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Original Article / 원저

식약처 승인 아토피 피부염 의약품 국내 임상 시험의 특성
- ClinicalTrials.gov 등록 임상시험을 중심으로-

황미리[1] · 안재현[2] · 제하경[1] · 김수영[1] · 정현아[3]
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Characteristics of Clinical Trials in Korea for Atopic Dermatitis
- Focus on ClinicalTrials.gov Registered Clinical Trials -

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Abstract

Objective : This study summarized the characteristics of clinical trials for atopic dermatitis medicines approved by the Ministry of Food and Drug Safety(MFDS). This study may be a reference for the design of clinical trials of atopic dermatitis herbal medicine treatment which may be carried out later.

Method : The characteristics of the clinical trial were analyzed for clinical trials registered with ClinicalTrials.gov, CRIS, and the Korea Health Industry Development Institute among the clinical trial approval statuses posted on the website of the MFDS.

Result : 1. Clinical trial drugs were developed in various formulations such as oral medicines, injections, dermatologic agents, and similar proportions. Relatively little clinical trials were found for herbal medicine.
2. In the control evaluation test, most of the treatments for the control group were performed with placebo using Vehicle.
3. In most clinical trials, one intervention group was in the form of a parallel assignment with only one treatment.
4. The age of the subjects was 11 out of 28 studies including minors, and clinical trials targeting minors were also found to be significant.
5. In the case of atopic dermatitis, the cases of subacute chronic or atopic dermatitis more than 6 months or more than 1 year were often used.
6. Most clinical trials were divided into mild to moderate atopic dermatitis or moderate to severe atopic dermatitis. The SCORAD index, EASI, IGA, BSA, and NRS were used as the evaluation criteria.

7. Regulations for the drugs used prior to the trial period for the treatment of atopic dermatitis vary somewhat from one clinical trial to another.
8. IGA was used most often as a primary efficacy tool, and SCORAD index, EASI, and NRS were also used.

Key words : Atopic Dermatitis, Clinical Trials, MFDS, Drug

I. 서 론

아토피 피부염은 소양감, 태선화 등을 동반하는 만성염증성 피부질환의 일종으로 그 원인은 아직까지 명확하게 밝혀지지 않았다[1]. 그러나 아토피 피부염은 전 세계적으로 점차 증가하는 추세로 해외 연구에서 10년간 약 2~3배가량 증가한 것으로 보고된바 있다[2]. 또한 국내에서 학동기 소아를 대상으로 전국적으로 시행한 아토피 피부염의 유병률 조사에서도 1995년 15.3%, 2000년 17.0%, 2006년 21.0%, 2010년 27.0%로 점차 증가하는 것으로 나타났다[3].

아토피 피부염 환자에서 증상 치료를 위해 항히스타민제, 경구 스테로이드제, 국소 스테로이드제, 면역억제제 등의 다양한 약물이 사용되고 있으나[4] 장기간 사용시 각종 부작용 및 내성 등으로 새로운 약물 개발에 관한 필요성이 지속적으로 제기되고 있다[6].

그러나 실제로 임상시험을 통과하여 시판 허가를 받는 의약품은 많지 않은 실정이며 특히 한약제로 개발된 아토피 피부염 치료제가 시판허가를 받은 경우는 전무한 상태이다. 더욱이 한약을 이용한 아토피 치료제의 경우 의약품보다는 보습 크림 등의 화장품 제형 개발 위주로 연구가 이뤄지고 있는 실정으로[2] 이는 한방 치료제의 임상시험 설계 및 진행에 대한 어려움, 제형 개발의 어려움, 처방의 문제 등의 다양한 원인이 있을 것으로 생각된다.

이에 저자는 현재 국내에서 아토피 피부염의 치료제 개발을 위하여 시행되고 있는 의약품 임상시험의 특징에 대하여 정리하여 향후 한약 외용제, 경구약 등의 임상시험 설계에 참고하고자 한다.

