



Sublingual immunotherapy and quality of life

Adrienne M. Laury^a, Rodney J. Schlosser^b, and Sarah K. Wise^a

Purpose of review

Sublingual immunotherapy (SLIT) has been shown to be a new and promising treatment for people with various allergic syndromes. Several studies have examined its efficacy. However, significantly fewer investigations have explored its specific impact on the patient's quality of life (QOL).

Recent findings

SLIT has an excellent safety profile, superior in many ways to subcutaneous immunotherapy (SCIT). Additionally, SLIT significantly decreases the use of allergy medications, as well as decreasing the money spent on allergy symptom control. Finally, SLIT has been shown to improve the patient's QOL when compared to placebo or even second-generation antihistamines.

Summary

Increasing data support the use of SLIT as a well tolerated, cost-effective, and time-efficient modality for the treatment of multiple allergic syndromes. However, additional studies are needed, particularly QOL studies which compare SLIT to the FDA-approved SCIT.

Keywords

quality of life, safety, subcutaneous immunotherapy, sublingual immunotherapy

INTRODUCTION

Approximately one out of every four people is affected by some form of allergic syndrome, including rhinitis, conjunctivitis, atopic dermatitis, urticaria, asthma, and food allergies [1]. In comparison to other chronic disease states, allergy ranks third in the prevalence among children and fifth in all age groups [2]. Americans spend nearly 8 billion dollars a year in direct (management strategies) and indirect (missed work) costs for allergy-related issues [3]. Needless to say, with this significant impact, several medical therapies have been developed in hopes of reducing this disease burden. Currently, immunotherapy is the only treatment option that offers a potential lifetime 'cure' for the atopic patient by actually altering their immune system. For the last century, subcutaneous immunotherapy (SCIT) has been the mainstay for administering immunotherapy antigens. However, the necessity for frequent injections and not infrequent adverse reactions has raised significant concerns. Conversely, sublingual immunotherapy (SLIT) has more recently gained acceptance as an alternative route of administration for effective and well tolerated antigen delivery. Although it has yet to be approved by the United States Food and Drug Administration, SLIT has become increasingly popular because of its noninjection delivery, excellent safety profile, and efficacy

comparable to SCIT. In fact, several studies have shown similar decreases in rhinitis, asthma symptom scores, and medication use when comparing SCIT and SLIT [4–6]. Although its efficacy has been examined and validated in numerous studies, the influence of SLIT on patient's quality of life (QOL) has only more recently been explored.

SAFETY: QUALITY OF LIFE'S MOST BASIC REQUIREMENT

To begin an evaluation of QOL, one of the first concerns must be the protection and propagation of that life. Therefore, one would be remiss to discuss SLIT and QOL without first examining its safety profile. When comparing SLIT with the FDA-approved and historical 'standard' SCIT, one can note several differences in safety. Adverse reactions

^aDepartment of Otolaryngology – Head and Neck Surgery, Emory University, Atlanta, Georgia and ^bDepartment of Otolaryngology – Head and Neck Surgery, Medical University of South Carolina, Charleston, South Carolina, USA

Correspondence to Sarah K. Wise, MD, MSCR, Emory University, 550 Peachtree Street, MOT 9th Floor, Atlanta, GA 30308, USA. Tel: +1 404 778 3381; fax: +1 404 686 4540; e-mail: skmille@emory.edu

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KEY POINTS

- SLIT is a well tolerated means of managing various allergic syndromes and has been shown to have fewer adverse reactions versus SCIT.
- After 3 years of use, SLIT is more cost-effective and time efficient than traditional pharmacotherapy regimens in treating allergic syndromes.
- SLIT has been shown to significantly improve QOL during its implementation, as well as 2 years after its discontinuation.

