

The mountain cedar model in clinical trials of seasonal allergic rhinoconjunctivitis

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ABSTRACT

Background: Clinical trials of seasonal allergic rhinoconjunctivitis use the mountain cedar (*Juniperus ashei*) season as the predominate model.

Objective: To evaluate clinical trials of rhinoconjunctivitis using mountain cedar, to present analysis of pollen counts during 18 seasons, and to discuss the model.

Methods: The medical literature was searched for clinical trials performed using mountain cedar either in or out of season. Pollen counts were recorded and analyzed for the duration of 18 seasons.

Results: Thirty-eight trials were identified. Of these, 1 evaluated onset of allergy, 8 were immunotherapy trials, 28 were pharmaceutical clinical trials, and 1 studied symptoms elicited in a pollen challenge chamber trial. Many generic equivalency trials are unreported. In the 18 years of counts in the Texas Hill Country, a dependable and intense pollen density was present in every season. The combination of dependable seasons without confounding pollens, the large number of allergic patients, and the ability to concentrate resources in one geographic area has made mountain cedar allergy a mainstay for therapeutic trials for allergic rhinoconjunctivitis.

Conclusion: Mountain cedar allergy presents a dependable and durable model of allergic rhinoconjunctivitis.

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Introduction

A major consideration in evaluating therapies for seasonal allergic rhinitis is choosing the appropriate model to study. In the evaluation of immunotherapy and pharmacotherapy, the mountain cedar (*Juniperus ashei*, Cupressaceae) season has proven to be a robust and dependable natural model of rhinoconjunctivitis. The mountain cedar tree of the south-central United States presents an unparalleled natural model to study allergic rhinoconjunctivitis. Unlike all other plants in the United States, mountain cedar pollinates during the winter months. The tree is a dioecious species with the mature male tree as the pollinating form. The mountain cedar tree is considered by many to be a difficult-to-control nuisance that wastes water and crowds out other foliage.¹ Others note the value of the tree in some areas prone to high erosion. The tree can be found as dense as several hundred plants per acre, and a male tree can produce 1 billion grains of pollen. During times of intense pollination, pollen is released with such density that fire departments are summoned because the pollen clouds resemble dense

smoke. In the Hill Country of Texas, pollen counts as high as 86,000 grains/m³ have been recorded, with counts of 10,000 to 20,000 grains/m³ being common. Mountain cedar grows in the Texas Hill Country, the Arbuckle Mountains of Oklahoma, and some areas of the Ozarks of Arkansas and southern Missouri, with 8.6 million acres involved in Texas alone, and with especially dense growth and pollination in the Hill Country of South Texas, also known as the Edwards Plateau.² In South Texas, mountain cedar pollen is the most common cause of allergic rhinoconjunctivitis.

In the order Coniferales, Cupressaceae is the most allergenic family.³ The major extractable allergen in mountain cedar has been reported to be Jun a 1, a glycoprotein homologous to the major allergens Cha o 1 from Japanese cypress and Cry j 1 from Japanese cedar.^{4,5} Jun a 1 and its homologues contain pectate lyase activity, with one of the major IgE epitopes occurring within the active enzyme site.⁶ As such, virtually all of the major allergens from the Cupressaceae species worldwide contain this conserved epitope (R. Goldblum, MD, oral communication, 2013). Studies of the crystal structure of Jun a 1 suggest that the parallel β -helix structure provides a steric hindrance to enzyme activity and thereby makes it a potent antigen.⁷ A second antigen, Jun a 3, has been isolated and sequenced and its structure modeled.^{8,9} Jun a 3 and related proteins, Cry j 3 from Japanese cedar and Cup s 3 from Italian

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Table 1
Mountain cedar studies of allergic rhinitis