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II. 본 론

1. 연구 대상

식품의약품안전처 의약품통합정보시스템에 공고된 임상시험승인현황 의약품 중 대상 질환이 아토피 피부염인 임상시험을 대상으로 하였다. 검색결과 총 43개의 임상시험이 승인받은 것으로 나타났는데 이중 기존 연구의 연장 승인을 받은 연구 2개를 우선 제외하였다. 이들 임상 시험들의 구체적인 임상시험 정보를 수집하기 위하여 아래의 사이트에서 연구 계획서를 검색하였다.

1) ClinicalTrials.gov

위의 식약처의 승인을 받은 임상시험들 중 미국 국립 의학 도서관에서 운영하고 있으며, 약 200여개 국가에서 시행 중인 임상시험 정보를 공개하고 있는 ClinicalTrials.gov에 등록되어 있는 연구 계획서를 검색하였다. 검색결과 총 24개의 연구 계획서가 검색되었다.

2) CRIS(Clinical Research Information Service)

질병관리본부 산하 국내에서 진행되는 임상시험 및 임상연구 온라인 등록 시스템인 CRIS(cris.nih.go.kr)에서 '아토피 피부염'으로 검색되는 연구 중 의약품(Drug)에 해당하는 연구를 검색하여 확인한 총 2개의 연구 계획서를 찾을 수 있었다. 이 중 1개의 연구계획서는 ClinicalTrials.gov와 중복되는 정보로 대상에서

제외하였다.

3) 보건산업진흥원(www.khidi.or.kr)

위의 임상시험 정보 데이터베이스에서 검색되지 않는 임상시험 중 보건산업진흥원의 연구지원을 받아 진행된 연구의 연구보고서를 검색하여 3개의 연구 계획정보를 연구 대상에 추가하였다.

위의 데이터베이스에서 임상시험 정보를 정리한 후 중복되는 경우를 제외하고 최종적으로 28개의 임상시험 정보를 대상으로 하였다.

2. 연구 항목

위의 데이터베이스에서 임상시험 정보를 알 수 있는 경우에는 위 데이터베이스의 정보를 바탕으로 하여 임상시험 정보를 분석하였다. 공개되지 않은 항목이 있는 경우에는 공개된 항목만을 분석하였다.

분석한 항목은 아래와 같다.

① 중재 약물의 종류
- 약물 투약 방법
- 한약/양약
- 대조군에 대한 처리
- 임상시험 기간

② 임상시험단계

③ 피험자수

④ 임상시험설계
- 임상시험 형태
- 시험군 배정
- 선정기준
- 제외기준
- 유효성 평가 도구

III. 결 과

1. 중재 약물의 종류

1) 약물 투약 방법

사용한 약물의 종류를 경구약, 외용제, 주사제로 분류하였다. 28개 임상시험 중 경구약을 대상으로 한 임상시험은 총 9개였으며 외용제 8개, 주사제는 11개로 서로 비슷한 비율로 임상시험이 이뤄지고 있음을 알 수 있었다(Table 1).

2) 한약/양약

29개 임상시험 중 자운고, 황련해독탕, 단미 엑스제 등 한약을 중재 약물로 시행한 임상시험은 외용제 1개, 경구제 2개로 총 3개였으며 이를 제외한 25개는 모두 양약에 해당하였다.

3) 대조군에 대한 처리

28개 임상시험 중 3개의 시험은 단일군 시험으로 별도의 대조군이 존재하지 않았다. 1개의 연구는 중재군 2군을 저용량군과 고용량군으로 나누어 임상시험을 진행하였다. 이를 제외한 24개의 연구에서는 주로 약물의 Vehicle을 활용한 위약(Placebo)을 이용하여 연구를 진행하였다(Table 1).

4) 임상시험 기간

피험자 개인별 임상시험 기간의 경우 평균 16.8주로 나타났다. 이 같은 임상시험 기간의 경우 약물의 종류별로 다소 차이가 있었는데 먼저 가장 짧게 나타난 것은 외용제로 최단 4주, 최장 12주로 평균 약 7주간 약물을 투약하고 방문을 하는 것으로 나타났다.

다음으로 주사제의 경우 최장 4주, 최장 164주간 진행되는 것으로 나타났고 평균 23.4주 동안 진행되는 것으로 나타났는데 이는 단회 투약 후에 약물의 지속효과를 평가하기 위에 방문하는 것까지 모두 포함된 수치였다.

