Quality of life in allergic rhinitis patients treated with intralymphatic immunotherapy (ILIT): A 19-year follow-up

Yasmin K. Adlany, MMSc,[a] Lara Šošić, MD,[a] Gabriela Senti, MD,[b] Claudia C. V. Lang, MD,[c] Brunello Wüthrich, MD,[a] Thomas M. Kündig, MD,[a,c] and Pål Johansen, PhD[a,c] *Zurich, Switzerland*

Background: In 2002-2005, we conducted a phase I/II clinical trial where a new allergy immunotherapy (AIT) route was introduced: intralymphatic immunotherapy (ILIT). Ultrasound guidance allowed injection of allergen directly into inguinal lymph nodes. Grass pollen–allergic patients received 3 injections with 1-month intervals. The short ILIT was more patient-friendly, required lower dosing, and was comparable with SCIT regarding short-term efficacy, which was used as a reference.
Objective: Nineteen years after ILIT, the same patients were followed up to assess the long-term effect on quality of life and efficacy of the treatment.
Methods: Patients who received ILIT and SCIT in 2002-2005 and an additional group of patients, who completed SCIT in 2015-2018, were recruited. All participants received a trial-specific in-house questionnaire and a standardized Rhinoconjunctivitis Quality of Life Questionnaire. Data were recorded off- (February 2021) and on- (May-June 2021) season. Descriptive statistics were applied.
Results: Of 58 and 54 patients who originally received ILIT or SCIT, 25 (43%) and 29 (54%) patients, respectively, returned the questionnaires for analysis. Four (16%) and 3 (11%) of the ILIT and SCIT patients, respectively, developed complete protection against grass pollen–mediated rhinitis, whereas another 15 (60%) and 20 (69%) expressed satisfaction with the received AIT. In both groups, any persistent symptoms were reported as mild. Medication usage in the ILIT and SCIT groups was comparable. Nineteen (76%) and 23 (79%) patients, respectively, expressed satisfaction with their AIT.
Conclusions: Grass pollen ILIT leads to long-term significant improvement in rhinitis-associated quality of life 19 years after treatment, and the ILIT quality-of-life effect was not inferior to that of SCIT. (J Allergy Clin Immunol Global 2023;2:43-50.)

Key words: *Allergen immunotherapy, intralymphatic immunotherapy, rhinoconjunctivits, quality of life, symptom scores, RQLQ(S)*

Allergic rhinitis is an IgE-mediated, chronic inflammatory disease of the nasal mucosa that is triggered by the inhalation of perennial or seasonal allergens (such as grass pollen). Most common symptoms include rhinorrhea, nasal itching, sneezing, nasal congestion, and symptoms of allergic conjunctivitis,[1,2] and approximately one-quarter of all Europeans are affected.[3]

Allergy immunotherapy (AIT) is the criterion standard for the treatment of allergies, especially for allergic rhinitis. For more than 100 years, this method comprised the administration of gradually increasing doses of allergen over a specific amount of time in either preseasonal or perennial settings with a total treatment duration of typically 3 years. The targeted result of AIT is a dampening of pathological immune responses toward natural exposure to allergens, for example, grass or tree pollen, with a decrease in allergic symptoms. The most common route of AIT is subcutaneous (subcutaneous immunotherapy [SCIT]), but more recently, sublingual immunotherapy (SLIT) is taking up much of the market. Other still more experimental routes are epicutaneous, intradermal,[4] nasal,[5] and oral applications, which have been reviewed in the past. The efficacy of AIT is often correlated with the allergen dosage[6] but is often also compromised by poor patient compliance.[7,8] Limitations of the maintenance dosage are possibly occurring allergic side effects.[9]

In 2002, we proposed a new AIT approach where the AIT extract was injected into a subcutaneous lymph node.[10] This so-called intralymphatic immunotherapy (ILIT) comprised the sonography-guided injection of allergens directly into an inguinal lymph node. In the first clinical ILIT trial, grass pollen–allergic patients received 3 injections with 1-month intervals, and the results revealed that ILIT was safer, faster, and more patient-friendly than SCIT, with comparable efficacy. Several other ILIT trials[11-18] and systematic reviews[19-21] later confirmed the results from the original study. However, a long-term follow-up of patients with hay fever treated with ILIT was never done. Therefore, we aimed to assess the long-term effect of grass pollen ILIT in patients from the original first-in-human trial.[10] Nineteen years after the original study, the participating patients were asked to report on quality of life (QOL) as well as long-term efficacy using a

From [a]the Department of Dermatology, University of Zurich, [b]University Hospital Zurich, and [c]the Department of Dermatology, University Hospital Zurich, Raemistrasse 100, Zurich.

This investigator-initiated study was supported by funding from the University Hospital Zurich and the University of Zurich, Department of Dermatology, Zurich, Switzerland.
Disclosure of potential conflict of interest: G. Senti and T. M. Kündig are shareholders of Saiba AG, which develops allergy therapeutics for animals. P. Johansen and T. M. Kündig have received financial support from Allergy Therapeutics Ltd, which develops immunotherapies for human. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication March 31, 2022; revised September 9, 2022; accepted for publication September 9, 2022.
Available online October 27, 2022.

Corresponding author: Pål Johansen, PhD, University Hospital Zurich, University of Zurich, Gloriastrasse 31, Zurich, Switzerland. E-mail: pal.johansen@usz.ch.

2772-8293

https://doi.org/10.1016/j.jacig.2022.09.007

Abbreviations used

AIT: Allergy immunotherapy
ILIT: Intralymphatic immunotherapy
QOL: Quality of life
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ(S): Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
VAS: Visual analogue scale

standardize Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) as well as an in-house questionnaire.

