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Potential Cost Savings by Switching from Subcutaneous to Intralymphatic Insect Venom Immunotherapy

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Keywords
Venom immunotherapy · Intralymphatic immunotherapy · Cost analysis · Allergy

Abstract
Introduction: IgE-mediated bee venom allergy can be treated with allergen-specific immunotherapy (AIT). Subcutaneous immunotherapy (SCIT) is time and cost intensive due to the repeated consultations, but the costs are justified by the high risk of potentially life-threatening allergic reactions, including anaphylaxis. However, intralymphatic immunotherapy (ILIT) offers potential to reduce treatment costs due to a significant reduction in injections and a shorter duration of therapy. Therefore, we calculated the cost savings that arise when switching from SCIT to ILIT. ***Methods:*** Treatment protocols for ILIT were based on previous ILIT studies. Treatment protocols for SCIT were based on routine treatment at the University Hospital Zurich (USZ). The treatment costs were calculated based on the internal hospital information system (KISIM). ***Results:*** The calculations revealed a potential two-fold reduction in treatment costs if ILIT is used instead of SCIT in patients with bee venom allergy. The costs could be reduced from EUR 11,612.59 with SCIT to EUR 5,942.15 with ILIT over 5 years. ***Conclusions:*** This study shows that bee venom ILIT has a cost-benefit potential for health insurances and patients, which should encourage further ILIT studies and which should be taken into account when considering future implementation of ILIT in the standard care of venom allergy.

Introduction

Allergen or venom immunotherapy (AIT or VIT) for the treatment of IgE-mediated bee venom allergy is important as allergic reactions to bee stings affect up to 25% of the European/America/Swiss population, and of these, 3.5% may react to a sting with a life-threatening systemic reaction [1]. In Switzerland, an average of 3–4 insect-venom-related deaths are registered each year [2]. For these patients, VIT with repeated and controlled application of bee venom allergen is the only causal treatment that can prevent such IgE-mediated hypersensitivity reactions. The mechanism, by which AIT or VIT provides long-term protection, includes the stimulation of T helper type 1 cells (TH1).

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Thus, AIT mediates an immune skewing from the pathology-associated TH2- to the rather protective TH1 immune response, which follows the inhibition of IL-4-induced IgE production through increased production of IFN-γ [3, 4]. Moreover, AIT can stimulate T regulatory cells that dampen hypersensitivity reactions in part through secretion of IL-10 and TGF-β [5]. The remodeling of this immunological microenvironment also facilitates production of allergen-specific IgG, especially IgG4, which have allergen-neutralizing properties. The result is venom tolerance [3, 4], but also the anergic state of effector granulocytes including mast cells and basophils [6]. In conclusion, this may result in long-term clinical benefits and improved quality of life (QoL) [7]. Despite these documented benefits and a protection rate of 75–85% after completion of therapy [8], a fraction of patients that would benefit from VIT is still reluctant to treatment, primarily due to the average treatment duration of 5 years. No fix number of required injections for bee venom SCIT exists, and longer therapy is associated with better clinical efficacy [9–12]. If there is an increased risk of severe anaphylaxis or in patients with mastocytosis, treatment may be lifelong [1, 13]. In addition to the time required by both patient and physician, there is a cumulative cost to the health care system for numerous consultations and injections during maintenance therapy of VIT [14, 15]. A shorter or more effective bee venom AIT would be of significant personal and societal impact [16].

An alternative route of AIT with direct lymph-node administration of the allergen (ILIT) has already shown promising results in various studies, especially for the treatment of pollinosis, with a significantly shorter treatment duration with the same effectiveness as conventional SCIT [17–24]. The majority of these studies on ILIT were conducted in patients with allergic rhinoconjunctivitis. Local and systemic reactions were reduced upon ILIT with birch and grass pollen allergens [20–26], and the clinical efficacy of ILIT was comparable to SCIT [19]. Less side effects and comparable efficacy with lower doses were reasoned by the low number of mast cells and basophils in the lymph nodes, as well as the fact that protective T- and B-cell responses are expected to be generated in the lymph node, making antigen presentation and stimulation of IgG synthesis more efficient when the allergen is administered directly to the lymph node [27, 28]. For the treatment of bee venom allergy, two clinical ILIT studies have been conducted [29].

