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Efficacy and safety of specific immunotherapy with aeroallergens in the management of atopic dermatitis: A systematic review and meta-analysis

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Abstract--Specific immunotherapy with standardized aeroallergens can reduce symptoms and increase the quality of life in some atopic diseases. This therapy is still controversial for atopic dermatitis (AD). Hence, a meta-analysis to assess efficacy and safety of specific immunotherapy with aeroallergens on patients with AD could provide an oversight on advantages and limitations of the therapy. We systematically searched several databases for relevant studies published Randomized controlled trials (RCTs) up to October 2020. Studies involving all ages and gender with AD who treated with specific immunotherapy employing aeroallergens compared with placebo/control. Seven studies RCTs were identified with 832 participants. Significantly decreased of SCORAD values favoring immunotherapy were observed (MD: -5.42; 95% CI -10.31, - 0.52; $p=0.03$). VAS score was significantly decreased (MD: -1.21; 95% CI -2.10, -0.31; $p=0.008$). However, immunotherapy showed no significant local and systemic adverse events ((RR 1.77; 95% CI 0.98, 3.19, $p=0.06$); (RR 0.69; 95% CI 0.16, 3.01, $p=0.62$)) and IgG4 *Dermatophagoides farinae* (MD: 92.36, 95% CI -89.14, 273.87; $p=0.32$). Our meta-analysis reported moderate-level evidence of specific aeroallergen immunotherapy that effective and safe for AD patients.

Keywords--Atopic dermatitis, specific immunotherapy, aeroallergens, SCORAD, VAS, vaccine.

Introduction

Allergic diseases in the world including Indonesia are increasing. One allergic disease is Atopic Dermatitis (AD) which is a serious condition that disrupts the quality of life of affected individuals and can interfere with the growth and development of children. AD is a chronic inflammatory skin disease, that involves relapsing symptoms, whose onset is generally related to a patient's or family's atopic history such as asthma and allergic rhinitis. This disease is often associated with impaired skin barrier function, allergen sensitization, and recurrent skin infections (Leung et al., 2011; Ng et al., 2018). Prevalence of AD in children ranges from 0.2-24.6% and AD in adults about 1-3% (Silverberg & Hanifin, 2013). Other studies reported in the Dermatology and Venereology outpatient clinic at Dr. Soetomo General Academic Hospital Surabaya shows the prevalence of AD in children has increased in 2007-2011 (Sihaloho & Indramaya, 2015). A study by Yolanda et al. (2018) reported women are the most common patients with AD and the most often chief complaint are pruritus.

Several AD therapeutic approaches have been established, which include promoting skin hydration, emollients, allergen avoidance, and the use of antihistamines or corticosteroids during the exacerbation phase. However, while these therapies can relieve symptoms, their use is often not effective enough, and the recurrence rate is still high. Some AD patients require long-term systemic treatment that can cause side effects (Garnacho-Saucedo et al., 2013). At present, there has been increased information about the use of immunotherapy in AD. Allergen immunotherapy has been used for more than a century to reduce symptoms of atopic disease that caused by aeroallergens, but its efficacy in AD is still controversial. Successful specific immunotherapy induces an established order of long time medical tolerance towards allergens, by ensuing a gradual reduction of signs and symptoms and reducing the need for pharmacotherapy (Mueller et al., 2018).

Specific immunotherapy works by desensitizing Mast cells and basophils, which initially induces Treg cells which will release Interleukin -10 (IL-10) and Tumor Growth Factor-beta (TGF- β). These can suppress effector cells which cause allergic inflammation such as Mast cells, basophils, and eosinophils. Besides, IL-10 and TGF- β produce IgG4 and IgA. IgG4 indirectly limits the activation of IgE. For specific long-term effects, immunotherapy can reduce the IgE-to-IgG4 ratio and number of Mast cells and eosinophils (Głobińska et al., 2018). In AD, increasing of serum IgE is possible, but normal level of IgE could not rule out the diagnosis of AD since IgE is one of the minor criteria proposed by Hanifin- Rajka. Elevated IgE levels can be due to parasitic or other non-allergic infections (Bonita et al., 2019; Prameswari et al., 2017). Desensitization is defined as the rapid administration of an increased dose of an allergen or drug in which effector cells are made less reactive or unreactive to the IgE-mediated immune response. Based on several studies on dust mite immunotherapy, allergen immunotherapy may be considered in certain patients with sensitive AD and suggested to be the only etiologic treatment (Ridolo et al., 2018). This study aimed to evaluate the efficacy and safety of specific immunotherapy for treating AD.

