



Comparative costs of subcutaneous and sublingual immunotherapy

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Purpose of review

This article describes the most recent comparative cost evaluations for subcutaneous (SCIT) and sublingual (SLIT) immunotherapy.

Recent findings

Only one recent article compares the costs of SCIT and SLIT in America. No American publications assess direct and indirect costs together. Few studies outside of America assess these costs in detail.

Summary

Limited data exist on the direct and indirect costs of SCIT and SLIT in the United States. Studies suggest that SLIT may be more affordable when taking indirect costs into account. Costs for SLIT may be more contained if physicians are more selective in the number and volume of antigens utilized per patient. Recent Food and Drug Administration approval of select sublingual tablets in America is changing the payment methodology for SLIT in America. Limited data on the cost in America call for further American studies on this topic.

Keywords

allergy, cost, insurance, subcutaneous immunotherapy, sublingual immunotherapy

INTRODUCTION

Allergy immunotherapy (AIT) is currently the only form of allergy management that alters the course of the disease by changing the body's response to allergens on a cellular level. Initiation of AIT has been shown to prevent the development of new allergies, decrease the prevalence of asthma in allergic rhinitis patients, and allow for decreased use of allergy medication, which may be sustained for years following the completion of therapy [1]. Immunotherapy should be offered to patients with allergic rhinitis who have inadequate control of symptoms with pharmacologic therapy, with or without environmental controls. Patients who are offered immunotherapy as a treatment alternative must ultimately decide whether AIT is the right treatment plan to undertake. This is a very individualized decision as immunotherapy carries potentially serious risks (anaphylaxis), incurs additional expenses, and takes several years to complete with often a delayed onset of symptom control. In the United States, AIT can be administered via the traditional subcutaneous route [subcutaneous immunotherapy (SCIT)] or through a sublingual route [sublingual immunotherapy (SLIT)]. Both types of immunotherapy require positive immunoglobulin E-mediated allergy documented

either on skin testing or using in-vitro methods. When SCIT or SLIT is initiated, the duration of treatment lasts anywhere between 3 and 5 years [2,3]. Both methods have proven effective in multiple studies [3–8], with continued beneficial effects at 10 and 8 years after cessation of SCIT [9] and SLIT [10], respectively. It is unclear whether one form is more effective than the other [11–14].

SCIT has been the traditional approach to allergy management in the United States. Although SLIT has been utilized in Europe for decades, it has only recently gained popularity in the United States. SLIT is generally well tolerated, with mild side-effects localized to the mouth and throat region. Systemic reactions to SLIT are reported at 0.056%, with no reported fatalities [15,16], supporting its safety for administration outside of the office

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KEY POINTS

- Limited data exist on the direct and indirect costs of SCIT and SLIT in the United States.
- Studies suggest that SLIT may be less costly when taking indirect costs into account.
- Recent FDA approval of select sublingual tablets in America is changing the payment methodology for SLIT in America.
- Costs for SLIT may be more contained if physicians are more selective in the number and volume of antigens utilized per patient.

setting. There have been rarely reported cases of anaphylaxis with SLIT, which has prompted the protocol for the first dose to be given in a physician's office under direct observation for at least 30 min [17,18]. After the first dose, SLIT is generally administered at home with the patients following up with the prescribing physician at varying time periods to assess symptom control and to obtain additional vials when necessary.

SLIT has traditionally been administered as liquid antigen placed under the tongue (sublingual drops). Vials of liquid antigen are either produced by the prescribing physician's office or outsourced to a company that formulates and compounds the vials. This form of SLIT is not currently Food and Drug Administration (FDA) approved and is therefore paid for out of pocket, with variable costs reported among practices. In 2014, SLIT tablets for grass (Grastek, Merck, New Jersey, USA and Oralair, GREER, North Carolina, USA) and ragweed (Ragwitek, Merck, New Jersey, USA) gained FDA approval and are now available for administration. It is recommended that the first administration of the tablet, like the sublingual drops, be given in a physician's office with a 30-min observation period [19–22].

