Intralymphatic immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis*

Minh P. Hoang[1,2,3], Kachorn Seresirikachorn[1,2], Wirach Chitsuthipakorn[4,5], Kornkiat Snidvongs[1,2]

[1] Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[2] Endoscopic Nasal and Sinus Surgery Excellent Center, King Chulalongkorn Memorial Hospital, Bangkok, Thailand
[3] Department of Otolaryngology, Hue University of Medicine and Pharmacy, Hue University, Vietnam
[4] Center of excellence in Otolaryngology Head & Neck Surgery, Rajavithi Hospital, Bangkok, Thailand
[5] Department of Otolaryngology, College of Medicine, Rangsit University, Bangkok, Thailand

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Abstract

Background: Intralymphatic immunotherapy (ILIT) is a new route of allergen-specific immunotherapy. Data confirming its effect is restricted to a small number of studies.

Methodology: A systematic review with meta-analysis was conducted. The short-term (<24 weeks), medium-term (24-52 weeks), and long-term (>52 weeks) effects of ILIT in patients with allergic rhinoconjunctivitis (ARC) were assessed. The outcomes were combined symptom and medication scores (CSMS), symptoms visual analog scale (VAS), disease-specific quality of life (QOL), specific IgG4 level, specific IgE level, and adverse events.

Results: Eleven randomized controlled trials and 2 cohorts (483 participants) were included. Compared with placebo, short term benefits of ILIT for seasonal ARC improved CSMS, improved VAS and increased specific IgG4 level but did not change QOL or specific IgE level. Medium-term effect improved VAS. Data on the long-term benefit of ILIT remain unavailable and require longer term follow-up studies. There were no clinical benefits of ILIT for perennial ARC. ILIT was safe and well-tolerated.

Conclusion: ILIT showed short-term benefits for seasonal ARC. The sustained effects of ILIT were inconclusive. It was well tolerated.

Key words: allergy, IgE, intralymphatic immunotherapy, pollinosis, allergic rhinitis

Introduction

The Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines and the International Consensus Statement on Allergy and Rhinology suggest allergen-specific immunotherapy (AIT) for patients with moderate to severe allergic rhinoconjunctivitis (ARC) who were not improved by medications[1,2]. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are the standard treatments of AIT[3,4]. However, these conventional treatments require a long treatment duration, for example, SCIT requires 50-80 injections over 3 years[5]. Intralymphatic immunotherapy (ILIT) is a form of AIT that can modify the IgE mediated hypersensitivity of ARC[3]. ILIT aims to improve the efficacy of AIT by administering specific allergens directly into the lymphoid organs[5], based on the "geographic concept of immunogenicity" that the immune responses can be initiated only in secondary lymphatic organs such as lymph nodes[6,7]. Inguinal and cervical lymph nodes are chosen as the injection sites of ILIT because they are superficially accessible[5]. Inguinal lymph nodes are 1 to 1.5 cm in size which can be detected by ultrasound as hypoechoic nodules. Specific allergens are injected into these lymph nodes by using a 28-gauge needle under ultrasound guidance. Current ILIT protocols suggest three injections into the lymph nodes over a period of eight weeks[8,9]. These protocols require fewer injections and a shorter treatment duration than conventional AIT. Thus, ILIT becomes an alternative treatment option for patients with ARC who did not adhere to the conventional AIT[10].

The efficacy of ILIT on allergen tolerance and mitigation of the

ARC severity has been demonstrated[8], resulting in the increasing ILIT acceptance[11]. While the long-term benefits of SCIT and SLIT have been reported[12], there is insufficient data regarding the long-term effects of ILIT. There is also a lack of systematic reviews and meta-analyses assessing the effectiveness and adverse events of ILIT. This systematic review aims to evaluate the efficacy and safety of ILIT in treating patients with ARC.

Materials and methods

The study protocol was submitted to the PROSPERO (reference number CRD42020188260). This systematic review was conducted in accordance with The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13]. Electronic searches with MEDLINE, SCOPUS, and EMBASE were conducted. Manual searches for the references of the included studies and the additional sources were conducted. The date of the last search was 21 July 2020. Combinations of the MESH terms and text words were "rhinitis, allergic", "allergic rhinitis", "nasal allergy", "hay fever", "rhinoconjunctivitis", "lymph nodes", "lymph*", "intralymph*", "intralymphatic immunotherapy", and "injection, intralymphatic".

Eligibility criteria

Clinical trials of ILIT in patients with ARC were included. Patients with ARC at any age were eligible. The diagnostic criteria of ARC followed the ARIA guidelines. The ARC diagnosis was confirmed by either skin prick test (SPT) or serum-specific IgE[14]. Studies with mixed populations of ARC and nonallergic rhinitis were included if data of the patients with ARC were reported separately. Protocols of ILIT with any type of specific allergen, dosage, treatment duration and follow-up period were accepted. Randomized controlled trials (RCTs) which assessed the effects of ILIT compared with either placebo or standard AIT (SCIT or SLIT) were eligible for the assessment of ILIT effectiveness. All clinical studies with any study design (e.g. case series, cohort, clinical controlled trial, etc.) were eligible for the assessment of ILIT safety. Conference abstracts and studies published in languages other than English were excluded.