마지막으로 경구약의 경우 최단 8주, 최장 20주로 평균 14.8주 동안 임상시험이 이루어지는 것으로 나타났다.

2. 임상시험단계

임상 시험의 단계의 경우 1상 임상시험이 2개, 1/2상에 해당하는 임상시험이 3개, 2상이 6개, 2/3상 1개, 3상 14개, 4상이 1개였으며 연구자 주도 임상시험으로 단계 설정이 명확하지 않은 시험이 1개 있었다(Table 1).

3. 피험자 수

피험자 수의 경우는 최저 13명, 최대 2300명으로 평균은 467.3명이었다. 이 중 다기관에서 수행된 연구는 총 23개로 이들 연구의 피험자 수는 평균 583.8명이었다. 반면 단일기관에서 수행된 연구는 총 5개로 이들 연구의 피험자 수는 40.3명으로 나타났다(Table 1).

4. 임상시험 설계

1) 임상시험 형태

연구설계는 전체 임상시험 중 3개의 시험에서는 단일군에 대해서 동일한 약물이 투약되는 단일군 시험(Single Group Assignment)으로 진행되었다. 나머지 시험 중 1개에서는 교차시험(Cross-over Study)으로 설계되었으며 이를 제외한 나머지 24개의 연구는 모두 평행 설계(Parallel Assignment)로 시험이 진행되었다(Table 1).

2) 시험군 배정

전체 임상시험 28개 중 단일군 시험을 제외한 25개의 시험에서는 모두 무작위 배정으로 설계되었으며 임상시험 눈가림은 피험자와 시험자 모두에게 맹검이 진행되는 이중 맹검으로 이루어졌다(Table 1).

5. 선정기준

각각 임상시험의 목적에 따라 나이, 체중 등의 기준을 달리 적용하고 있었다(Table 2). 이중 성별, 나이, 아토피 피부염 병력 및 중증도에 대한 정보만을 별도로 정리해보았다.

1) 성별

Phase I에 해당하는 1개의 임상시험에서는 약물의 안정성과 약동학을 보기 위해서 건강한 성인 남성만을 대상자로 하였으며 이를 제외한 27개의 임상시험에서는 모든 성별을 대상으로 하였다.

2) 나이

피험자의 나이를 크게 18세 이상을 성인, 12세 이상 18세 미만을 청소년, 12세 미만을 아동으로 구분하였을 때 성인만을 대상으로 한 임상시험은 총 17건이었으며 청소년만을 대상으로 한 임상시험이 1건, 아동만을 대상으로 한 임상시험이 2건이었다. 청소년과 성인 모두를 대상으로 한 임상시험은 6건이었으며 아동과 청소년만을 대상으로 한 임상시험이 1건, 유아, 청소년, 성인 모두를 대상으로 한 임상시험도 1건이었다.

3) 아토피 피부염에 대한 병력

전체 임상시험 중 1개의 임상시험은 건강한 성인 남성을 대상으로 한 시험으로 아토피 피부염을 앓지 않은 사람을 대상으로 했으며 나머지 27개의 임상시험은 건강한 사람을 제외하고 아토피 피부염을 앓고 있는 환자들을 대상으로 하였다.

먼저 아토피 피부염에 이환 된 기간을 기준으로 명시를 한 임상시험은 15개가 있었다. 이 중 4개의 임상시험은 아급성과 만성(Subacute, Chronic) 아토피 피부염 환자를 대상으로 하였으며 4개 임상시험 모두 6개월 이상 아토피에 이환 된 경우를 아급성과 만성 아토피 피부염의 기준으로 보았다.

다음으로 11개의 임상시험은 모두 만성(Chronic) 아토피 피부염 환자를 임상시험 대상자로 하였는데 구체적인 기간은 임상시험마다 다소 차이가 있었다. 6개의 임상시험에서는 1년 이상 이환 된 경우를 만성 아토피 피부염의 기준으로 하였으며 1개의 임상시험에서는 1년 이상, 4개의 임상시험에서는 3년 이상 이

Table 1. Clinical Trials List and Designs.

