

Subcutaneous Injection Immunotherapy for Optimal Effectiveness

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KEYWORDS

- Immunotherapy • Subcutaneous • Injection • Asthma
- Allergic rhinitis • Atopic dermatitis • Oral allergy syndrome

In 1911, Leonard Noon published in *The Lancet* a description of his treatment of patients suffering from grass pollen-induced hay fever. In keeping with immunologic thinking of the day, he hypothesized that these individuals were uniquely sensitive to a toxin contained in the grass pollen, and that by a series of injections of increasing amounts of grass pollen extract he could induce protective antibodies against this toxin.¹ In an era when there was no effective symptomatic treatment for respiratory allergies, the practice of subcutaneous injection immunotherapy spread rapidly, and was extended to a wide range of allergens and conditions. Thus, in 1930 John Freeman, who had succeeded Noon in the initial treatment at St Mary's Hospital in London,² described the method of "Rush Inoculations" with examples, not only of using grass pollen extract but also extracts of horse dander and autogenous house dust, to treat patients with both hay fever and asthma.³ Subcutaneous immunotherapy has been successfully employed for the entire range of inhalant allergens, including pollens, animal danders, house dust mites, and fungi as well as for allergy to insect stings, especially flying Hymenoptera and various species of ants. Despite this extension of subcutaneous immunotherapy to other allergens and other allergic conditions, the basic approach, that of a series of graded increasing doses followed by a prolonged series of maintenance injections, has changed little over the course of the 100 years that it has been employed.

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DISEASE INDICATIONS FOR SUBCUTANEOUS INJECTION IMMUNOTHERAPY

Allergic Rhinitis and Asthma

Allergic rhinitis and asthma often occur together in response to allergen exposure. When John Bostock first described hay fever, he spoke of “a periodic affection of the eyes and chest.”⁴ The hay fever patients of Noon and Freeman also often complained of symptoms of asthma, and they reported that there was improvement in both hay fever and asthma with the injections of Timothy pollen extract.² The effectiveness of appropriate subcutaneous injection immunotherapy for allergic rhinitis and asthma has been repeatedly confirmed in single studies. Cochrane Collaboration meta-analyses have combined the results from many of these studies. An analysis of 15 randomized controlled trials conducted between 1950 and 2006 in subjects with seasonal allergic rhinitis revealed an overall reduction in symptoms in the immunotherapy group with a standard mean difference (SMD) of -0.73 and in 13 trials an SMD for medication use of -0.57 . Both of these reductions were highly significant.⁵

Randomized controlled studies of perennial allergic rhinitis have been conducted less frequently than those for seasonal rhinitis; however, there are studies with house dust mite extracts that suggest clinical efficacy in this condition as well. In a small but carefully conducted study in 36 adults with severe allergic rhinitis due to house dust mite allergy uncontrolled by regular antiallergic drugs, a maintenance dose of *Dermaphagoides pteronyssinus* extract was administered for 12 months.⁶ Compared with baseline, respiratory symptoms scores were reduced significantly (58%) in the active group, but not significantly (32%) in the placebo group. Medication scores were not significantly reduced in either the active group (20%) or the placebo group (no change).

The most recent Cochrane Database Systematic Review of injection allergen immunotherapy for asthma included 87 randomized controlled trials published through 2005 in the meta-analysis.⁷ The investigators found a significant reduction in asthma symptoms (MSD -0.59) based on findings in 35 studies. There was a reduction of medication requirement (SMD -0.53) based on 21 studies, as well as significantly reduced allergen-specific bronchial hyperreactivity (4.1-fold) with some reduction in nonspecific bronchial hyperreactivity (2.2-fold).

