainly, SLIT offers more leeway than SCIT but still it is always necessary to advise caution with the administration of any form of immunotherapy. The recently reported case of anaphylaxis related to SLIT administration (for inhalant allergies)[44] appears to be a case where there was no progression from low safe doses to higher doses.

At last, it is important to emphasize that this study is not inferring that SCIT should be discarded. This study suggests that SLIT should be one more tool in the allergy practitioner's armamentarium.

REFERENCES

1. Curtis HH. The immunizing cure of hay fever. Med News, New York 77:16, 1900.
2. Canonica GW, and Passalacqua G. Non Injections routes for immunotherapy. J Allergy Clin Immunol 111:437–448, 2003.
3. Bouquet J. The new ARIA guidelines: Putting science into practice. Clin Exp Allergy Rev 2:38–43, 2002.
4. Bousquet J, and the ARIA Workshop Group. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 108(suppl 5):242–245, 2001.
5. Kagi MK, and Wuthrich B. Different methods of local allergen-specific immunotherapy. Review article. Allergy 57:379–388, 2002.
6. Bellanti JA, and Settipane RA. Sublingual immunotherapy: A procedure whose time has come? Asthma Allergy Proc 28:1–2, 2007.
7. Hansel FK. Treatment of hay fever. In Allergy of the Nose and Paranasal Sinuses. St. Louis: CV Mosby, 755, 1936.
8. Vaughan WT, and Black JH (Eds.). Pollens and pollinosis, other inhalant allergy. In Practice of Allergy, 3rd ed. St. Louis: CV Mosby Co., 697–698, 1954.
9. Ruddy LW. Why sublingual therapy in otolaryngologic allergy? Trans Am Soc Oph Otol All 17:93–102, 1976.
10. Dickey LW. Sublingual antigen testing and therapy for inhalants, foods and petrochemicals, In Clinical Ecology. Dickey L (Ed). Springfield, IL: Charles C. Thomas Publisher, 544–553, 1976.
11. Hansel FK. Sublingual testing and therapy. A comparison with injectable methods. Trans Am Soc Ophtalmol Otolaryngol Allergy 11:93–103, 1972.
12. Kleine-Tebbe J, Ribel M, and Herold DA. Safety of a SQ-standardized grass allergen tablet for sublingual immunotherapy: A randomized, placebo-controlled trial. Allergy 61: 181–184, 2006.
13. Andre C, Vatrinet C, Galvain S, et al. Safety of sublingual-swallow immunotherapy in children and adults. Int Arch Allergy Immunol 121:220–234, 2000.
14. Van Deusen MA, Angelini BL, Cordoro KM, et al. Efficacy and safety of oral immunotherapy with short ragweed extract. Ann Allergy Asthma Immunol 78:573–579, 1997.
15. 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 33:206–210, 2003.
16. Frati F, Moingeon P, Marcucci F, et al. Mucosal immunization application to allergic disease: Sublingual immunotherapy. Allergy Asthma Proc 28:35–39, 2007.
17. Leatherman BD, Owen S, Parker M, et al. Sublingual immunotherapy: Past, present, paradigm for the future? A review of the literature. Otolaryngol Head Neck Surg 136:S1–S20, 2007.
18. Cox LS, Linnemann DL, Nolte H, et al. Sublingual immunotherapy: A comprehensive review. J Allergy Clin Immunol 117:1021–1035, 2006.
19. Wilson DR, Torres Lima R, and Durham SR. Sublingual immunotherapy for allergic rhinitis: Systematic review and meta-analysis. Allergy 60:4–12, 2005.
20. Bagnasco M, Passalacqua G, Villa G, et al. Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy is allergic volunteers. Clin Exp Allergy 31: 54–60, 2001.
21. Morris DL. Current use of sublingual-swallow immunotherapy. Curr Opin Otolaryngol Head Neck Surg 9:179–180, 2001.
22. Brown JL, and Frew AJ. The efficacy of oro-mucosal immunotherapy in respiratory allergy.Clin Exp Allergy 31:8–10, 2001.
23. Bousquet J. Sublingual immunotherapy: From proven to putative rapid relief of allergic symptoms. Allergy 60:1–3, 2005.
24. Akdis M, Scmidt-Weber C, Jutel M, et al. Mechanisms of allergen immunotherapy. J World Allergy Org 16:65–69, 2004.
25. Ciprandi G, Fenoglio D, Cirillo I, et al. Sublingual immunotherapy: An update on immunologic and functional effects. Allergy Asthma Proc 28:40–43, 2007.
26. Della Volpe A, D'Agostino GW, Varricchio AM, and Mansi N. Sublingual allergen-specific immunotherapy in allergic rhinitis and related pathologies: Efficacy in a paediatric population. Int J Immunopathol 15:35–40, 2002.