The so-far published ILIT studies all suggest that treatment time can be significantly reduced by changing from SCIT to ILIT. Hence, ILIT is a potentially cost-effective alternative to SCIT, not only from the patient's perspective but also from a health policy perspective [30]. By now, no cost-saving studies with ILIT have been published. Therefore, the current study aimed at comparing the cost-effectiveness of bee venom SCIT and ILIT, assuming comparable clinical efficacy. The two bee venom studies formed the basis for calculating the potential cost savings of ILIT, based on total medication and treatment costs of SCIT versus ILIT.

Materials and Methods

Data Collection and Analysis

Data on costs for the treatment of bee venom allergy by AIT were collected at USZ between October 2020 and February 2021. The cost of ILIT was calculated by applying the ILIT trial therapy scheme described in clinical bee venom ILIT trials [29]. The cost of SCIT was calculated based on a hymenoptera ultrarush and maintenance scheme used at the allergy ward of the USZ. Cost savings were considered from the perspective of the Swiss healthcare system. Using the Clinic Information System (KISIM), the treatment costs were converted into total tax points with the tax point value of EUR 0.89, which was valid for the financial year 2021. The material costs for the allergen extract were added, the prices of which were taken from KISIM and the 2020 Swiss Federal Office of Public Health (FOPH) list of specialties. The comparison of ILIT and SCIT was performed on two levels. First, we compared the costs for the first year of SCIT and ILIT, as there is still insufficient knowledge about the long-term effects of ILIT. Second, we compared the costs for the remaining 4 years of bee venom AIT based on a total 5-year SCIT therapy with 58 injections and an ILIT, which would require seven injections over 5 years (three injections in the first year and one ILIT injection in the each of the following 4 years).

Costs of a SCIT during the First Year

The bee venom SCIT begins with a 1-day ultrarush. The ultrarush follows USZ guideline-compliant clarifications and is appropriate and safe. These clarifications include an initial consultation with a specialist, which lasts an average of 45 min and is followed by an intradermal test and venous blood collection. The total costs for the intradermal test comprise test material, the preparation of test material, the intradermal test, and 20 min of treatment. Additional costs arise through laboratory tests (total IgE, antigen-specific IgE, antigen-specific IgG4, and tryptase) and medical services in the absence of the patient. The latter includes a non-formalized report and patient-file study, which is charged as a 70-line report to the referring doctor or the cost of credit and a 5-min patient-file study.

The ultrarush starts after prophylactic administration of an antihistamine (e.g., Xyzal 5 mg). Six subcutaneous injections of a non-depot aqueous bee venom extract with increasing concentrations are performed at 30-min intervals and later at 60-min intervals and under continuous monitoring until the cumulative dose of 111.1 μg bee venom extract is reached [4]. After the last injection, the patient should be monitored for another 4 h [4]. During the initial therapy, patients are at the clinic for a total of