	No.	Title	Number of gruoups	Drug	Control	Allocation	Design	Masking	Duration(Wks)	Phase	Sample size	Multi-center
Internal medicine	1	The Effectiveness of Montelukast on Atopic Dermatitis in Koreans	2	Montelukast	Placebo	RCT	Crossover	Double	18	Not Applicable	54	X
	2	A Study of Long-term Baricitinib (LY3009104) Therapy in Atopic Dermatitis (BREEZE-AD3)	8	Baricitinib	Placebo	RCT	Parallel Assignment	Double	16	3	1500	O
	3	A Study of Baricitinib (LY3009104) in Combination With Topical Corticosteroids in Adults With Moderate to Severe Atopic Dermatitis (BREEZE-AD7)	3	Baricitinib	Placebo	RCT	Parallel Assignment	Double	16	3	300	O
	4	Study of Baricitinib (LY3009104) in Adults With Moderate to Severe Atopic Dermatitis (BREEZE-AD2)	4	Baricitinib	Placebo	RCT	Parallel Assignment	Double	16	3	750	O
	5	A Study to Evaluate Upadacitinib in Adolescent and Adult Subjects With Moderate to Severe Atopic Dermatitis	4	Upadacitinib	Placebo	RCT	Parallel Assignment	Double	16	3	810	X
	6	Study Evaluating Efficacy and Safety of PF-04965842 in Subjects Aged 12 Years And Older With Moderate to Severe Atopic Dermatitis (JADE Mono-2)	3	PF-04965842	Placebo	RCT	Parallel Assignment	Double	12	3	375	O
	7	Study to Evaluate Efficacy and Safety of PF-04965842 With or Without Topical Medications in Subjects Aged 12 Years and Older With Moderate to Severe Atopic Dermatitis (JADE EXTEND)	2	PF-04965842	Placebo	RCT	Parallel Assignment	Double	12	3	2300	O
	8	Study Evaluating Efficacy and Safety of PF-04965842 and Dupilumab in Adult Subjects With Moderate to Severe Atopic Dermatitis on Background Topical Therapy (JADE Compare)	5	PF-04965842 Dupilumab	Placebo	RCT	Parallel Assignment	Double	20	3	700	O
	9	Clinical trials of HH01 for adult atopic dermatitis	2	Hwanglyeonhaedok-tang	Placebo	RCT	Parallel Assignment	Double	8	3	100	X
Dermatologic agents	10	A Phase I Study of HY209 Gel in Healthy Male Volunteers for Atopic Dermatitis	7	HY209 gel	Placebo	RCT	Parallel Assignment	Double	4	1	56	X
	11	A Study to Evaluate the Safety and Efficacy of PAC-14028 Cream in Adults With Atopic Dermatitis	4	PAC-14028 cream	Placebo	RCT	Parallel Assignment	Double	8	2	192	X
	12	CAPTAIN-AD: Clinical Study of AmorePacific's TRPV1 Antagonist in Atopic Dermatitis	2	PAC-14028 cream	Placebo	RCT	Parallel Assignment	Double	8	3	240	O
	13	A Study to Evaluate the Safety and Efficacy of PAC-14028 Cream in Pediatric Atopic Dermatitis	4	PAC-14028 cream	Placebo	RCT	Parallel Assignment	Double	4	1/2	56	O
	14	Efficacy, Safety and Dose Finding Trial of Topical Jaungo Application in Atopic Dermatitis Patients	2	Jaungo	Placebo	RCT	Parallel Assignment	Double	4	2	34	O

