Ten-Year Experience with Sublingual Immunotherapy for Juniper Pollenosis

ABSTRACT

RATIONALE: Juniper species are major spring allergens in the southwestern USA. We previously reported a study of sublingual immunotherapy (SLIT) for Juniper pollenosis in 2005. Over the last ten years, we have gradually expanded the use of SLIT for this allergen. This study summarizes our results.

METHODS: Pollen counts for J. Asheii and J. Scropulorum typically start to rise in mid-March in our area of southwest Colorado. Patients are contacted in early January to begin the SLIT program. Patients receive 2 vials of J. Scropulorum (Rocky Mountain Juniper, Greer Labs)) extract containing a total of 150-200 micrograms of protein. Maintenance dose is one dropper (6 micrograms) every 3 or 4 days until late May. Patients are instructed to place the drops under the tongue for at least one to two minutes, and then expectorate the remainder. Pollen counts are observed during the season using a Rotorod sampler. Patients are then contacted by phone or office visit in May for assessment of efficacy.

RESULTS: For the 2014 season, 165 patients were treated with Juniper SLIT. 77 of these patients were monosensitized. 149 (90%) patients reported positive results. Side effects were mostly local oral discomfort. There were no systemic reactions. In the 2013 season, there were 53 patients reporting 79% positive results.

CONCLUSIONS: Juniper SLIT may be an effective form of immunotherapy when given pre-co-seasonally at the doses studied.

BACKGROUND

Juniper species are major spring allergens in the southwestern United States, in Europe, and in Japan. Mountain cedar (Juniperus asheii) is a prominent allergen in central Texas and into New Mexico, and Rocky Mountain Juniper (Juniperus scropulorum) is predominant into the Colorado plateau. The term “cedar fever” has been used to describe this severe form of allergic rhinoconjunctivitis. In Europe, these species are referred to as cypress, and are major allergens in southern Europe to the Middle East. Japan also has a significant problem with seasonal allergic rhinitis (SAR) to cedar species which has been termed “a national affliction”(1). In 2005, we presented a small study comparing subcutaneous rush immunotherapy (SCIT) with sublingual immunotherapy (SLIT) in patents monosensitized to Juniper (2). The results suggested that use of single allergen SLIT for Juniper may be efficacious. Meanwhile, at least two European studies appeared using SLIT for cypress pollen allergy. One placebo controlled study of 76 patients showed a reduction in medication usage when SLIT was administered pre-co-seasonally in cypress allergic patients (3). In another study, SLIT was compared to SCIT during year round administration. Markers of allergic inflammation were assessed in nasal lavage fluids and clinical symptom scores were graded. Both SCIT and SLIT for cypress pollen showed similar reductions in inflammatory markers and clinical symptoms (4). Japanese researchers have published a number of studies pertaining to the use of cedar SLIT with positive results in both
adults and children (5,6,7). SLIT for cedar pollenosis has been approved by insurers in Japan beginning in 2014 (1).

SLIT is becoming more widely used in the USA with the recent FDA approval of grass and ragweed pollen extracts, which are available commercially (9). However, non-standardized extracts, such as Juniper, are unlikely to be approved for SLIT in the near future. We began using Juniper SLIT on a small scale in 2005. Initially, these patients were monosensitized to Juniper, and had difficulty with access to physician’s offices for the use of SCIT. As reports of positive efficacy became clear, the number of patients treated increased markedly over the last three years. This report summarizes our experience with Juniper SLIT in the southwestern United States over the last 10 years.

METHODS

In 2005 we began compiling a registry of patients who were monosensitized to Juniper species (J. Asheii and J. Scropulorum). Patients would be contacted in early January and offered the SLIT program as an option for immunotherapy. Patients were given informed consent regarding the experimental nature of SLIT, possible side effects, and uncertain coverage by insurers. Patients received two vials of extract containing 2cc. (150-200 micrograms) of J. Scropulorum (Greer Laboratories) with 8cc of glycinerated diluent (ALK Abello). Patients were given a build-up phase with a gradually increasing number of drops over a one week period until they reached a full dropperful (0.7cc containing 6 micrograms of protein). They would then be instructed to place one dropperful under the tongue and retain it for at least a minute before expectorating the remainder. Doses during the maintenance period were given twice a week at home, and extracts were kept refrigerated. Using this schedule beginning in late-January, the full 20cc. of extract would be enough to last in most cases until the end of Juniper season in May. That is a total of 28 doses lasting approximately 14 weeks.

Patients were contacted following the pollen season by phone, office follow up, and an online survey. We used a modified version of the Rhinitis Quality of Life Questionnaire (RQLQ). Patients were asked to report on symptoms, medication usage, side effects, compliance, and, finally, whether they would like to continue with SLIT as an option. In 2010, we expanded the definition of monosensitized to include patients with symptoms of SAR mainly during cedar season, with positive skin prick tests to Juniper, and otherwise mild SAR controlled with medication (clinically monosensitized). Pollen counts were obtained in our local area by standard methods using a Rotorod Sampler (IMS Health).

