

Changes in Immunologic Indicators During Allergen-Specific Immunotherapy for Allergic Rhinitis and Determinants of Variability: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background: To date, there are no generally recognized biomarkers for allergen immunotherapy (AIT) and even the changes in immunological indicators during AIT are inconsistent in different publications.

Objective: This study was conducted to quantify the immunological changes that occur during AIT and identify the determinants of heterogeneity.

Methods: Randomized controlled trials of AIT published in the past 10 years were searched in Medline, Embase and Cochrane CENTRAL. Data on immunological indicators were extracted, and the characteristics of the included studies were collected. Meta-analysis and meta-regression were conducted for each indicator. The study was registered on the PROSPERO website (CRD42020176127).

Results: We reviewed 1898 studies. Forty-six studies met the inclusion criteria, and 31 studies were included in the quantitative analyses. Subset analyses by time demonstrated that serum allergen-specific IgE (sIgE) of AIT patients increased in the first 12 months, then decreased and became slightly lower than that of control patients. Allergen-specific IgG4 (sIgG4) was elevated in the AIT group during and after treatment. IgE-blocking factor (IgE-BF) was increased and IgE-facilitated allergen binding (IgE-FAB) was reduced in AIT patients. Both of them of the 2 factors were associated with clinical efficacy in the multivariate regression analysis. sIgE/sIgG4 decreased in AIT patients, while there was no change in total IgE.

Conclusion: The levels of serum sIgE and sIgG4 during AIT showed a time-dependent pattern. IgE-BF and IgE-FAB should be further investigated as biomarkers for predicting and monitoring AIT efficacy.

Keywords

desensitizations, immunologic, allergen immunotherapy, rhinitis, allergic, meta-analysis, biomarkers

Introduction

Allergen immunotherapy (AIT) is currently the only etiological treatment for IgE-mediated allergic diseases, as it can modify the immune responses of individuals, alleviate allergen-induced symptoms and prevent disease progression. Currently, most of the efficacy assessment in AIT are subjective evaluations and the psychometric validation is absent.¹ The allergen provocation test is relatively objective, but it can hardly reproduce natural allergen exposure in real-life situations and the methodology varies a lot.¹ In this regard, biological markers,

which help to predict clinical outcomes, monitor therapy effects, and indicate severe adverse events during AIT, are needed to provide reliable evidence for precise

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decision making and avoid unnecessary time and health economic costs.

Candidate biomarkers can be classified into the following domains: IgE, IgG, inhibitory activity for IgE, basophil activation, cytokines and chemokines, and cellular biomarkers.² However, to date, there are no generally recognized biomarkers and even the changes in immunological indicators during AIT are still controversial. Allergen-specific IgE (sIgE) and IgG4 (sIgG4) are the most widely explored immunological indicators used in clinical trials of AIT. One study demonstrates an increase in sIgG4 in responders compared with non-responders during AIT, indicating the correlation between sIgG4 and clinical efficacy,³ but both sIgE and sIgG4 show a time-dependent change pattern, which may lead to the heterogeneous results between studies with different duration of treatment. Inhibitory activity for IgE, namely IgE-facilitated allergen binding (IgE-FAB) and IgE-blocking factors (IgE-BF), appear to be promising biomarkers for clinical efficacy,² since the correlation between them and symptom score has been demonstrated in some studies.^{4,5} The results of other biomarkers from clinical studies are also conflicting and do not show direct clinical relevance.²

By conducting a systematic review and meta-analysis of randomized controlled trials, this study aimed to quantify the effect of AIT for AR on biological parameters mainly in the first three domains and identify the factors that are responsible for the heterogeneity.

Method

Search Strategy and Selection Criteria

Studies published in the past 10 years were found by searching EMBASE, Medline and Cochrane Central Register of Controlled Trials via Ovid SP. The search was performed on January 28, 2020 based on the following keywords: rhinitis, allergic; rhinitis, allergic, perennial; rhinitis, allergic, seasonal; desensitization, immunologic; sublingual immunotherapy; and immunotherapy. Animal studies were excluded and there was no restriction on language. The detailed searching strategy in Medline can be seen in Supplement.

Randomized controlled trials (RCTs) were eligible if they met all the following criteria: contained at least one interventional group of AIT (SLIT or SCIT) and a controlled group not exposed to AIT and/or biological agents that might influence the immune system (such as monoclonal antibodies); the participants should be diagnosed with AR according to their clinical history and allergen tests, including skin prick test, serum allergen-specific IgE (sIgE) or nasal provocation test; the outcome measures included at least one kind of immunological parameter. Other studies, such as

nonrandomized controlled trials and observational studies, were not considered. Trials for intradermal, epicutaneous, intralymphatic or intranasal immunotherapy were also excluded.

Data Extraction

Two researchers independently reviewed the publications and extracted the data. Any disagreement was resolved by discussion or by a third reviewer. Details were extracted into the customized data sheet. For immunological indicators, arithmetic means of raw data and log-scaled data, geometric means of raw data and log-scaled data, and mean changes of log-scaled data from baseline were collected. Other information that could be the source of heterogeneity was collected: publication year, location of trials, methodology (blind or nonblind study design, intervention of control group), inclusion criteria (age limit, inclusion threshold of serum sIgE), characteristics of participants (sample size, proportion of women, ratio of polysensitization, ratio of concomitant asthma, the rate of loss to follow-up, etc.), protocol of AIT (up dosing duration, category of allergen, type of vaccine, route of administration, etc), details of measurement (time interval between AIT initiation and measurement, measurement method, whether in or out of the pollen season) and clinical efficacy (combined symptom and rescue medication score, CSMS; or total symptom score, TSS). For studies using continuous AIT, repeated measurements of each biological indicator at different time points were collected. For some studies designed as preseasonal or coseasonal AIT for pollen allergy, only data in the first treatment period were collected.

Data Analyses

For all analyses, the statistical unit was group rather than study. For example, if a multi-armed RCT used repeated measure design, each single measurement of a biomarker in each interventional arm was treated as a group. The heterogeneity was quantified by using the Q test. Outcomes were synthesized using the random-effect model if the heterogeneity between groups was considerable ($I^2 > 50\%$). Because we presumed that the changes in biomarkers were time-dependent, subgroup analyses by time were performed after general synthesis if applicable. Characteristics of studies that might influence the outcomes were put into univariate random-effects meta-regression separately. An intercept was allowed to capture intergroup variability not modeled by the explanatory variables. Potential effect modifiers in unadjusted regression analyses with a p-value < 0.05 were included in the multivariable model using the stepwise selection method. The amount of heterogeneity explained by the

model and the residual heterogeneity were denoted by R^2 and I^2 .

Data for sIgE and sIgG4 were transformed to means and standard deviations on the $\log_{10}$ scale⁶ and then analyzed in the units of $\log_{10}$ -kU/L and $\log_{10}$ -mg/L, respectively. The mean difference (MD) and 95% confidence interval of each indicator were used in meta-analyses. Clinical efficacy was denoted by the MD in CSMS or TSS between the AIT group and control group, and all the scores were adjusted to the same scale with a maximum score of 3. All analyses were performed using the meta package of R (i386 3.6.2 version, the R Foundation, Vienna, Austria). The study was registered on the PROSPERO website (CRD42020176127).

Results

The search yielded a total of 1897 publications from 3 databases and 1 study from the references of literature. Of these, 31 RCTs met the inclusion criteria and were included in the quantitative synthesis. The selection

process of studies is described in Figure 1. Quantitative analyses were available for 6 serum indicators: sIgE, sIgG4, IgE-BF, IgE-FAB, total IgE (tIgE) and sIgE/sIgG4.

