Allergen Immunotherapy for a Teenager with Seasonal Allergic Rhinitis Due to Grass Pollen: Subcutaneous or Sublingual Route?

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CASE PRESENTATION

The patient is a 16-year-old female high school student from the Midwestern United States who has experienced symptoms of sneezing, rhinorrhea, nasal itching, and obstruction each spring for the last 2 years. Her symptoms begin in late May and persist until early July. Her family recognized these symptoms as being due to grass pollen allergies because her father experiences similar symptoms at that time of year and has been diagnosed as having hay fever due to grass pollen. She saw a physician who prescribed antihistamines the first year. Because they did not provide adequate relief, the following season she was prescribed first a nasal steroid spray, and when that had not provided relief by mid-June, a combination antihistamine and corticosteroid spray. This helped, but only partially. The persistent symptoms impacted her quality of life because she is an avid softball player who frequently plays outdoors in the afternoon. Other than the 6 weeks from May to July, she experiences no persistent nasal symptoms, nor does she notice coughing, wheezing, or shortness of breath during the grass pollen season. In the fall, after the second year of symptoms, she consults an allergist/immunologist seeking more effective treatment for her anticipated grass pollen symptoms the coming spring.

INTRODUCTION

The young woman in the case report presents a very straightforward indication for allergy immunotherapy (AIT). She has a family history of seasonal allergic rhinitis due to grass and she presents with a 2-year history of classic allergic rhinitis symptoms occurring during the grass pollination season in the temperate regions of the United States. She has no other seasonal or perennial rhinitis symptoms, she does not have accompanying asthma, she has not had an adequate response to symptomatic therapy, and her quality of life is adversely impacted by her symptoms. It would be important to establish that failure of antiallergic drugs in her case is not due to either poor adherence to treatment or inadequate technique with nasal sprays. Any concerns about potential side effects of drugs should be elicited and discussed. To complete the indication for grass pollen AIT, objective confirmation of IgE sensitization to the grass pollens that predominate in her part of the country is required, either *in vivo* by skin prick testing or *in vitro* by measurement of allergen-specific IgE. Her symptoms may be treated with either subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT); there are arguments favoring each of these approaches that will be discussed in the succeeding sections.

PRO-SCIT/Con-SLIT POSITION

The case for SCIT (Harold Nelson)

Clinical effectiveness in grass pollen allergic rhinitis. Beginning with the publications of Noon and Freeman in 1911,[1,2] SCIT has been reported to be an effective treatment for grass-induced allergic rhinitis. One of the first controlled studies of injection immunotherapy was conducted with grass pollen extract.[3] A later study of preseasonal SCIT in subjects with severe grass-induced allergic rhinitis, who had failed treatment the previous season with symptomatic treatment, demonstrated 60% and 80% reductions, respectively, in symptoms and rescue medication use compared with placebo during the grass pollen season.[4] A large study of SCIT with grass pollen extract was conducted in the United Kingdom in the setting of specialist hospital practice.[5] Again, subjects had had inadequate response the previous year to symptomatic treatment. In the group receiving the same dose of timothy grass pollen extract as had been used in the previously mentioned study, reductions in symptoms and medication use were 32% and 41%, respectively, compared with placebo. However, subjects receiving only 1/10 of the high dose of timothy extract experienced improvements of only 22% in symptoms and 16% in medication use compared with placebo. From this study, we can deduce the appropriate dose for grass-SCIT. The effective high dose contained 20 μg of the major allergen of timothy, Phl p 5, whereas the marginally effective dose contained 2 μg. Although doses higher than 20 μg of Phl p 5 have not been tested, 4.4% of subjects receiving the highest dose experienced systemic reactions (non−life-threatening), suggesting that higher doses might not have an acceptable level of safety. Thus, approximately 20 μg of Phl p 5 appears to be appropriate for maintenance dosing of SCIT for treatment of allergic rhinitis caused by timothy and probably for other northern pasture grasses, because all members of this group are highly cross-reactive with timothy. However, although the temperate grasses of the United States are highly cross-reactive,

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Abbreviations used
AIT- Allergy immunotherapy
RCT- Randomized controlled trial
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual immunotherapy
SMD- Standardized mean difference

other grasses that coexist or predominate in the southern and western states, such as Bermuda, Bahia, and Johnson grass, have little or no shared allergenicity with timothy.[6]

Modification of the natural history of allergic rhinitis. There is evidence that SCIT with grass pollen extracts modifies the underlying immune process[7] and alters the natural history of allergic rhinitis.[8-12] Several studies have reported that patients who were initially monosensitized and received AIT were at greatly reduced risk for developing additional sensitizations. Most of these studies have been in patients receiving house dust mite extracts,[8] but a retrospective comparison of 7182 patients receiving AIT for 4 years to various allergens compared with 1214 patients receiving only drug treatment reported new sensitizations after 7 years in 27% of the AIT-treated patients compared with 77% of the drug-only—treated patients.[9] In this report, 20% of the AIT-treated subjects received grass pollen extracts. Of perhaps more interest is the ability of AIT to reduce the chance of patients with only allergic rhinitis developing asthma.[10] Children with allergic rhinitis due to grass and/or birch pollen with no evidence of asthma received 3 years of AIT to 1 or both pollen extracts and then were followed for 7 years after discontinuation of AIT.[10] Follow-up was obtained after 10 years in 147 subjects. At that time those who had received active treatment continued to have a reduced risk of having developed asthma (16 of 64) compared with the untreated controls (24 of 53) with a significant longitudinal treatment effect ($P = .0075$).