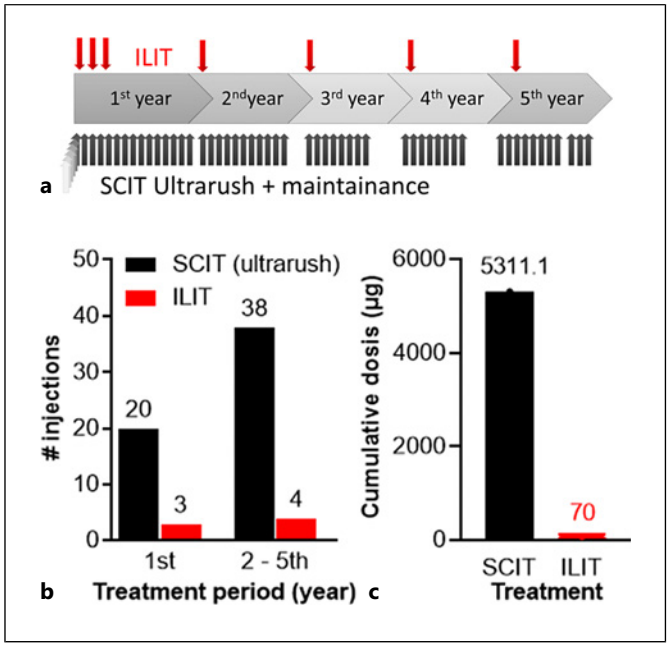

Fig. 1. ILIT and SCIT dose and dose number regimen. **a** The therapy scheme for bee venom allergy with ILIT (red arrows) and SCIT (white/grey arrows). Overall dose numbers (**b**) and allergen dose (**c**) of ILIT (red bars) and SCIT (black bars) during 5 years of therapy.

about 8 h. The treatment costs for the ultrarush include the administration of the hymenoptera venom, 4 h posttreatment surveillance in the clinic, and 90 min of consultation and treatment by the allergologist. Medication costs result from two units of the registered dry substance allergen product (Pharmalgen *Apis mellifera* from ALK-Abelló).

After initiation by a 1-day ultrarush procedure, the SCIT is continued with a maintenance dose after 1, 3, and 7 weeks, including 20 min treatment, 2 h observation, and a 30-min follow-up consultation. This serves to determine any side effects and intolerance of the therapy and is used to plan the continuation of therapy. After this period, the maintenance dose is applied every 4–6 weeks (4 weeks in the first year, 5 weeks in the second year, and 6 weeks in the following years). A maintenance treatment time of 20 min with another 30 min observation is required and applied for the cost analysis.

Although VIT can be maintained life-long for some patients, the cost calculation in the current study was based on a 5-year SCIT regimen (Fig. 1a) with 58 injections (Fig. 1b) and a cumulative dose of 5311.1 µg allergen extract (Fig. 1c). The number of injections includes six ultrarush injections, a maintenance phase with 14 injections in the first year, 11 injections in the second year, 24 injections in the following 3 years, and three injections at the end of completed therapy. Each injection is followed by 60 min of monitoring.

During the entire maintenance phase, the patients receive 1 mL of the aluminum hydroxide-absorbed bee venom extract Alutard SQ-U *A. mellifera* 100 µg (ALK-Abelló) at the USZ allergy ward. Prophylactic administration of an antihistamine is carried out before the injection and included in the cost analysis.

Costs of ILIT Therapy

Using the SCIT regimen of the USZ allergy ward, the knowledge from two bee venom-specific ILIT studies [29] as well as other ILIT studies [12–15, 17–21, 25, 27–31], a therapeutic regimen for bee venom ILIT was constructed (Fig. 1a, b). The therapeutic ILIT regimen consisted of three injections applied at 4-week intervals over 2 months. Each injection comprised 0.1 mL of the 100,000 SQ Alutard SQ-U *Apis mellifera*, which corresponds to 10 µg of bee venom extract. For the cost analysis, 2 h of monitoring was planned to follow each of the three ILIT sessions, since most of the allergic reactions occur during the first 2 h after completed injection [19]. As in SCIT, 30-min follow-up consultations are planned at weeks 4 and 8 after the second and third injection.

Prior to the first ILIT session, an initial 45 min consultation with an allergologist. An intradermal test and venous blood collection are performed as for SCIT. Similarly, a 70-line report is and total IgE, allergen-specific IgE, allergen-specific IgG4, and tryptase are analyzed from blood. Treatment costs include the three injections of bee venom extract and 3 times patient monitoring for 2 h after the first injection and 1 h each after the second and third injection. Medication costs result from a prophylactic antihistamine and one 5 mL vial (Alutard SQ-U *A.pis mellifera* from ALK-Abelló) containing 100,000 SQ of bee venom allergen extract. Since only 0.1 mL per injection is necessary, one vial may be used for several treatments and for other patients receiving bee venom ILIT in a timely manner. Of note, the shelf life of Alutard allows to keep the preparation for a maximum of 6 months after opening. Since the use of the extract in ILIT was not defined yet, we assumed an annual vial (5 mL) per patient in the cost calculations. The costs of an emergency kit containing adrenaline, antihistamine, and prednisolone were not considered for the estimation of either SCIT or ILIT costs.