METHODS

Study design and ethics

This was a single-center, descriptive cross-sectional study conducted in Zurich, Switzerland. The study followed the consort 2010 statement[22] and comprised the development of a questionnaire, identifying potential subjects, recruitment, and evaluation of the QOL in patients with allergic rhinitis. Ethical approval from the Cantonal Ethics Committee of Zurich was granted in January 2021 (BASEC no. 2020-02369), the study was classified according to the Human Research Act as an HRO trial of category A (Ordinance of Human Research with the exception of Clinical Trials), and the study was registered at clinicaltrials.gov (NCT05037955). Approval for collecting patient data from the clinical information system at the University Hospital Zurich was obtained from the Hospital Data Governance Board (DUP-78). Written informed consent was obtained from all participants before study entrance.

Follow-up allergic rhinitis-QOL questionnaires, including Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities

A study-specific questionnaire to assess QOL in the original ILIT-trial patients was designed by the authors (see Form F1 in this article's Online Repository at www.jaci-global.org). Using a structured concept, 19 questions regarding demographics, symptoms, daily activity, overall mood, antiallergic medication, further immunotherapy, and an overall personal bottom line with close-ended multiple-choice answers were asked. The answers were used for patient characterization and to compare SCIT and ILIT regarding outcome. The study participants also received a standardized questionnaire: Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities, RQLQ(S).[23,24] The RQLQ(S) consisted of 28 questions with 7 standardized answers. The answers were measured in parameters scoring 0 to 6 points where "0" meant "does not apply" and "6" meant "applies fully." Higher scores indicate higher correlation with allergic symptoms. Both questionnaires were in German language.

In the original trial, the participants were asked to record ocular (red eyes and itchy eyes) and nasal (congestion, itching, and sneezing) symptoms during the grass pollen season. At that time, a nonstandardized questionnaire was used and the symptoms were scored on a visual analogue scale (VAS) from 0 (lowest score) to 10 (highest score). To be able to compare the VAS scores with the RQLQ(S) scores, the VAS scored was transformed to the RQLQ(S) scale from 0 to 6.

Identifying the target group

The study participants were identified through study documentation from the original trial.[10] The documentation contained details such as names, addresses, phone numbers, and partly the e-mail addresses. Each patient was first contacted by phone. Subsequent contacts were in part by email or by surface mail.

For better comparison of the true treatment efficacy, another group of SCIT-treated patients was included. These patients were recruited from the allergy outpatient clinic at the University Hospital Zurich, who provided the required information such as age, sex, medical history, and AIT history. Forty potential study participants were identified and contacted by phone or mail.

Eligibility criteria

All eligible participants took part in the original study in 2002-2005 and had to give their written informed consent before taking part in the current trial. The control group included only patients who had finished SCIT for grass pollen at the University Hospital of Zurich between 2015 and 2018. All study participants were more than 18 years old and understood written and spoken German language.

Exclusion criteria included everyone who was not part of the original study or, for the SCIT control groups, did not complete SCIT between 2015 and 2018. Participants who did not return their written consent or did not fill out all forms correctly were excluded.

Procedures

On ethical approval in January 2021, the trial phase began in February 2021 and lasted through June 2021. During the first contact by phone and by e-mail, candidate participants were shortly informed about the follow-up study. After agreeing to the terms, each participant received patient information, informed consent form, and questionnaires by surface mail in February 2021. In May 2021, the standardized RQLQ(S) questionnaire was sent to all included study participants. Pollen counts were obtained from the *MeteoSwiss*, the Swiss federal office for meteorology and climatology.

Settings and locations where the data were collected

The study took place in the Dermatology Department of the University Hospital of Zurich, Switzerland, from January 2021 until February 2022. The recruitment took place in January and February 2021. Three researchers were involved in data collection and analysis. All data were safely locked and encrypted. Only the participating party had access to the data collection.

Statistical analysis

The gathered data were analyzed using descriptive statistics. The data were analyzed using PRISM v8.0.0 from GraphPad (San Diego, Calif). Two-tailed Mann-Whitney *U* test or Kruskal-Wallis test with Dunn's correction for multiple comparison was applied for statistical assessment of the recorded RQLQ(S) scores. Comparisons of ocular and nasal symptom scores for baseline and after 1, 3, and 19 years were made using a mixed-model analysis with Sidak's multiple comparison test. Contingency analyses were done using 2-sided Fisher exact test. For all statistical analysis, the significance level was set at 95%.

RESULTS

Patient characteristics

Of the 112 originally participating patients, 54 participants were included in the study, of whom 25 were in the ILIT group and 29 patients received SCIT (Fig 1). The rest could not be reached because of outdated or invalid contact details (n = 53), death (n = 2), or lack of consent (n = 3). Eighteen participants were included in the control group (SCIT).

The demographic data are presented in Table I. Briefly, there were more male patients both in SCIT (61%) and in ILIT (76%), but the sex distribution did not differ between SCIT and ILIT (P = .249). None of the participants were younger than