Study selection process and data extraction

Two authors (MPH and WC) independently screened the titles and abstracts of the studies based on predetermined eligibility criteria. Full texts of the screened studies were obtained for the final study selection. Two authors (MPH and KSe) separately performed data extraction. If there was incomplete data during the data collection, the corresponding author of that study was contacted for additional data. Disagreements over the selection and extraction processes were resolved by thoroughly discussing among the authors or by consulting the fourth author (KSn). The extracted data included: sample size, age, gender, allergen extract, dosage, interval between the injections, booster dose, and follow-up period. The effects of ILIT were assessed after finishing three injections at <24 weeks for short-term effects, 24-52 weeks for medium-term effects, and >52 weeks for long-term effects.

Outcome measures

Primary outcomes were the combined symptom and medication score (CSMS), symptom score (SS), medication score (MS), visual analog scale (VAS) of ARC symptoms, and disease-specific quality of life (QOL). These outcomes are recommended by the European Academy of Allergy and Clinical Immunology (EAACI) and the Food and Drug Administration (FDA) as primary outcomes for AIT trials[15]. The CSMS is equally weighted between the SS and MS, and reflects both the symptom severity and the intake of rescue medication[15]. Secondary outcomes were specific IgG4 level, specific IgE level, and adverse events. Adverse events were categorized as local reaction, systemic reaction, anaphylaxis, and death.

Quality of the included studies

Two authors (MPH and WC) independently evaluated the quality of the included studies. Risks of bias were assessed according to the Cochrane Collaboration's tool[16] to determine the quality of each RCT. Five domains were evaluated which included random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Each domain was determined as "low risk" of bias when the methods of the domain were sufficiently described, "high risk" when the respective domain has not been mentioned, or "unknown risk" when the domain was mentioned but insufficiently described. The quality of non-randomized studies was assessed by the methodological index for non-randomized studies (MINORS) with 8 domains for non-comparative studies or 12 domains for comparative studies[17]. Each domain had a score ranging from 0 to 2. The total MINORS score of non-comparative studies was 0-16 or 0-24 for comparative studies. A total score of non-comparative studies below 11 and comparative studies below 16 represented high risk of bias.

Data synthesis and statistical analysis

Meta-analysis was performed by using Review Manager (RevMan) version 5.4[18]. Dichotomous data were analyzed and reported as risk ratio (RR) and 95% confidence interval (CI). Continuous data were presented as mean difference (MD) or standardized mean difference (SMD), standard deviation (SD), and 95% CI. The standard error, median, range, and 95% CI were interpreted if the SD was not provided or could not be calculated. Discrepancies in the treatment effects among the trials were evaluated using heterogeneity (I2) statistics. An I2 of <40%, 40-60% and >60% represented "low", "moderate" and "substantial" heterogeneity, respectively. When heterogeneity was low, a fixed-effect model was used. A random-effects model was used

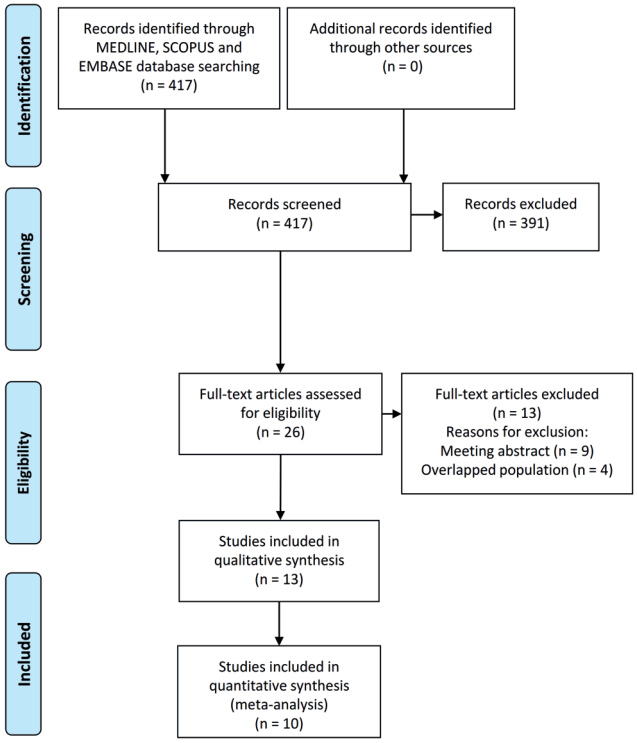

Figure 1. Flow diagram of study selection for the systematic review and meta-analysis.

if the heterogeneity was high for a more conservative estimate of the differences.

Subgroup analyses

Subgroup analyses by ARC subtype, age of the participant, and injection interval were conducted to assess the treatment effects and to explore the heterogeneity.

Results

Study selection

The electronic and manual searches retrieved 417 studies. Title and abstract screening removed 391 studies. Full-text screening for eligibility excluded 13 studies. Thirteen studies (11 RCTs and 2 cohorts) were included in the qualitative synthesis[8,9,19-29] of which 10 RCTs were included in the quantitative synthesis[8,19-22,24-28]. A flowchart of the study selection is illustrated in Figure 1.