RESULTS

From 2005 to 2010, few patients participated. These patients typically lived in remote areas, such as the Navajo Reservation, where access to medical facilities was severely limited. In 2010, the number of patients increased (Fig.1), but still only amounted to a few dozen until 2012 when utilization approached 50 patients. During the 2014 season, 165 patients participated. A total of 365 patient-years experience are now reported, involving approximately 10,220 doses given. In 2014, 77 of 165 (47%) patients were monosensitized by skin test, the rest were considered clinically monosensitized. Table 1 shows a summary of patients treated, the percent
monosensitized, and the percent of children under 15. The rate of positive results is defined by improved symptom scores, lower medication usage and willingness to continue with the SLIT program in the future. Juniper pollen counts are shown for the ten year period. Cedar pollen first appears in our area around March 15\textsuperscript{th}. Peak levels of the pollen usually occur within two or three weeks of April 15\textsuperscript{th}, and there was significant variation in levels. 2014 happened to be a relatively low year, with the count just under 1000 grains/cu.meter. This could influence the results for this year.

![Graph showing pollen count from 2005 to 2014](image)

**Figure 1. Year of treatment vs. number of patients**

The percentage of patients reporting positive results ranged from 75\% in the 2009 and 2010 seasons to 90\% or greater during the 2011 and 2014 seasons. Males and females were equally represented. In 2014, there were 59 children in the group under the age of 15 (35\%). In 2013 there were 18 children out of 53 total patients (34\%). Side effects were reported by up to 17\% of patients. The most common complaint was oral itching, less frequent side effects included itching in the soft palate, indigestion, and heartburn. There were no systemic symptoms in any of the patients during the ten year period involving approximately 10,220 doses prescribed. Non-compliance rates, as judged by failure to complete the prescribed course entirely, were less than 10\% in the 2012-2014 seasons, perhaps due to the bi-weekly dosing schedule. However, “front end” non-compliance rates were very high. Notices went out to 247 patients in January of 2014 and 165 (66\%) of the patients subsequently received the treatment.
<table>
<thead>
<tr>
<th>Year</th>
<th>#patients</th>
<th>%mono</th>
<th>%peds</th>
<th>%positive</th>
<th>peak pollen</th>
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<td>83</td>
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<td>0</td>
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Table 1.

DISCUSSION

Mountain cedar pollen provides an excellent model for the study of SAR treatment (8). Our experience demonstrates that sublingual desensitization to Juniper pollen on a pre-co-seasonal schedule may be efficacious at rates comparable to subcutaneous immunotherapy. Advantages of the sublingual route include ease of administration, an excellent side effect profile, and lowered cost compared to subcutaneous immunotherapy. SLIT is particularly useful in children and about 35% of patients in our SLIT program are under the age of 15. Parents report excellent compliance in kids with the bi-weekly doses, and the taste with glycerinated diluent is not unpleasant.

Although widely practiced in other parts of the world, adoption of SLIT has been slow in the USA (9). Barriers to the more widespread use of SLIT include the lack of FDA approval for non-standardized extracts, concerns about liability related to side effects, a general distaste for “off label” prescribing, and billing uncertainties. Despite these barriers, allergists in the USA will be increasingly prescribing the commercial SLIT preparations for grass and ragweed pollen. Unfortunately, the FDA seems unlikely to approve the use of non-standardized extracts, such as Juniper, for SLIT use. Furthermore, the cost of standardizing multiple extracts is prohibitive for small allergy supply houses (T. Greer, personal communication). As patients become aware of SLIT availability, there may be confusion as to why allergists are unable to provide this service for severe local allergy symptoms such as “cedar fever”.

A number of factors are also contributing to a change in immunotherapy prescribing in the USA. Remote allergy providers are contracting with primary care physicians to offer allergy testing and immunotherapy. Patients are given presumably low dose allergy extracts to administer at home with no direct involvement of local Board Certified allergists. Many ENT physicians, including those in our community, are adopting low dose year round SLIT as offered by a number of online, remote allergy sites (Allergy Choices). Such protocols have questionable efficacy at best. Finally, as of 2014, pharmaceutical companies have entered this market offering grass and ragweed...
SLIT products, which are effective, but at a retail cost of about $1500/season. Concurrently, these changes are taking place at a time of rapid change in the US healthcare system. Government and third party payers are moving toward a reimbursement system that rewards value over volume. Although subcutaneous immunotherapy has been shown to be cost effective in previous studies (10), it may be even more cost effective when used in selected patients, such as our monosensitized population, by the sublingual route.

This report is based on clinical experience and is not a placebo controlled trial. To date, I have been unable to find any studies from the USA regarding the use of SLIT for Juniper desensitization, despite a number of studies from abroad as previously noted. Such trials are urgently needed to document the true response of patients to this form of therapy. Allergists should be the thought leaders in their communities regarding the use of any form of immunotherapy. The ability of allergists to offer a safe, efficacious, and lower cost form of immunotherapy as a preventive modality in treating cedar pollen allergic disease would be a good start toward healthcare value.

REFERENCES


8. The mountain cedar model in clinical trials of seasonal allergic rhinoconjunctivitis.