In general, the cost of SLIT (sublingual drops) is determined by the number and volume of antigens added to a 10 ml treatment vial. The volume of antigen utilized may range from 0.4 to 1.0 ml. The cost of SLIT significantly increases when the volume of antigen is increased from 0.4 to 1.0 ml. Since the SLIT tablet is FDA approved, it is covered by insurance companies in varying degrees across the United States. With the development and approval of these tablets (and likely more to follow), more uniform pricing may be seen in the future. Cost evaluations for these new oral tablets in America have not yet been reported. The cost of the tablets is likely to change in the next several years as additional tablets become available and more pharmaceutical companies develop similar products for administration.

Studies looking at the economic favorability of SLIT are prevalent in the European literature, but there is a paucity of data in the American literature. This is likely due to the variability of allergen administration and dosage in the United States. In Europe, where SLIT is prevalent, it is common to treat patients with a select few representative allergens regardless of how many positive allergens are identified on allergy tests. In the United States, most practitioners administering SCIT treat with multiple allergens, attempting to cover the majority of the positive allergens identified on allergy tests. There is no consensus in the United States on the appropriate dosing or number of antigens that should be mixed in a single vial for SLIT. There does, however, seem to be a consensus toward treating with fewer antigens when offering SLIT to patients.

COMPARATIVE COSTS OF SUBCUTANEOUS AND SUBLINGUAL IMMUNOTHERAPY IN AMERICA

Only one publication has evaluated the comparative costs of SCIT and SLIT in America. As this study was in 2012, SCIT was the only form of immunotherapy that was FDA approved, and SLIT tablets were not yet available in America. Therefore, the costs were calculated under the premise that SLIT was paid for out of pocket, and SCIT was covered by insurance. In this study, Medicare and eight preferred provider organizations were evaluated with regards to direct costs incurred with SCIT. Direct costs were calculated based on the percentage of coverage for the injections, serum vial fees, weekly copays, and insurance plan deductibles. This study did not calculate the indirect costs associated with SCIT, which may include time off work for travel and appointments, gas mileage, vehicle wear, and parking fees. Insurance companies were found to cover between 60 and 100% of the costs for SCIT. Insurance plans with higher deductibles, higher weekly copays, and lower coverage for services were noted to have significantly higher costs for SCIT. It was suggested that SLIT might be a more affordable option for patients with these insurance plans [23].

This study also compared the cost of SCIT with that of SLIT based on reports from 13 allergy practices across the United States. The cost of SLIT was noted to have substantial variability among these practices due to the variable volume and numbers of antigen utilized. For most practices, the cost of SLIT could be contained at \$500–1200 per year if the number of antigens utilized was less than 10. These costs exceeded \$2100 per year when the number of antigens approached 25. When accounting for direct and indirect costs together, these results

suggested that SLIT may be the more affordable option, especially when the number of antigens in the vial is limited to less than 10 [23]. However, evaluations that specifically quantify indirect costs in America have not been reported.

COMPARATIVE COSTS OF SUBCUTANEOUS AND SUBLINGUAL IMMUNOTHERAPY OUTSIDE OF AMERICA

Dranitsaris evaluated the economics of SCIT and SLIT for seasonal grass-induced allergic rhinitis in Canada [5]. Direct and indirect costs were evaluated in four treatment scenarios which included patients receiving SLIT with Oralair for 6 months per year over 2–3 years; patients receiving SLIT with Grazax (ALK-Abello A/S, Hoersholm, Denmark; Timothy grass) for 12 months per year over 2–3 years; patients receiving SCIT weekly for 6 months, then monthly for 2–3 years; and patients receiving SCIT for 7 months each year for 2–3 years. Indirect costs that affected the SCIT groups included patient travel (gas, public transportation) and time off of work (estimated as 2 h per visit). The most cost-effective scenario was noted for the group receiving Oralair. During the first year of treatment, Oralair was noted to be \$2471 and \$948 less expensive than year round and seasonal SCIT, respectively. Over the second and third years, Oralair was noted to be \$868 and \$1883 less expensive than year round and seasonal SCIT, respectively. Grazax was noted to be less expensive than year-round SCIT, but more expensive than seasonal SCIT for the first year. During the second and third years, Grazax was the most expensive treatment group. The pharmacy cost of Grazax was reported to be 2.5 times that of Oralair, leading to the difference in cost estimates [24]. The outcomes from this study were noted to be in agreement with a similar evaluation conducted in Germany [25].