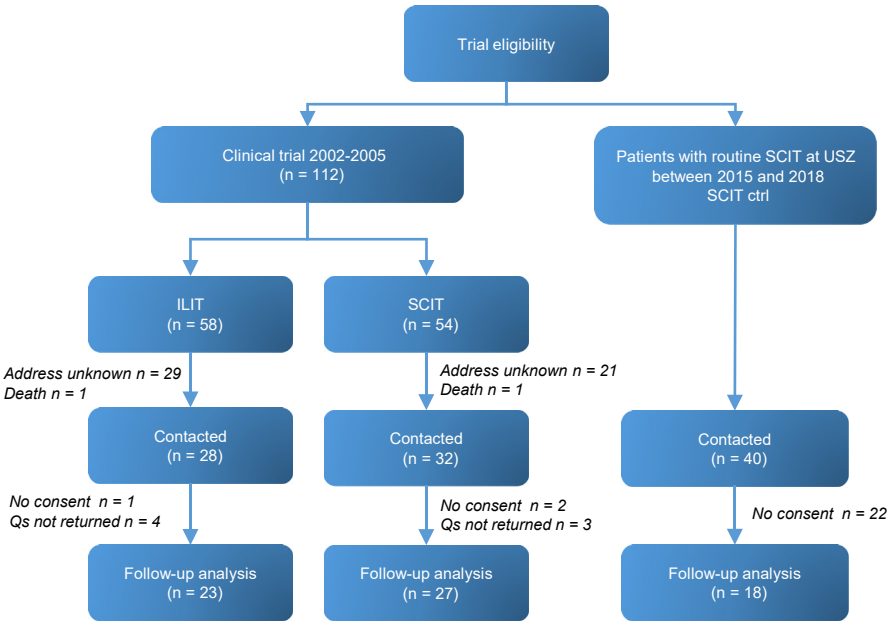

FIG 1. Flowchart of subject disposition. Study participants were recruited from patients taking part in the original ILIT vs SCIT study from 2002 to 2005 (cf Senti et al[10]). In addition, a cohort of SCIT efficacy controls was recruited from patients who received and completed SCIT as a routine AIT at the Allergy Unit of University of Zurich between 2015 and 2018 (SCIT ctrl). *Qs*, Questionnaires; *USZ*, University of Zurich.

TABLE I. Sociodemographic and clinical profile of the study groups

Characteristic	ILIT	SCIT	*P* value*
Sex			
Male	19 (76)	17 (59)	
Female	6 (24)	12 (41)	.249
Age (y)			
<30	0 (0)	0 (0)	
30-39	0 (0)	2 (7)	
40-49	7 (28)	9 (31)	
50-59	9 (36)	7 (25)	
>59	9 (36)	11 (37)	.654
Residential environment			
Urban	8 (32)	16 (55)	
Rural	17 (68)	13 (45)	.106
Allergy type			
Atopic eczema	1 (4)	1 (3)	
Allergic asthma	5 (20)	7 (24)	
Foods	1 (4)	4 (14)	
Animal dander	3 (12)	3 (10)	
Dust mites	5 (20)	3 (10)	
Insect stings	3 (12)	2 (7)	
Other	5 (20)	1 (3)	
None	13 (52)	13 (44)	.625

Values are n (%).
Of note, several questions had more than 1 possible answer.
*Two-sided Fisher exact test.

30 years, whereas 8 (33%) and 11 (39%) of the ILIT and SCIT participants, respectively, were older than 59 years. The mean and median age brackets in both treatment groups were 50 to 59 years old, with a light shift toward younger patients in the ILIT group. However, the age distribution did not differ between SCIT and ILIT ($P = .249$). Although there was some apparent imbalance in the rural and urban distribution of the study participants, with more rural residents in ILIT and more urban residents in SCIT, the contingencies did not meet statistically significant differences ($P = .106$). Table I also summarizes the type of allergies and co-sensitizations reported by the study participants, a parameter that also was not significantly different between the 2 treatment groups ($P = .625$).

Health-related QOL

The in-house questionnaire also scored the baseline symptom history (Table II). Twelve patients in ILIT (48%) and 13 patients in SCIT (46%) had no allergic symptoms at baseline. One patient in both ILIT (4%) and SCIT (4%) had perennial symptoms. Off-season symptoms were primarily allergic asthma (20% in ILIT, 25% in SCIT). The main season for recurring symptoms was spring (March, April, May) for 19 ILIT (76%) and 22 SCIT (76%) patients, followed by summer for 14 ILIT (56%) and 15 SCIT (54%) patients. The main manifestations included runny and itchy nose and itchy and red eyes. Of 25 ILIT patients, 2 (8%) reported neither nasal nor eye symptoms. In terms of antiallergic medications, 3 patients receiving ILIT (12%) and 11 receiving SCIT (38%) reported daily usage of drugs during the season peak after finishing their AIT. Six patients (24%) in the ILIT group and 7 (24%) in the SCIT group declared no need of antiallergic usage.

When asked about the overall clinical benefit of the original immunotherapy from 2002 to 2005, 4 (16%) and 3 (10%) patients reported complete symptom relief on ILIT or SCIT, respectively. Fifteen ILIT (60%) and 20 SCIT (69%) patients reported overall treatment benefit, whereas 4 ILIT (16%) and 6 SCIT (21%) patients reported no treatment benefit. Hence, the majority in both

TABLE II. In-house questionnaire regarding symptoms, general well-being, treatment benefit, and treatment satisfaction after ILIT/SCIT 19 y earlier

Characteristic	ILIT	SCIT
Seasons with symptoms present		
Spring (March-May)	19 (76)	22 (76)
Summer (June-August)	14 (56)	16 (55)
Autumn (September-November)	0 (0)	2 (7)
Winter (December-February)	1 (4)	4 (14)
All year	1 (4)	1 (4)
No symptoms	2 (8)	2 (7)
Nasal symptoms		
Running nose	20 (80)	26 (90)
Loss of smell	2 (8)	2 (7)
Sneezing	24 (96)	24 (83)
Congestion	12 (48)	15 (52)
None	1 (4)	0 (0)
Eye symptoms		
Itchy eyes	24 (96)	26 (93)
Red eyes	17 (68)	17 (61)
Puffy eyes	8 (32)	12 (43)
Watery eyes	10 (40)	17 (59)
None	1 (4)	0 (0)
General symptoms		
Coughing	7 (28)	5 (18)
Dyspnea	7 (28)	6 (21)
Headache	2 (8)	5 (18)
Fatigue	7 (28)	11 (39)
None	12 (48)	14 (48)
Restrictions of daily life activities		
Daily activities (at work/home)	2 (8)	2 (7)
Socializing	2 (8)	0 (0)
Outdoor activities	12 (48)	15 (54)
None	13 (52)	14 (48)
Mood affection by symptoms		
I avoid company	2 (8)	0 (0)
I feel uncomfortable	5 (20)	7 (25)
I avoid leaving the house	3 (12)	5 (18)
I avoid activities	3 (12)	2 (7)
None	18 (72)	17 (59)
Invested time to follow treatment plan		
A lot of time	3 (12)	14 (48)
A little of time	18 (72)	14 (48)
No effort	4 (16)	1 (4)
Usage of medication after finishing treatment		
None	6 (24)	7 (24)
Antiallergics (maximum 1×/wk)	5 (20)	3 (10)
Antiallergics (>1×/wk)	11 (44)	8 (28)
Antiallergics daily	3 (12)	11 (38)
Medication type		
Eye drops	12 (48)	18 (62)
Nasal sprays	6 (24)	15 (52)
Inhalers	6 (24)	8 (28)
Antiallergics (pills)	17 (68)	21 (72)
None	5 (20)	2 (7)
Treatment benefits		
Long-term relief	4 (16)	3 (10)
Improvement	15 (60)	20 (69)
No improvement	4 (16)	6 (21)
Increase in symptoms	2 (8)	0 (0)
Treatment recommendation		
Yes	19 (76)	23 (79)
No	6 (24)	6 (21)