	No.	Title	Number of gruoups	Drug	Control	Allocation	Design	Masking	Duration(Wks)	Phase	Sample size	Multi-center
Dermatologic agents	15	Randomized, double-blind, multicenter, Parallel Assignment, placebo-controlled therapeutic exploratory study for the validation and safety of CP001 for patients with atopic dermatitis	3	CP001	Placebo	RCT	Parallel Assignment	Double	8	2	144	O
	16	Double-blind, randomized, placebo-controlled, Parallel Assignment, multicenter, Phase II clinical trial to assess the dose-response of HL009 in pediatric patients with mild and moderate atopic dermatitis.	4	HL-009 gel	Placebo	RCT	Parallel Assignment	Double	8	2	219	O
	17	A 6-week, double-blind, randomized trial to evaluate the efficacy and safety of Elidel 1% cream for patients aged 2 to 11 years with a mild to moderate facial atopic dermatitis intolerant or dependent on topical corticosteroids , Placebo-controlled, 12-week multicenter trial consisting of a 6-week open-label trial	2	Elidel cream 1%	Placebo	RCT	Parallel Assignment	Double	12	4	200	O
injections	18	Safety and Efficacy of ADSTEM Inj. in Patients With Moderately Subacute and Chronic Atopic Dermatitis	1	ADSTEM Inj.	None	None RCT	Parallel Assignment	None	12	1	13	O
	19	Safety and Efficacy of FURESTEM-AD Inj. in Patients With Moderately Subacute and Chronic Atopic Dermatitis (AD)	1	FURESTEM-AD Inj.	None	None RCT	Parallel Assignment	None	4	1/2a	34	O
	20	Study of Autologous Total Immunoglobulin G Therapy for Atopic Dermatitis	2	Autologous immunoglobulin	Placebo	RCT	Parallel Assignment	Double	8	2/3	51	X
	21	Safety and Efficacy of FURESTEM-AD Inj. in Patients With Moderate to Severe Chronic Atopic Dermatitis(AD)	2	FURESTEM-AD Inj.	Placebo	RCT	Parallel Assignment	Double	12	3	194	O
	22	Tralokinumab Monotherapy for Moderate to Severe Atopic Dermatitis - ECZTRA 2 (ECZema TRAlokinumab Trial no. 2) (ECZTRA 2)	6	Tralokinumab	Placebo	RCT	Parallel Assignment	Double	16	3	780	O
	23	Open-label Study of Dupilumab (REGN668/SAR231893) in Patients With Atopic Dermatitis	1	Dupilumab	None	None RCT	Parallel Assignment	None	164	3	2000	O
	24	Study to Assess the Efficacy and Long-term Safety of Dupilumab (REGN668/SAR231893) in Adult Participants With Moderate-to-Severe Atopic Dermatitis (CHRONOS)	3	Dupilumab	Placebo	RCT	Parallel Assignment	Double	8	3	740	O

	No.	Title	Number of gruoups	Drug	Control	Allocation	Design	Masking	Duration(Wks)	Phase	Sample size	Multi-center
injections	25	A Study of Lebrikizumab in Participants With Persistent Moderate to Severe Atopic Dermatitis	4	Lebrikizumab	Placebo	RCT	Parallel Assignment	Double	12	2	212	O
	26	Study of Dupilumab (REGN668/SAR231893) Monotherapy Administered to Adult Patients With Moderate-to-Severe Atopic Dermatitis (SOLO 2)	3	Dupilumab	Placebo	RCT	Parallel Assignment	Double	16	3	708	O
	27	A Dose Ranging Placebo-Controlled Double-Blind Study to Evaluate the Safety and Efficacy of Tezepelumab in Atopic Dermatitis	4	Tezepelumab	Placebo	RCT	Parallel Assignment	Double	16	2b	300	O
	28	Ⅰ/Ⅱa clinical research to evaluate the safety and effectiveness of EBI-H (Auto-derived activated lymphocyte) for subacute above medium severity and chronic atopic dermatitis patients	2	EBI-H	None	RCT	Parallel Assignment	Double	12	1/2a	23	O