Sensitivity to Insect Stings

Injection immunotherapy with the venoms of the flying Hymenoptera (honeybee, yellowjacket, hornet, and wasp) is of well-established efficacy. This therapy is recommended for all patients who have experienced a systemic reaction to an insect sting and who have specific IgE to venom allergens demonstrated by skin testing or in vitro testing, with the exception of children 16 years and younger whose reactions are limited to cutaneous systemic signs and symptoms.^{8,9}

Allergic reactions to ant stings are also common, especially the Imported Fire ant in the southern United States and the Jack Jumper ant in Australia. For these insects whole-body extracts are employed for injection immunotherapy, their efficacy being supported by clinical observations¹⁰ and double-blind studies,¹¹ respectively.

Systemic reactions to biting insects are occasionally reported, but there are only isolated reports of use of injection immunotherapy for their treatment, and effective commercial extracts are not available.⁸

Atopic Dermatitis

Atopic dermatitis has not traditionally been considered an indication for injection immunotherapy, although it frequently coexists with or precedes allergic rhinitis and asthma and is characterized in many patients by positive skin tests and high IgE levels. The

most clearly recognized allergic trigger for atopic dermatitis is food allergy. Roughly a third of infants and young children with atopic dermatitis show relevant sensitivity to one or more foods.¹² The evidence for a role of other allergens either by inhalation or through contact with the skin is more circumstantial.¹³ However, in addition to several anecdotal accounts of improvement in atopic dermatitis with injection immunotherapy, at least 3 reports of placebo-controlled studies have been published.^{14–16} In the first of these studies, 26 children and adults with atopic dermatitis out of 52 originally randomized completed 2 years of injection therapy with a variety of inhalant allergens including house dust, danders, feathers, molds, and grass.¹⁴ Thirteen of 16 treated with all the allergens to which they reacted improved compared with only 4 of 10 who improved on placebo. One of two monozygotic twins with atopic dermatitis flaring during the grass pollen season was given injections of grass pollen extract while her twin received placebo. After 2 years of blinded treatment, skin symptoms during May improved significantly in the grass-treated patient compared with her placebo-treated twin.¹⁵ Recently, a larger study was reported of 1 year of injection therapy with 3 widely differing doses of house dust mite extract in adults with atopic dermatitis.¹⁶ Treatment was initiated in 89 subjects, 51 of whom completed the study. Doses of house dust mite extract were 1/5000th, 1/50th, and 1/5th the customary monthly injection maintenance dose for respiratory allergy, and were given weekly. The reduction in atopic dermatitis score after 2 months was significantly greater in the highest compared with the lowest dose, and there was less use of topical corticosteroids with the 2 higher doses. The results of these studies suggest that there may be a role for injection immunotherapy in atopic dermatitis. However, further studies are needed to confirm this benefit and also to better define the population likely to respond.

Food Allergy and the Oral Allergy Syndrome

Injection of food extracts as treatment for food allergy was tried repeatedly in the early decades after the introduction of immunotherapy. There were occasional reports of success, such as John Freeman's induction in a young boy of tolerance to cod liver oil by inoculations of fish extract by a rush protocol.³ However, the overall results were felt to be inconsistent, and parenteral food desensitization was not generally recommended.¹⁷ The possibility was reexamined for peanut allergy as it became evident that this sensitivity was responsible for many of the anaphylactic deaths due to food ingestion, and that there was little tendency for this sensitivity to spontaneously remit.¹⁸ A 1-year randomized, controlled study was conducted, with 6 peanut-allergic subjects receiving rush induction followed by maintenance injections.¹⁹ All treated subjects reached the projected maintenance dose, and experienced increased tolerance to oral peanut challenge and decreased skin test reactivity to peanut; however, a median of 33 injections was required to reach maintenance and there was a median of 9 systemic reactions per subject during the buildup to maintenance. After achieving maintenance, all subjects continued to experience systemic reactions (median 15), and 3 subjects required dose reduction with complete or partial loss of the acquired tolerance to peanut. The conclusion was that injection immunotherapy with unmodified peanut extract was not a clinically viable option.

