별첨 1 자료추출 및 비뚤림위험 평가

1. 자료추출

연번(Ref ID)	3
1저자(출판연도)	Bogacz_Piaseczynska 2022
연구특성	• 연구수행국가*: Poland • 연구대상자 모집기간: 2022
연구대상	• 연구대상: Moderate-to severe AD a minimum of one year – 질환명: 아토피피부염 – 알레르겐: House Dust Mites • 환자수 : 37(21/16) ⇒ 34 (20/14) • 평균연령: 중재군 18.5 ±11.3, 대조군 20.1 ±8.3
중재법	• 알레르겐 면역요법 방법: SCIT, Subcutaneous immunotherapy
비교중재법	• 위약: Placebo Inj. (Oral antihistamines, such as desloratadine and topical medications)
추적관찰 및 결과변수	• 추적관찰기간: 12개월 • 순응도: 중재군 95.2%, 대조군 87.5%
결과분석방법	• 결과변수: EASI (Eczema Area and Severity Index), BSA (body surface area) scale, At least 3 points on the IsGA (investigator global assessment) scale, Dermatology Life Quality of Index (DLQI) – Statistica version 8.12 (SoftPol, Cracow, Poland) – The non-parametric tests : not normally distributed – The Wilcoxon test: differences between the groups. – The ANOVA test : to compare scale scores. Differences were considered significant when p 〈 0.05.

연구결과-안전성

• SRs: Systemic reactions, LRs: Local reactions, SAEs: Severe Adverse Events

구분	시점 (개월)	중재군, (명)			대조군, (명)			p -value
		Events	Total	%	Events	Total	%	
SRs	12	1	31		0	16		–
	18	9	112	8%	20	55	10.7%	–
LRs	12	5	31		0	16		–
SAEs	12	NR	31		NR	16		–

연구결과-효과성

• 결과변수: EASI (Eczema Area and Severity Index)

결과 지표	측정 시점	중재군			대조군			p-value	비고
		Mean [median]	SD [IQR/range]	Total (명)	Mean [median]	SD [IQR/range]	Total (명)		
EASI	기저	43	8.2	21	39	10.3	16		
	12M	21	5.9	20	32	12.8	14		Final 값

결론	– AD 환자와 단일감작 HDM 환자의 알레르기 항원 면역요법은 위약군에 비해 치료 1년 후 질병의 임상과정을 개선함. 추가 연구 필요함
Funding	Funding: This research received no external funding.

* 제 1저자 기준

연번(Ref ID)	68
1저자(출판연도)	Sanchez Caraballo 2012
연구특성	• 연구수행국가*: 콜롬비아 • 연구기관: • 연구대상자 모집기간: 2009.9.~2010.1.
연구대상	• 연구대상: AD for more than 2 years with/without Asthma/Rhinitis – 질환명: 아토피피부염 – 알레르겐: House Dust Mites, dog dander, pollen grains • 환자수 : 60(31/29) • 평균연령: 중재군 8 (3~24), 대조군 8 (3~25)
중재법	• 알레르겐 면역요법 방법: SCIT, Subcutaneous immunotherapy
비교중재법	• Pharmacotherapy: Oral antihistamines, emollients, topical steroids, and tacrolimus were administrated in staggered steps according the severity of symptoms
추적관찰 및 결과변수	• 추적관찰기간: 6개월, 12개월 • 순응도: 미보고
결과분석방법	• 결과변수: SRs: Systemic reactions, Scoring Atopic Dermatitis (SCORAD) • Efficacy of treatment, reduction of drugs, wheal sizes, total IgE, and specific IgE and IgG4 were compared between both groups using the Mann-Whitney test. Because the effect of immunotherapy is detectable after several months of treatment, evaluation of effectiveness was performed based on protocol analysis; Proportions were analyzed using contingency tables, and the Fisher exact test was conducted. • *P 〈 0.05 was considered statistically significant.* • *For the primary outcome (clinical response), a sample size of 58* subjects would provide a statistical power of 80% to detect a mean difference of 30%.
연구결과-안전성	• SRs: Systemic reactions

결과지표	시점 (개월)	중재군, (명)			대조군, (명)			p -value	비고
		Events	Total	%	Events	Total	%		
SRs	12	0	31		0	29		-	

연구결과-효과성

• 결과변수: SCORAD 〉50: Severe AD – Mean Diff.