Table 2. Inclusion Criteria of Clinical Trials

	No.	Age	gender	Inclusion Criteria
Internal medicines	1	≥2 and ≤6	all	•The ages of 2 to 6 years old, 54 children with moderate to severe atopic dermatitis diagnosed by the criteria of Haniffin and Rajka were included in the study. •Volunteer children with moderate to severe atopic dermatitis were recruited from the Pediatric Allergy and respiratory Center of the SoonChunHyang University Hospital (Seoul, Korea). At the time of recruitment, written consent was obtained. The ethical committee at the SoonChunHyang University Hospital approved the trial. •Volunteers who agreed by their parents. •The severity of their disease was assessed by modified SCORAD index.
	2	≥18	all	•Have been diagnosed with moderate to severe Atopic Dermatitis for at least 12 months. •Have had inadequate response or intolerance to existing topical (applied to the skin) medications within 6 months preceding screening. •Are willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period). •Agree to use emollients daily.
	3	≥18	all	•Have been diagnosed with moderate to severe atopic dermatitis for at least 12 months. •Have had inadequate response to existing topical (applied to the skin) medications within 6 months preceding screening. •Are willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period). •Agree to use emollients daily.
	4	≥18	all	•Have been diagnosed with moderate to severe Atopic Dermatitis for at least 12 months. •Have had inadequate response or intolerance to existing topical (applied to the skin) medications within 6 months preceding screening. •Are willing to discontinue certain treatments for eczema (such as systemic and topical treatments during a washout period). •Agree to use emollients daily.
	5	≥12 and ≤75	all	•Active moderate to severe atopic dermatitis defined by Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Body surface area (BSA), and pruritus •Candidate for systemic therapy or have recently required systemic therapy for atopic dermatitis

	No.	Age	gender	Inclusion Criteria
Internal medicines	6	≥12	all	• Evidence of a personally signed and dated informed consent document indicating that the subject or their parent(s)/legal guardian, if applicable, have been informed of all pertinent aspects of the study. • Male or female subjects of 12 years of age or older, at the time of informed consent and body weight greater than or equal to 40 kg. Adolescent subjects below the age of 18 years old will only be enrolled in this study if instructed by the sponsor and approved by the country or regulatory/health authority. If these approvals have not been granted, only subjects aged 18 years and older will be enrolled. • Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures. • Must have completed the full treatment period of a qualifying Phase 3 study OR must have completed the full rescue treatment period of a qualifying Phase 3 study (if applicable). • Female subjects who are of childbearing potential (which includes all female subjects aged 12 years and older, regardless of whether they have experienced menarche) must not be intending to become pregnant, currently pregnant, or lactating. The following conditions apply: 1.Female subjects of childbearing potential must have a confirmed negative pregnancy test prior to randomization. 2.Female subjects of childbearing potential must agree to use a highly effective method of contraception for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. • Female subjects of non childbearing potential must meet at least 1 of the following criteria: 1.Have undergone a documented hysterectomy and/or bilateral oophorectomy; 2.Have medically confirmed ovarian failure; or 3.Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle stimulating hormone (FSH) level confirming the postmenopausal state. All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential. • Must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study. • Must agree to avoid use of prohibited medications throughout the duration of the study.
	7	≥12	all	
	8	≥18	all	•Male or female subjects aged 18 years or older at the time of informed consent •Diagnosis of atopic dermatitis (AD) for at least 1 year and current status of moderate to severe disease (>= the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4) •Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with medicated topical therapy for AD for at least 4 weeks, or who have required systemic therapies for control of their disease. •Must be willing and able to comply with standardized background topical therapy, as per protocol guidelines throughout the study •Female subjects who are of childbearing potential must not be intending to become pregnant, currently pregnant, or lactating. The following conditions apply: 1.Female subjects of childbearing potential must have a confirmed negative pregnancy test prior to randomization; 2.Female subjects of childbearing potential must agree to use a highly effective method of contraception for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. •Female subjects of non-childbearing potential must meet at least 1 of the following criteria: ○Have undergone a documented hysterectomy and/or bilateral oophorectomy; ○Have medically confirmed ovarian failure; or ○Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle stimulating hormone (FSH) level confirming the postmenopausal state. All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential. -If receiving concomitant medications for any reason other than AD, must be on a stable regimen prior to Day 1 and through the duration of the study