Patients allergic to several pollens and to latex experience oral symptoms on ingestion of specific fruits and vegetables. Case reports of immunotherapy with pollen mixes and multiple-allergen mixes reported improved tolerance and decreased sensitivity to the implicated fruits and vegetables.^{20,21} Several series were reported of the effect of birch pollen immunotherapy on sensitivity to apples.^{22–24} These nonrandomized studies reported decreased symptoms in comparison with untreated controls on ingestion of apples and, in one report, hazelnuts. A double-blind, double-dummy

placebo-controlled study of both sublingual and subcutaneous immunotherapy with birch pollen extract was conducted in 74 subjects, 69% of whom reported oral allergy symptoms on ingestion of apples.²⁵ In this study, the oral symptoms on follow-up apple challenge decreased in all groups, but significantly only in those receiving placebo. Thus the final answer on immunotherapy for the oral allergy syndrome remains to be determined.

USE OF SPECIFIC ALLERGENS FOR SUBCUTANEOUS IMMUNOTHERAPY

Pollens

The initial study by Noon and Freeman employed Timothy grass pollen extract. Subsequently many pollen extracts have been proved to be effective when administered in adequate doses by injection. Among the allergens employed in the studies reviewed in the meta-analysis of injection immunotherapy in seasonal allergic rhinitis were ragweed (12 studies), mixed grass (16 studies), Timothy (5 studies), *Parietaria* (6 studies), birch (4 studies), orchard grass (2 studies), cedar (3 studies), and Bermuda and *Juniperus ashei* (1 study each).⁷ Pollen extracts were also used in 27 of the studies reviewed in the meta-analysis of injection immunotherapy for asthma, including Bermuda grass, orchard grass, Timothy grass, velvet grass, sweet vernal grass, perennial rye grass, birch, olive and ragweed.⁵

House Dust Mites

In keeping with the importance of house dust mite allergy in asthma, 42 of 88 studies reviewed in the meta-analysis of injection immunotherapy for allergic asthma employed house dust mite extract, in almost all instances *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*.⁷ Extracts of house dust mites have been used in virtually all studies reporting immunotherapy for perennial allergic rhinitis.

Animal Dander

Animal dander extracts, primarily cat or dog, were employed in 10 of the studies reviewed for the meta-analysis of injection immunotherapy for asthma.

Fungi

Three double-blind, placebo-controlled studies have been conducted in Europe with either *Cladosporium* or *Alternaria* extracts.^{26–28} All 3 studies were small but used well-defined mold spore seasons and partially purified, standardized extracts. All 3 studies demonstrated significant improvement with active treatment compared with placebo in symptoms, medication use, or both.

It is unclear whether the results of these 3 European studies can be used to support the efficacy of fungal therapy in the United States. Despite the obvious clinical importance of fungal allergy in the United States, there are distinct problems with fungal immunotherapy: (1) the presence of hundreds of thousands of different species of fungi, (2) lack of accurate information on exposure patterns for most fungal species, (3) generally poor quality of commercially available fungal extracts, and (4) lack of commercial extracts for many of the clinically implicated fungal genera.^{29,30}

Cockroach

No adequately controlled studies are available to assess the efficacy of cockroach extract. However, 3 commercially available cockroach extracts have been assayed for potency, and found to have potencies of 1735 to 8570 BAU/mL. This level would suggest that therapeutic doses can be achieved, at least with the most potent of

the 3 extracts. Only glycerinated extracts of cockroach should be used, because of the high degree of autodigestion in aqueous preparations.