27. Pajno GB, Morabito L, and Parmiani S. Clinical and immunological effects of long term immunotherapy in asthmatic children sensitized to mites: A double-blind placebo-controlled study. Allergy 55:842–849, 2000.
28. Hirsch Th, Sahn M, and Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. Pediatr Allergy Immunol 8:21–27, 1997.
29. Saporta D, and McDaniel AB. Safety and efficacy comparison of multiple-antigen subcutaneous immunotherapy with multiple-antigen sublingual Immunotherapy. ENT J 86:493–497, 2007.
30. Leatherman BD. AAOA consensus sublingual immunotherapy dosing protocol. AAOA Today 28:3–4, 2007.
31. Baker SP. The use of sublingual drop therapy in allergy. In Clinical Ecology. Dickey L (Ed). Springfield, IL: Charles C. Thomas Publisher, 554–555, 1976.
32. Madonini E, Agostinis F, Barra R, et al. Safety and efficacy evaluation of sublingual allergen-specific immunotherapy. A restrospective multicenter study. Int J Immunopathol Pharmacol 13:27–81, 2000.
33. Grosclaude M, Bouillot P, Alt R, et al. Safety of various dosage regimens during Induction of sublingual immunotherapy. Int Arch Allergy Immunol 129:248–253, 2002.
34. Feliziani V, Lattuada G, Parmiani S, and Dall'Aglio PP. Safety and efficacy of sublingual rush immunotherapy with grass allergen extracts. A double blind study. Allergol Immunopathol 23:224–230, 1995.
35. Samburgo R, Puccinelli P, Burastero SE, and Di Rienzo V. The efficacy of sublingual immunotherapy for respiratory allergy is not affected by different dosage regimens in the induction phase. Allergol Immunopathol 31:329–337, 2003.
36. Potter PC. Update on sublingual immunotherapy. Ann Allergy Asthma Immunol 96:S22–S25, 2006.
37. Durham SR, Walker SM, Varga EM, et al. Long term clinical efficacy of grass pollen immunotherapy. N Eng J Med 341: 468–475, 1999.
38. 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 52:914–920, 1997.
39. Bousquet J, Scheinmann P, Guinnepain MT, et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: A double-blind, placebo-controlled study. Allergy 54:249–260, 1999.
40. Clavel R, Bousquet J, and Andre C. Clinical efficacy of sublingual-swallow immunotherapy: A double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. Allergy 53:493–498, 1998.
41. Hurst DS, Gordon BR, Fornadley JA, and Hunsaker DH. Safety of home based and office allergy immunotherapy: A multicenter prospective study. Otol Head Neck Surg 121: 553–561, 1999.
42. Li JT, Lockey RF, Bernstein L, et al. Allergen immunotherapy: A practice parameter. Ann Allergy Asthma Immunol 90:1–40, 2003.
43. Pfeiffer GO. Sublingual diagnosis and treatment. Trans Am Soc Ophtalmol Otolaryngol Allergy 15:109–113, 1975.
44. Dunsky EH, Goldstein MF, Dvarin DJ, and Belecanech GA. Anaphylaxis to sublingual immunotherapy. Allergy 61:1235, 2006.
45. Antico A, Pagani M, and Crema A. Anaphylaxis by latex immunotherapy. Allergy 61:1236–1237, 2006.
46. Nelson HS. Allergen immunotherapy: Where is it now? J Allergy Clin Immunol 119:769–777, 2007.
47. Finegold I. Allergen immunotherapy: Present and future. Allergy Asthma Proc 28:44–49, 2007.
48. Ruddy LW. Why sublingual therapy in otolaryngologic allergy. Trans Am Soc Ophtalmol Otolaryngol Allergy 17:93–102, 1976.
49. Lombardi C, Gani F, Landi M, et al. Quantitative assessment of the adherence to sublingual immunotherapy. J Allergy Clin Immunol 113:1219–1220, 2004.
50. Bousquet J, Demoly P, and Michel FB. Specific immunotherapy in rhinitis and asthma. Ann Allergy Asthma Immunol 87:38–42, 2001.
51. Braman SS, Barrows AA, DeCotiis BA, et al. Airway hyperresponsiveness in allergic rhinitis. A risk factor for asthma. Chest 91:671–674, 1997.
52. Cook PR, Bryant JL, Davis WE, et al. Systemic reactions to immunotherapy: The American Academy of Otolaryngic Allergy Morbidity and Mortality Survey. Otolaryngol Head Neck Surg 110:487–493, 1994.
53. Linna O, Kokkonen J, and Lukin M. A 10 year prognosis for childhood allergic rhinitis. Acta Paediatr 81:100–102, 1992.
54. 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 109:251–256, 2002.
55. 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 99:450–453, 1997.
56. Fornadley JA, Corey JP, Osguthorpe JD, et al. Allergic rhinitis: Clinical practice guideline. Otolaryngol Head Neck Surg 115:115–122, 1996.
57. Gordon BR, and Veling MC. Safety of beta blockade during intradermal dilution testing, quantitative testing, or immunotherapy. Presented at the American Academy of Otolaryngic Allergy Annual Meeting, Toronto, CA, September 15, 2006.
58. Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO). Allergy 62: 317–324, 2007.
59. Roder E, Berger M, Hop W, et al. Sublingual immunotherapy is not effective in symptomatic youngsters in primary care. J Allergy Clin Immunol 119:892–898, 2007. □