Method

Literature selection

Literature searches were undertaken in Cochrane Central Register of Controlled Trials, PubMed, and Directory of Open Access Journals (DOAJ) databases from inception to October 10, 2020 for all relevant randomized controlled trials (RCTs) on specific immunotherapy with aeroallergens. Particularly, all relevant studies were addressed by using keyword “atopic dermatitis” and “immunotherapy”. The search was limited to original research with full text available in English. All eligible studies were addressed by testing the strategies. Reviewers (SA, D, MAU, CDR, CRSP) also assessed all the citations of any relevant articles to broaden our search. Study searches included the participants who were diagnosed with dermatitis/ eczema and were not restricted by genders and age.

Data extraction and quality assessment

Relevant information including the first author, year of publication, study design, number of populations, atopic dermatitis prevalence, and specific immunotherapy treated were identified and extracted. We included all published RCTs with intervention using immunotherapy with standardized aeroallergens for single or mixed allergens by the sublingual, subcutaneous, intradermal, compared with placebo and evaluating the effect of specific immunotherapy in AD treatment. For this study, the participants of all genders and ages were diagnosed as AD by doctors. We excluded literature with other specific dermatitis such as irritant contact dermatitis. Outcomes were as follows: Scoring Atopic Dermatitis (SCORAD), Visual Analog Score (VAS), Serum IgG4 *Dermatophagoides farinae*, specific IgE *Dermatophagoides farinae*, and Adverse Events. Five reviewers (SA, D, MAU, CDR, CRSP) independently extracted data by titles, abstract, and full texts. The available clinical characteristics data were extracted and tabled. The risk of bias was assessed by the Cochrane Risk of Bias tools. Disagreement was resolved by discussion until a consensus was reached.

Data synthesis and statistical analysis

For continuous data, we calculated individual and pooled statistics as mean differences (MD) where studies used the same outcome measure, reported with 95% confidence interval (CI), where possible. We planned to contact the author if the paper didn't have details about the statistic data of the study. Forest plots were created to present the prevalence and the corresponding 95% CI of mean differences and clinical characteristics, respectively. We used I^2 statistics to assess heterogeneity among the studies. I^2 values from 0% to 50% indicated low heterogeneity, I^2 between 50% and 75% indicated moderate heterogeneity, and I^2 more than 75% indicated high heterogeneity. If $I^2 < 50\%$, we used the fixed benefit model to pool the data. Contrarily, when $I^2 > 50\%$, we used the random effect model. The threshold of statistical significance was set to be $p < 0.05$. We planned to undertake sensitivity analysis to explore any statistical heterogeneity. We used a funnel plot to test publication bias. All analyses and plots were performed and created with Review Manager (version 5.3).

Results

Search results, characteristics of the included studies, and methodological quality

We initially identified 635 articles by our search, including 446 from PubMed, 83 from Directory of Open Access Journals (DOAJ), and 106 from Cochrane Central Register of Controlled Trials. After removing the duplicates, 572 articles remained. From titles and abstract screening, 556 were excluded. 16 potentially eligible articles were assessed by full-text review. Of these 16 studies, 5 review articles, 3 non RCTs, and 1 non-English full-text articles, were further excluded. 7 studies met our selection criteria and included the data we needed to investigate (Figure 1).