Participants

There were 483 participants (54.9% male). The mean age was 33.2 years. There were no patients younger than 15 years old. Ten RCTs assessed seasonal ARC patients. One RCT[19] and two cohorts assessed perennial ARC patients[9,23]. Three studies assessed only patients with moderate to severe ARC[21,24,27]. Characteristics of the included studies are shown in Table 1.

Intervention

Inguinal lymph nodes were the site of allergen administration in 12 studies[8,19-29]. One study used cervical lymph nodes[9]. Pollen extracts were administered in 10 studies that assessed seasonal ARC patients[8,20-22,24-29]. In the 3 studies of patients with perennial ARC, mixed allergen extracts (house dust mites, dog, and cat dander)[23], house dust mite allergen extracts[9], and a recombinant MAT–Feld1 from cat dander[19] were used in each study. Non-standardized allergen extracts were used in 2 studies[23,28]. The interval between the ILIT injections was 4 weeks in 12 studies[8,9,19,21-29], and 2 weeks in 1 study[20]. Escalating doses were administered in 2 studies[19,22] and fluctuating doses in 1 study (due to adverse events)[23]. The other 10 studies administered the

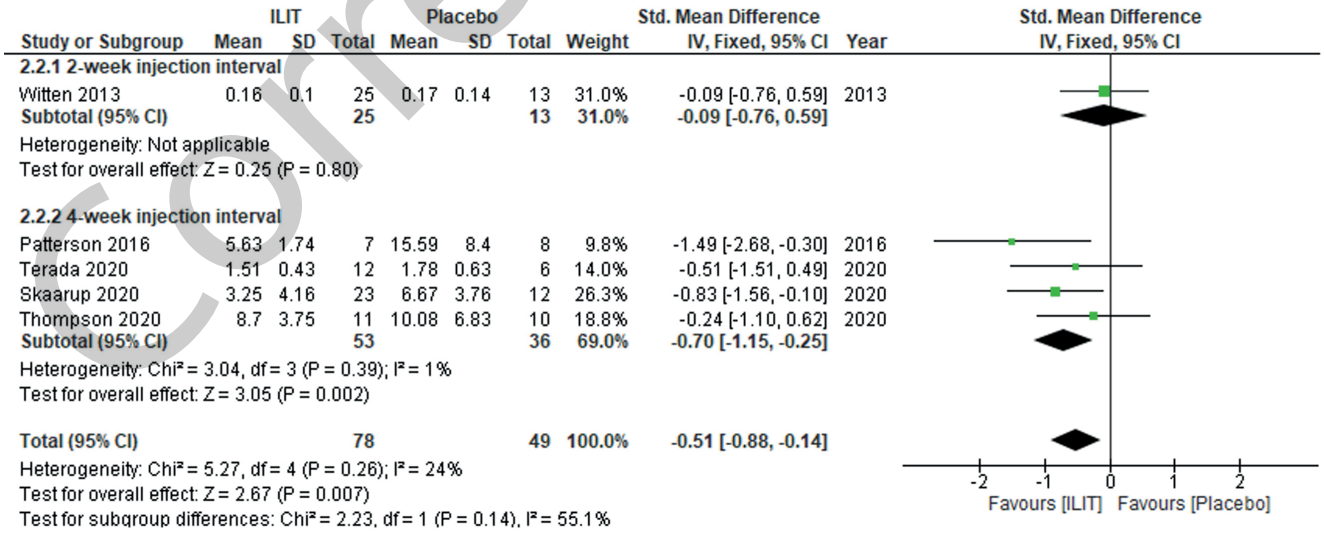

Figure 2. Short-term improvement in combined symptom and medication score and subgroup analysis by injection interval: intralymphatic immunotherapy versus placebo. ILIT = intralymphatic immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

Table 1. Characteristics of the included studies.