Latex

Four patients with anaphylactic sensitivity to latex underwent injection immunotherapy with a commercial latex extract.³¹ All had reduction in skin tests, 3 had latex exposure without symptoms, and the other had reduced symptoms. The same commercial extract was employed in a 6-month study in 24 subjects with urticaria, rhinitis, or asthma due to latex exposure; 16 received active treatment and 8 received placebo.³² Systemic reactions occurred with 9% of injections. Following treatment there was significant improvement in the latex glove challenge and a strong trend toward improvement in bronchial and nasal symptoms on inhalation challenge in the active treatment group, without improvement in the controls. A different commercial latex extract was employed in a double-blind, placebo-controlled study of 23 latex-allergic subjects, most of whom had asthma.³³ Systemic reactions (SRs) were observed with 30% of injections and in 82% of patients receiving active treatment. Most SRs were mild and no subject withdrew because of SRs. There was no difference in the change from baseline in the diary-reported rhinoconjunctivitis or cutaneous symptoms between the active and placebo groups. On the basis of these reports injection therapy for latex sensitivity cannot be considered an established therapeutic approach, especially in view of the absence of an approved commercial extract in the United States.

EXTRACT DOSING FOR INJECTION THERAPY

A wide range of doses of allergen extracts are employed in subcutaneous injection immunotherapy in the United States.³⁴ The results of double-blind, placebo-controlled studies of dosing in injection therapy suggest that many of the doses being employed are clinically ineffective.^{35,36}

Effective doses of allergen extract for injection immunotherapy can only be determined by placebo-controlled studies. Except for the ragweed studies, most of these studies have been conducted in Europe where there is no common method of extract standardization. Therefore, to be able to combine all of the studies of extract dosing, the only available method is to express the dose as the major allergen content of the extract delivered at maintenance, even though this method presents problems related to differing monoclonal antibodies employed for the determinations. The doses that have been proved to give good clinical responses for those extracts, which have been standardized, are listed in **Table 1**. Also listed are doses that have produced definitely inferior results, sometimes no better than placebo. It must be noted that the range of effective major allergen dosing is fairly narrow; except for house dust mites and *Alternaria*, most values are between 10 and 20 μg .

Information regarding effective dosing by major allergens is useful only if the major allergen content is known for the commercially available allergen extracts. Of the United States standardized or nonstandardized extracts, only those of short ragweed list information on major allergen content. The content is listed in Food and Drug Administration units that are approximately equal to micrograms. Also, the content of major allergen varies quite widely from company to company, even in standardized extracts. Nevertheless, many of the extract-manufacturing companies have analyzed their own and other companies' products for major allergen content, so this information can often be obtained. **Table 2** lists the mean allergen content of multiple samples of United States extracts provided by one extract company.

Table 1 Effective maintenance doses for injection immunotherapy by major allergy content			
Allergen Extract	Major Allergen	Range of Effective Doses	Less Effective or Ineffective Doses
Grasses	Phl p 5 or other group 5 allergens	15 µg ³⁷ 18.6 µg ³⁸ 20 µg ³⁹	2 µg ⁴⁰
Birch	Bet v 1	3.28 µg ⁴¹ 12 µg ⁴²	Not determined
Short ragweed	Amb a 1	6 µg ⁴³ 11 µg ⁴⁴ 12.4 µg ⁴⁵ 24 µg ⁴⁶	0.6 µg ⁴⁵ 2.0 µg ⁴⁶
<i>Dermatophyoides</i>	Der p 1Der f 1	7 µg ⁴⁷ 10 µg ⁴⁷	0.7 µg ⁴⁸
Cat dander	Fel d 1	11.3 µg ⁴⁹ 15 µg ⁵⁰ 17.3 µg ⁵¹	3 µg ⁵² 3 µg ⁵³
Dog dander	Can f 1	15 µg ⁵⁴	3 µg ⁵⁴
<i>Alternaria</i>	Alt a 1	1.6 µg ²⁸	Not determined

Multiple Allergen Mixes

The vast majority of controlled studies of injection immunotherapy have employed only a single extract.^{5,7} On the other hand, the common practice in the United States is to administer a mixture of allergens.⁵⁵ The English and non-English medical literature was searched up to 2007 for reports of multiple allergen immunotherapy. Five studies, all administering extracts by injection, were identified that employed