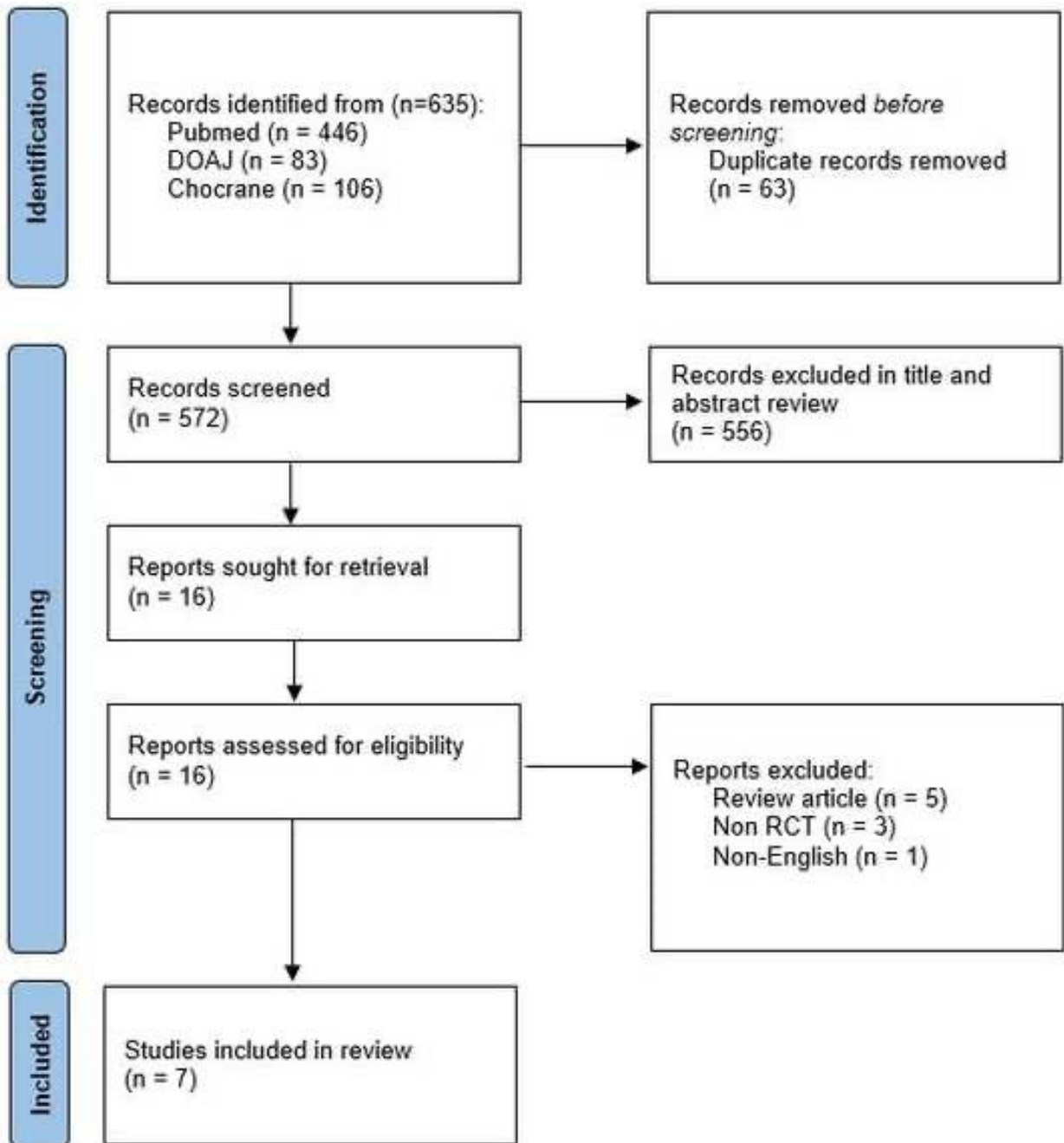


Figure 1. Flow diagram of study selection

A total number of 832 patients were included in these chosen studies. The main characteristics of patients and studies included are described in Table 1. The included articles consisted of 7 RCTs studies. One study was from the USA, two from China, and four from Europe. In term of population characteristic, 4 trials studied adults, 1 trial studied children, and 2 trials studied both children and

adults. The 7 included studies were all RCTs with intervention using immunotherapy. Of these, 3 trials studied sublingual immunotherapy (SLIT), 2 trials studies subcutaneous immunotherapy (SCIT), 1 trial studied both SCIT and pharmacotherapy, and 1 trial studied both SLIT and pharmacologic topical and/or systemic treatment. We didn't undertake sensitivity analysis because of the small numbers of studies that contributed to the analysis.