Source	Agents or effect studied	No. of patients	Evaluation	Environment
Black, ¹⁷ 1929	Injection immunotherapy	39	Efficacy	Natural season
Miller et al. ²⁰ 1964	Injection immunotherapy	34	Efficacy	Natural season
Pence et al. ²¹ 1976	Injection immunotherapy	32	Efficacy	Natural season
Hirsch et al. ²² 1981	Injection immunotherapy	14	Efficacy	Natural season
Lee et al. ²³ 1982	Injection immunotherapy	76	Efficacy	Natural season
Ramirez, ¹⁸ 1984	Onset of allergy in population	234	Define natural history	Natural season
Ratner et al. ²⁷ 1985	Acrivastine tablets	119	Efficacy	Natural season
Reid et al. ¹⁹ 1988	Injection immunotherapy	38	Efficacy	Natural season
Fling et al. ²⁴ 1989	Injection immunotherapy	14	Efficacy	Natural season
Parker et al. ²⁵ 1989	Injection immunotherapy	51	Efficacy	Natural season
Ratner et al. ³¹ 1992	Fluticasone propionate nasal spray vs beclomethasone dipropionate nasal spray	313	Efficacy	Natural season
Van Bavel et al. ³² 1994	Fluticasone propionate nasal spray vs terfenadine tablets	232	Efficacy	Natural season
Ratner et al. ⁴⁷ 1994	Azelastine nasal spray	251	Safety and efficacy	Natural season
Kozma et al. ³³ 1996	Fluticasone propionate nasal spray vs terfenadine tablets	232	Cost-efficacy ratios	Natural season
Howland et al. ³⁴ 1996	Fluticasone propionate nasal spray	304	Efficacy	Natural season
Williams et al. ²⁸ 1996	Acrivastine plus pseudoephedrine capsules vs acrivastine capsules vs pseudoephedrine capsules	676	Efficacy	Natural season
Ratner et al. ³⁵ 1996	New formulation of flunisolide nasal spray vs previous formulation of flunisolide nasal spray	216	Safety, tolerability, efficacy	Natural season
Ratner et al. ³⁶ 1998	Fluticasone propionate nasal spray vs loratadine tablets vs. combination fluticasone propionate nasal spray plus loratadine tablets	600	Efficacy	Natural season
Hampel et al. ⁴⁸ 1999	Levocabastine nasal spray	270	Efficacy	Natural season
Hampel et al. ²⁹ 2002	Ebastine capsules with or without food	652	Efficacy	Natural season
Ratner et al. ³⁰ 2002	Tecastemizole tablets	885	Efficacy	Natural season
Atkinson et al. ³⁷ 2005	Rofleponide nasal spray vs mometasone furoate nasal spray	660	Efficacy	Natural season
Ratner et al. ⁴⁹ 2005	Olopatadine nasal spray	667	Efficacy and safety	Natural season
Ratner et al. ³⁸ 2006	Ciclesonide nasal spray	726	Efficacy	Natural season
Ratner et al. ³⁹ 2006	Ciclesonide nasal spray	327	Efficacy and safety	Natural season
Hampel et al. ⁵⁰ 2006	Olopatadine nasal spray	675	Quality of life and dose selection	Natural season
Martin et al. ⁴⁰ 2006	Fluticasone propionate nasal spray vs montelukast tablet	736	Efficacy	Natural season
Martin et al. ⁴¹ 2007	Fluticasone furoate nasal spray	641	Dose selection	Natural season
Ratner et al. ⁵³ 2008	Azelastine nasal spray vs fluticasone propionate nasal spray vs combination of azelastine nasal spray and fluticasone propionate nasal spray	151	Efficacy	Natural season
Jacobs et al. ⁴² 2009	Fluticasone furoate nasal spray	302	Efficacy	Natural season
Andrews et al. ⁴³ 2009	Fluticasone furoate nasal spray vs fexofenadine tablets	875	Efficacy	Natural season
Van Bavel et al. ⁵¹ 2009	Azelastine nasal spray	536	Efficacy and safety	Natural season
Hampel et al. ⁵⁴ 2010	Azelastine nasal spray vs fluticasone nasal spray vs combination of the 2 in single nasal spray device	610	Efficacy	Natural season
Ratner et al. ⁴⁴ 2010	Ciclesonide nasal spray	707	Efficacy, safety, and dose selection	Natural season
Jacobs et al. ²⁶ 2011	Pollen concentration	42	Pollen dose-response in environmental chamber	Environmental chamber
Howland et al. ⁵² 2011	Azelastine nasal spray	506	Efficacy	Natural season
Ratner et al. ⁴⁵ 2012	Ciclesonide nasal spray	671	Efficacy and safety	Natural season
Van Bavel et al. ⁴⁶ 2012	Beclomethasone dipropionate nasal aerosol	340	Efficacy and safety	Natural season