The main information about the studies included in quantitative analyses is presented in Table 1. All the studies were placebo controlled and double blinded except four studies that included an open controlled group.^{5,7-9}

Allergen-Specific IgE

One hundred nine groups from 26 studies were included in the analysis for sIgE. According to the time interval (month) between AIT initiation and measurement, these groups were roughly divided into the following 8 subsets: 1 m, 2 m, 3-4 m, 5-6 m, 7-8 m, 12 m, and 24-36 m, post-treatment (12-24 m after cessation). The results of subset analyses showed that the average sIgE level in the AIT groups was higher than that in the control groups from 1 m to 7-8 m ($P < 0.0001$). In the 12 m subset, the

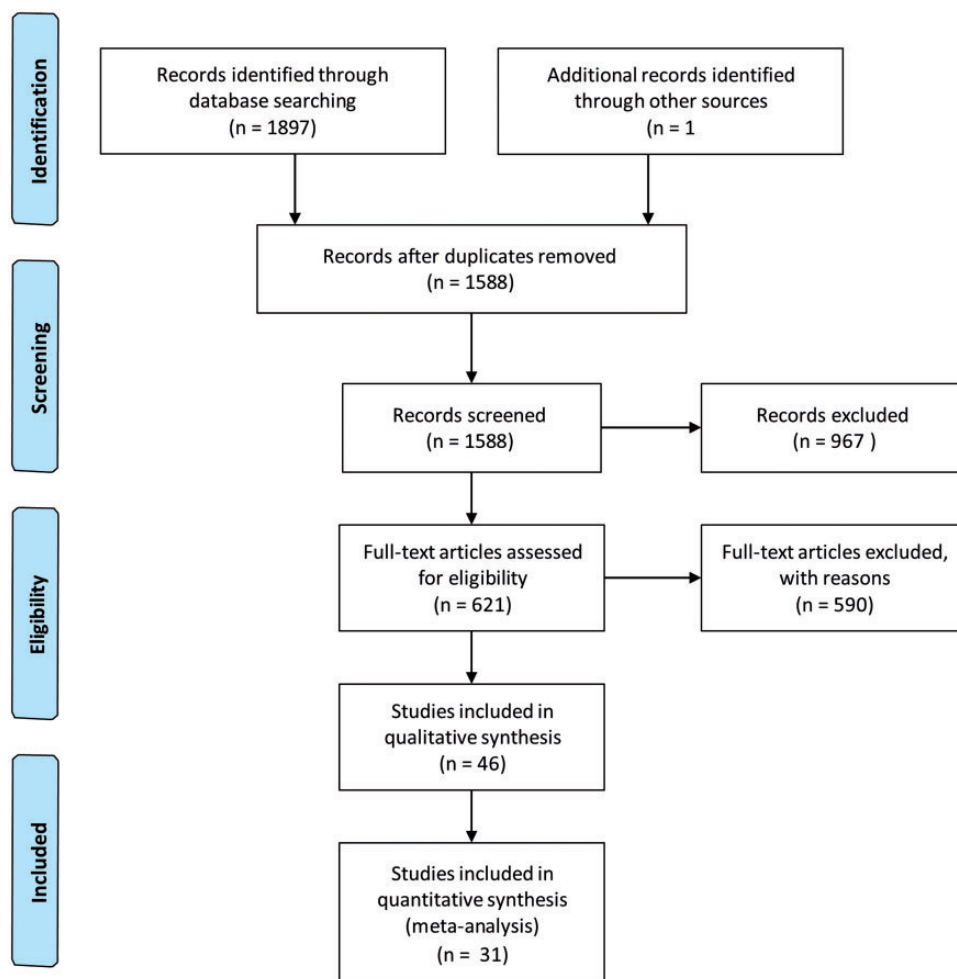


Figure 1. PRISMA flow diagram.

Table 1. Main Characteristics of the Studies Included in the Meta-analysis.

Authors	Publication Year	Location	Intervention	Sample Size	Allergen	Maintenance Dose	No. of Arms	Biomarkers	Ref.
Bergmann	2013	Europe	SLIT tablet	509	HDM	300 IR 500 IR	3	slgE, slgG4	10
Cox	2012	USA	SLIT tablet	473	Pollen mixture	300 IR	2	slgE, slgG4	11
Didier	2009	Europe	SLIT tablet	628	Pollen mixture	100 IR 300 IR 500 IR	4	slgE, slgG4	12
Gunawardana	2018	UK	SLIT tablet	23	HDM	12 SQ-HDM	2	slgE, slgG4, IgE-BF	13
Martinez-Cocera	2010	Spain	SCIT	46	<i>Phleum pratense</i>	800 STU (2 µg of Phl p 5 major allergen)	2	slgE, slgG4	7
Pfaar	2012	Germany	SCIT	149	Pollen mixture	10,000 SQ-U	2	slgE, slgG4, IgE-BF	14
Roux	2016	Canada	SLIT tablet	355	HDM	100 IR 300 IR 500 IR	4	slgE, slgG4	15
Sreelmach	2009	Poland	SLIT drop	50	Pollen mixture	300 IR	2	slgE, tlgG4, tlgE	16
Wahn	2009	Europe	SLIT tablet	278	Pollen mixture	300 IR	2	slgE, slgG4	17
Kristian Reich	2011	Europe	SLIT tablet	276	<i>Phleum pratense</i>	75,000 SQ	2	slgE, slgG4, IgE-BF	18
Peter Couroux	2018	Canada	SLIT tablet	219	Birch	2 DU 7 DU	4	slgE, slgG4, IgE-BF, IgE-FAB	19
Durham	2010	Europe	SLIT tablet	634	<i>Phleum pratense</i>	12 DU	2	slgE, slgG4, IgE-BF	20
Laurssen	2018	Europe	SLIT tablet	812	<i>Phleum pratense</i>	75,000SQ	2	slgE, slgG4	21
Makela	2018	Europe	SLIT tablet	637	Birch	0.5 DU 1 DU 2 DU 4 DU 7 DU	7	slgE, slgG4	22
Masuyama	2018	Japan	SLIT tablet	458	HDM	12 DU	2	slgE, slgG4	23
Nolte	2016	North America	SLIT tablet	1482	HDM	10,000 JAU	2	slgE, slgG4	24
Shamji	2012	UK	SCIT	410	<i>Phleum pratense</i>	12 SQ-HDM 10,000 SQ-U 1,00,000 SQ-U	3	slgE, slgG4, IgE-BF, IgE-FAB	4
Bozek	2013	Poland	SLIT drop	108	HDM	540 IR	2	slgE, tlgE	25
Bozek	2016	Poland	SCIT	60	Pollen mixture	10,000 AUM	2	slgE, slgG4, slgE/slgG4	26

(continued)

Table 1. Continued.

Authors	Publication Year	Location	Intervention	Sample Size	Allergen	Maintenance Dose	No. of Arms	Biomarkers	Ref.
Bozek Chaker	2014	Poland	SLIT drop	78	Pollen mixture	240 IR	2	slgE, tlgE	27
	2016	UK	SCIT	37	<i>Phleum pratense</i>	30,000 SQ	3	slgE, slgG4, tlgE, IgE-FAB	28
Cortellini Gallego	2010	Italy	SLIT drop	27	<i>Alternaria</i>	2,500 RU	2	slgE, slgG4	29
	2010	Spain	SCIT	64	HDM (Depigmented and polymerized extracts)	More than 17.5 µg	2	slgE, slgG4, slgE/slgG4	30
Mosges	2018	Germany	SCIT	198	<i>Lolium perenne</i> (peptide)	Derp and 14 µg derf	4	slgE/slgG4	31
						70 µg		slgE, slgG4, slgG, IgE-FAB	
						170 µg			
Pfaar	2012	Germany	SCIT	195	Pollen mixture (Depigmented 500 DPP (31.5 µg Phi) and polymerized extracts)	370 µg	2	slgE, slgG4	32
Prieto	2010	Spain	SCIT	39	Alt a 1	0.2 µg	2	slgG4	33
Schmid	2014	Denmark	SCIT	24	<i>Phleum pratense</i>	1,00,000 SQU	2	slgE, BAT, IgE-FAB, IgE-BF	5
Shao	2014	China	SLIT drop	264	HDM	50 µg	2	slgE, slgG4, slgE/slgG4	8
Song	2014	China	SCIT	102	HDM	1,00,000 SQ	2	slgE	9
Wang	2013	China	SLIT drop	120	HDM	75 µg	2	slgE, slgG4	34
Xian	2020	China	SLIT drop	70	HDM	SLIT: 200 STU SCIT: 1,00,000 SQ	3	slgE, slgG4	35

SQ-U: standardized quality-units; IR: Index of reactivity; DU: has been used as a standardized potency unit; JAU: Japanese allergy unit (10,000 JAU =6 SQ-HDM).

difference in the sIgE between the AIT groups and control groups became insignificant ($P=0.08$). Then, in the 24–36 m and posttreatment subsets, the level of sIgE in the AIT groups was lower than that in the control groups ($P=0.01$) (Figure 2, forest plot see Supplementary Figure S1).