Table 2 Representative mean content of major allergens in some United States standardized and nonstandardized extracts			
Allergen Extract	Concentration	Major Allergen	Mean Content of Major Allergen
Short ragweed	1:10 wt/vol	Amb a 1	520 µg/mL
Timothy grass	100,000 BAU/mL	Phl p 5	660 µg/mL
Kentucky blue grass (June)	100,000 BAU/mL	Poa p 5	300 µg/mL
Orchard grass	100,000 BAU/mL	Dac g 5	740 µg/mL
Bermuda grass	10,000 BAU/mL	Cyn d 1	225 µg/mL
<i>Dermatophagoides pteronyssinus</i>	10,000 AU/mL	Der p 1	67 µg/mL
		Der p 2	69 µg/mL
<i>Dermatophagoides farinae</i>	10,000 AU/mL	Der f 1	65 µg/mL
		Der f 2	80 µg/mL
Cat dander	10,000 BAU/mL	Fel d 1	40 µg/mL
A.P. dog (H.S.)	1:100 wt/vol	Can f 1	140 µg/mL
Dog dander	1:10 wt/vol	Can f 1	5.4 µg/mL

Each mean major allergen content represents analyses of multiple extracts from several extract manufacturers. Data were provided by Greg Plunkett, PhD, ALK-Abelló, Round Rock, TX, September 2010.

more than 2 non-cross-reacting extracts in therapy.⁵⁶ Three of the 5 demonstrated clinical efficacy, 2 for allergic rhinitis^{35,57} and 1 for asthma in children,⁵⁸ while 2 did not.^{59,60} In the allergic rhinitis studies showing efficacy, ragweed-allergic subjects were matched for severity of symptoms during one pollen season. The ragweed component of their multiple allergen immunotherapy was then either eliminated or reduced by 95%, in both cases resulting in significant reduction in control of symptoms during the ensuing ragweed pollen season. In the asthma study, children were treated with all inhalants giving positive skin tests, but at several different maintenance doses. The 2 highest doses (1:5000 wt/vol and 1:250 wt/vol for each allergen extract) resulted in many fewer children with asthma at the end of the study, with the higher dose showing the best results.

An additional study of preseasonal immunotherapy for grass pollen-induced rhinitis and asthma⁶¹ was not included in the review of multiallergen immunotherapy. In this study, subjects received 2 to 10 allergens in addition to grass extract or placebo in their treatment mix. Only 18 subjects participated; however asthma symptom-medication scores (SMS) were reduced significantly by immunotherapy (74%) with a trend for improvement in SMSs for rhinitis as well (43%).

Extract Dosing in Children

The study of injection immunotherapy for childhood asthma demonstrated that maximum concentrations of 1:5000 wt/vol resulted in greater reduction in asthma than placebo, but it was less effective than the 1:250 wt/vol dose of each of the extracts included in the treatment.⁵⁸ Otherwise there are very few studies of pediatric dosing and no consensus as to whether the dose should be different from that employed in adults. In 2 studies, in which immunotherapy was shown to reduce the incidence of new sensitization, the doses employed were less than those proven effective in adults. Thus, a dose containing 7 µg Der p 1 is recommended in adults,^{47,48} whereas in the study in 2- to 6-year-olds the maintenance dose contained 2 µg Der p 1⁶² and in the study of 5- to 8-year-olds the maintenance dose contained 3.5 µg Der p 1.⁶³ It is therefore possible that lower doses than are required by adults may be effective in young children.