Table 1. Characteristic of trials included in the review

Trial	Methods	Participant	Intervention (n)	Comparison (n)	Primary outcome	Secondary outcome
Liu, 2019	DB, RCT	239 patients, 18-60 years old, 10<SCORAD<40, positive SPT results to DF stimulation	DF drops (SLIT): 36 weeks High Dose treatment (n=60) Medium Dose treatment (n=60) Low Dose treatment (n=59)	Placebo group (n=60)	SCORAD Pharmacotherapy medication score	Skin lesion area DLQI Safety assessment (adverse drug reaction)
Werfel, 2006	DB, RCT	89 patients, 18-55 years old with chronic AD, allergic sensitization HDM, SCORAD >40	SCIT DF : 12 months Increasing dose Group 2 : 20SQ-U to maintenance dose 2000 SQ-U (n=28) Group 3: 20.000 SQ-U (n=33)	Constant dose of 20 SQ-U (active placebo group) n=28	SCORAD	
Pajno, 2007	DB, RCT	56 patients, Children age 5-16 years with atopic dermatitis (SCORAD>7), sensitization to dust mites	SLIT DP and DF 18months (n=28)	Placebo (n=28)	SCORAD VAS	Adverse event
Qin, 2013	RCT	107 patients, with chronic AD, 18-46 years of age, moderate AD, sensitization to DF	12 months SLIT DF (n=58)	Only pharmacotherapy (n=49)	Patients compliance SCORAD Daily drug scores VAS score IgG4 level	
Novak, 2012	DB, RCT	168 patients, 18-66 years of age, moderate – to severe AD, positive SPT DP and DF	SCIT (n=112) 18 months	Placebo (n=56)	SCORAD DLQI IgE and IgG Adverse reaction	
Sanchez Caraballo & Cardona Villa, 2012	RCT	60 patients, 3-25 years of age, Clinical history of AD >2years, IgE sensitization to DF and DP,	SCIT + pharmacotherapy (n=31)	Pharmacotherapy (n=29)	SCORAD Total IgE and specific IgE and IgG4 Levels Adverse event	

Di Rienzo, 2014	OL, RCT	SCORAD>15 57 patients, 5-18 years of age, clinical history of chronic mild to moderate AD, not requiring regular use of inhaled corticosteroids, sensitization to DP and/or DF (SPT), positive patch test HDM, SCORAD 8-40	SLIT HDM (72 weeks) standardized extracts + Pharmacologic topical and/or systemic treatment 72 weeks (n=30)	Pharmacologic topical and/or systemic treatment (n=27)	SCORAD	Cutaneous symptoms (VAS) Investigator judgment on efficacy from baseline
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AD, Atopic dermatitis; HDM, House dust mite; SPT, skin prick test; SCORAD, SCORing Atopic Dermatitis; SCIT, subcutaneous immunotherapy; SLIT, Sublingual immunotherapy; DP, *Dermatophagoides pteronyssinus*; DF, *Dermatophagoides farinae*; VAS, visual analog scale; DB, Double-blind; RCT, Randomized controlled trial; OL, Open label.

Risk of bias

Five researchers independently assessed the risk of bias of included studies by Cochrane Collaboration's Risk of Bias tool. In our meta-analysis, the risk of bias mostly was moderate. We assessed the risk of bias during random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, analysis of incomplete outcome data, selective reporting, and other bias (Figure 2).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Di Rienzo 2014	+	+	●	●	●	?	?
JM Sanchez 2012	?	?	●	●	+	+	+
Liu 2019	+	+	+	+	●	+	+
Novak 2012	+	+	?	+	●	+	?
Pajno 2007	+	+	?	?	+	●	?
Qin 2013	+	+	?	?	●	+	+
Werfel 2006	+	?	?	●	+	●	?