Costs of an SCIT during the Second to Fifth Year

As mentioned, the cost calculations for SCIT imply 11 injections in the second year and 27 injections in the following years of the 5-year treatment. As in the first year, costs incur for each 20 min treatment by the allergologist, 1 mL of the aluminum hydroxide-absorbed bee venom extract "Alutard SQ-U *A. mellifera* continuation treatment" and the administration of a prophylactic antihistamine. From the second year on, each injection is followed by 30 min of monitoring. Furthermore, at the third- and fifth-year follow-up, an intradermal test is repeated and a laboratory analysis of total IgE, IgE, IgG, and tryptase is made from blood.

Costs of an ILIT during the Second to Fifth Year

Since there is no evidence in clinical trials for a long-term protection against further bee stings after 2 months of ILIT treatment, we recommend annual maintenance ILIT for another 4 years. For the cost calculation, four annual booster injections with 10 µg, i.e., 0.1 mL of bee venom extract with 100,000 SQ are planned. As for SCIT, intradermal tests and analysis of antibodies and tryptase from blood are repeated in the third- and fifth-year follow-up. The medication costs consist of an annual 5 mL vial (Alutard SQ-U *Apis mellifera* from

Table 1. Costs of bee venom SCIT and ILIT during the first year of treatment

Cost factor	Costs (EUR)	
	SCIT	ILIT
Initial consultation	158.28	158.28
Intradermal test	87.65	87.65
Medical service in the absence of patient	82.79	82.79
Laboratory	117.50	117.50
Ultrarush (1st ambulant SCIT)	1,275.76	n.a.
2nd to 14th ambulant SCIT*	2,378.68	n.a.
1st to 3rd ambulant ILIT*	n.a.	1,106.05
Follow-up visits (3×)	369.31	369.31
Ultrasound (3×)	n.a.	404.25
Total cost per patient	4,469.97	2,325.83

Costs in Euro were calculated using a therapy scheme based on 20 SCIT injections and 3 ILIT injections during the first year. Additional costs derive from consultation, intradermal test report, other medical services, and follow-ups. For ILIT, there are further costs due to the use of an ultrasound. *incl. medication and monitoring. n.a., not applicable.

ALK-Abelló). We based our calculations on four injections during the second to fifth year after completed ILIT with a cumulative dose of 40 μg.

Results

Costs of SCIT and ILIT during the First Year of Immunotherapy

The calculations show significantly higher total costs for a bee venom SCIT with 15 sessions and 1,511.1 μg bee venom extract than for a bee venom ILIT with 3 sessions and 30 μg bee venom extract (Table 1). Prior to ultrarush, there are costs for a 45-min initial consultation (EUR 158.28), 30 min confectioned prick-/scratch testing and blood draw (EUR 87.65) with a pre-interventional laboratory (EUR 117.5), and medical services, including report, in absence of the patient (EUR 82.79). The costs for the pretreatment examinations are EUR 446.22. The subsequent ultrarush treatment, including medication, supervision, and monitoring totals EUR 1,275.76.

Each maintenance treatment during the first year costs EUR 166.33, with EUR 94.95 for the medical service, EUR 60.55 for the bee venom allergen extract, EUR 0.82 for the prophylactic administration of an antihistamine, and EUR 10.01 for 30 min monitoring. For the first three maintenance injections, one 2-h and two 1-h monitoring are required, therefore, the costs for the first maintenance treatment is CHF 196.37, while the second and third treatments costs CHF 176.34. The three follow-up consultations during the first 7 weeks cost additionally CHF 369.31. In overall, the first year of SCIT (pretreatment consultation, ultrarush, and maintenance) with 14 injections amounts to an average total cost of CHF 4,469.97.