cypress, are members of the pathogenesis-related proteins.^{10–12} Schwietz et al.¹³ investigated cross-reactivity among 12 Cupressaceae and 1 Taxodiaceae species (Japanese cedar). They found positive skin prick test results in 10 patients with mountain cedar allergy. In in vitro studies, these species were found to have shared antigens, and it has been speculated that for both testing and immunotherapy, it may be possible to use one component-based extract.¹³

Eastern red cedar (*Juniperus virginiana*) is much more widespread across the eastern United States.³ However, the pollen from eastern red cedar does not appear to be as dominant an allergen as is seen in mountain cedar regions.^{14,15} Several characteristics may provide insight. First, the density of growth, and therefore pollen production, is not as high as that seen for mountain cedar. Second, the outer waxy cuticle of the pollen is thicker, making the major allergenic protein, Jun v 1, potentially less accessible. Third, the other major allergenic protein, Jun v 3, has not been detected in pollen extracts, likely because of a mutation leading to a stop codon within the complementary DNA sequence.¹⁶

Cedar hay fever was described by Black¹⁷ in 1929. He found that with skin tests, there was cross-reaction of mountain cedar pollen with Port Oxford cedar (*Chamaecyparis lawsoniana*) pollen found primarily in Oregon and California. He demonstrated that with desensitization with either pollen there was improvement in symptoms in those with mountain cedar allergy.

In 1984, Ramirez¹⁸ studied 234 mountain cedar allergic patients and found that 34% were allergic to mountain cedar only. That group of 34% had lower IgE levels and required longer exposure intervals (mean, 14.4 years) on moving to South Texas to develop allergic sensitization than the atopic individuals (mean, 5.7 years) with multiple allergies.¹⁸ A subsequent study confirmed a mountain cedar allergic subgroup of individuals with single positive skin test results and no other signs of atopy.¹⁹

In recent years, multiple trials using this model have been performed annually. This report will present the published trials to date, present summaries of mountain cedar pollen counts and weather conditions during the past 18 years, and discuss the mountain cedar clinical model of allergic rhinoconjunctivitis.

Methods

A computerized search was conducted for clinical trials in MEDLINE and PubMed using the following keywords: mountain cedar, cedar fever, and *Juniperus ashei*. In addition, the bibliographies of those articles identified were reviewed for additional references. Pollen counts measured with a Burkhard sampler were recorded by Paul H. Ratner, MD, at Sylvana Research in San Antonio, Texas, for 18 years. Simple descriptive statistics were used to summarize pollen count data. Cumulative area under the curve was used to represent the magnitude of seasonal exposure to mountain cedar pollen, which was compared with seasonal rainfall and temperature data using a generalized linear modeling approach.

Results

Thirty-eight clinical trials of mountain cedar allergy were identified. Most were performed in the Hill Country of Texas. One trial contrasted the differences in persons with allergy to mountain cedar only with those who had multiple allergies.¹⁸ Eight immunotherapy trials have been reported.^{17,19–25} Twenty-eight pharmaceutical trials have been reported, including phase 3 studies. One environmental chamber study has been reported.²⁶ Table 1 presents a summary of those studies.