SPECIAL CONSIDERATIONS IN CHILDREN

Age for Beginning Immunotherapy

Caution has been advised regarding initiating injection immunotherapy in children younger than age 5 years.^{64–66} Among the perceived problems are difficulty in communicating with the child regarding SRs (ie, the health care provider recognizing a systemic reaction) and that injections can be traumatic for very young children.⁶⁵ Balanced against these concerns are recent reports from Europe regarding the safety and efficacy of injection immunotherapy in young children^{67,68} and the reports of the long-lasting, disease-modifying actions of immunotherapy (Table 3). In a report from Spain, data were presented on 239 children aged 1 to 5 years treated with injection therapy. In 6689 injections there was only one systemic reaction, which occurred 90 minutes following an injection of house dust mite extract and which rapidly responded to treatment.⁶⁷ A report from Italy gave results from 592 children aged 3.5 to 10.5 years with severe asthma. These children were contrasted with 590 non-atopic children from the clinic.⁶⁸ After 3 years, the immunotherapy group showed greater improvement in symptoms, medication use, spirometry, and evidence of sensitivity compared with the drug-treated control group. Clinical adverse events were characterized as mild and transient.

Table 3 Prevention by subcutaneous injection immunotherapy for new sensitizations in monosensitized patients						
Study,^{Ref.} Year	Condition	Age (years)	Number	Follow-Up	New Sensitization	P Value
Des Roches et al, ⁶² 1997	Asthma (house dust mite)	2–6	22 treated 22 controls	3 y (end of treatment)	Active 55% Controls 100%	<.001
Purello-D'Ambrosio et al, ⁶⁹ 2001	Asthma or allergic rhinitis Multiple-single allergens	≥14, mean 22.5	7182 treated 1214 controls	Treated 4 y Follow-up 3 y	Active 26.95% Controls 76.77%	<.0001
Pajno et al, ⁶³ 2001	Asthma (house dust mite)	5–8	75 treated 63 controls	Treated 3 y Follow-up 3 y	Active 24.6% Control 66.7%	.0002
Inal et al, ⁷⁰ 2007	Asthma or rhinitis (house dust mite)	6–16	45 SCIT 40 SLIT 62 Controls	5 y	Active 29.7% (no difference SCIT/SLIT) Control 53.3%	.002

Modification of Disease

Prevention of new sensitizations in monosensitized patients

Several studies have reported that injection immunotherapy in monosensitized children or young adults decreases the number who develop new sensitivities not only during the course of immunotherapy but also for several years after treatment is discontinued (see [Table 3](#)). A similar protection has not been reported in polysensitized patients.

Prevention of progression from rhinitis to asthma

The main evidence that injection immunotherapy decreases the likelihood of asthma developing in patients who only have rhinitis comes from the Preventive Allergy Treatment (PAT) study, conducted in 6 European pediatric centers.⁷¹ The children, aged 6 to 14 years, were required to have symptomatic allergic rhinitis only to grass and/or birch and have no asthma during an initial observational year. One hundred and sixty-three children were then randomized to injection immunotherapy with Timothy and/or birch pollen extracts (n = 79) or were untreated controls (n = 72) during 3 years of the treatment phase of the study. At the end of 3 years, asthma had developed in 24% of the 79 children receiving injection immunotherapy and in 44% of the 76 control children. Follow-up observations on the children made 7 years after immunotherapy was discontinued showed no waning of the protective effect, with asthma in 25% of 64 treated subjects and in 45% of 53 control subjects.⁷²

DURATION OF TREATMENT AND PERSISTENCE OF EFFECT

Duration of Treatment

The onset of efficacy of injection immunotherapy is quite rapid, with good results reported following a single preseasonal course of treatment.³⁸ Most randomized studies are of just 1 year; however, in 2 studies of 3 years' duration, there was progressive improvement with each year of treatment.^{37,73} A 3-year duration of injection immunotherapy is also supported by studies showing persisting benefit for several years following 3 to 4 years of injection immunotherapy.^{62,63,72-76}

Persistence of Benefit After Discontinuation of Treatment

Multiple lines of evidence indicate that the beneficial effects of injection immunotherapy persist after completion of a course of treatment of adequate length and sufficient dosing. The suppression of both development of new sensitivities in monosensitized patients and development of asthma in patients with allergic rhinitis has been shown to persist, with little evidence of diminution for 3 to 7 years.^{63,69,72}