Figure 2. Risk of bias in included studies

SCORAD

A meta-analysis of five studies comprising a total of 355 patients reported a significant effect between SCORAD and AD patients who were treated with specific immunotherapy in random-effects model pooling in that result (MD: -5.42; 95% CI: -10.31- 0.52) (Di Rienzo et al., 2014; Novak et al., 2012; Pajno et al, 2007; Sanchez Caraballo & Cardona Villa, 2012; Werfel et al., 2006). The heterogeneity was high ($I^2 = 96\%$), hence the random-effect model was applied for these outcomes (Figure 3).

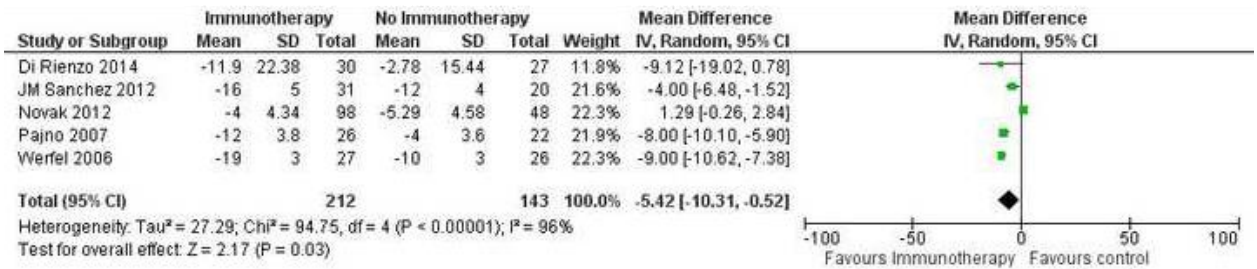


Figure 3. Forest plots of participants with atopic dermatitis showing end of treatment differences in SCORAD

VAS (Visual analog scale)

Two studies with 141 participants reported this outcome (Di Rienzo et al., 2014; Qin et al., 2014). A meta-analysis of VAS scores showed significant improvement in end-of-treatment of specific immunotherapy (MD: -1.21; 95% CI: -2.10, -0.31, I²=0%) (Figure 4).

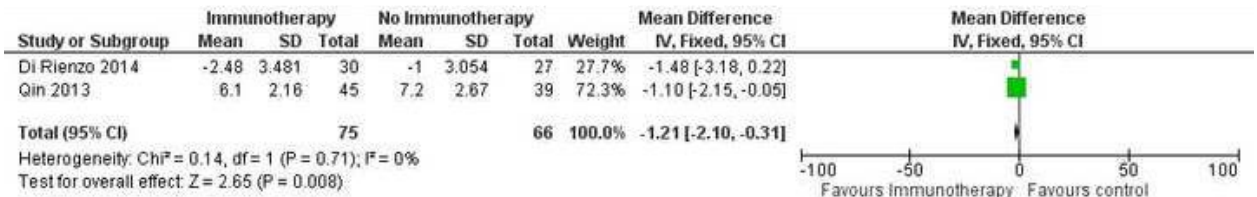


Figure 4. Forest plots of participants with atopic dermatitis showing changed VAS

Serum IgG4 *Dermatophagoides farinae*

A meta-analysis of two studies with 141 participants found no significant increase in serum IgG4 *Dermatophagoides farinae* (MD: 157.62, 95% CI -153.76, 469.0, I² = 99%) (Qin et al., 2014; Sanchez Caraballo & Cardona Villa, 2012) (Figure 5).

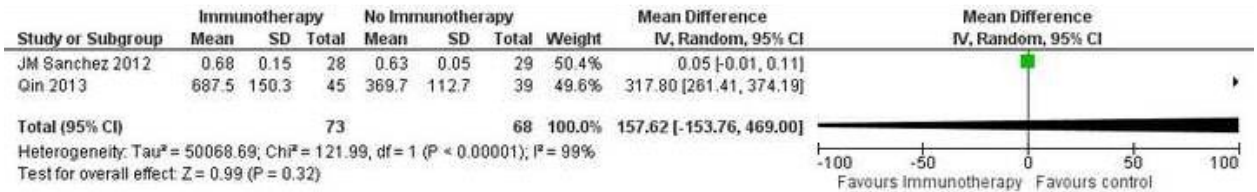


Figure 5. Forest plots of participants with improvement of serum IgG4 *Dermatophagoides farinae*

IgE *Dermatophagoides farinae*

IgE *Dermatophagoides farinae* were reported in two studies and were measured before and after treatment (Cardona et al., 2014; Novak et al., 2012). The results of a study conducted by Novak et al. (2012), shown there is a significant

difference in specific *Der. p* and *Der. f* ($p < 0.01$ and $p \leq 0.01$), however Sanchez Caraballo & Cardona Villa (2012) showed there was no significant difference in total and specific *Der. p* and *Der. f*.