In univariate meta-regression analyses, the time interval was the factor that explained the largest amount of heterogeneity ($R^2=53.04\%$, $P<0.0001$; Supplementary Table S1). The results of the multivariate model are shown in Table 2. An R^2 of 66.8% and an I^2 of 84.91% demonstrated that some other factors affecting sIgE levels were not included in this model.

Allergen-Specific IgG4

One hundred groups from 19 studies were classified into the same subsets as above. The results of subset analyses

demonstrated that after 1 month of AIT, the sIgG4 titer in the AIT groups became significantly higher than that in the control groups (<0.0001). This trend remained at approximately 24 months after AIT initiation, with small fluctuations. In the posttreatment subset (2–24 months after treatment cessation), the level of sIgG4 was still significantly higher in the AIT groups than in the controls ($P<0.0001$; Figure 3; forest plot see Supplementary Figure S2). However, 2 studies, which suggest no significant changes in sIgG4 during AIT, were not included in the quantitative analyses because of insufficient data on sIgG4.^{36,37}

The result of the univariate meta-regression analysis was shown in Supplementary Table S2. In multivariate regression, route of AIT and time interval were covariates for sIgG4 (Table 3, $R^2=41.09\%$, $I^2=94.05\%$). Compared to the SLIT tablet, SCIT was associated

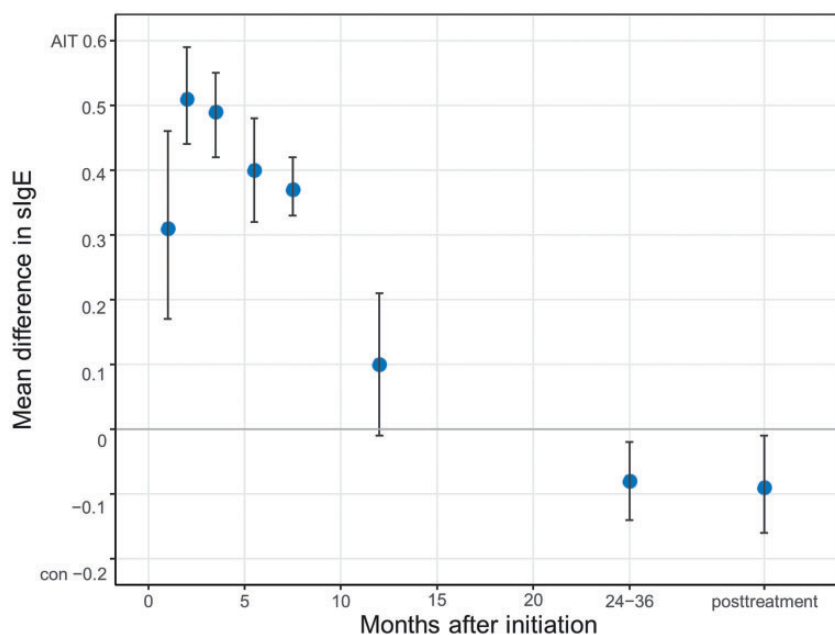


Figure 2. Changes in sIgE in the AIT group compared to the control group by subset analysis. Blue dots: mean difference between AIT groups and control groups. Vertical bars: 95% CIs. The positive end of the y axis indicates higher sIgE levels in the AIT groups.

Table 2. Multivariate Meta-regression Model of Serum sIgE.

Factors	Estimated β	95% CIs	P value
Polysensitization ratio (%)	0.003	0.001, 0.004	0.004
Months after initiation (reference: 1 m)			
2–3 m	0.175	0.017, 0.334	0.0301
4–8 m	0.042	–0.111, 0.195	0.5920
12 m	–0.107	–0.269, 0.053	0.1934
24–36 m	–0.299	–0.495, –0.104	0.0027
Posttreatment	–0.260	–0.455, –0.064	0.0092
Female ratio (%)	0.017	0.011, 0.022	<0.0001
Intercept	–0.639	–0.960, –0.318	<0.0001

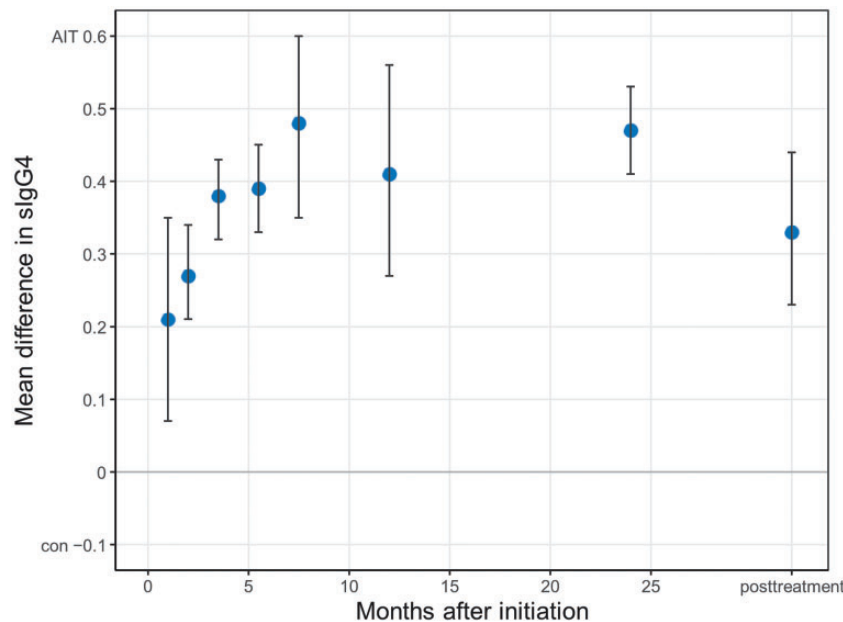


Figure 3. Changes in sIgG4 in the AIT group compared to the control group by subset analysis. Blue dots: mean difference between the AIT groups and control groups. Vertical bars: 95% CIs. The positive end of the y axis indicates higher sIgG4 levels in the AIT groups.

Table 3. Multivariate Meta-regression Model of Serum sIgG4.

Factors	Estimated β	95% CIs	P value
Route (reference: SLIT tablet)			
SCIT	0.5562	0.4237, 0.6686	<0.0001
SLIT drop	-0.2383	-0.4165, -0.0601	0.0088
Months after initiation (reference: 1 m)			
2-3 m	0.2696	0.1566, 0.3826	<0.0001
4-8 m	0.3491	0.2357, 0.4626	<0.0001
12 m	0.3387	0.2060, 0.4713	<0.0001
24 m	0.4169	0.2102, 0.6236	<0.0001
Posttreatment	0.2168	0.0775, 0.3562	0.0023
Intercept	0.0486	-0.0563, 0.1536	0.3638

with a higher level of sIgG4 ($\beta = 0.56$), while the SLIT drop was related to a relatively lower sIgG4 level ($\beta = -0.24$), which indicated that SCIT might induce more pronounced serum sIgG4 than the SLIT drop and SLIT tablet, and the SLIT tablet might induce more sIgG4 production than the SLIT drop. Moreover, compared to 1 month of AIT, a longer duration of treatment was associated with a higher sIgG4 level, as was the posttreatment subset.