Of the 28 pharmaceutical trials using this model, 4 were of oral antihistamines.^{27–30} Sixteen trials were of corticosteroid nasal sprays.^{31–46} Six trials were of antihistamine nasal sprays.^{47–52} Two trials investigated a combination of a nasal antihistamine and a nasal corticosteroid.^{53,54} A pediatric trial using the mountain cedar model has not been performed. The minimal age for enrollment of any of these pharmaceutical trials was 12 years. Additional clinical trials, including a large number of generic nasal spray equivalent trials, have been performed and are not reported in the literature.

The first environmental chamber trial using mountain cedar pollen as the antigen has been reported by Jacobs et al.²⁶ That trial demonstrated that the pollen could provoke symptoms in individuals who were sensitive to the skin test and had a history of symptoms. Healthy, nonallergic controls in that chamber study developed minimal symptoms.

San Antonio pollen data were examined for the years 1994 to 2012. The mean, range, and SE of mountain cedar pollen counts by

weeks for 18 pollen seasons are presented in Figure 1. Although variability within seasons was seen, high counts in San Antonio were present in every season with similar patterns. Six of the 18 seasons revealed brief overlap at the end of the mountain cedar season with the spring season Arizona ash pollination. To ensure the adequate capture of symptom occurrence in mountain cedar studies, most protocols require 3 consecutive days with pollen counts of greater than or equal to 50 grains/m³ to initiate trials. Across the years analyzed, that condition was present at earliest by December 7 and at the latest by December 30. The duration of the seasons averaged 51 days. The earliest that counts were consistently below 50 grains/m³ was January 31, and the latest was February 21 (Fig 2). We did not observe an association between cumulative pollen count for a season and total rainfall or average temperature ($P = .56$ and $P = .88$, respectively; data not shown).

Discussion

Allergic rhinoconjunctivitis is a significant medical disorder that affects as many as 40 million persons in the United States. Symptoms include nasal itching, nasal congestion, sneezing, and ocular tearing and itching. Substantial socioeconomic costs are attributed to this syndrome.

As noted in the “Results” section, multiple studies have shown efficacy of immunotherapy for those with mountain cedar allergy. Five decades ago, annual pollen counts were published in a 10-year study in San Antonio by Fein and Kamin.⁵⁵ Mountain cedar counts were similar to those published in this article. As demonstrated in this current report by the counts performed at Sylvana Research, substantial counts are present for 7½-week intervals on the average. Levitin and Van de Water⁵⁶ demonstrated that mountain cedar pollen concentrations could be forecast with some accuracy, although given the regularity of the counts, forecasting may have little value in the Texas Hill Country. Although climate change appears to be affecting worldwide patterns and intensities of aeroallergens,⁵⁷ the data presented in this report do not reveal changes in mountain cedar pollen duration or intensity during 18 seasons.

Perhaps the most difficult decision in a natural season allergy study is the start date for screening, particularly if there will be a placebo run-in phase. If the study is initiated too soon, there will

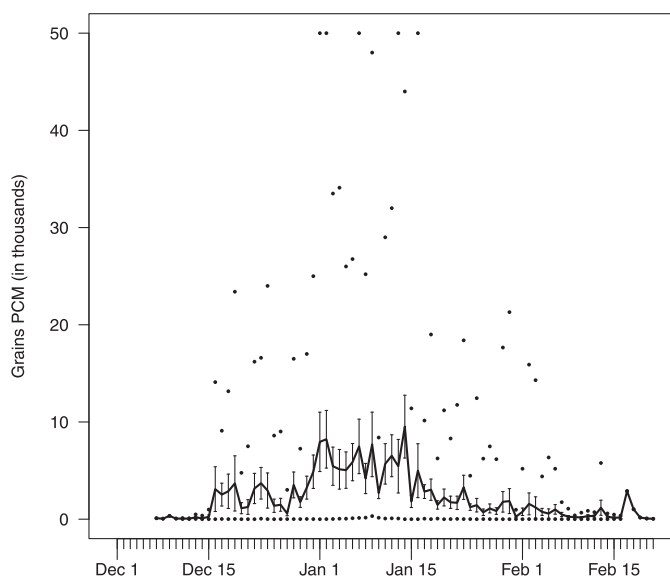


Figure 1. Mean $\pm$ 1 SEM daily pollen counts of the 1994 to 2012 mountain cedar pollen seasons. Points represent minimum and maximum daily counts.