Local adverse events

Six studies comprising a total of 651 patients reported the local adverse event in specific immunotherapy (Di Rienzo et al., 2014; Liu et al., 2019; Novak et al., 2012; Pajno et al., 2007; Qin et al., 2014; Sanchez Caraballo & Cardona Villa, 2012). The heterogeneity was moderate ($I^2 = 54\%$), hence the random-effect model was applied for these outcomes. A meta-analysis showed there were no significant local adverse events in AD patients who were treated with immunotherapy (RR 1.77; 95% CI: 0.98, 3.19, $I^2 = 54\%$) (Figure 6).

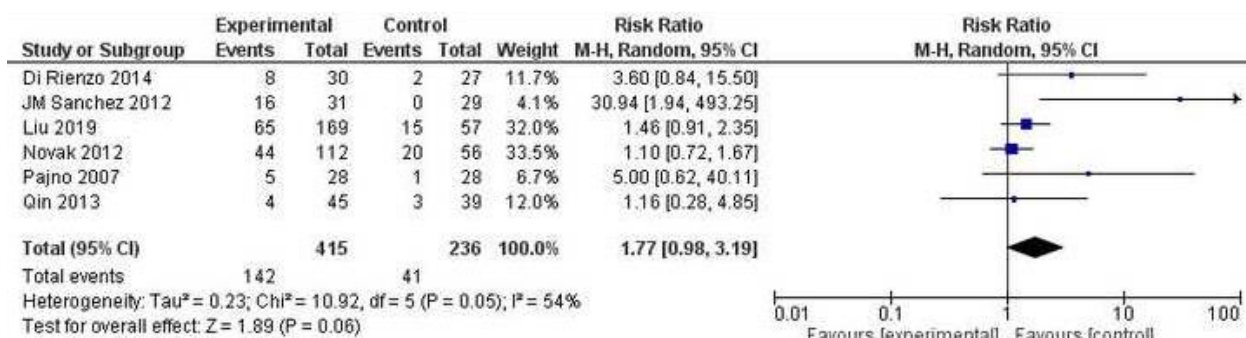


Figure 6. Forest plots of participants with atopic dermatitis showing local adverse events

Systemic adverse events

We found no significant for systemic adverse events for trials of specific immunotherapy. In six studies with 651 participants reported systemic adverse events (RR 0.69; 95% CI: 0.16, 3.01, $I^2 = 35\%$) (Di Rienzo et al., 2014; Liu et al., 2019; Novak et al., 2012; Pajno et al., 2007; Qin et al., 2014; Sanchez Caraballo & Cardona Villa, 2012) (Figure 7).

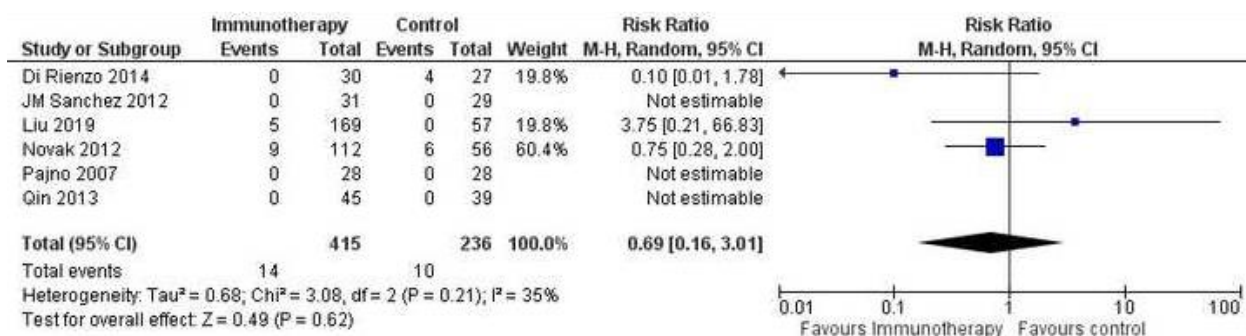


Figure 7. Forest plots of participants with atopic dermatitis showing systemic adverse events