Values are n (%).
Of note, several questions had more than 1 possible answer.

treatment groups reported to have benefited from their given AIT, with 76% and 79% for ILIT and SCIT, respectively. Two of the 25 patients who received ILIT (8%) reported an increase in allergic manifestations after treatment. In the SCIT group, none of the trial patients reported further clinical impairment after immunotherapy. On asking the trial patients whether they would recommend the received AIT to other, 19 of 25 ILIT patients (76%) and 23 of 29 SCIT patients (79%) replied with a "yes."

In the original trial, the trials participants were asked to score clinical symptoms at baseline as well as 1 and 3 years post-immunotherapy. For this, a nonstandardized questionnaire was applied, and the symptoms were scored on a VAS. To further test the long-term effects of ILIT and SCIT, we compared total rhinitis and conjunctivitis scores from the original trials with those obtained in the current 19-year follow-up. As illustrated in Fig 2, both ILIT and SCIT caused a significant ($P < .0001$) reduction in ocular (Fig 2, *A*) and nasal (Fig 2, *B*) symptoms within 1 to 3 years of treatment. A further reduction of symptoms was recorded at the 19-year follow-up in trial participants who received ILIT ($P < .05$), with the median ocular scores dropping from 0.99 (0.51-1.68) to 0.50 (0.00-1.25) after 19 years. Likewise, the median nasal score reduced from 1.3 (95% CI, 0.68-2.180) after 3 years to 0.75 (0.00-1.25) after 19 years. For trial participants who originally received SCIT, the median ocular and nasal scores changed negligibly from 0.78 (0.33-1.32) to 0.75 (0.25-1.5) or 1.04 (0.62-1.44) to 1.25 (0.75-2.00), respectively.

Analysis of RQLQ(S) off- and in-season

Symptoms were recorded off-season (February) and in the pollen season (May-June). The highest scores off-season were associated with the domains activities, practical problems (carrying tissues, rubbing nose/eye), and nasal and eye symptoms (Fig 3, *A*). When comparing the median total RQLQ(S) score (Fig 3, *B*) in the ILIT group (0.1100; 95% CI, 0.000-0.250) with that from the SCIT group (0.760; 95% CI, 0.140-1.570), we observed a statistically significantly lower score in patients who had received ILIT ($P = .017$). The score difference of 0.6 was larger than the minimal important difference reported for RQLQ(S),[24] hence, suggesting lower prevalence of off-season allergic symptoms in patients who received ILIT compared with patients who received SCIT. The strongest single contributors to the lower score in the ILIT were less impaired activities and less eye symptoms.

For the in-season RQLQ(S) analysis, we again compared the individual domains and total scores for patients who received ILIT or SCIT 19 years earlier, but we also included a recent SCIT group as control for the expected score 3 to 6 years after completing AIT. The domains with the highest scores were the same categories as off-season, but with the addition of the domain sleep (Fig 3, *C*). As expected, the median scores were higher than off-season, but the increase was little and the scores were lower in the ILIT groups for all 7 symptom domains. However, the domain differences did not reach statistical significance when corrected for multiple comparisons (Table III). Interestingly, when comparing the median total scores (Fig 3, *D*) in the 3 treatment groups, including the more recent SCIT control, we observed a significantly lower score in the ILIT groups (0.440; 95% CI, 0.000-0.870) than in the more recent SCIT control group (1.155; 95% CI, 0.510-1.490). This means that even 19 years after completion, ILIT provided reduced symptoms compared with the

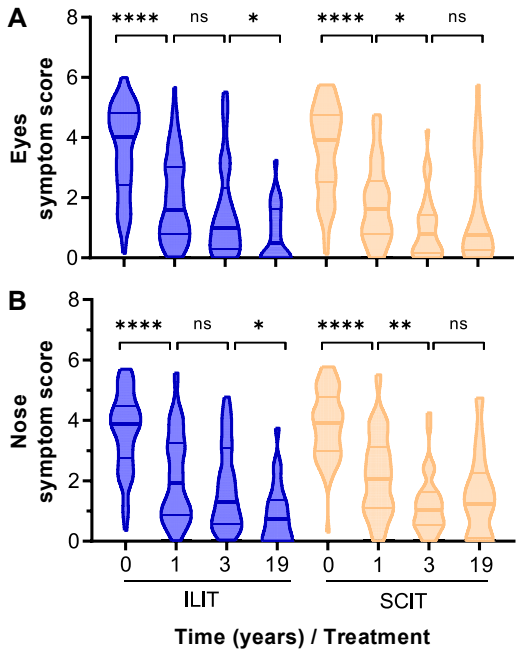

FIG 2. Total ocular and nasal symptoms scores as recorded in-season at baseline and after 1, 3, and 19 years of AIT. Patients who received ILIT (blue) or SCIT (orange) recorded the on-season ocular (**A**) and nasal (**B**) allergy-related symptoms. At baseline, 1, and 3 years posttreatment, a nonstandardized VAS was used to record nasal congestion, itching, and sneezing. At 19 years, the RQLQ(S) form was used to record the same. For ocular symptoms, red and itchy eyes were recorded. The VAS scores from 0 to 10 were transformed to a 0- to 6-scale so as to be comparable with the RQLQ(S) scores. Violin plots with median and with 25% and 75% quartiles are shown. A mixed-model analysis was performed with Sidak's multiple comparison tests. *ns*, Not significant. $*P < .05$. $**P < .01$. $****P < .0001$.