IgE-Blocking Factors

Data from 25 groups from 7 studies were available for analyses. The time interval between the first dose of vaccine administration and measurement ranged from 1 month to 24 months. Overall synthesis showed that the MD between the AIT and control groups was 0.20 (95% CI: 0.15, 0.26, Figure 4).

Table S3 in the Supplement shows the result of the univariate regression analyses. In the multivariate regression model, the up dosing duration ($\beta = 0.004$; 95% CI: 0.002, 0.006; $P = 0.0001$) and clinical outcome ($\beta = -0.612$; 95% CI: -1.036, -0.188; $P = 0.0047$) were independently associated with sIgE-BF. I^2 was 96.52%, R^2 was 60.66% and the P value for intercept was 0.281.

IgE-Facilitated Antigen Binding

Thirteen groups from 4 studies were analyzed. The mean difference in IgE-FAB was -0.18 (Figure 5(A)) indicating that IgE-FAB levels were reduced in the AIT groups compared with controls. Regression analyses revealed that among those potential modifiers, only clinical outcome was correlated with IgE-FAB ($\beta = 0.3823$; 95% CI: 0.0694, 0.6952; $P = 0.0166$; Table S4). The intercept was insignificant, while the residual heterogeneity (I^2) was 93.4%. However, one study, which was not included in the analysis due to inappropriate data, illustrated that the change ratios of IgE-FAB in the SLIT group and control group were similar after treatment despite significant differences in clinical efficacy and immunological indicators, such as sIgE, sIgG4, sIgA and IgE-BF.³⁸

tIgE

Only 4 groups from 4 studies were enrolled to synthesize the data about tIgE. The time point of measurement ranged from 2-3 months to 36 months after AIT. All the results showed no difference between the AIT and control groups after AIT ($I^2 = 0.0\%$), which was the

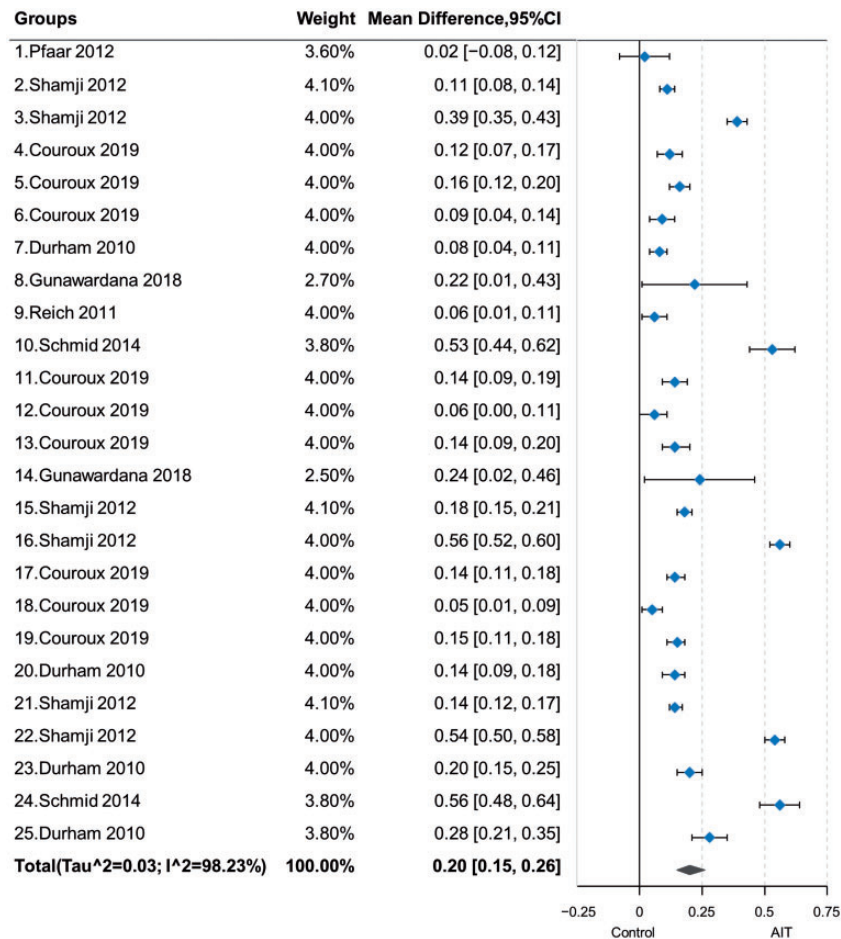


Figure 4. Forest plot for IgE-BF. Groups were sorted by time interval.

same as the study conducted by Sakurai.³⁹ The overall estimated value of tIgE was 0.02, with a 95% CI of -0.03 to 0.07 (Figure 5(B)).

sIgE/sIgG4

Three groups from 3 studies were included in the analyses of sIgE/sIgG4. One group measured the antibodies 36 months after AIT, while the other 2 measured them 12 months after AIT. The results showed that AIT had a negative impact on the ratio of sIgE/sIgG4 (Figure 5 (C)). The mean difference was -0.43, and the 95% CI was -0.62 to -0.23. A similar result was reported narratively in another study.⁴⁰

Other Indicators

One study reported decreased serum sIgA after 1 year of SLIT compared with baseline levels,³⁶ while another study showed no changes in sIgA during 4 months of SLIT.³⁸ These 2 studies also showed no change in sIgG1 after SLIT, but 2 studies exhibited increased

sIgG1 after preseasonal⁴¹ and 10 weeks of SCIT.³⁷ Only 1 study reported steady sIgM levels during 4-month SLIT.³⁸

Increased serum IFN- γ was reported in 2 studies,^{35,42} while 3 studies reported no changes after 1-2 years of AIT.⁴³⁻⁴⁵ One study revealed decreased IL-4, paralleled by increased IL-10 and TGF- β after 6 months of SCIT.⁴² Another 2 reported no changes in IL-5 and IL-10 in either the SCIT or SLIT group after 1-3 years of treatment.^{35,44} Starchenka et al conducted a transcriptomic analysis in patients receiving grass allergoid immunotherapy and found that simultaneous polarization of cytokines towards Th1 (IL-12, IL-18, IL-27), Th2 (IL-4) and Treg (IL-2, IL-27) responses occurred after 5 weeks of SCIT.⁴⁶

Four studies investigated T-cell clones with controversial results: two studies^{42,45} indicated that there was no change in Foxp3+ Tregs; however, the other two found that Foxp3+ Tregs were upregulated after AIT.^{35,39} IL-10⁺Tr1 was reported to be upregulated after AIT.⁴⁵ For Th1 and Th2, one study⁴⁵ showed no