DLQI (Dermatology Life Quality Index)

Liu et al. (2019), reported that specific immunotherapy and placebo groups had a decrease in DLQI. We did not find the data of standard deviation. Another report by Novak et al. (2012), showed no difference between treatment groups.

Discussion

Our meta-analysis result found that specific immunotherapy with standardized extract of aeroallergens in AD patient can significantly reduce the SCORAD. From the number of total populations included in our study, we are confident that our result represents the global population. Besides, studies that include also from various countries. In some studies, reduction of SCORAD will be seen after nine months of therapy using specific immunotherapy (Novak, 2007). Another study showed that the specific immunotherapy treated group with AD saw a statistically significant improvement over the control group in SCORAD. Since the study by Pajno et al. (2007) of SLIT was in children, and Novak et al. (2012) of SCIT was in adults, it is difficult to make comparisons (Novak et al., 2012; Pajno et al., 2007, Sanchez Caraballo & Cardona Villa, 2012). Some studies showed SCORAD in adults was more variate than children, which was due to population factor, ages, race, genetic, diet, and sample size (Inoue et al; 2014; Karim et al., 2019). Clinical manifestations can be calculated by the SCORAD but that is not always correlated with total IgE level (Prakoeswa et al., 2020). A recent meta-analysis also showed a significant reduction in SCORAD, which included in the latest study (Tam et al., 2016). SCORAD and Eczema Area and Severity Index (EASI) are some of the recommended results of the assessment signs for AD patients (Schmitt et al., 2007).

We also investigated changes in the VAS score. VAS score represents pruritus scale that was the dominant symptom in AD patients (Umborowati et al., 2020). Our study showed that VAS significantly reduced. Our meta-analysis was limited due to only two studies reporting this outcome and minimal population. But evidence from another study showed improvement in VAS (Ma & Muzhapaer, 2010). The VAS score based on neurobiophysics and physiology was used to assess the patients' subjective symptoms. This score can be a subjective evaluation reflecting the quality of life of the patient (Novak, 2007). The first few studies reported symptomatic skin improvement after active therapy and significant improvement (Ring, 1982; Warmer et al., 1978). Irwanto et al. (2019), reported severity of AD was related with sleep problems, that could decrease the quality of life the patients, their cognitive function and behavioral patterns. The decreased SCORAD and VAS values after the use of specific immunotherapy therapy are evidence of their efficacy in improving the quality of life for AD patients. The new study by Liu et al. (2019) showed significant decreased in DLQI of AD patients. Previous study reported the positive correlation between the severity of AD in children evaluated with SCORAD which was assessed with IDQLI, and this study showed severity of AD can improve parents' QOL which was assessed by FDLQI (Al Robaee & Shahzad, 2010; Marciniak et al., 2017; Monti et al., 2011).

The increase in IgG4 *Dermatophagoides farinae* was not significant in the findings of our meta-analysis. The data from Sanchez Caraballo & Cardona Villa (2012) and Qin et al. (2014) showed significant results whereas Novak et al. (2012) showed no significant results. One study in this systematic review showed no significant difference in the decrease of specific IgE while another study reported significant difference in the decrease before and after treatment (Novak et al., 2012; Sanchez Caraballo & Cardona Villa, 2012). The study by Endaryanto & Irmawati (2018) showed SLIT could decrease serum IgE, eosinophil count, and TH2 cytokines' level. The different results could be depending on the allergen concentration of the immunotherapy extract used (Feng et al., 2018). In our review the findings were limited due to the heterogeneity and small study size, treatment protocols in types and doses of allergen, and duration of therapy. Some studies show an increase in IgG4 seen since the first month of therapy, while another study showed that after 70 days of specific immunotherapy therapy will increase specific IgA, IgG1, and IgG4 and the increase in IgG4 concentration from 10 to 100-fold (Głobińska et al., 2018; Jutel et al., 2003; Jutel et al., 2005). There is no guideline concerning sIgG4 as a biomarker to predict clinical effect of immunotherapy treatment (Chen et al., 2017).