more recent SCIT control. No statistical difference in the total RQLQ(S) score was observed between the original SCIT group (0.940; 95% CI, 0.920-1.790) and ILIT, showing an equally high potency in symptom reduction on-season. There was also no significant difference between the 2 SCIT groups, revealing that SCIT maintained good effect even after all those years. Of note and according to the local pollen counts during 2021 (Zurich, Switzerland; 558 m ASL), grass blooming started in the second half of April. Strong blooming (100-250 grains/m^3) was recorded for a period of approximately 25 days end of May and beginning of June.

DISCUSSION

Long-term, randomized controlled AIT trials have confirmed that AIT can modify the allergic disease with reduced symptoms and medication in patients with allergic rhinitis[25] and most recently, Fritzsching et al[26] demonstrated at least 9-year effectiveness of AIT in a real-life study of nearly 50,000 outpatients with allergic rhinitis and asthma. Despite being effective, a huge majority of patients with allergic rhinitis do not choose AIT as treatment or is nonadherent to AIT[27] mostly due to the long treatment duration, with interventions that may cause significant cuts in daily life, at least short-term. Nearly 20 years ago, we therefore suggested an alternative and shorter AIT method[28] that was reasoned on classical vaccination for stimulation of neutralization antibodies, comparable to childhood vaccines.[29] The first grass pollen ILIT trial was conducted in 2002-2005 and comprised patients with allergic rhinoconjunctivitis.[10] The trial showed that ILIT (58 patients) resulted in fewer side effects, but triggered faster and equally good efficacy compared with SCIT (54 patients) with regard to rescue medication, symptoms (VAS), and tolerance in nasal provocation tests measured over 3 years. The primary objective of ILIT was reached with a cumulative dose that was only 1/1000th of that used for SCIT in the control group. Before this human trial, preclinical observations in mice had already shown that using a direct lymphatic route as method of choice increased efficacy while lowering the required dose to reach endpoints.[30-35] The relatively stronger clinical and preclinical effects were explained by the inefficiency of subcutaneously administered allergens or antigens to reach the lymphatic system. Only a small fraction of SCIT dose reached the lymphatic organs and was able to trigger allergen-specific immune reactions. By administering the AIT dose directly into the lymph node, the whole dose is available to the lymphatic tissue.[10]

In 2010-2011, Hylander et al[17] conducted a double-blind, placebo-controlled study for intralymphatic grass and birch pollen immunotherapy with a good outcome. All patients tolerated the treatment well without any severe adverse events and showed a reduction in allergic symptoms during the following pollen season. One of the latest studies by Hoffmann et al[15] included a 3-year follow-up randomized placebo-controlled trial in 36 patients suffering from grass pollen–induced allergic rhinitis. After 3 preseasonal ILIT injections, the results showed a significant reduction in grass pollen allergy symptoms and in the use of rescue medication after the first pollen season.[11] A randomized trial conducted by Konradsen et al[13] and Patterson et al[16] showed benefit of ILIT in young patients with rhinoconjunctivitis and asthma. Both latter studies showed that ILIT was well tolerated by adolescents without any severe side effects and, importantly, symptom relief after the third injection. Indeed, a recent systematic review and meta-analysis of 10 trials with 483 patients revealed that ILIT was mostly well tolerated and had good short-term outcomes with regard to improvement of symptoms, but did not show a difference in QOL before and after the treatment.[20] Another meta-analysis included 11 studies with 452 patients and showed ILIT to be safe, but not effective, in terms of symptom reduction.[19] Finally, a last meta-analysis included 17 clinical trials with 644 patients and showed that ILIT was a safe and fast way to reduce allergic symptoms and additional medication use.[21] Of note, ILIT has also been tested for the treatment of sensitization to animal dander and house dust mite[36-40] as well as bee venom.[41]

Hence, although ILIT has shown promising results, major drawbacks for possible efficacy claims have been the low number and small size of the trials, no standard trial design, and the lack of long-term follow-up. Indeed, despite the fact that ILIT has been discussed for nearly 20 years, no study so far followed the trial patients and the obtained effect for longer than 3 years.[10,15] For this reason, the current study aimed to reach the patients who received grass pollen allergen ILIT in the very first trial of this kind in 2002. Of the 58 patients who originally received ILIT 19 years back in time, we could reach 26 patients, of which 25 were included in the study and returned the questionnaires for full analysis. Nineteen of the 25 ILIT patients (76%) were reported to be symptom free or to have had less seasonal symptoms after ILIT as compared with before ILIT. The ILIT effect was comparable to the effect obtained in 29 patients