Studies have also been conducted that show persisting benefit for the symptoms of allergic rhinitis and allergic asthma. Specific immunotherapy to grass was discontinued after 3 to 4 years of treatment in 108 patients who had responded well to treatment.⁷⁵ Each year there was an increased number of patients with recurrent rhinitis symptoms, reaching 31% by the third year after discontinuation. In a placebo-controlled study, 32 subjects who had received grass injection immunotherapy for 3 or 4 years were randomized to continue to receive either maintenance injections of Timothy or placebo.⁷⁶ After 3 years, there was no difference in symptoms during the grass pollen season between the 2 groups. A small, open study of injection grass immunotherapy was conducted between 1988 and 1991. The participants were followed up prospectively through the grass pollen seasons of 1997 and 2003, 6 and 12 years after the discontinuation of treatment.⁷⁷ After 12 years there were still fewer symptoms, fewer new sensitizations, and a strong trend for less seasonal asthma in the treated group.

Injection immunotherapy was discontinued in a group of patients who had received house dust mite extract for from 12 to 96 months and had become symptom free.⁷⁴ Over the 3 years following discontinuation, approximately half the patients relapsed. The likelihood of relapse correlated inversely with both the duration of immunotherapy and the degree of immediate skin test suppression they experienced during treatment. On the basis of these studies the usual recommendation is that immunotherapy be continued for 3 to 5 years before discontinuation is considered.

ADHERENCE TO SUBCUTANEOUS INJECTION IMMUNOTHERAPY

Because injection immunotherapy is usually administered in a medical facility, it is easy to determine whether a patient receives the treatment. Several investigators have examined the percentage of patients who have discontinued the treatment of their own volition before completing the planned 3-year course of injections. In 2 university clinics, approximately half of the patients discontinued treatment; the major contributing factor was the inconvenience of the treatment.^{78,79} A much lower rate of discontinuation was reported from a large private clinic where only 12% of 1033 patients prescribed injection immunotherapy failed to complete at least 3 years of treatment.⁸⁰ Again inconvenience was a major contributor, as were concurrent medical conditions, change of residence, and adverse reactions. Patient-initiated withdrawals during 3 years of immunotherapy administered intranasally, sublingually, or subcutaneously were compared in 2774 children in southern Italy.⁸¹ Patient withdrawals over the 3 years were 73.2% for intranasal, 21.5% for sublingual, and 10.9% for subcutaneous injection immunotherapy. The principal reason for withdrawal from intranasal was local nasal symptoms (57%). Major reasons for withdrawal from sublingual were cost (36%) and ineffectiveness (25%), and cost (40%) and inconvenience (24%) were reasons for withdrawal from subcutaneous.

COMPARATIVE EFFECTIVENESS OF SUBCUTANEOUS AND SUBLINGUAL IMMUNOTHERAPY

The relative effectiveness of sublingual and subcutaneous immunotherapy either in the short-term or long-term is not established. The data available to assess relative effectiveness consists of meta-analyses of reports of treatment of allergic rhinitis by the two methods, comparative results when the same investigator treated similar patients by the two methods, and studies with patients randomized to treatment by the two methods.

Systematic reviews of published articles on treatment of allergic rhinitis by sublingual immunotherapy (SLIT)⁸² and injection immunotherapy (SCIT)⁵ were conducted for the Cochrane Collaboration. Twenty-two double-blind, placebo-controlled trials involving 979 patients were included in the SLIT meta-analysis. There was an oval reduction in symptoms (SMD -0.42) and medication use (SMD -0.43). Fifty-one studies with 2871 subjects met the criteria for randomized trials of SCIT. The overall improvement in symptoms was SMD -0.73 and for medications SMD -0.57, suggesting a possible greater efficacy of SCIT over SLIT.