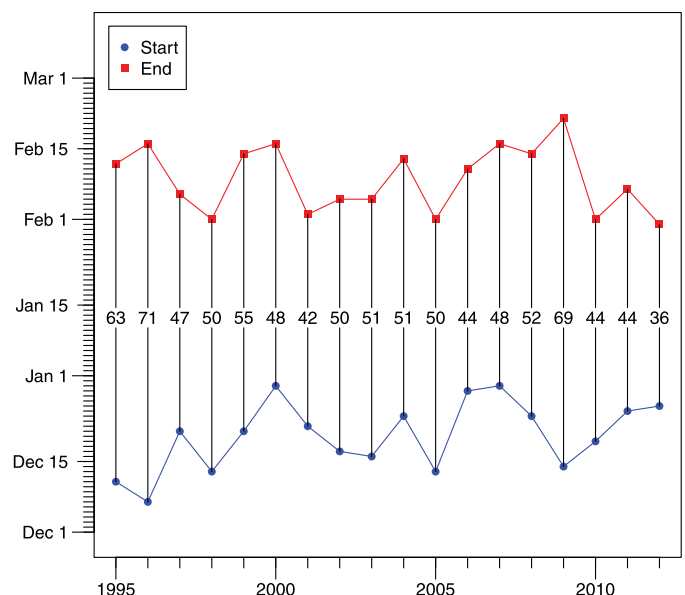


Figure 2. The start and end times of adequate mountain cedar pollen counts (y-axis) by end of seasons (x-axis). The centrally located numbers represent the length of the pollen season in days.

be a large number of randomization failures. If the study is started too late, many potential participants will have self-treated with excluded medications. In the cedar model, the requirement for 3 consecutive days of 50 grains/m³ appears to yield sufficient but not excessive symptoms. The reported pharmaceutical trials used a variety of inclusion criteria, such as total nasal symptom scores, for randomization criteria and required moderate to severe symptoms. The number of randomization failures is not provided in most of the reports. Therefore, the 3-day pollen count standard for initiating trials is not evaluable. A theoretical disadvantage of the mountain cedar model is for symptomatic responses to very dense pollen to overwhelm therapy of limited efficacy. The pharmaceutical trials reported were successful, so that potential disadvantage cannot be assessed.

For a pivotal New Drug Application submission, the mountain cedar model is accepted for 1 of the 2 required phase 3 trials for any new molecular submittal for treatment of allergic rhinoconjunctivitis. Any other seasonal pollen can be used for the second trial.⁵⁸

In a large San Antonio study, Calabria et al.⁵⁹ demonstrated that mountain cedar was the tree most commonly associated with positive skin test results, with 43% of atopic patients experiencing sensitivity. Because of the large numbers of persons highly sensitive to this pollen, it is anticipated that the chamber model using mountain cedar pollen will be useful for future studies of pharmacotherapy and immunotherapy, as well as the assessment of molecular and genetic characteristics of acute inflammation. Bernstein⁶⁰ has anticipated that in the future specific allergen provocation tests in a chamber may be used as a criterion for inclusion in a study to provide a more homogeneous group.

Thus far, there are no reports of sublingual immunotherapy for the treatment of mountain cedar allergy. Both the natural season and the environmental chamber model would appear to be appropriate for studying this mode of therapy.

Mountain cedar allergy presents a durable model that has become a mainstay of therapeutic trials for allergic rhinoconjunctivitis. There are a number of reasons for the success and potential of this model: (1) a unique season during most of which no other confounding seasonal pollen is present; (2) a very large population of symptomatic potential individuals; (3) antigens well characterized by structure and sequence; (4) the logistical ability to concentrate study resources in one geographic area; and (5) as demonstrated by the data presented in this study, the intensity and consistency of the pollen distribution.

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