First author, Year	Patients (n)	Allergy	Mean age (year)	Male (%)	ILIT Allergen extracts	ILIT dose per injection	Booster Dose	Control	Interval (weeks)	Follow up (weeks)	Anaphylaxis events
Senti [8], 2008	112	Grass pollen	34	65.1	AHA grass pollen extract	1000 SQU	No	SCIT: same extract with ILIT	4	144	NR
Senti[19], 2012	20	Cat dander	30.8	30	AHA MAT–Feld1	1 µg 3 µg 10 µg	No	Placebo: AHA and saline	4 ± 3 days	55	NR
Witten [20], 2013	43	Grass pollen	35.4	58.1	Alutard, Phleum pratense, ALK-Abelló	1000 SQU	No	Placebo: saline	2	14	NR
Hylander [21], 2016	36	Birch / Grass pollen	33.3	61.1	AHA birch or grass pollen extract	1000 SQU	No	Placebo: Alutard, ALK Abéllo	4	36	NR
Patterson [22], 2016	15	Grass pollen	NR	NR	AHA grass pollen extract Center-Al Phleum pratense	50 PNU 100 PNU 250 PNU	No	Placebo: saline with phenol	4	10	NR
Lee[23], 2017	11	HDM, cat, and dog	41.6	36.4	Aqueous causal allergen extracts	Various doses	No	NR	4	42	Yes
Hellkvist[24], 2018	51	Birch and grass pollen	31.8	68.6	ALK Alutard 5-grasses and ALK Alutard Birch	1000 SQU	No	Placebo: saline and albumin	4	24-36	NR
Wang[9], 2019	81	HDM	34.5	53.1	Standardized house dust mite allergen extracts	50 TU	No	NR	4	52	NR
Konradsen [25], 2020	26	Birch and/ or grass pollen	22.3	61.5	Alutard birch or grass pollen	1000 SQU	Yes	Placebo: ALK diluent	4	92-104	NR
Skaarup[26], 2020	36	Grass pollen	30.7	52.8	ALK 225 Soluprick Phleum Pratens	1000 SQU	Yes	Placebo: isotonic saline	4	144	NR
Terada[27], 2020	18	Japanese cedar pollen	43	33.3	Japanese cedar pollen extract	20 JAU	No	Placebo: saline	4	130	NR
Thompson [28], 2020	21	Mountain cedar pollen	37.6	42.9	Mountain cedar pollen, ALK-Abelló	1:2000 w/v	No	Placebo: glycerin and saline	4	15-19	NR
Weinfeld[29], 2020	13	Grass ± birch pollen	NR	NR	ALK Alutard 5-grasses	1000 SQU	Yes	Placebo: ALK diluent*	4	84	NR

* placebo booster; ILIT, intralyphatic immunotherapy; SCIT, subcutaneous immunotherapy; AHA: aluminium hydroxide-adsorbed; SQU, standardized quality units; PNU, protein nitrogen units; JAU, Japanese allergy units; TU, therapeutic units; NR, not reported; ALK, Allergologisk Laboratorium København.

same dosage throughout the study. Preseason booster doses were given in 3 studies[25,26,29]. Five studies had follow-up periods longer than 52 weeks[8,25-27,29].

Comparisons

Ten of the 11 RCTs compared ILIT with placebo[19-22,24-29] and 1 RCT compared ILIT with the conventional SCIT[8].

Outcomes

Combined symptom and medication score (CSMS)

Five RCTs compared CSMS in patients with seasonal ARC between the ILIT and placebo[20,22,26-28]. The short-term effect of ILIT on the CSMS improvement favored ILIT (SMD -0.51, 95%CI -0.88 to -0.14, p<0.01, 5 RCTs)[20,22,26-28]. An I2 of 24% represented low heterogeneity. Data are illustrated in Figure 2. There was no

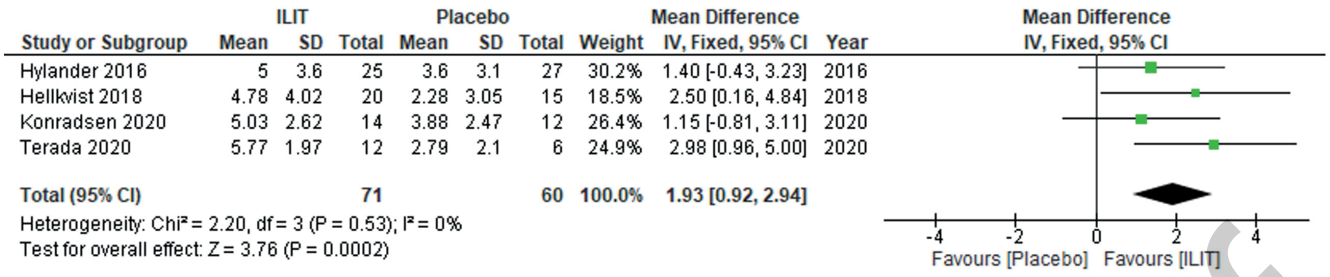

Figure 3. Medium-term improvement in visual analog scale in allergic symptoms: intralymphatic immunotherapy versus placebo. ILIT = intralymphatic immunotherapy; CI = confidence interval; df = degrees of freedom.

study assessing medium-term effect. The long-term effect of ILIT was not different from placebo (MD -3.62, 95%CI -7.61 to 0.37, p=0.08, 1 RCT)[26].

Visual analog scale (VAS) of seasonal allergic symptoms

Four RCTs compared the VAS of seasonal allergic symptoms between the ILIT and placebo[21,24,25,27].The short-term effect on VAS improvement (MD 2.98, 95%CI 0.96 to 5.00, p<0.01, 1 RCT) [27], and the medium-term effect (MD 1.93, 95%CI 0.92 to 2.94, p<0.01, 4 RCTs) favored ILIT[21,24,25,27]. Data are illustrated in Figure 3. An I2 of 0% represented low heterogeneity. The long-term effect of ILIT was not different from placebo (MD 0.43, 95%CI -2 to 2.86, p=0.73, 1 RCT)[27].