to SCIT can range from local to systemic and mild to life threatening. Local reactions, which can manifest as erythema, pruritus, and swelling at the injection site, are fairly common, with a frequency ranging from 26 to 82% of patients and 0.7–4% of injections [7]. On the other hand, systemic reactions, although less frequent, are undeniably more concerning. Near-fatal anaphylaxis secondary to SCIT occurs on the order of 23 episodes per year or 5.4 episodes per 1 million injections, whereas actual fatalities occur once for every 2.5 million injections [8]. Alternatively, in a review by Cox, SLIT administration was examined in 4378 patients. For the nearly 1.2 million doses administered, not one serious life-threatening reaction was reported [9]. Additionally, only 0.27% of doses resulted in any type of local adverse reaction – most commonly oral itching, rhinorrhea, or nausea. In 2011, a Cochrane review of 49 randomized, placebo-controlled trials examining SLIT also failed to identify a single life-threatening event or use of adrenaline for an anaphylactic reaction [10¹¹]. Similar findings have been reported for the pediatric population [11]. In 2012, Calderon *et al.* [12] directly examined the 11 reported episodes of nonfatal anaphylaxis associated with SLIT (no fatalities have been reported to date) and compared them to the evidence-based safety profile of SCIT. In this review, Calderon *et al.* [12] estimated that these 11 cases equate to approximately one case of anaphylaxis per 100 million SLIT administrations or per 526 000 treatment years versus SCIT which has an estimated one case of anaphylaxis per 33 300 injections or per 4160 treatment years.

Overall, based on the available studies, the safety profile of SLIT appears superior to SCIT, particularly when it comes to systemic and life-threatening reactions. This, in turn, likely improves QOL not only through the rarity of adverse reactions, but also by endorsing the patient's ability to safely undergo treatment in their own homes rather than requiring a weekly trip to their doctor's office to ensure that a possible anaphylactic event is

appropriately managed. However, as with any method of immunotherapy, caution should be exercised when starting and accelerating SLIT. A thorough patient history and frequent reassessments, observing for local or systemic reactions, is still recommended throughout the treatment. Additionally, the authors advise that each SLIT patient be required to maintain a nonexpired epinephrine auto-injector with them throughout their treatment course.

PHARMACOTHERAPY DISCONTINUATION: TEMPORAL AND MONETARY EFFECTS ON THE QUALITY OF LIFE

Outside of immunotherapy, there are countless medical therapies available to reduce the allergic symptoms. From second-generation antihistamines, to nasal steroid sprays, to leukotriene inhibitors, billions of dollars are spent annually on medications to alleviate the allergic symptoms [3]. These medications require a perpetual schedule of administrations that may substantially alter a patient's QOL. With immunotherapy, the possibility of complete discontinuation of allergy medications may become a reality. Multiple trials have shown a significant reduction in the medication use with the initiation of SLIT [10¹¹,11,13,14]. In 634 grass pollen allergy patients, Dahl *et al.* [15] showed a 38% reduction in medication use with the implementation of SLIT. Additionally, an improvement of QOL may be implied from a monetary standpoint. The literature consistently finds that immunotherapy for 3 years is cost-effective when compared to pharmacotherapy [16¹⁷]. This result applies to children, adolescents, and adults; seasonal and perennial allergic rhinitis; and different types of allergy. The cost-effectiveness of immunotherapy versus pharmacotherapy additionally improves if the lasting effect following cessation of immunotherapy is considered, and more so if indirect costs are added.

PATIENT'S PERCEPTION: OBJECTIFYING PATIENTS' SUBJECTIVE VIEWS OF QUALITY OF LIFE

Patient's perception of a medical therapy's effect on the QOL is a relatively newly considered, yet powerful means, by which one can validate a drug's efficacy. Although allergic rhinoconjunctivitis symptoms are rarely life threatening, several studies have shown a substantial impact on patients' QOL and daily functioning, including daytime sleepiness, impaired social functioning, mood and cognition disturbances, and diminished productivity [17–20]. Although a patient's subjective impression of the

efficacy of a medication is important, a validated assessment method is required for the evidence-based analysis. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is a validated, forced-choice questionnaire which has been utilized in multiple studies on SLIT and QOL. Over the last few years, at least six high-quality clinical studies have utilized this scoring system (Table 1). Ciprandi *et al.* [21] indicated that QOL can be improved in polysensitized patients with allergic rhinitis who are treated with SLIT. Additionally, these authors showed that this significant improvement can often be accomplished by treating with only one or two antigens. Woody *et al.* [22] demonstrated comparable results in patients with multiantigen sensitivities. Additionally, the authors also showed that QOL improvements continued postescalation during the maintenance phase of SLIT [22]. In one of the first large-scale North American trials involving SLIT, Nelson *et al.* [23] showed that QOL significantly improved after one season of SLIT treatment in patients with Timothy grass allergy, whereas Blaiss *et al.* [24] showed a similar result in children. Finally, two recent studies were identified that sought to examine SLIT's effect on grass-pollen allergic patients' QOL over the long term. In Didier *et al.*'s [25[■]] evaluation of 633 patients, treated for either 2 or 4 months with SLIT versus placebo over 3 seasons, the authors noted statistically significant improvement in the RQLQ scores at season 1, increasing improvement by season 2, and maintained improvement in season 3. Additionally, Durham *et al.* [26] were the first to show that SLIT for grass allergen, even 2 years after discontinuation (5 years after initiation),