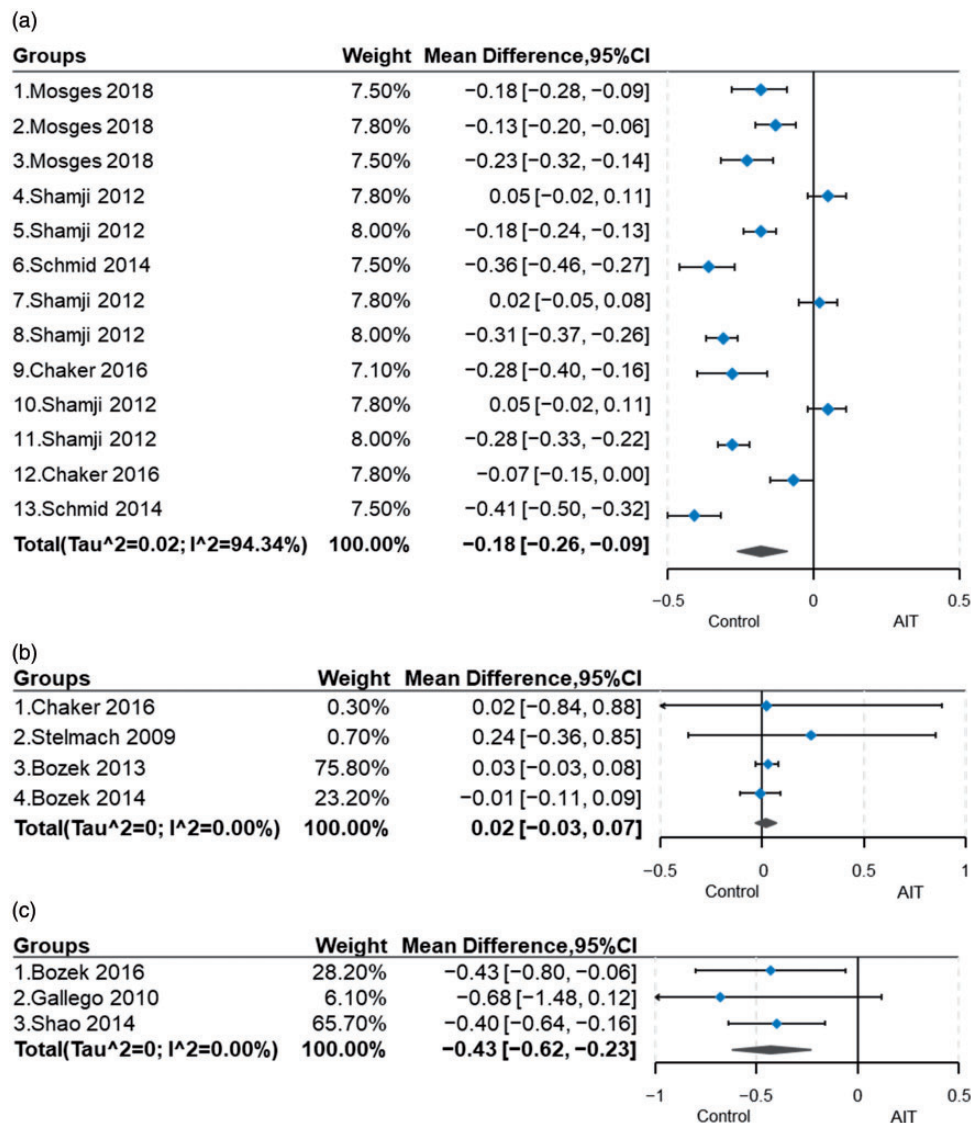


Figure 5. Forest plot for IgE-FAB (A), tIgE (B) and sIgE/sIgG4 (C). Groups were sorted by time interval.

change, while another study⁴² reported that Th1 was upregulated and Th2 was downregulated.

In studies addressing basophil activation, two favored lower expression of CD203c in BAT in AIT groups than placebo groups after 12-18 months of AIT.^{36,47} Two studies found no intergroup difference after a relatively shorter duration of treatment (2-4 months).^{48,49} One study demonstrated reduced expression of CD63 in the SCIT group after 6 months of treatment.⁴²

Discussion

In the subset analysis by time, we found that the level of serum sIgE showed a pattern of time-dependent change during AIT. A shorter course of AIT (<12 months) led to an increase in sIgE compared to the control, while

sIgE decreased in patients following a longer duration of AIT and became lower than the controls after 24-36 months of AIT. This was verified in a meta-regression model in which the time interval between AIT initiation and sIgE measurement had a biphasic association with sIgE. This variation over time can partly explain the heterogeneity of sIgE levels among studies. The results also showed that AIT had a persistent suppressive impact on sIgE up to approximately 12 to 24 months after treatment, favoring the prolonged immune effect of AIT. Another 2 explanatory factors in the multivariate model were the ratio of females and the ratio of polysensitization. A meta-analysis demonstrated that the incidence of AR in childhood is higher in males, but this tendency changes towards females in adolescence, while in adults, there is no gender-specific

difference.⁵⁰ However, the literature reporting gender differences during AIT is limited. One retrospective study suggests no difference in sIgE between males and females,⁵¹ but more research is needed to verify whether gender is a confounder. Higher serum sIgE levels in polysensitized patients than in monosensitized patients after AIT have been reported previously.^{52,53} In our regression model, the coefficient for polysensitization ratio (%) was 0.003, indicating that polysensitization status might have a modest correlation with higher sIgE levels. However, most of the studies do not give a clear definition of polysensitization and do not distinguish sensitization to cross-reactive components from genuine sensitization to multiple allergen sources. In addition, some studies use single-allergen AIT for all patients, while others use a mixture of different allergen extracts. These may cover the influence of sensitization status on immunological changes during AIT. sIgG4 remained at a higher level in the AIT group than in the control group during the whole treatment and even at 2-24 months posttreatment, which was confirmed by regression analysis. However, unlike sIgE, the route of AIT (SCIT, SLIT drop and SLIT tablet) was an independent variable of serum sIgG4 level. Since the immune mechanisms associated with SCIT and SLIT are thought to be similar, with a critical role in inducing Th1 and Treg cell responses,⁵⁴ this discrepancy may be caused by different pharmacologic properties, adjuvant systems, treatment protocols, efficacious doses and adherence to treatment. For example, adjuvants such as aluminum salts in the formulation of SCIT products help to improve immune tolerability and boost antibody production.⁵⁵ Whether the different influence of SCIT, SLIT drop and SLIT tablet on sIgG4 are applicable to other antibody subtypes and whether this relates to the controversial clinical results of these 3 routes need to be further studied. In the present study, clinical efficacy was unrelated to the variation in sIgE and sIgG4, disproving their roles as biomarkers for AIT. This was also in accordance with the current evidence supporting the hypothesis that other subtypes of antibodies except for sIgG4 also contribute to the establishment of long-term tolerance induced by AIT.⁵⁶

IgE-BF and IgE-FAB are quantified functional indicators of serum inhibitory effects for IgE. IgE-BF indicates the extent to which several factors can hinder sIgE from binding to its allergen and thus prevent allergic responses and clinical symptoms.² An increase in IgE-BF after AIT and its association with clinical outcomes has been reported.⁴ Furthermore, one study demonstrated that an increase in IgE-BF after 4 months of AIT may predict the clinical response after 1 year of treatment.⁵⁷ Our results also showed a higher level of IgE-BF in AIT patients than in controls and a significant correlation between IgE-BF and clinical efficacy, but the data

were insufficient to prove its predictive value. IgE-FAB indicates the binding of the allergen-IgE complexes to FcεRII (CD23) on the surface of B cells, which has been used as a surrogate rate-limiting step for the subsequent processing of allergen.² In accordance with previous literature,^{58,59} our results also revealed an AIT-induced reduction in IgE-FAB and a positive correlation between clinical efficacy and IgE-FAB. Therefore, IgE-BF and IgE-FAB should be further investigated as markers for predicting and monitoring AIT efficacy. However, the detection instrument for IgE-BF sold by ADVIA Centaur is no longer produced, which limits its availability in further investigations. The serum sIgG4 level was not a covariate of IgE-BF and IgE-FAB during AIT, which favors the critical role of other antibodies in IgE inhibitory activities. However, clinical trials about the dynamic posttreatment changes in IgE-BF and IgE-FAB are currently lacking, and this needs to be investigated in future studies. The effect of AIT on other molecules and cells varies between studies and has been described briefly as above.