For ILIT, the preliminary examinations cost EUR 446.22, as for SCIT. For the ILIT therapy itself, EUR 475.92 is charged per treatment, including ultrasound costs (EUR 134.75/treatment) and bee venom allergen (EUR 100.9/treatment). In addition, EUR 0.82 and EUR 40.04 (first injection), respectively, EUR 20.02 (second and third injections) are charged for administration of antihistamine and for 2-, respectively, 1-h monitoring. The three follow-up consultations during the first 8 weeks cost additionally EUR 369.31. In total, costs for the three treatments and consultation with the specialist, ultrasound, and monitoring result in an amount of EUR 2,325.83.

Costs of SCIT and ILIT Maintenance during the Second to Fifth Year of Treatment

The 4 years of continued maintenance confirm lower costs with ILIT (four sessions with 40 μg) compared to SCIT. For SCIT, the pertreatment costs are EUR 166.33, similar to the maintenance treatment during the first year. Further costs of EUR 822.08 arise for follow-up visits after 3 and 5 years and are comprised of twice EUR 123.10 for consultation with allergologist, twice EUR 87.65 for intradermal tests and blood collection, twice EUR 117.50 for the laboratory tests, and 2 times EUR 82.79 for medical services in absence of the patient. In total, the costs for SCIT maintenance during the second to fifth year of treatment with 38 injections amount EUR 7,142.62.

Table 2. Costs of a SCIT and ILIT during the second to fifth year of treatment

Cost factor	Costs (EUR)	
	SCIT	ILIT
Follow-up consultation (after 3rd and 5th year)	246.2	246.2
Intradermal test	175.3	175.3
Laboratory (IgE, tryptase)	235	235
Medical service in absence of patient	165.58	165.58
4th to 7th ambulant ILIT*	n.a.	2,255.24
15th to 52nd ambulant SCIT*	6,320.54	n.a.
Ultrasound (4×)	n.a.	539
Total costs per patient	7,142.62	3,616.32

The costs in Euro were calculated based on 38 SCIT injections and 4 ILIT injections for the remaining 4 years of treatment. After 3 and 5 years, there are additional costs for two follow-up consultations, clinical tests, laboratory tests, and other medical services. *incl. medication and monitoring. n.a., not applicable.

Since a longer duration of therapy with hymenopteran venom and a higher cumulative dose shows better protection against recurrence of bee stings [32, 33], a maintenance phase seems reasonable also with ILIT. Hence, an additional annual dose of 0.1 mL the bee venom 100,000 SQ solution was planned for 4 years following the three ILIT injections in the first year. This incurs an annual cost of EUR 698.56 for treatment, 1-h monitoring, medication (EUR 302.7/treatment, whole vial), and antihistamine. In addition, follow-up controls after the 3 and 5 years of ILIT generate costs of EUR 822.08, similar to that for SCIT. In total, 4 years of ILIT maintenance with an annual intralymphatic booster injection would cost EUR 3,616.32 (Table 2).

Cost Savings with ILIT

Compared to the costs of bee venom SCIT (EUR 4,469.97), bee venom ILIT (EUR 2,325.83) would cause EUR 2,144.14 in cost reductions after 1 year of treatment. This corresponds to a cost reduction by 52% or a factor of 2. The cost reduction is mainly due to the reduced number of maintenance treatment sessions with consultations and injections. No ultrarush is used in ILIT, which contributes with EUR 1,275.76 of the total costs savings. The costs for the intradermal test, laboratory diagnostics, as well as reports and medical services in the absence of the patient are identical for ILIT and SCIT and therefore do not contribute to cost differences.