continued to have a significant impact on QOL, with a relative difference of 25–32%. This was one of the first studies that confirmed SLIT's ability to modify a disease process and provide long-term improvement in QOL even after cessation.

Enhancements in the QOL measures have also previously been shown in children and adults with allergic rhinitis when receiving SCIT as well as when using various nonimmunotherapy treatments [27–29]. However, although published over 5 years ago, Rak *et al.*'s [30] examination of grass SLIT and QOL is of particular note in that it is the only study the authors could identify to date which indicated that SLIT alone had a greater QOL benefit than loratadine alone. This is the only known QOL study which directly compares antiallergy pharmacotherapy and SLIT.

QUALITY OF LIFE: FUTURE DIRECTIONS

Although the popularity of SLIT has grown rapidly in the last decade and multiple studies have resulted in a clearer understanding of its efficacy and safety, data are still limited examining SLIT's effect on patients' QOL. Future research is needed which directly compares SCIT and SLIT and their relative effects on QOL. Similar studies could also be performed comparing SLIT and various other antiallergy pharmacotherapies to determine the relative rates of improvement in RQLQ. Finally, long-term data (5 and 10 years) need to be obtained regarding SLIT's effect on QOL, because as an immunomodulator, long-term efficacy is where immunotherapy should truly stand out.

Table 1. Six recent studies which examine SLIT's effect on patients' QOL				
Author	# of patients	QOL assessment tool	EBM grade	Results
Ciprandi <i>et al.</i> 2010 [21]	167	RQLQ	2b	QOL improvement with SLIT in polysensitized patients; improvement can be significant even with only one or two antigens
Woody <i>et al.</i> 2012 [22]	38	mRQLQ	2b	QOL improvement after escalation and during maintenance phase of SLIT
Nelson <i>et al.</i> 2011 [23]	439	RQLQ	1b	QOL improvement with one season's treatment with SLIT for timothy grass
Blaiss <i>et al.</i> 2011 [24]	345	RQLQ	1b	QOL improvement in children with one season's treatment with timothy grass SLIT
Didier <i>et al.</i> 2011 [25 [■]]	633	RQLQ	1b	SLIT significantly improved QOL scores compared to placebo; this improvement escalated over the first 2 years and was maintained in year 3
Durham <i>et al.</i> 2012 [26]	238	RQLQ	1b	QOL improvement maintained 2 years after the cessation of SLIT

This table includes number of patients, QOL measure, EBM grade, and generalized results. (m)RQLQ, (mini)Rhinoconjunctivitis Quality of Life Questionnaire; SLIT, sublingual immunotherapy.

CONCLUSION

Throughout the last 2 decades, SLIT has been shown to be a viable and efficacious alternative to SCIT. However, more recently, it has also been shown to have a significant impact on patients' QOL. This can take the form of an improved safety profile when compared to the traditional immunomodulator therapy – SCIT, or by its QOL improvements from a monetary or temporal standpoint. Additionally, over the last decade, SLIT has been shown to significantly improve validated QOL ratings for both allergic rhinitis and asthmatic patients; in children and adults; and for short and long periods of time. These findings have made SLIT not only a viable alternative, but also at times a preferred treatment mechanism for many of the millions of Americans afflicted each year by allergic syndromes.

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Conflicts of interest

R.J. Schlosser is a consultant for BrainLab, Sunovion, and Olympus. Dr Schlosser also receives grant support from Medtronic, Arthrocare, and NeilMed, and is on the speaker's bureau for NeilMed.

The remaining authors have no conflicts of interest to declare pertaining to this article.

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 295).

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