The increased sIgE and total IgE is one of the standards for a confirmatory diagnosis of allergy and are frequently elevated in AD (Darsow et al., 2011). In therapy with specific immunotherapy, there will be an increase in the initial few months followed by a decrease in sIgE after 6 to 12 months of therapy. Several studies have shown that long-term specific immunotherapy therapy for 2 to 3 years reduces sIgE (Blumberga et al., 2011; Vickery et al., 2014). Increases of IgG4 levels are associated with Interferon-gamma (IFN- γ), IL-10 and TGF- β (Endaryanto, 2019; Vitaliti et al., 2014). In another study, the IgE/IgG4 ratio can be used as biomarkers for the efficacy of specific immunotherapy (Głobińska et al., 2018). However, You et al. (2017) reported the serological biomarkers did not correlate with clinical improvement of AD patients. Future trials could investigate the level of sIgG4 and sIgE at 2 or 3 years after specific immunotherapy, with larger sample size, same concentrations, to find the correlation with clinical responses.

Apart from sIgE and IgG4, several aspects that affect AD are age and race. One study showed that children with AD had lower levels of CLA + IFN- γ TH1 T cells than adults, whereas adults with AD had elevated IL-22 (Leung, 2015). In our meta-analysis, there was a wide distribution of age in the subject populations of the included studies, and accordingly it is possible that the immune responses could be different in the outcome. AD sufferers are also affected by race, and research showed that African American children with AD have a 1.7-fold higher risk of those with European-American children, while Tackett et al. stated that people of colour have a 3.37 higher risk of being moderate to severe AD, followed by the Latino race with 0.64 times and Caucasians with 0.6 times higher risk (Shaw et al., 2011; Tackett et al., 2020).

One of genes that affects race is the *FLG* (*Filaggrin*) gene. *FLG* gene loss-of function mutations are the most widely studied genetic link to AD across ethnic groups, and some studies show it is mostly in European followed by Asian AD cases (Kaufmann et al., 2018). On histologic appearance, Asians with AD appear

more psoriasiform, leading to increased epidermal hyperplasia and more parakeratosis. Psoriasiform dermatitis in Asian patients with AD is due to IL-9 and IL-22. The difference in appearance is because of the epidermal gene expression between Asians, Caucasians, and colored people (Brunner et al., 2017; Li et al., 2016).

Local and systemic adverse events showed no significant differences with specific immunotherapy in our study. The reactions shown were dizziness, swelling of the mouth, face, itching of the lips, rhinitis, erythema, and some reactions will recover without treatment. The systemic reaction shown included flare-ups of eczematous, urticarial lesion, and asthma (Novak et al., 2012; Pajno et al., 2003). Cardona et al. (2014) reported the risk factor of systematic reaction was the age of patients under 20 years while another study found there was no fatality due to specific immunotherapy after more than 25 years of clinical use (Antico & Fante, 2014).

Several limitations were noted in our study including heterogeneity of ages, race, genetic, clinical manifestation, diet, sample size, allergen types, route, protocol, doses, and length of therapy (Durham & Penagos, 2016). Not all studies used placebo, some studies gave pharmacotherapy as their comparison treatment. It is debatable whether clinical improvement is due to immunotherapy only or effect of other treatment since its mechanism is still unknown. Our meta-analysis reported potential effect of aeroallergen immunotherapy in reducing SCORAD and VAS, with relatively minimal adverse events and no fatality report in the included studies. Further animal research is needed to determine the mechanism of action of immunotherapy in AD.

Conclusion

Our meta-analysis reported moderate-level evidence of specific aeroallergen immunotherapy that effective and safe for AD patients. However, there were certain limitations in this study related to heterogeneity and the lack of studies.

Acknowledgments

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