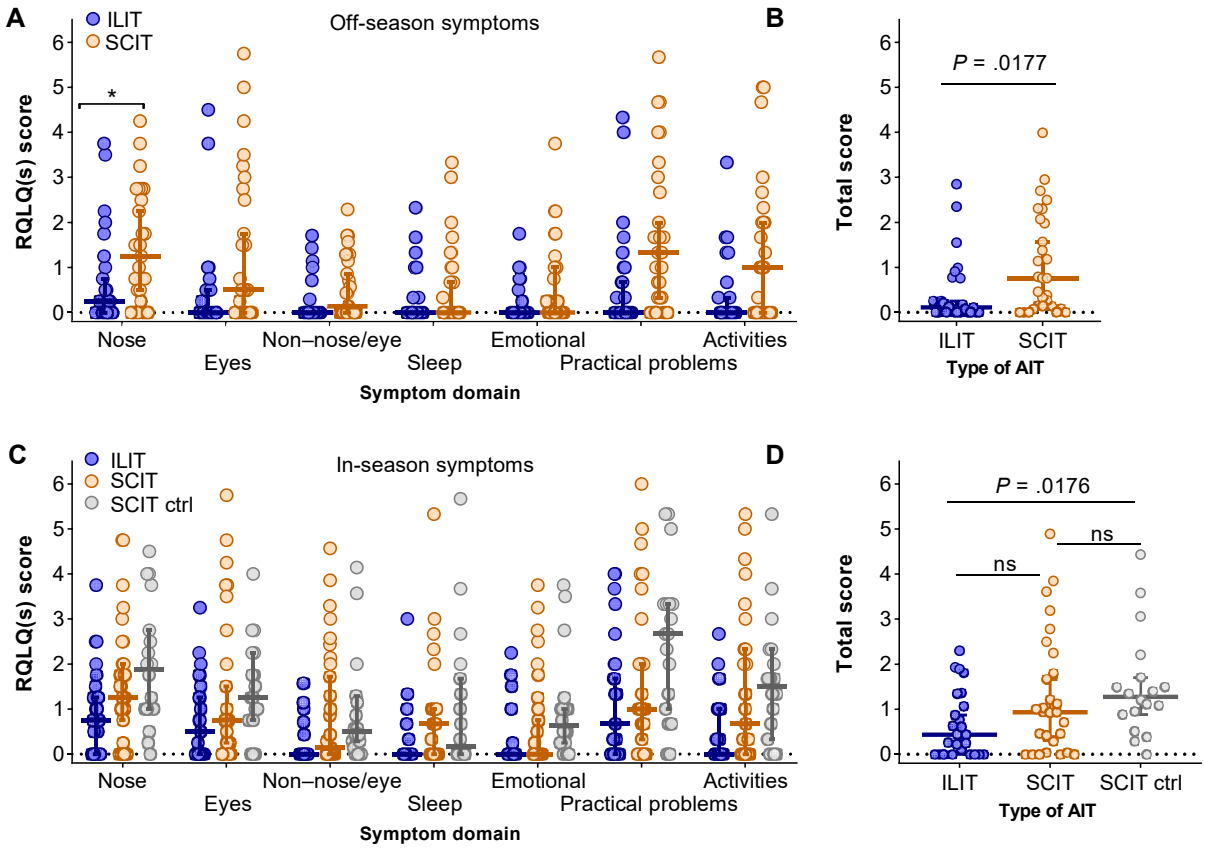

FIG 3. Total and domain RQLQ scores as recorded off-season (February 2021) and in-season (May/June 2021) for patients who received AIT. Patients who received ILIT (blue) or SCIT (orange) 19 years earlier recorded the current off-season (**A** and **B**) and in-season (**C** and **D**) allergy-related symptoms using the standardized RQLQ(S). An additional SCIT control group (gray) comprised patients who completed SCIT 3 to 6 years earlier and was added to the in-season analysis as reference for expected treatment effect. Individual domain scores (Fig 3, *A* and *C*) and total scores (*B* and *D*) are shown as well as median and 95% CIs. Analysis of the off-season total score (Fig 3, *B*) by 2-tailed Mann-Whitney *U* test revealed that ILIT patients had statistically significant lower score than patients who received SCIT ($P = .0177$). Analysis of the in-season total score (Fig 3, *D*) by Kruskal-Wallis test with Dunn's correction revealed that patients who received ILIT 19 years earlier had a statistically significant lower score ($P = .0176$) than patients who finished SCIT 3 to 6 years ago. No difference was determined between ILIT and SCIT and between SCIT and control SCIT. *ctrl*, Control. *$P < .05$.

who completed SCIT 17 years earlier. Moreover, and to control for the treatment efficacy, a second and more recent SCIT group was included in the current study. This second SCIT group represents the general and expected treatment effect of SCIT. Surprisingly, the 19-year ILIT effect was comparable and noninferior to the 3- to 6-year SCIT effect. Furthermore, when comparing rhinitis and conjunctivitis symptoms recorded at baseline and during the first 3 years of ILIT or SCIT, we found that ILIT-treated patients showed symptom improvement at 19 years as compared with 3 years posttreatment, whereas this was not the case for SCIT-treated patients. Of course, some of the ILIT effect may well be due to a natural change in the course of the allergic disease, as it is known that rhinitis symptoms, at least in a fraction of the patients, can become milder with time, especially in younger persons.[42,43] However, for the patients included in the current study, patients receiving SCIT were only slightly older than the patients receiving ILIT, the median age in both treatment groups being 50 to 59 years. Moreover, although the original study was randomized for sex, age, and urban or rural residency, a higher fraction (68%) of the study participants in the ILIT group was of rural residents with typically more grass pollen allergen exposure, whereas most (55%) of the SCIT patients were living in urban areas with typically less pollen exposure. The latter therefore does not suggest that ILIT patients show more improvement and less symptoms than SCIT patients did due to the less pollen exposure. However, because farmers typically are at a lower risk of reporting pollen allergies, and rural residents are typically less affected by allergies than persons from urban areas,[44] the overall and long-term clinical effect of ILIT and SCIT may be confounded by regional differences in the 2 test cohorts. Finally, the noninferiority as compared with the simultaneous or the more recent SCIT demonstrate that the ILIT effect was not short-lived or lost. Hence, with fewer interventions, shorter treatment time, and less AIT material, long-term effect of ILIT seems feasible.