결과 지표	측정 시점	중재군			대조군			p-value
		Mean [median]	SD [IQR/range]	Total (명)	Mean [median]	SD [IQR/range]	Total (명)	
SCO-RAD	12M	22.09	3.90	31	27.11	5.48	29	
		-15.4	3.19	31	-10.5	5.52	29	0.0001

결론	• 알레르기 항원 특이 면역요법이 진드기 알레르기 항원에 대한 면역 및 IgG4 반응을 유도할 수 있고 임상적으로 효과적이고 안전하며 아토피성 피부염 관리에 중요한 도구로 제안될 수 있음을 시사함. • 아토피성 피부염 환자의 새로운 감작을 예방하는 데 있어 면역요법의 영향을 평가하기 위해서는 추가 연구가 필요함
Funding	• The authors do not have any conflict of interests to declare.

* 제 1저자 기준

<table>
<tr><td>연번(Ref ID)</td><td>320</td></tr>
<tr><td>1저자(출판연도)</td><td>Novak 2012</td></tr>
<tr><td>연구특성</td><td>• 연구수행국가*: 독일
– Recruited at 21 centers in Germany
• 연구대상자 모집기간: 2007. 3. ~ 2009. 1.</td></tr>
<tr><td>연구대상</td><td>• 연구대상: Moderate to severe AD duration 〉2 years
– 질환명: 아토피피부염
– 알레르겐: House Dust Mites
• 환자수 : 168 (112/56) ⇒ ITT(107/55) , PP(76/39)
• 평균연령: 18~66세</td></tr>
<tr><td>중재법</td><td>• 알레르겐 면역요법 방법: SCIT, Subcutaneous immunotherapy</td></tr>
<tr><td>비교중재법</td><td>• Basic medication + Placebo</td></tr>
<tr><td>추적관찰 및
결과변수</td><td>• 추적관찰기간: 3개월, 6개월, 12개월, 18개월(76주)
• 순응도: 중재군 67.8%, 대조군 69.6%</td></tr>
<tr><td>결과분석방법</td><td>• 결과변수: SRs: Systemic reactions, Scoring Atopic Dermatitis (SCORAD), DLQI (Dermatology Life Quality of Index) score, Immunonologic markers
• (AUC) values for both the total SCORAD and the use of basic medication (the ‘‘medication score’’) over the 18-month treatment period. The 1-sided or Wilcoxon rank-sum test was used for all primary analysis variables to show superiority or inferiority of the SCIT-treated group compared with the placebo-treated group.
• Subgroups were specified after the primary analysis in an exploratory analysis.</td></tr>
<tr><td>연구결과-안전성</td><td>• SRs: Systemic reactions
<table>
<tr><th rowspan="2">시점
(개월)</th><th colspan="3">중재군, (명)</th><th colspan="3">대조군, (명)</th><th rowspan="2">p
-value</th></tr>
<tr><th>Events</th><th>Total</th><th>%</th><th>Events</th><th>Total</th><th>%</th></tr>
<tr><td>18</td><td>9</td><td>112</td><td>8%</td><td>20</td><td>55</td><td>10.7%</td><td>-</td></tr>
</table></td></tr>
<tr><td>연구결과-효과성</td><td>• 결과변수: 증상점수 - SCORAD〉50: Severe AD, Mean Diff.
<table>
<tr><th rowspan="2">측정
시점</th><th colspan="3">중재군</th><th colspan="3">대조군</th><th rowspan="2">p-
value</th></tr>
<tr><th>Mean
[median]</th><th>SD
[IQR/range]</th><th>Total
(명)</th><th>Mean
[median]</th><th>SD
[IQR/range]</th><th>Total
(명)</th></tr>
<tr><td rowspan="2">18M</td><td>24.5</td><td>11.66</td><td>107</td><td>44.8</td><td>12.56</td><td>55</td><td></td></tr>
<tr><td>-33</td><td>13.8</td><td>107</td><td>-17.5</td><td>12.5</td><td>55</td><td></td></tr>
</table></td></tr>
<tr><td>결론</td><td>• 진드기 추출물을 이용한 면역치료는 아토피피부염 환자 치료가 효과적이고 안전하며, 특히 HDM에 민감하게 반응하는 중증 환자의 경우, 가치있는 추가 치료법으로 간주됨</td></tr>
<tr><td>Funding</td><td>• Supported by LETI Pharma GmbH, Germany. LETI Pharma GmbH was involved in the design and conduct of the study and provided logistical support during the trial.
• Employees of the sponsor worked with the investigators to prepare the statistical analysis plan, but the analyses were performed by Pierrel Research Europe.</td></tr>
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* 제 1저자 기준