One RCT compared the VAS scores between ILIT and SCIT in patients with seasonal ARC. Both ILIT and SCIT improved the VAS scores when compared with the baseline. There were no differences between ILIT and SCIT in both the medium-term effect (MD 0.02, 95%CI -0.35 to 0.39, p=0.92, 1 RCT) and the long-term effect (MD 0.33, 95%CI -0.04 to 0.71, p=0.08, 1 RCT)[8].

Symptom score (SS)

Three RCTs assessed SS between the ILIT and placebo[20,25,28]. The short-term effect of ILIT on SS was not different from placebo (SMD -0.28, 95%CI -0.74 to 0.18, p=0.23, 3 RCTs). An I2 of 0% represented low heterogeneity.

Medication score (MS)

Three RCTs assessed MS between the ILIT and placebo(20,25,28). The short-term effect of ILIT on MS was not different from placebo (SMD -0.14, 95%CI -0.16 to 0.29, p=0.48, 3 RCTs). An I2 of 0% represented low heterogeneity.

Disease-specific quality of life

Four RCTs assessed the disease-specific QOL score[19,20,24,25], of which 3 RCTs assessed seasonal ARC[20,24,25] and 1 RCT assessed perennial ARC[19]. The Asthma Quality of Life Questionnaire was used in 1 RCT[25]. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was used in 2 RCTs[20,24]. The short-term effect of ILIT was not different from placebo (SMD -0.4, 95%CI -1.21 to 0.42, p=0.34, 2 RCTs)[20,24]. The validated mini RQLQ was used in 1 RCT which assessed perennial ARC. There was no statistical difference between ILIT and placebo but the data could not be extracted[19].

Subgroup analysis by pediatric subgroup

There was no study assessing pediatric patients.

Subgroup analysis by ARC subtype

One RCT studied patients with perennial ARC[19]. The mini RQLQ were assessed and showed no statistical difference between ILIT and placebo (data not shown). The CSMS, SS, MS, and VAS were not assessed in this study.

Subgroup analysis by injection interval

Subgroup analysis by injection interval was performed. The short-term effect on CSMS improvement favored the 4-week interval of ILIT over placebo (SMD -0.70, 95%CI -1.15 to -0.25, p<0.01, 4 RCTs)[22,26-28]. An I2 of 1% represented low heterogeneity. Benefit of the 2-week interval of ILIT was not shown (SMD -0.09, 95%CI -0.76 to 0.59, p=0.8, 1 RCT)[20].

Specific IgG4 level

Eight RCTs assessed specific IgG4 level between the ILIT and placebo[19-21,24-27,29]. One RCT assessed specific IgG4 level only for preseason booster dose[29]. Data from 2 RCTs were not extracted due to selecting outcome bias[24,27]. The short-term effect of ILIT increased specific IgG4 level (SMD 0.7, 95%CI 0.16 to 1.24, p=0.01, 4 RCTs)[19-21,26]. An I2 of 48% represented moderate heterogeneity. There were no differences in the medium-term effect (SMD 0.37, 95%CI -0.03 to 0.78, p=0.07, 4 RCTs, I2 = 9%)[21,25,26,30] and the long-term effect (MD -0.02, 95%CI -0.72 to 0.68, p=0.95, 1 RCT)[26]. Data are illustrated in Figure 4.

Specific IgE level

Eight RCTs assessed specific IgE level between ILIT and placebo[19-21,24-28]. Data were not provided in one RCT[27]. The ILIT effects did not decrease the specific IgE level at any time point: short-term (SMD 0.01, 95%CI -0.27 to 0.3, p=0.92, 6 RCTs)[19-