The same United Kingdom group conducted studies on the use of SLIT and SCIT for seasonal allergic rhinitis due to grass pollen. In 1989, they recruited 40 patients with severe hay fever unresponsive to symptomatic therapy.³⁸ Patients were administered a preseasonal course of either Timothy pollen extract or placebo by injection. During the ensuing grass pollen season, the active-treatment group had a reduction in total symptoms of 61% and reduction of medication use of 79% compared with the placebo-treated group. Fifty-six patients with grass pollen-induced allergic rhinitis

were recruited in 1998 and randomized to SLIT or placebo.⁸³ The SLIT was of 9 to 14 months' duration by the beginning of the grass pollen season, with a monthly cumulative dose of Timothy 225 times that administered in the SCIT study. Reduction in symptoms in the active-treatment group during the grass pollen season of 1999 was 28% and medication use was reduced by 45% compared with placebo, although neither result was statistically significant. Global assessment of improvement was significant in the active group, but the magnitude of the difference from placebo was about half that observed in the previous SCIT study for patient-reported outcomes.

A placebo-controlled comparison study of treatment of allergic rhinitis due to birch pollen, uncontrolled by symptomatic therapy, was conducted in Denmark.⁴¹ Seventy-one subjects were observed during one birch pollen season, then randomized to injection therapy or sublingual therapy with a cumulative monthly dose 225 times that in the SCIT group. Both groups had significant reductions in symptoms and medication compared with the placebo group. There were no statistically significant differences between those receiving SCIT and SLIT. However, compared with the placebo group the reduction in symptoms and medication use in the SCIT group was 70% and 33% greater, respectively, than in the SLIT group.

The response of perennial allergic rhinitis in patients sensitized only to house dust mites to immunotherapy with house dust mite extract administered either by injection or sublingually was compared in 193 patients.⁷³ The cumulative monthly SLIT dose in this study was only 3 times that used for SCIT. Clinical improvement during 3 years of immunotherapy was progressive and similar in the two groups. After discontinuation, the subjects were followed for an additional 3 years. There was no increase of symptoms in the SCIT group, but symptoms increased significantly in the third follow-up year in the SLIT group. SCIT was also significantly better for reduction in nasal airway resistance and prick skin tests to house dust mites.

Thus by all 3 data sets, there is a suggestion of a superior response to SCIT compared with SLIT; however, this conclusion is very tentative and many more studies are needed.

SUMMARY

Immunotherapy by the subcutaneous injection of increasing doses and then maintenance doses of extracts of inhalant allergens has been practiced with only minor changes for 100 years. Controlled clinical trials have established its efficacy in treating allergic rhinitis, asthma, and stinging insect sensitivity, and there are preliminary data to suggest a favorable response in some patients with atopic dermatitis. It is not recommended for treating primary food allergy, but may benefit the oral allergy symptoms associated with pollen sensitivity. The best documented responses are to extracts of pollens, house dust mites, and animal danders, and to venom and whole-body extracts of stinging insects. There is limited support for its use in fungal and latex allergy, and to date there is no documentation of efficacy with cockroach extracts. The response to subcutaneous injection immunotherapy is very dose dependent, with doses one-fifth or one-twentieth of the effective doses often offering little or no benefit. Dosing is best expressed as the major allergen content of the maintenance dose. This practice is limited by the availability of data on the major allergen content of commercially available extracts in the United States. Treatment with mixtures of non-cross-reacting extracts has been proved to be effective in injection immunotherapy, provided the concentration of each extract is adequate. Among the exciting findings with subcutaneous injection immunotherapy is its

disease-modifying actions. These actions include blocking the development of new sensitivities in monosensitized patients, blocking the progression to asthma in patients with allergic rhinitis, and persistence of treatment effects up to 7 to 10 years following discontinuation of a 3-year course of treatment. Studies comparing the outcome with subcutaneous injection and sublingual-swallow approaches to immunotherapy are inadequate, but the limited data available suggest that subcutaneous injection may be somewhat more effective than sublingual administration.

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