A recent evidence-based cost evaluation in the United Kingdom compared SLIT with Grazax to SCIT [26]. The evaluation included the costs of the allergens, supplies, staff, symptomatic medications, and productivity loss. SLIT was estimated to require 13 office visits per year, whereas SCIT was estimated to require 46 office visits per year. Estimations of staff and supply costs were obtained through expert opinion. The estimations of symptomatic therapy utilization, hours spent at work with decreased productivity, and hours missed from work were extrapolated from previous reports on SCIT and SLIT. Both groups received immunotherapy for 3 years, with the assumption that the effects would be sustained for the following 3 years. Cumulative costs were assessed during the fourth through 10th years based on symptomatic medication

utilization and productivity loss. Results demonstrated an overall cost reduction of £2869 (\$4554) for SLIT with Grazax when compared with SCIT over a 3-year period. Additionally, the cost gap between SCIT and SLIT continued to increase over the following 7 years, with a cost difference of £3378 (\$5362) favoring SLIT at the end of the 10th year. This article also analyzed the cost effect of changing maintenance injections from every 4 to 6 weeks. This change led to a difference of £1926 (\$2934) between SCIT and SLIT by 10 years [26].

COMPARISONS BETWEEN HEALTH SYSTEMS AND FUTURE DIRECTIONS

Although the direct and indirect costs in these other reports may be similar to those encountered in America, extrapolation of these results to the American system is imperfect. It is common practice in Europe to prescribe only select antigens for SLIT, as opposed to in America where multiple allergens are typically administered. This American practice increases the direct costs for SLIT when compared with European practices. Additional limitations in extrapolating results between these studies are the variable healthcare models present in the reported countries. Private insurers are the predominant payers in America, whereas universal healthcare is common in Canada and the United Kingdom [4]. Extrapolation of the reported indirect costs is imperfect as these are variable not only between countries, but also between cities within the United States.

SLIT in America is undergoing a transition. Currently, off-label utilization of liquid allergen extracts dominates in America, with each individual practice dictating the costs. As more SLIT options gain FDA approval, the cost for SLIT may become more standardized, becoming more dependent on insurance copays and deductibles. At the present time, Merck offers online coupons for Grastek and Ragwitek, limiting costs to \$25 per month for the first year. Compared with the costs reported for SLIT in the aforementioned studies, this may be a more affordable option totaling only \$300 for the first year. However, following the first year, the cost becomes dependent on insurance prescription plans.

As SLIT costs are partially dependent on the number of antigens prescribed, SCIT may be the more economic option for some polysensitive patients in America. Regardless of newer SLIT tablets gaining FDA approval in the future, patients requiring treatment with multiple allergens may still find SCIT to be more affordable. Oralair has attempted to target the polysensitized patient by covering multiple grasses in one tablet (Timothy, Orchard, Perennial Rye, Kentucky Blue Grass, and Sweet Vernal). FDA approval of

other combination SLIT tablets may be a future cost saving measure. Currently, the effects of combining various sublingual tablets are not known, and this practice is not recommended.

CONCLUSION

The cost of immunotherapy in America is a complex topic, and the recent FDA approval of SLIT tablets has added to this complexity. Few cost comparisons between SCIT and SLIT exist in the literature, and no American studies take direct and indirect costs into account. It is anticipated that more SLIT tablets will gain FDA approval in the upcoming years, and the American payment system for immunotherapy will continue to evolve toward a more insurance-dependent system. Further cost analyses in America are warranted to allow cost saving measures to be implemented if necessary.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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