2. 비뚤림위험 평가

연번(Ref ID)		3
1저자(출판연도)		Bogacz_Piaseczynska 2022
영역	비뚤림위험	사유
Adequate sequence generation (무작위 배정순서 생성)	■ 낮음 □ 높음 □ 불확실	This randomised, placebo-controlled, double-blind 12-month trial was performed in the Clinical Outpatient Allergy Department between 2021 and 2022.
Allocation concealment (배정순서 은폐)	■ 낮음 □ 높음 □ 불확실	The randomisation procedure with random selection relied on the use of computer-generated numbers by the use of a coin flip generator (Excel, 2021, Microsoft). Finally, 21 subjects received SCIT, and 16 participants formed the placebo group. The groups were comparable at baseline in most of the variables
Blinding of participants and personnel (연구 참여자, 연구자에 대한 눈가림)	■ 낮음 □ 높음 □ 불확실	Thirty-seven patients were individually randomised in comparable numbers to one of **two "parallel" groups using a double-blind method** (Figure 1).
Blinding of outcome assessment (결과평가에 대한 눈가림)	□ 낮음 □ 높음 ■ 불확실	언급없음
Incomplete outcome data addressed (불충분한 결과자료)	□ 낮음 □ 높음 ■ 불확실	During the 12 months of observation, the number of AD exacerbations in the study group was significantly lower compared with the placebo: 1.4 vs. 2.9 per patient during 12 months of observation for $p < 0.05$. - SCIT (n=20), Placebo (n=14)
Free of selective reporting (선택적 보고)	■ 낮음 □ 높음 □ 불확실	• SRs: Systemic reactions, LRs: Local reactions, SAEs: Severe Adverse Events • 결과변수: EASI (Eczema Area and Severity Index)
Other bias : Funding (그 외 비뚤림)	■ 낮음 □ 높음 □ 불확실	**Funding:** This research received no external funding.