During the VIT maintenance phase from the second to the fifth year, another EUR 3,526.3 could be saved by changing from SCIT (EUR 7,142.62) to ILIT (EUR 3,616.32). Again, the cost savings derive primarily from the reduction in consultations and injections (38 for SCIT vs. 4 for ILIT). In the second year, the reduction from 11 to a single injection produces costs savings of EUR 1,131.07. In the third year, the reduction from eight to a single injection results in cost savings of EUR 632.08. In the fourth year and fifth year, the reduction from 19 to two injection generates cost savings of EUR 1,763.15. As illustrated in Figure 2, the cost differences between SCIT and ILIT increase with each year of treatment. Overall, ILIT with three injections in the first year and the four booster injections in the following 4 years would cost approximately EUR 5,942.15. Compared to the equivalent SCIT costs of EUR 11,612.59, this represents 51.1% or a 2-fold cost reduction.

Discussion

One argument for introducing ILIT as an alternative to SCIT is that ILIT generates lower treatment- and health-related cost. In this work, the direct treatment costs associated with bee venom ILIT was calculated, described, and compared to the costs associated with bee venom SCIT. The hypothesis that a change in VIT treatment regime from SCIT to ILIT would produce cost savings for patient and health insurance was based on the assumption that bee venom ILIT and SCIT are equally effective for the treatment of patients with bee venom hypersensitivity. The generated data revealed that the overall and per-patient treatment, medication, and other VIT-related costs were markedly lower with ILIT than of SCIT. Our calculations suggest that the total VIT costs can be halved from almost EUR 12,000 to less than EUR 6,000 if ILIT were to be used instead of SCIT for the 5 years treatment of bee venom allergy. The costs are minimized mainly by the reduced number of consultations and

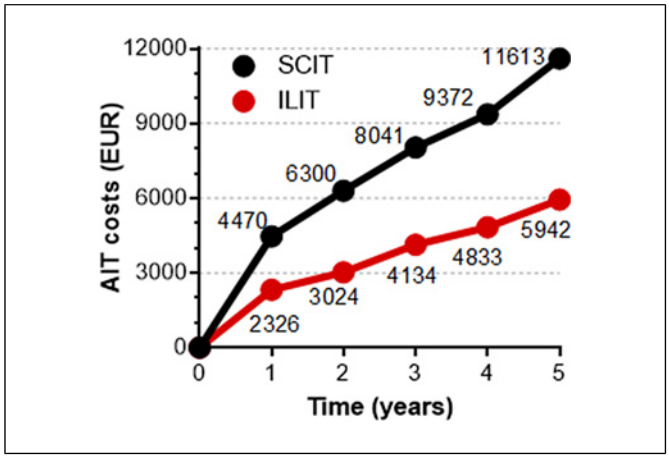

Fig. 2. Overall and cumulative costs during 5 years of SCIT or ILIT treatment. The cumulative AIT costs per patient in Euro were calculated for 58 SCIT injections for 5 years (20 injections in first year and 38 injections in the following years), while ILIT comprised totally seven injections (three in first year, and one in each the following 4 years).

injections in ILIT (totally seven in ILIT vs. 58 in SCIT). Moreover, the time- and cost-intensive initiation procedure with ultrarush is eliminated by changing from SCIT to ILIT. From the patient's point of view, this enables cost savings through less travel costs and reduced absenteeism from work or school.

Two jointly published bee venom ILIT studies have shown that protection can be comparable to SCIT based on the results from bee sting provocations [29]. The level of protection was achieved with a 15- to 20-fold reduction in the number of injections and doctor visits and a 150- to 200-fold reduction in the amount of bee venom extract applied. Furthermore, the authors hypothesized that due to the lower dose of applied allergen and due to fewer injections, fewer and less treatment-associated allergic reactions, including severe anaphylaxis should be expected during venom ILIT than during venom SCIT. By consequence and in addition to already saved treatment costs, further and indirect costs savings may be expected with ILIT, e.g., less emergency medication and less medical treatment of side effects due to therapy. In a study on hymenopteran immunotherapy, systemic reactions were observed in 19.3% of the administered injections during the initiation phase of bee venom SCIT (mostly mild and easily treated) and severe systemic reactions occurred in 4.6% of the administered injections, which were mainly observed at higher doses (100 μg) during the maintenance phase [34]. Severe anaphylaxis can lead to hospitalization (until the following day), which costs EUR 2,660 at the local hospital (USZ). Depending on the severity of anaphylaxis or in case of a longer hospitalization, the costs may increase. Since ILIT uses only 10% of the dose of SCIT, we may assume that anaphylaxis occurs 10 times less with ILIT than with SCIT due to the immunological response and the absence of mast cells in the lymph nodes. Indeed, studies have shown fewer adverse events [20–23, 30] and less likelihood of anaphylaxis [35–37] with ILIT than with SCIT.