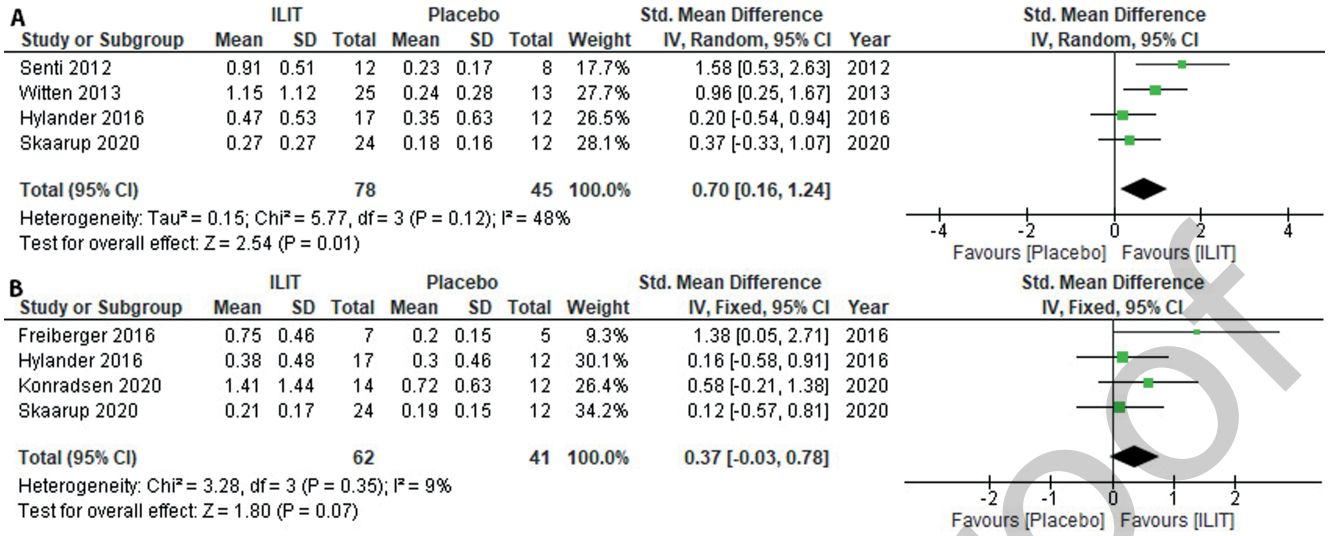

Figure 4. Change on specific IgG4 level: intralymphatic immunotherapy versus placebo. (A) Short-term. (B) Medium-term. ILIT = intralymphatic immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

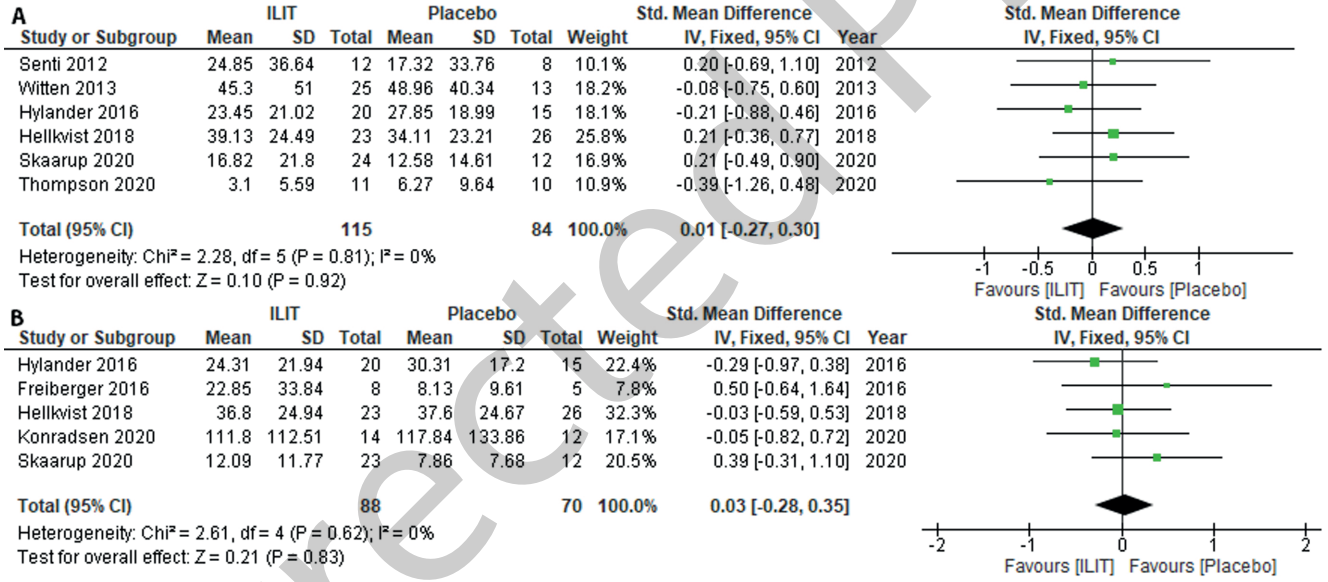

Figure 5. Change on specific IgE level: intralymphatic immunotherapy versus placebo. (A) Short-term. (B) Medium-term. ILIT = intralymphatic immunotherapy; CI = confidence interval; df = degrees of freedom; Std. mean difference = standardized mean difference.

[21,24,26,28], medium-term (SMD 0.03, 95%CI -0.28 to 0.35, p=0.83, 5 RCTs)[20,21,25,26,30], and long-term (SMD 0.18, 95%CI -0.52 to 0.88, p=0.62, 1 RCT)[26]. An I2 of 0% represented low heterogeneity in all meta-analyses. Data are illustrated in Figure 5. One RCT compared between the ILIT and SCIT, the effects of SCIT significantly decreased specific IgE level in all 3 periods: short-term (MD 6.40, 95%CI 1.85 to 10.95, p<0.01, 1 RCT), medium-term (MD 5.58, 95%CI 1.03 to 10.13, p=0.02, 1 RCT), and long-term (MD 7.54, 95%CI 3.18 to 11.09, p<0.01, 1 RCT)[8].

Adverse events

All the 11 included RCTs assessed the safety of ILIT and reported adverse events. ILIT had more local reactions than placebo but there were no differences in systemic adverse events. Data are illustrated in Table 2. ILIT had fewer adverse events than SCIT (RR 0.28, 95%CI 0.12 to 0.64, p<0.01, 1 RCT)[8]. Anaphylaxis and death were assessed in a total of 989 ILIT injections (2 cohorts and 11 RCTs), there was no death but two (0.2%) anaphylaxis events were reported[23].