연번(Ref ID)		68
1저자(출판연도)		Sanchez Caraballo 2012
영역	비뚤림위험	사유
Adequate sequence generation (무작위 배정순서 생성)	☐ 낮음 ☐ 높음 ■ 불확실	• This is an open label, controlled, randomized study. Patients were enrolled during September 2009 to January 2010. • After a baseline, patients were stratified according to sensitization pattern in monoand poly-sensitized and randomized to receive immunotherapy and pharmacotherapy (active group) or only pharmacotherapy (control group).
Allocation concealment (배정순서 은폐)	☐ 낮음 ☐ 높음 ■ 불확실	• 언급없음
Blinding of participants and personnel (연구 참여자, 연구자에 대한 눈가림)	☐ 낮음 ■ 높음 ☐ 불확실	• This is an open label, controlled, randomized study.
Blinding of outcome assessment (결과평가에 대한 눈가림)	☐ 낮음 ■ 높음 ☐ 불확실	• Single-Blinded Placebo-Controlled - At the beginning of the study 26 patients had a self-reported adverse reaction after eating some food but in 24 of these patients the clinical history was not clear and had a negative prick test.
Incomplete outcome data addressed (불충분한 결과자료)	■ 낮음 ☐ 높음 ☐ 불확실	• Change in symptoms evaluated with objective and subjective scales at different time points. Blue: Active group. Red: Control Group. • Figure 2: SCORAD: Scoring Atopic Dermatitis, VAS: Analog Visual Scale, SS: Subjective Scale. $P \leq 0.05$; $n = 60$; • Figure 3: $n = 60$;
Free of selective reporting (선택적 보고)	■ 낮음 ☐ 높음 ☐ 불확실	• 안전성 결과변수: Systemic reactions • 효과성 결과변수: Scoring Atopic Dermatitis (SCORAD) • Change in Sensitization Pattern in Both Groups after One Year. After one year, change in pattern sensitization in both groups were observed (Table 2).
Other bias : Funding (그 외 비뚤림)	■ 낮음 ☐ 높음 ☐ 불확실	• The authors do not have any conflict of interests to declare.

연번(Ref ID)		320
1저자(출판연도)		Novak 2012
영역	비뚤림위험	사유
Adequate sequence generation (무작위 배정순서 생성)	■ 낮음 □ 높음 □ 불확실	• This was a randomized, double-blind, placebo-controlled, parallel group study.
Allocation concealment (배정순서 은폐)	□ 낮음 □ 높음 ■ 불확실	• ~ randomly assigned to add-on therapy with SCIT treatment or to placebo, in addition to their basic medication, in an allocation ratio of 2:1 (Fig 1). • A simple randomization procedure (computerized random numbers) was used.
Blinding of participants and personnel (연구 참여자, 연구자에 대한 눈가림)	□ 낮음 □ 높음 ■ 불확실	• 연구참여자 및 연구자에 대한 눈가림은 불확실함
Blinding of outcome assessment (결과평가에 대한 눈가림)	□ 낮음 ■ 높음 □ 불확실	• The primary efficacy end points were the total SCORAD scores and the use of basic medication (ie, cumulative application of topical medication and overall consumption of systemic medication), both over the 18-month treatment period. Secondary efficacy was provided by quality-of-life questionnaires with the use of the Dermatology Life Quality Index (DLQI), evaluated for the whole treatment period and for the heating period from September to February. • Adverse reactions reported by the patient or noted by the investigator were documented during the whole study according to the European Academy of Allergy and Clinical Immunology scale
Incomplete outcome data addressed (불충분한 결과자료)	■ 낮음 □ 높음 □ 불확실	• Median improvement of the AUC of the SCORAD over 18 months was 6% in the actively treated group versus the placebo-treated group, and median improvement of the AUC of the medication score over 18 months of treatment was 32% in the actively treated group versus the placebo-treated group in the ITT set. • As shown in Table III, total SCORAD was statistically significantly lower (P 5.02) for the ITT study population, with a median reduction of the AUC of the total SCORAD of 18% in the actively treated group versus the placebo-treated group. • This effect was also seen in the PP study population, although it did not reach statistical significance (P 5 .03).
Free of selective reporting (선택적 보고)	□ 낮음 ■ 높음 □ 불확실	• SRs: Systemic reactions, Scoring Atopic Dermatitis (SCORAD), DLQI (Dermatology Life Quality of Index) score, Immunonologic markers • Subgroups were specified after the primary analysis in an exploratory analysis.
Other bias : Funding (그 외 비뚤림)	□ 낮음 ■ 높음 □ 불확실	• Supported by LETI Pharma GmbH, Germany. LETI Pharma GmbH was involved in the design and conduct of the study and provided logistical support during the trial. • Employees of the sponsor worked with the investigators to prepare the statistical analysis plan, but the analyses were performed by Pierrel Research Europe.