Our study investigated the pattern of change in sIgE and sIgG4 and identified the correlation between IgE-BF, IgE-FAB and clinical outcomes, but there were limitations. The major limitation of this study was not including maintenance dose as a covariate when performing meta-regression because a standard to normalize the different units of various allergen products is lacking, and comparison between different units is not possible. However, we can presume that the maintenance dose is a crucial independent variable for immunological parameters according to the results of some dose-ranging trials. Another problem was that clinical efficacy in some studies was evaluated only at the end of the trial, but the immunological indicators were repeatedly measured at several time points, so there was a time gap between clinical outcomes and immunological indicators in some groups. This might lead to an underestimated association between the 2 factors.

Conclusion

The level of serum sIgE in patients receiving AIT increased in the first year and then decreased over time. AIT induced an increase in the level of sIgG4 during treatment and after treatment cessation. However, the levels of serum sIgE and sIgG4 had no correlation with clinical efficacy. Following AIT, IgE-BF increased and IgE-FAB was reduced. Both factors were associated with clinical efficacy in the multivariate regression model. However, because only a limited number of RCTs were included in the analyses, further studies are needed to determine the role of IgE-BF and IgE-FAB as efficacy biomarkers for AIT.

Author Contributions

Juan Meng was responsible for study conception, design and supervision. Study screening, data extraction and data analysis were performed by Zihan Jiang and Hao Xiao. The manuscript was written, reviewed and edited by Zihan Jiang, Shixi Liu and Juan Meng.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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Figure s1. Forest plot for sIgE. Subset analyses by time is shown in the plot.

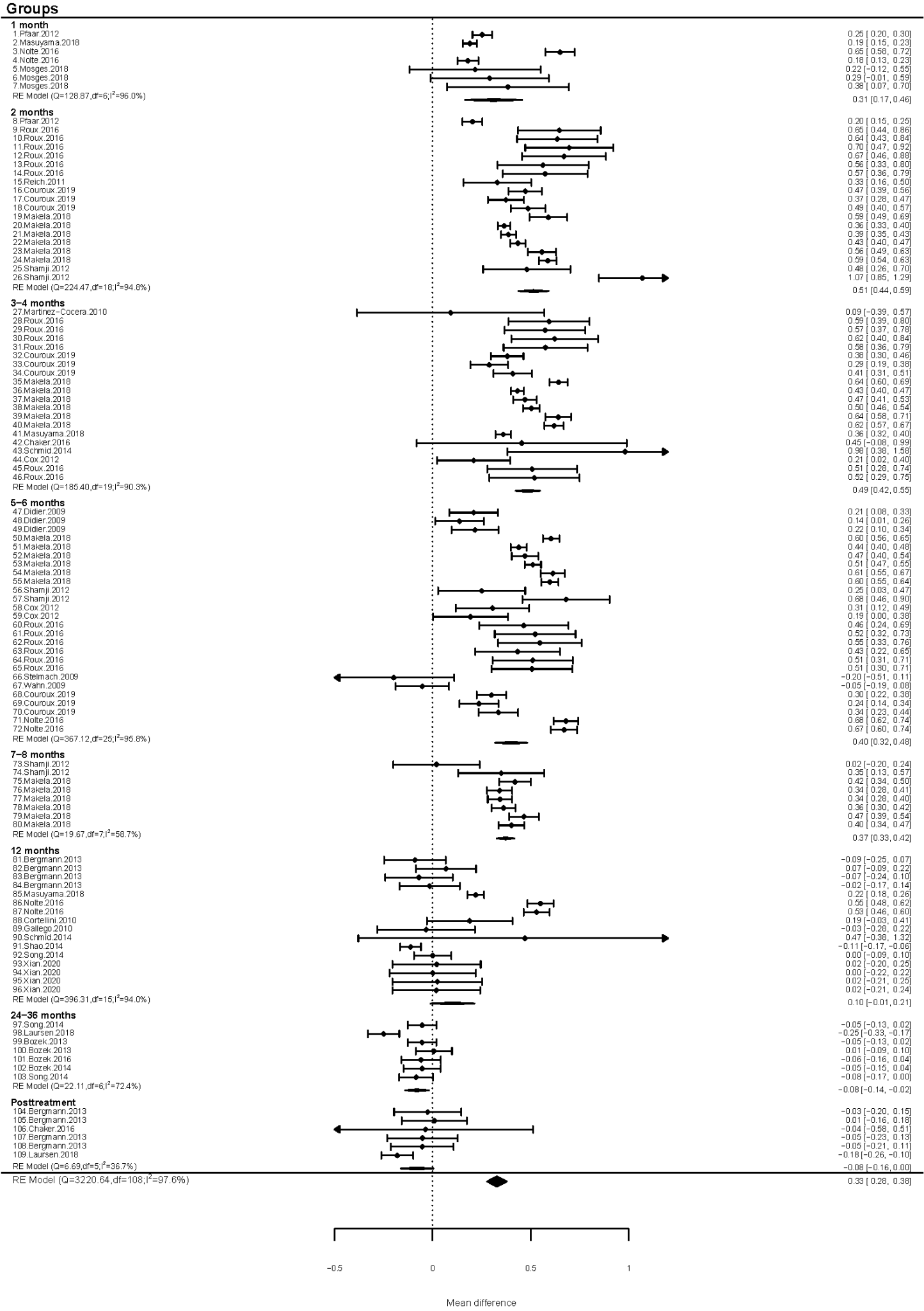


Table s1. Univariate meta-regression for sIgE

Factors	R^2(%)	β	95%CIs	P
Asthma ratio (%)	0	-0.0015	-0.0035, 0.0006	0.1575
Baseline sIgE	0	-0.1760	-0.3666, 0.0146	0.0703
Female ratio (%)	10.95	0.0112	0.0049, 0.0174	0.0004
Up-dosing duration (day)	11.90	-0.0031	-0.01, -0.001	0.0018
Year of publication	19.68	0.0308	0.0174, 0.0443	<0.0001
Sample size	18.68	0.0003	0.0001, 0.0004	<0.0001
Time point (reference: 1 m)	53.04			<0.0001
2-3 m		0.1950	0.0588, 0.3312	0.0050
4-8 m		0.0813	-0.0543, 0.2170	0.2399
12 m		-0.2040	-0.3546, -0.0533	0.0080
24-36 m		-0.3896	-0.5579, -0.2212	<0.0001
posttreatment		-0.3754	-0.5639, -0.1868	<0.0001
Polysensitization ratio (%)	27.71	0.0055	0.0039, 0.0071	<0.0001
Drop-out rate (%)	0	0.0039	-0.0036, 0.0113	0.3090
Age(adult)	21.65			<0.0001
Children		-0.2702	-0.4338, -0.1066	0.0012
Elderly		-0.4003	-0.5944, -0.2061	<0.0001
Kind of allergen (reference: HDM)	9.90			0.3246
Pollen		0.0589	-0.0260, 0.1439	0.1740
Alternaria		-0.0648	-0.3689, 0.2394	0.6764
Location (reference: Europe)	17.66			<0.0001
North America		0.1874	0.1010, 0.2737	<0.0001
Asia		-0.2328	-0.3647, -0.1009	0.0005
Type of vaccine (reference: standard extract)	1.87			
Others		-0.1992	-0.4218, 0.0234	0.0795
Pollen season (reference: out of season)	18.51			0.0064
In season		0.1817	0.0891, 0.2744	0.0001
Inclusion criteria about sIgE (reference: >0.70kU/L)	13.25			<0.0001
>0.35kU/L		-0.3581	-0.5058, -0.2103	<0.0001
None		-0.985	-0.2636, 0.0666	0.2422
Detection method (reference: chemiluminescence immunoassay)	25.76			<0.0001
Other methods		-0.4319	-0.6199, -0.2439	<0.0001
Route (reference: SCIT)	32.16			<0.0001
SLIT liquid		-0.2342	-0.4088, -0.0596	0.0086
SLIT tablet		0.1871	0.0925, 0.2816	0.0001
Clinical outcome	36.21	0.3377	0.2243, 0.4512	<0.0001