Quality of the included studies

Most of the 11 RCTs had risks of selection bias and attrition bias (Figure 6). There were low risks of bias in allocation concealment (55% of the RCTs), incomplete outcome data (55%), random sequence generation (70%), blinding of outcome assessment

Table 2. Risk ratios of adverse events: Intralymphatic immunotherapy vs placebo.

Adverse events	Number of studies	ILIT		Placebo		Risk ratio (95% CI)	p value
		Number of injections	Number of events	Number of injections	Number of events		
Local reactions							
Local lymph node swelling [19-21,24,26]	6	368	102	265	5	7.53 (1.82, 31.15)	0.01
Local redness[21,24,28,29]	4	194	43	169	0	16.75 (4.1, 68.41)	<0.01
Local itching[21,24,29]	3	161	23	139	10	5.48 (1.80, 16.68)	<0.01
Systemic reactions							
Skin[19,21,24,26,29]	5	281	10	223	1	2.93 (0.85, 10.02)	0.09
Eye/nasal symptoms[19-21,24,26,27,29]	7	404	47	283	25	1.17 (0.73, 1.87)	0.52
Headache/fatigue[19,20,24,26,29]	5	307	22	220	12	1.25 (0.62, 2.53)	0.53
Pulmonary symptoms[19,20,29]	3	136	6	72	4	0.74 (0.23, 2.42)	0.62
Abdoment/nausea[19-21,24,29]	5	284	11	205	8	0.81 (0.37, 1.78)	0.60
Anaphylaxis[19-22,24-29]	10	536	0	408	0	NA	NA

Abbreviations: ILIT, intralymphatic immunotherapy; CI, confidence interval; NA, not applicable.

(80%), and selective reporting (80%). When the quality of 2 cohorts was assessed, both of them had high risks of bias. The total MINORS scores of these studies were 9[23] and 10[9] out of 16.

Discussion

This systematic review demonstrated the short-term benefits of ILIT in treating seasonal ARC patients compared with placebo. The short-term effects of ILIT significantly improved the CSMS and VAS.

AIT is a step-up treatment for patients with ARC who were not improved by pharmacotherapies[31]. Nevertheless, SLIT needs high compliance and SCIT requires more than 70 injections over 3-5 years[32]. As a result, most patients with ARC feel unsatisfied with the inconveniences of these conventional AITs[33]. ILIT, a new form of AIT that requires 3 intralymphatic injections over 2 months, could be a potential alternative for these patients.

The benefits of ILIT for treating patients with ARC have been postulated and investigated in recent years[3]. Direct intralymphatic injection enhances the availability of allergen in secondary lymphoid organs[5]. An animal experiment demonstrated that the antigens that reached the lymph nodes after intralymphatic administration were 100-fold higher than those after subcutaneous injection at the same dose[34]. A human study revealed that the allergen fragments reached the deep subcutaneous lymph nodes 20 minutes after the intralymphatic injection into a superficial inguinal lymph node[10]. On the contrary, only a small fraction of antigen reached the lymph nodes after 24 hours of subcutaneous administration with the same dose at 10 cm above the contralateral superficial lymph node[10]. ILIT requires a lower total dose than the conventional AIT. The 3-year cumulative dose of SCIT is 1,000-fold higher than ILIT[8]. In addition, the treatment duration of ILIT is shorter. For these reasons, ILIT should be considered as another option of AIT[11].

The short-term and medium-term beneficial effects were shown for ILIT on VAS improvement. The reduction of CSMS reflected an improvement in symptom severity and/or a decrease in the usage of rescue medications[15]. The short-term benefit of ILIT on CSMS reduction was demonstrated in this review. However, the standardized mean difference of around 0.5 may not be clinically significant. The medium-term benefit of ILIT on improving CSMS remained unavailable and the long-term benefit was not shown. Disease specific quality of life, symptom score, and medication score were not different between the ILIT and control groups. Discordance between VAS, CSMS and disease specific quality of life, symptom score raises a concern that the effects of ILIT should not be overstated. Unlike the effect of other AITs on specific IgE level[7], ILIT did not decrease the specific IgE level at any time point. Although the IgG4 level was increased after ILIT, this effect deteriorated after 24 weeks. This finding was similar to the effect on CSMS[26]. The short-term benefit on CSMS was demonstrated in the 4-week injection interval but not the 2-week interval in this study. This finding suggested that the 2-week interval was not enough time for adequate immune responses. The allergen-specific immune responses, including memory B-cell formation and affinity maturation need sufficient time to develop after allergens are present in lymph follicles[35].