Allergic rhinitis can significantly impair the QOL in affected patients. Having the option of a faster way to reach long-term symptom relief might be able to help a great number of patients worldwide to attain an improved QOL. We demonstrated that long-term outcome in patients treated with ILIT was similar to the

TABLE III. Analyses of RQLQ(S) score changes from off-season to in-season for ILIT and SCIT

	ILIT			SCIT		
Domain	Off-season	In-season	Δ RQLQ(S) score*	Off-season	In-season	Δ RQLQ(S) score*
Nose	0.740	0.930	0.190	1.405	1.534	0.129
Eyes	0.530	0.810	0.280	1.319	1.414	0.095
Non–nose/eye	0.251	0.285	0.034	0.547	1.025	0.478
Sleep	0.320	0.333	0.014	0.586	0.966	0.379
Emotional	0.240	0.380	0.140	0.603	0.741	0.138
Practical problems	0.693	1.240	0.546	1.644	1.678	0.034
Activities	0.426	0.587	0.160	1.241	1.424	0.183
Total	0.458	0.652	0.195	1.048	1.255	0.207

The changes for ILIT and SCIT were not statistically different as analyzed by a multiple *t* test with *post hoc* corrections (Holm-Sidak).
*Δ RQLQ(S) score is the difference between in-season RQLQ(S) score and off-season RQLQ(S) score.

criterion standard SCIT. For more than 75% of the trial participants, improved QOL and symptom reduction were reported to last for at least 19 years after treatment and these effects in ILIT-treated trial participants were noninferior to results obtained in the SCIT group. Considering the period, the allergen quantity, the possible side effects, and the compliance of each individual patient, we can say that ILIT might have come one step closer to becoming a new treatment route in the future. Here, ILIT is not suggested to replace SCIT in general, but to act as a complement for patients who either find SCIT too time consuming or who fear the risk of treatment-associated allergic side effects due to the higher number of injections in SCIT than in ILIT.

Study limitations

Considering the small sample size, around half the patients participating in the original study could not be recruited because of outdated contact details or death (not related to the allergy). This limited our participant selection to the subjects we were able to reach. Moreover, the criterion standard of monitoring AIT efficacy is to use a combined symptom-medication score, throughout the season. In the current study, quantitative medication use was not recorded and the RQLQ(S) questionnaire represents 1 week during the peak pollen season and not the whole pollen season. Nonetheless, analyzing the gathered data, the results show potential long-term efficacy of ILIT as a method for treating allergy. There is, however, the necessity for further trials with larger sample sizes to assess the safety and efficacy of ILIT more precisely.

We thank Christel Weiß and Kamran Alibeik for help in statistical analysis, and Valentine Homère for help with questionnaires. We are also grateful for the financial support from Truus und Gerrit van Riemsdijk Stiftung (Vaduz, Lichtenstein).

Clinical implications: This study describes and demonstrates long-term efficacy of ILIT for the treatment of rhinoconjunctivitis due to sensitization to grass pollen allergens.

REFERENCES

1. Wuthrich B, Schindler C, Leuenberger P, Ackermann-Liebrich U. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). Swiss Study on Air Pollution and Lung Diseases in Adults. Int Arch Allergy Immunol 1995;106:149-56.
2. Wuthrich B, Schindler C, Medici TC, Zellweger JP, Leuenberger P. IgE levels, atopy markers and hay fever in relation to age, sex and smoking status in a normal adult Swiss population. SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) Team. Int Arch Allergy Immunol 1996;111:396-402.
3. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J 2004;24:758-64.
4. Slovick A, Douiri A, Muir R, Guerra A, Tsioulos K, Haye E, et al. A randomised placebo-controlled trial investigating efficacy and mechanisms of low-dose intradermal allergen immunotherapy in treatment of seasonal allergic rhinitis. In: Efficacy and Mechanism Evaluation (EME). Southampton, UK: NIHR Journals Library; 2016.
5. Passalacqua G, Canonica GW. Local nasal specific immunotherapy for allergic rhinitis. Allergy Asthma Clin Immunol 2006;2:117-23.
6. Calderon MA, Larenas D, Kleine-Tebbe J, Jacobsen L, Passalacqua G, Eng PA, et al. European Academy of Allergy and Clinical Immunology Task Force report on 'dose-response relationship in allergen-specific immunotherapy. Allergy 2011;66:1345-59.
7. Liu W, Zeng Q, He C, Chen R, Tang Y, Yan S, et al. Compliance, efficacy, and safety of subcutaneous and sublingual immunotherapy in children with allergic rhinitis. Pediatr Allergy Immunol 2021;32:86-91.
8. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases. Allergo J Int 2014;23:282-319.
9. James C, Bernstein DI. Allergen immunotherapy: an updated review of safety. Curr Opin Allergy Clin Immunol 2017;17:55-9.
10. Senti G, Prinz Vavricka BM, Erdmann I, Diaz MI, Markus R, McCormack SJ, et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. Proc Natl Acad Sci U S A 2008;105:17908-12.
11. Hellkvist L, Hjalmarsson E, Kumlien Georen S, Karlsson A, Lundkvist K, Winqvist O, et al. Intralymphatic immunotherapy with 2 concomitant allergens, birch and grass: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 2018;142:1338-41.e9.
12. Hellkvist L, Hjalmarsson E, Weinfeld D, Dahl A, Karlsson A, Westman M, et al. High-dose pollen intralymphatic immunotherapy: two RDBPC trials question the benefit of dose increase. Allergy 2022;77:883-96.
13. Konradsen JR, Grundstrom J, Hellkvist L, Tran TAT, Andersson N, Gafvelin G, et al. Intralymphatic immunotherapy in pollen-allergic young adults with rhinoconjunctivitis and mild asthma: a randomized trial. J Allergy Clin Immunol 2020;145:1005-7.e7.
14. Skaarup SH, Graumann O, Schmid J, Bjerrum AS, Skjold T, Hoffmann HJ. The number of successful injections associates with improved clinical effect in intralymphatic immunotherapy. Allergy 2021;76:1859-61.
15. Skaarup SH, Schmid JM, Skjold T, Graumann O, Hoffmann HJ. Intralymphatic immunotherapy improves grass pollen allergic rhinoconjunctivitis: a 3-year randomized placebo-controlled trial. J Allergy Clin Immunol 2021;147:1011-9.
16. Patterson AM, Bonny AE, Shiels WE II, Erwin EA. Three-injection intralymphatic immunotherapy in adolescents and young adults with grass pollen rhinoconjunctivitis. Ann Allergy Asthma Immunol 2016;116:168-70.
17. Hylander T, Latif L, Petersson-Westin U, Cardell LO. Intralymphatic allergen-specific immunotherapy: an effective and safe alternative treatment route for pollen-induced allergic rhinitis. J Allergy Clin Immunol 2013;131:412-20.
18. Hylander T, Larsson O, Petersson-Westin U, Eriksson M, Kumlien Georen S, Winqvist O, et al. Intralymphatic immunotherapy of pollen-induced rhinoconjunctivitis: a double-blind placebo-controlled trial. Respir Res 2016;17:10.
19. Aini NR, Mohd Noor N, Md Daud MK, Wise SK, Abdullah B. Efficacy and safety of intralymphatic immunotherapy in allergic rhinitis: a systematic review and meta-analysis. Clin Transl Allergy 2021;11:e12055.
20. Hoang MP, Seresirikachorn K, Chitsuthipakorn W, Snidvongs K. Intralymphatic immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. Rhinology 2021;59:236-44.
21. Werner MT, Bosso JV. Intralymphatic immunotherapy for allergic rhinitis: a systematic review and meta-analysis. Allergy Asthma Proc 2021;42:283-92.
22. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg 2012;10:28-55.
23. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 1991;21:77-83.
24. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. J Allergy Clin Immunol 1999;104:364-9.

25. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999; 341:468-75.
26. Fritzsching B, Contoli M, Porsbjerg C, Buchs S, Larsen JR, Elliott L, et al. Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: results from the REACT study, a retrospective cohort study. Lancet Reg Health Eur 2022;13:100275.
27. Bender BG, Lockey RF. Solving the problem of nonadherence to immunotherapy. Immunol Allergy Clin North Am 2016;36:205-13.
28. Senti G, Johansen P, Kundig TM. Intralymphatic immunotherapy. Curr Opin Allergy Clin Immunol 2009;9:537-43.
29. Bachmann MF, Kundig TM. Allergen-specific immunotherapy: is it vaccination against toxins after all? Allergy 2017;72:13-23.
30. Johansen P, Haffner AC, Koch E, Zepter K, Erdmann L, Maloy K, et al. Direct intralymphatic injection of peptide vaccines enhances immunogenicity. Eur J Immunol 2005;35:568-74.
31. Johansen P, Senti G, Gomez JMM, Kuendig TM. Medication with antihistamines impairs allergen-specific immunotherapy in mice. Clin Exp Allergy 2008;38:512-9.
32. Johansen P, Senti G, Gomez JMM, Wuthrich B, Bot A, Kundig TM. Heat denaturation, a simple method to improve the immunotherapeutic potential of allergens. Eur J Immunol 2005;35:3591-8.
33. Johansen P, Senti G, Martinez Gomez JM, Storni T, von Beust BR, Wuthrich B, et al. Toll-like receptor ligands as adjuvants in allergen-specific immunotherapy. Clin Exp Allergy 2005;35:1591-8.
34. Heinzerling L, Basch V, Maloy K, Johansen P, Senti G, Wuthrich B, et al. Critical role for DNA vaccination frequency in induction of antigen-specific cytotoxic responses. Vaccine 2006;24:1389-94.
35. Maloy KJ, Erdmann I, Basch V, Sierro S, Kramps TA, Zinkernagel RM, et al. Intralymphatic immunization enhances DNA vaccination. Proc Natl Acad Sci U S A 2001;98:3299-303.
36. Freiberger SN, Zehnder M, Gafvelin G, Gronlund H, Kundig TM, Johansen P. IgG4 but no IgG1 antibody production after intralymphatic immunotherapy with recombinant MAT-Feld1 in human. Allergy 2016;71:1366-70.
37. Senti G, Kuster D, Martinez-Gomez J, Steiner M, Rose H, Crameri R, et al. Intralymphatic allergen specific immunotherapy using modified recombinant allergen targeting the MHC class II pathway: a double-blind placebo-controlled clinical trial in cat dander allergic patients. Allergy 2009;64:74.
38. Park HJ, Kim SH, Shin YS, Park CH, Cho ES, Choi SJ, et al. Intralymphatic immunotherapy with tyrosine-adsorbed allergens: a double-blind, placebo-controlled trial. Respir Res 2021;22:170.
39. Lee SP, Jung JH, Lee SM, Joe E, Kang IG, Kim ST, et al. Intralymphatic immunotherapy alleviates allergic symptoms during allergen exposure in daily life. Allergy Asthma Immunol Res 2018;10:180-1.
40. Lee SP, Choi SJ, Joe E, Lee SM, Lee MW, Shim JW, et al. A pilot study of intralymphatic immunotherapy for house dust mite, cat, and dog allergies. Allergy Asthma Immunol Res 2017;9:272-7.
41. Chabot A, Senti G, Erdmann I, Prinz BM, Wüthrich B, Sosic L, et al. Intralymphatic immunotherapy (ILIT) with bee venom allergens: a clinical proof of concept study and the very first ILIT in human. Front Allergy 2022;3: 832010.
42. Di Lorenzo G, Leto-Barone MS, La Piana S, Ditta V, Di Fede G, Rini GB. Clinical course of rhinitis and changes in vivo and in vitro of allergic parameters in elderly patients: a long-term follow-up study. Clin Exp Med 2013;13: 67-73.
43. Danielsson J, Jessen M. The natural course of allergic rhinitis during 12 years of follow-up. Allergy 1997;52:331-4.
44. Tizek L, Redlinger E, Ring J, Eyerich K, Biederman T, Zink A. Urban vs rural – prevalence of self-reported allergies in various occupational and regional settings. World Allergy Org J 2022;15:100625.