Although compliance is typically high in treatment of hymenoptera allergy due to life-threatening reactions to stings [8], earlier ILIT studies in patients with rhinoconjunctivitis have suggested that compliance may be increased due to shorter treatment duration than when SCIT is utilized [19]. Although bee venom SCIT shows higher compliance than other SCIT, ILIT offers further optimization of long-term therapy. In a multicenter ILIT-bee venom study, treatment was completed with four injections in all 67 patients included in the study [29]. In a previous bee venom SCIT study, early treatment termination was observed in 16 of the 59 patients (27.1%) before [38]. Thus, ILIT offers great potential for patient-optimized therapy, while simultaneously reducing direct costs and probably indirect costs that are incurred due to disease-dependent absences from school and work [39] through increased compliance. In addition, the indirect costs associated with care-taking family members of children (informal care) are expected to be reduced as a result of less treatment sessions and higher compliance with ILIT than of SCIT [39].

Bee venom allergy represents a common health condition. Depending on the study, geography, inclusion criterion and demographics, the numbers of severe systemic reactions in the Swiss population vary. One in 12 Swiss adults was allergic to hymenopteran venom, and allergic systemic reactions manifested in 1 to 3 out of 50 persons [40, 41]. Furthermore, 3 to 4 deaths from insect venom allergy are reported annually in Switzerland [42], but it is generally recognized that the number of systemic reactions and deaths can be reduced by VIT [2]. Therefore, cost savings should not be considered only in relation to individual patients but should additionally show the economic impact in relation to the entire Swiss population. In principle, all patients with severe systemic reactions (severity III or IV, sometimes also severity II) can receive VIT, but only 70–80% of patients with a severe systemic reaction chose to receive VIT. Data from the USZ Allergy Ward showed that ca. 500 patients start bee venom-specific SCIT each year. If these 500 patients were treated with ILIT instead of SCIT, approximately EUR 1.8 million could have been saved over a period of

5 years. Assuming that the patients of the USZ represent 25% of all new patients with bee venom allergy in Switzerland and neglecting therapy discontinuations, this would account for EUR 11.34 million reduced treatment costs of bee venom VIT in 5 years. In addition, many patients come with wasp venom hypersensitivity. Hence, with the high proportion of patients in need of treatment, the extent of cost savings by switching from SCIT to ILIT would increase significantly.

Besides health-related aspects, further economic advantages of new AIT methods need to be demonstrated. Here, the change from SCIT to sublingual immunotherapy (SLIT) may represent a cost reduction. Recently, Mei Hardin and coworkers concluded that for adult patients with allergic rhino-conjunctivitis, the baseline total cost of SLIT per successful treatment outcome was USD 1,196, while that of SCIT was USD 2,691 for 1 year of treatment [43]. However, also Reinhold and Brüggenjürgen compared SCIT and SLIT in patients with allergic rhinitis and concluded that SCIT was predominant and cost-effective due to greater patient compliance and lower drug costs (EUR 1,159 vs. EUR 1,322) [44]. Of note, the latter study applied a different calculation model (Markov), which also takes quality-adjusted life years (QALY) in a 9-year horizon into consideration. Finally, Di Bona and coworkers [45] applied the Markov model and concluded that SCIT was slightly more expensive than SLIT (EUR 1,621 vs. EUR 1,582). However, while SCIT was more cost-effective with respect to direct costs, SLIT was more effective than SCIT with regard to indirect costs [45]. In all mentioned studies, AIT (SLIT or SCIT) was more cost-effective than symptomatic treatment with antihistamines and corticosteroids.