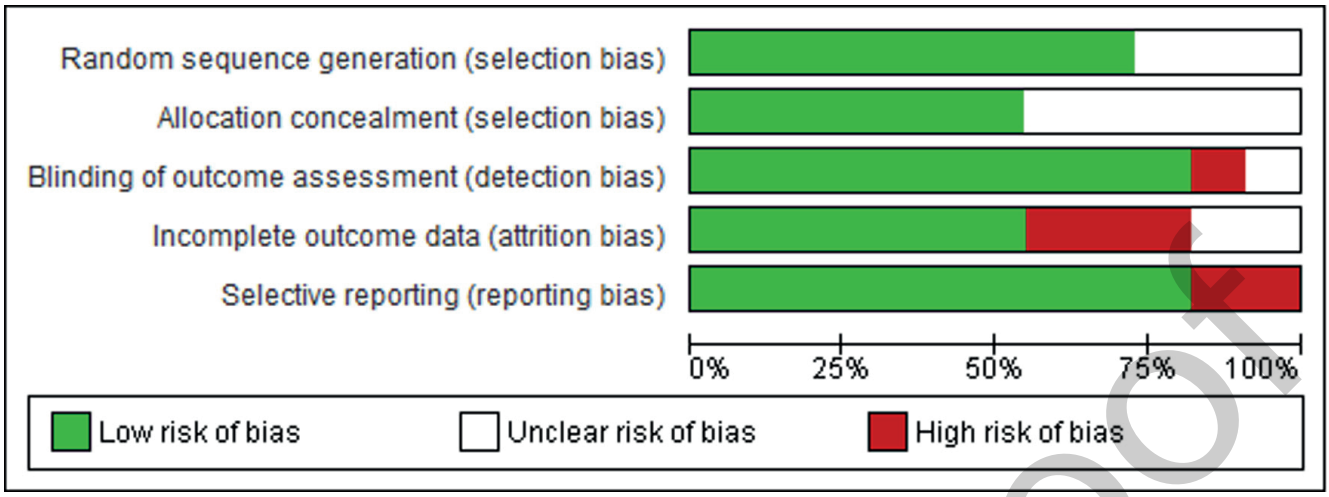

Figure 6. Each risk of bias item for each included study.

AIT is expected to provide long-term favorable therapeutic outcomes. However, this review did not demonstrate the long-term benefits of ILIT. There were only a few of the included RCTs that studied the long-term effects of ILIT. Two RCTs reported no long-term benefits of ILIT (after 52 weeks). The dosage of ILIT in these studies might be suboptimal[26,27]. This review could not demonstrate the optimal dose for long-term benefits of ILIT. Moreover, the ILIT protocols in most of the included studies were 3 injections of the same dose within 2 months. Escalating dose and/or booster dose might provide better therapeutic effects as well as long-term effects. The protocols with escalating dose and/or booster dose have not, however, been extensively investigated. Mixed results were reported by the studies that investigated a booster dose. Konradsen et al.[25] assessed the effects of one additional booster dose after one year. They demonstrated the clinical improvements in symptom score and medication score but the increased specific IgG4 level was maintained at the same level as the first pollen season (before the booster dose). In concordance with this finding, Weinfeld et al.[29] demonstrated that the preseason booster of ILIT decreased the eyes symptom score and increased the specific IgG4 level. In contrast, Skaarup et al.[26] reported that the preseason booster did not provide additional effects. Therefore, the benefits of booster injection were inconclusive.

ILIT had fewer adverse events than SCIT in both local and systemic reactions. Lee et al.[23] reported two anaphylaxis events in a cohort study. An aqueous non-standardized allergen extract was used in this cohort. Other studies that used standardized allergen extracts did not report any anaphylaxis or other severe systemic adverse events. ILIT also had risks of local reaction. Allergen extracts used in 9 out of the 11 RCTs were aluminum-based adjuvant. It is possible that aluminum increases the risk of local reaction. In addition, glycerin in glycerinated extract used by Thompson et al.[28] might be the cause of local redness.

The limitations of this systematic review were that the majority of studies assessed patients with seasonal ARC with only a few studies assessed perennial ARC. There were no pediatric patients included in the study. Multi-center trials with large sample sizes and long-term follow-up greater than 1 year are required to determine the standardized dose for ILIT and its long-term efficacy.

Conclusion

Evidence from 11 randomized controlled trials showed short-term benefits of ILIT for treating adult patients with seasonal ARC. These short-term benefits included improvements of the combined symptom and medication score and the visual analogue scale of ARC symptoms. The long-term effects were inconclusive due to a lack of studies. Benefits of ILIT for treating perennial ARC were inconclusive. There was no data for pediatric patients. ILIT was safe and well-tolerated.

Authorship contribution

MPH: study design, search, study selection, data collection, data analysis, drafting the article, and final approval; KSe: search, study selection, data collection, revising the article, and final approval; WC: search, study selection, revising the article, and final approval; KSn: conception, study design, data analysis, drafting the article, and final approval.

Conflict of interest

Kornkiat Snidvongs received Honoraria for speaking at symposia from Merck Sharp & Dohme, Mylan, and Menarini.
Minh P. Hoang, Kachorn Seresirikachorn, Wirach Chitsuthipakorn declare that they have no conflict of interest.

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Kornkiat Snidvongs
Department of Otolaryngology
Faculty of Medicine
Chulalongkorn University
1873 Rama 4 Road
Pathumwan
Bangkok 10330
Thailand

Tel: (+66) 2-256-4103
Fax: (+66) 2-252-7787
E-mail: drkornkiat@yahoo.com