Modification of the underlying immune status is also indicated by the persistence of remission of symptoms following discontinuation of a successful course of treatment.[11,12] One hundred eight Austrian patients who had responded well to 3 to 4 years of AIT with grass pollen extract had their treatment discontinued and were followed for evidence of recurrence of symptoms.[11] Over the initial 3 years of follow-up, approximately 30% had a relapse of their grass pollen—induced allergic rhinitis, following which the rate of relapse appeared to be even lower. A double-blind, placebo-controlled trial of discontinuation of grass pollen AIT was conducted in the United Kingdom after 3 to 4 years of active treatment.[12] Three groups were followed: one continued to receive maintenance injections of grass pollen extract, the second group received instead regular injections of placebo, while the third was a newly recruited cohort with sensitivity to grass similar to that of the other 2 groups before receiving their AIT. The third group demonstrated over the next 3 years that these were robust grass pollen seasons. The other 2 groups fared considerably better and did not differ from each other in symptoms or medication requirement. These 2 studies confirm prospectively, and in 1 with double-blinded controls, that SCIT with adequate doses and duration can induce long-lasting clinical benefit for most patients.

Safety of SCIT. Two major limitations in the use of SCIT are the concern over systemic reactions and the many clinic visits required over the projected treatment course of 3 to 4 years. The occurrence of systemic reactions is related to the dose and extract formulation. In a previously mentioned clinical trial of preseasonal grass immunotherapy, subjects received, following up-dosing, a maintenance injection of alum-precipitated timothy grass extract containing either 20 μg or 2 μg of the major allergen Phl p 5.[5] A 15-injection up-dosing over 8 weeks was used. Immediately following injections, wheezing or urticaria occurred only in those receiving the high dose; these reactions were all non—life-threatening and occurred in 4.4% of high-dose subjects.[5] One problem in applying these data to SCIT with grass pollen extract in the United States is that the extract in this study was alum precipitated. There is a line of alum-precipitated pollen extracts available in the United States (Center-Al, ALK-Abello', Round Rock, Texas) and direct comparison of comparable doses of the alum-precipitated grass pollen extract to unmodified glycerol-saline grass revealed a marked reduction in systemic reactions[13]; however, this study was performed before standardization and accompanying reduction in the potency of US grass pollen extracts. A recent report from the American Academy of Allergy, Asthma & Immunology (AAAAI)/American College of Allergy, Asthma & Immunology (ACAAI) Surveillance Study of Subcutaneous Immunotherapy reported that systemic reactions occurred in only 0.1% of injection visits and 1.9% of patients.[14] This suggests that the rate of systemic reactions with the US aqueous and glycerol-saline extracts is not markedly higher than that which has been reported with alum-precipitated extracts. The major concern is, of course, the possibility of a fatal reaction. In the last report of the Surveillance Study, 2 fatal reactions were reported in 28.9 million injection visits in allergy practices.[15] Most fatalities that have been identified in the last few decades have occurred in patients with unstable asthma, so the risk for a young patient with only allergic rhinitis to have a fatal reaction is considerably less.

The question is whether anything can be done to decrease the number of clinic visits required for a course of SCIT. Attention should be directed toward the period of up-dosing, because it is unlikely that a patient derives clinical benefit until close to the time they reach maintenance doses and monthly visits are less onerous than weekly or even twice weekly visits typical of the up-dosing period. Cluster regimens, with 2 or 3 injections per visit at 30-minute intervals, have been used to reduce the clinic visits during the period of up-dosing from at least 15[16] to 8.[17] There are no prospective studies of cluster versus conventional dosing regimens with pollen allergen extracts. With alum-precipitated house dust mite extracts, cluster dosing is tolerated at least as well as conventional dosing.[18]

SCIT versus SLIT. There are a number of ways to compare the efficacy of SCIT and SLIT. For example, the reduction in symptoms or medication use in studies with SCIT or SLIT can be compared with that with placebo by meta-analyses and the standardized mean differences (SMDs) that are generated for SCIT and SLIT can be compared. When this was done, the SMD of symptom scores and medication use in allergic rhinitis was −0.73 and −0.57, respectively, in 51 studies of SCIT and −0.49 and −0.32, respectively, in 49 studies for SLIT, suggesting greater efficacy for SCIT.[19] Eleven head-to-head comparisons of SCIT and SLIT were identified in the medical literature.[19] Again, these direct comparisons favored SCIT over SLIT, but in 9 of 11 studies SLIT was taken less than daily and a