To date, only few cost-effectiveness analyses of bee venom VIT exist [46–48]. Bee venom-specific SCIT showed positive and long-term clinical and psychological outcomes (anxiety reduction before re-sting, improved QoL, reduced reaction to stings), which were associated with a gain in QALYs [47]. Using QALYs, in addition to costs, the two dimensions "remaining life expectancy" (quantitative component) and "QoL" (qualitative component) are represented. In this context, the number of years in a certain health state (e.g., severe allergic reactions to insect stings) was multiplied by the respective utility value [39]. With bee venom SCIT, a reduction in cost per QALY was shown and, at the same time, a 4-fold increase in earning capacity (utility) was assumed. This suggests a long-term cost reduction with sustained SCIT compared with symptom-only therapy. Based on the current cost-analysis study for bee venom ILIT and further published report on ILIT in general, ILIT may provide an additional improvement in the long-term cost-effectiveness of bee venom VIT. Nevertheless, establishment of ILIT in pivotal phase III trials is necessary for an accurate health economic analysis on ILIT. Early health economic surveys during ILIT trials would provide data supporting future therapy and treatment pricing, but these differ from the standard treatment situation due to the specific setting (randomization, increased attention, forced care, better compliance, etc.). Therefore, in prospective ILIT studies, patient-specific economic data of economic relevance should be collected. Retrospectively, the collection of such data is more complicated, inaccurate and only associated with much effort. An incomplete list of data to collect in future ILIT trials would include therapy duration, required medical or nursing working time, drugs required, diagnostic examinations, the extent of additional services, time absent from work or school, and health-related QoL data [39]. Thus, in future cost-benefit analyses of ILIT, intangibles costs should be considered in addition to direct and indirect costs. As not all such data was collected in the previous ILIT studies, some parameters (e.g., proportion of Swiss bee venom allergy patients in treatment) had to be estimated in this work. Final costs may therefore slightly differ from the presented numbers. Nevertheless, the current calculations with data from previous studies suggest that there are significant cost savings with ILIT for health insurances and patients.

Because ILIT is still an experimental and not yet approved treatment option, there were limitations to the amount on available data related to ILIT efficacy and costs. Moreover, the SCIT regime may vary also between countries, regions, and therapeutic traditions, the direct costs of SCIT may vary slightly. The present calculations were based on a model with an average of 5 years of SCIT, 6 ultrarush and 52 maintenance injections. Due to limited data for ILIT, only direct costs were considered in the current study. Indirect costs, including lost resources (e.g., lost productivity due to absenteeism, travel costs, informal care, or premature death) and intangible costs (e.g., pain/suffering, stress) are associated with QoL or QALY and were neglected. For a comprehensive assessment of cost savings, all three types of costs (direct, indirect, and intangible costs) should be considered, as costs are often greater than direct health care expenditures [39]. The inclusion of indirect and intangible costs was beyond the scope of the current investigation and would of course be a more accurate cost savings model from a patient perspective, but we expect that the inclusion of indirect and intangible costs could further increase the potential cost savings of ILIT. However, in a liberal health marked, one may expect that the direct costs of marketed ILIT will be more expensive than what calculated here, otherwise, practicing allergologist and medical centers might not want to implement ILIT in their AIT repertoire.

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Statement of Ethics

Ethical approval and consent were not required as this study was based on publicly available data. Patient consents were not required as this study was based on publicly available data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Alexandra Chabot and Pål Johansen analyzed data, wrote the first draft, and finalized the manuscript. Claudia Lang, Peter Schmid-Grendelmeier, and Thomas Kündig provided strategic support and reviewed the manuscript. All the authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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