Groups



Table s2. Univariate meta-regression for sIgG4

Factors	R^2(%)	β	95%CIs	P
Asthma ratio (%)	2.05	0.0018	-0.0983, 0.0042	0.1385
Baseline sIgE	0	0.0466	-0.0737, 0.1670	0.1670
Baseline sIgG4	47.32	-0.3180	-0.4908, -0.1451	0.0003
Female ratio (%)	1.76	-0.0063	-0.0128, -0.0013	0.0128
Up-dosing duration (day)	9.19	0.0024	0.0002, 0.0046	0.0327
Year	13.81	-0.0007	-0.0115, 0.0101	0.8950
Sample size	0	-0.0001	-0.0002, 0.0001	0.1127
Time interval (reference: 1m)	22.99			<0.0001
2-3m		0.1341	0.0133, 0.2566	0.0296
4-8m		0.1972	0.0739, 0.3192	0.0014
12m		0.1988	0.0531, 0.3448	0.0075
24m		0.2653	0.0314, 0.4978	0.0262
posttreatment		0.1339	-0.0191, 0.2868	0.0862
Polysensitization ratio (%)	0	0	-0.0019, 0.0019	0.9998
Drop-out rate (%)	3.99	-0.0021	-0.0044, 0.0001	0.0603
Age (reference: adult)	11.31			
Children		-0.0519	-0.1709, 0.0671	0.3924
Kind of allergen (reference: HDM)	22.08			<0.0001
Pollen		0.0559	0.0186, 0.1409	0.0705
Alternaria		0.7335	0.4578, 1.0093	<0.0001
Location (reference: Europe)	13.31			<0.0001
North America		-0.0473	-0.1412, -0.0195	0.1652
Asia		-0.1478	-0.2802, -0.0154	0.0286
Type of vaccine (reference: standard extract)	2.13			
Non-standard extract		0.3815	0.2157, 0.5473	<0.0001
Pollen season (reference: out of season)	21.23			
In season		0.0437	-0.0263, 0.1138	0.3921
Inclusion criteria about sIgE (reference: >0.70kU/L)	0.68			
None		0.3395	0.1844, 0.4946	<0.0001
Detection method (reference: chemiluminescence immunoassay)	17.85			
Other methods		-0.0369	0.1889, 0.1151	0.6343
Route (reference: SLIT tablet)	13.05			<0.0001
SLIT drop		-0.1809	-0.3819, 0.0201	0.0777
SCIT		0.4430	0.3038, 0.5822	<0.0001
Clinical outcome	5.24	0.0869	-0.1200, 0.2938	0.1401

Table s3. Univariate meta-regression analyses for IgE-BF

factors	R^2(%)	β	95%CI	P
Year	0.28	-0.0122	-0.0279, 0.0036	0.1294
Location (reference: Europe)				
North American	5.59	-0.15	-0.2678, -0.0321	0.0126
Sample size	0	-0.0001	-0.0004, 0.0002	0.6628
Female ratio (%)	0	-0.0114	-0.0274, 0.0047	0.1667
Asthma ratio (%)	0	-0.2536	-0.7482, 0.2411	0.3150
Polysensitization ratio (%)	8.45	-0.2952	-0.4472, -0.1433	0.0001
Drop-out rate (%)	0	0.0015	-0.0812, 0.0843	0.9708
Kind of allergen (reference: HDM)				
Pollen	0	-0.0206	-0.2792, 0.2380	0.8760
Route (reference: SCIT)				
SLIT tablet	15.77	-0.2000	-0.3119, -0.0880	0.0005
Up-dosing duration (day)	21.97	0.0042	0.0024, 0.0060	<0.0001
Time (months)	4.18	0.0107	-0.0014, 0.0228	0.0826
Pollen season (reference: out of season)				
In season	0	-0.0578	-0.1789, 0.0633	-0.3494
Inclusion criteria about sIgE (reference: >0.70kU/L)				
None	6.31	0.1851	0.0075, 0.3626	0.0410
MD of sIgE	0	0.2109	-0.0643, 0.4862	0.1331
MD of sIgG4	5.65	0.1881	-0.0761, 0.4522	0.1629
Clinical outcome	16.79	-0.7295	-1.3057, -0.1533	0.0131

Table s4. Univariate meta-analyses for IgE-FAB

factors	R^2(%)	β	95%CI	P
Year	0	-0.0105	-0.0457, 0.0246	0.5566
Sample size	1.19	0.0004	-0.0001, 0.0009	0.0858
Female ratio (%)	0	0.0002	-0.0061, 0.0064	0.9612
Drop-out rate (%)	7.91	1.0894	-0.1040, 2.2829	0.0736
Type of vaccine (reference: standard extract)				
Non-standard	0	-0.0040	-0.2102, 0.2023	0.9698
Up-dosing duration (day)	0	-0.0023	-0.0068, 0.0021	0.3013
Time (month)	0	-0.0056	-0.0291, 0.0179	0.6393
Pollen season (reference: out of season)				
In season	0	0.0341	-0.2088, 0.2769	0.7833
Inclusion criteria about sIgE (reference: >0,70kU/L)				
None	1.64	-0.1462	-0.3271, 0.0347	0.1131
Clinical outcomes	37.94	0.3823	0.0694, 0.6952	0.0166

Methods

Searching Strategy in Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 28, 2020>

Search Strategy:

- 1exp rhinitis, allergic/ or exp rhinitis, allergic, perennial/ or exp rhinitis, allergic, seasonal/ (21017)
- 2allergic rhinitis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (17257)
- 3exp desensitization, immunologic/ or sublingual immunotherapy/ (10974)
- 4immunotherapy.mp. or exp Immunotherapy/ (308668)
- 53 or 4 (308668)
- 61 or 2 (28022)
- 7immunoglobulin.mp. or exp Immunoglobulins/ (922580)
- 8exp immunoglobulin a/ or exp immunoglobulin d/ or exp immunoglobulin e/ or exp immunoglobulin g/ or exp immunoglobulin m/ (214809)
- 9(IgE or IgA or IgG or IgM or IgD or antibod*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1245639)
- 107 or 8 or 9 (1442298)
- 115 and 6 and 10 (1928)
- 12exp animals/ not humans.sh. (4668289)
- 1311 not 12 (1832)
- 14limit 13 to yr="2009 -Current" (763)

Figure s1. Forest plot for sIgE. Subset analyses by time is shown in the plot.



Table s1. Univariate meta-regression for sIgE

Factors	R^2(%)	β	95%CIs	P
Asthma ratio (%)	0	-0.0015	-0.0035, 0.0006	0.1575
Baseline sIgE	0	-0.1760	-0.3666, 0.0146	0.0703
Female ratio (%)	10.95	0.0112	0.0049, 0.0174	0.0004
Up-dosing duration (day)	11.90	-0.0031	-0.01, -0.001	0.0018
Year of publication	19.68	0.0308	0.0174, 0.0443	<0.0001
Sample size	18.68	0.0003	0.0001, 0.0004	<0.0001
Time point (reference: 1 m)	53.04			<0.0001
2-3 m		0.1950	0.0588, 0.3312	0.0050
4-8 m		0.0813	-0.0543, 0.2170	0.2399
12 m			-0.3546,	
		-0.2040	-0.0533	0.0080
24-36 m			-0.5579,	
		-0.3896	-0.2212	<0.0001
posttreatment			-0.5639,	
		-0.3754	-0.1868	<0.0001
Polysensitization ratio (%)	27.71	0.0055	0.0039, 0.0071	<0.0001
Drop-out rate (%)	0	0.0039	-0.0036, 0.0113	0.3090
Age(adult)	21.65			<0.0001
Children		-0.2702	-0.4338,	0.0012
			-0.1066	
Elderly		-0.4003	-0.5944,	<0.0001
			-0.2061	
Kind of allergen (reference: HDM)	9.90			0.3246
Pollen		0.0589	-0.0260, 0.1439	0.1740
Alternaria		-0.0648	-0.3689, 0.2394	0.6764
Location (reference: Europe)	17.66			<0.0001
North America		0.1874	0.1010, 0.2737	<0.0001
Asia		-0.2328	-0.3647,	0.0005
			-0.1009	
Type of vaccine (reference: standard extract)	1.87			
Others		-0.1992	-0.4218, 0.0234	0.0795
Pollen season (reference: out of season)	18.51			0.0064
In season		0.1817	0.0891, 0.2744	0.0001
Inclusion criteria about sIgE (reference: >0.70kU/L)	13.25			<0.0001
>0.35kU/L		-0.3581	-0.5058,	<0.0001
			-0.2103	
None		-0.985	-0.2636, 0.0666	0.2422
Detection method (reference: chemiluminescence immunoassay)	25.76			<0.0001
Other methods		-0.4319	-0.6199,	<0.0001
			-0.2439	
Route (reference: SCIT)	32.16			<0.0001
SLIT liquid		-0.2342	-0.4088,	0.0086
			-0.0596	
SLIT tablet		0.1871	0.0925, 0.2816	0.0001
Clinical outcome	36.21	0.3377	0.2243, 0.4512	<0.0001

Figure s2. Forest plot for sIgG4. Subset analyses by time is shown in the plot.



Figure s2

Table s2. Univariate meta-regression for sIgG4

Factors	R^2(%)	β	95%CIs	P
Asthma ratio (%)	2.05	0.0018	-0.0983, 0.0042	0.1385
Baseline sIgE	0	0.0466	-0.0737, 0.1670	0.1670
Baseline sIgG4	47.32	-0.3180	-0.4908, -0.1451	0.0003
Female ratio (%)	1.76	-0.0063	-0.0128, -0.0013	0.0128
Up-dosing duration (day)	9.19	0.0024	0.0002, 0.0046	0.0327
Year	13.81	-0.0007	-0.0115, 0.0101	0.8950
Sample size	0	-0.0001	-0.0002, 0.0001	0.1127
Time interval (reference: 1m)	22.99			<0.0001
2-3m		0.1341	0.0133, 0.2566	0.0296
4-8m		0.1972	0.0739, 0.3192	0.0014
12m		0.1988	0.0531, 0.3448	0.0075
24m		0.2653	0.0314, 0.4978	0.0262
posttreatment		0.1339	-0.0191, 0.2868	0.0862
Polysensitization ratio (%)	0	0	-0.0019, 0.0019	0.9998
Drop-out rate (%)	3.99	-0.0021	-0.0044, 0.0001	0.0603
Age (reference: adult)	11.31			
Children		-0.0519	-0.1709, 0.0671	0.3924
Kind of allergen (reference: HDM)	22.08			<0.0001
Pollen		0.0559	0.0186, 0.1409	0.0705
Alternaria		0.7335	0.4578, 1.0093	<0.0001
Location (reference: Europe)	13.31			<0.0001
North America		-0.0473	-0.1412, -0.0195	0.1652
Asia		-0.1478	-0.2802, -0.0154	0.0286
Type of vaccine (reference: standard extract)	2.13			
Non-standard extract		0.3815	0.2157, 0.5473	<0.0001
Pollen season (reference: out of season)	21.23			
In season		0.0437	-0.0263, 0.1138	0.3921
Inclusion criteria about sIgE (reference: >0.70kU/L)	0.68			
None		0.3395	0.1844, 0.4946	<0.0001
Detection method (reference: chemiluminescence immunoassay)	17.85			
Other methods		-0.0369	0.1889, 0.1151	0.6343
Route (reference: SLIT tablet)	13.05			<0.0001
SLIT drop		-0.1809	-0.3819, 0.0201	0.0777
SCIT		0.4430	0.3038, 0.5822	<0.0001
Clinical outcome	5.24	0.0869	-0.1200, 0.2938	0.1401

Table s3. Univariate meta-regression analyses for IgE-BF				
factors	R^2(%)	β	95%CI	P
Year	0.28	-0.0122	-0.0279, 0.0036	0.1294
Location (reference: Europe)				
North American	5.59	-0.15	-0.2678, -0.0321	0.0126
Sample size	0	-0.0001	-0.0004, 0.0002	0.6628
Female ratio (%)	0	-0.0114	-0.0274, 0.0047	0.1667
Asthma ratio (%)	0	-0.2536	-0.7482, 0.2411	0.3150
Polysensitization ratio (%)	8.45	-0.2952	-0.4472, -0.1433	0.0001
Drop-out rate (%)	0	0.0015	-0.0812, 0.0843	0.9708
Kind of allergen (reference: HDM)				
Pollen	0	-0.0206	-0.2792, 0.2380	0.8760
Route (reference: SCIT)				
SLIT tablet	15.77	-0.2000	-0.3119, -0.0880	0.0005
Up-dosing duration (day)	21.97	0.0042	0.0024, 0.0060	<0.0001
Time (months)	4.18	0.0107	-0.0014, 0.0228	0.0826
Pollen season (reference: out of season)				
In season	0	-0.0578	-0.1789, 0.0633	-0.3494
Inclusion criteria about sIgE (reference: >0.70kU/L)				
None	6.31	0.1851	0.0075, 0.3626	0.0410
MD of sIgE	0	0.2109	-0.0643, 0.4862	0.1331
MD of sIgG4	5.65	0.1881	-0.0761, 0.4522	0.1629
Clinical outcome	16.79	-0.7295	-1.3057, -0.1533	0.0131

Table s4. Univariate meta-analyses for IgE-FAB

factors	R^2(%)	β	95%CI	P
Year	0	-0.0105	-0.0457, 0.0246	0.5566
Sample size	1.19	0.0004	-0.0001, 0.0009	0.0858
Female ratio (%)	0	0.0002	-0.0061, 0.0064	0.9612
Drop-out rate (%)	7.91	1.0894	-0.1040 , 2.2829	0.0736
Type of vaccine (reference: standard extract)				
Non-standard	0	-0.0040	-0.2102, 0.2023	0.9698
Up-dosing duration (day)	0	-0.0023	-0.0068, 0.0021	0.3013
Time (month)	0	-0.0056	-0.0291, 0.0179	0.6393
Pollen season (reference: out of season)				
In season	0	0.0341	-0.2088, 0.2769	0.7833
Inclusion criteria about sIgE (reference: >0,70kU/L)				
None	1.64	-0.1462	-0.3271, 0.0347	0.1131
Clinical outcomes	37.94	0.3823	0.0694, 0.6952	0.0166

Methods
Searching Strategy in Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 28, 2020>

Search Strategy:

- 1 exp rhinitis, allergic/ or exp rhinitis, allergic, perennial/ or exp rhinitis, allergic, seasonal/ (21017)
- 2 allergic rhinitis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (17257)
- 3 exp desensitization, immunologic/ or sublingual immunotherapy/ (10974)
- 4 immunotherapy.mp. or exp Immunotherapy/ (308668)
- 5 3 or 4 (308668)
- 6 1 or 2 (28022)
- 7 immunoglobulin.mp. or exp Immunoglobulins/ (922580)
- 8 exp immunoglobulin a/ or exp immunoglobulin d/ or exp immunoglobulin e/ or exp immunoglobulin g/ or exp immunoglobulin m/ (214809)
- 9 (IgE or IgA or IgG or IgM or IgD or antibod*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1245639)
- 10 7 or 8 or 9 (1442298)
- 11 5 and 6 and 10 (1928)
- 12 exp animals/ not humans.sh. (4668289)
- 13 11 not 12 (1832)
- 14 limit 13 to yr="2009 -Current" (763)