	No.	Age	gender	Inclusion Criteria
	9	≥19	all	• Typical clinical manifestations of intermittent or persistent atopic dermatitis for more than 6 months, • If the diagnostic criteria for Hanifin and Rajka are met. • Have been diagnosed with atopic dermatitis from two oriental medical doctors. • Those who have agreed in writing to the clinical trial agreement.
Dermatologic Agents	10	≥20 and ≤50	male	•Healthy male aged from 20 to 50 at screening test •Weight 45kg ~ 90kg with BMI 17kg/m2 ~ 27kg/m2 •No skin diseases, no skin damages(scars, tattoo, etc), no hairy skin
	11	≥19 and ≤70	all	•Male and female patients aged 19 - 70 years. •Who was diagnosed with Atopic Dermatitis according to Haniffin and Rajka criteria. •Whose affected BSA is over 5% and IGA score is 2 (mild) to 3 (moderate). •Who voluntarily agreed to participate in the study and signed an informed consent form.
	12	≥12 and ≤70	all	•Male and female patients aged 12 - 70 years. •Who was diagnosed with Atopic Dermatitis according to Haniffin and Rajka criteria. •Whose affected TBSA is over 5% and below 30%, and IGA score is 2 (mild) to 3 (moderate). •Who voluntarily agreed to participate in the study and signed an informed consent form.
	13	≥2 and ≤12	all	•Male and female patients aged 24 months - 12 years •Who was diagnosed with Atopic Dermatitis according to Haniffin and Rajka criteria, whose affected BSA is over 5% and IGA score is 2 (mild) to 3 (moderate). •Who has applied stable amount of emollients daily before baseline visit •Who voluntarily agreed to participate in the study and signed an informed consent form.
	14	≥5 and ≤65	all	•The diagnosis of AD will be made according to the criteria of Hanifin and Rajka •Age: 5 years to 65 years •objective SCORAD≤40, Diagnosis of Mild to Moderate Atopic Dermatitis (AD) •Exoriation≥1, Lichenification≥1, Dryness≥1 or Exoriation+Lichenification+Dryness≥3 •Participants who able to express intention •Participants willing to provide written informed consent
	15	≥17 and ≤64	all	• (Hanifin and Rajka diagnosis criteria) Those diagnosed with atopic dermatitis • Severity of SCORAD atopic dermatitis Objective index below 40 • A person who agrees to participate in the trial after hearing the details of the trial and agrees to observe the notice
	16	≥12 and ≤18	all	• Patients suffering from mild to moderate atopic dermatitis
	17	≥2 and ≤11	all	• Mild to moderate facial atopic dermatitis • Patients intolerant of, or dependent on, topical corticosteroids

	No.	Age	gender	Inclusion Criteria
Injections	18	≥19 and ≤70	all	•Of either gender, aged ≥19 and ≤70 years •Atopic dermatitis subjects who are coincident with Hanifin and Rajka diagnosis criteria •Subacute and chronic atopic subjects who have atopic dermatitis symptoms continually at least 6 months •Subjects with over moderate atopic dermatitis (SCORAD score 〉 20) •Subjects who understand and voluntarily sign an informed consent form
	19	≥20 and ≤60	all	•Of either gender, aged ≥20 and ≤60 years •Atopic Dermatitis subjects who are coincident with Hanifin and Rajka diagnosis criteria •subacute and chronic Atopic subjects who have Atopic Dermatitis symptoms continually at least 6 months •Subjects with over moderate atopic dermatitis(SCORAD score 〉 20) •Subjects who understand and voluntarily sign an informed consent form
	20	≥13	all	•Suitability of autologous blood donation criteria •Current standard medical therapies more than 2 months and moderate-to-severe atopic dermatitis •≥10% lesion body surface area (BSA) of atopic dermatitis involvement in area
	21	≥19	all	•Atopic Dermatitis subjects who are coincident with Hanifin and Rajka diagnosis criteria •Chronic Atopic Dermatitis that has been present for at least 3 years •EASI〉=12 at screening and baseline visit •IGA〉=3, SCORAD index〉=25, BSA 〉=10% of AD involvement at screegning and baseline visit •Subjects with documented record of inadequate response to the stable use of topical atopic dermatitis treatment within 24 weeks before participating in the study, or whom are inadvisable due to safety risks •Subjects who understand and voluntarily sign an informed consent form
	22	≥18	all	•Age 18 and above. •Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD. •Diagnosis of AD for ≥1 year. •Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable. •AD involvement of ≥10% body surface area at screening and baseline. •Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation
	23	≥18	all	•Participation in a prior clinical trial of dupilumab for AD and met one of the following: 1.Received study treatment and adequately completed the assessments required for both the treatment and follow-up periods of the parent studies (except studies listed in b) as defined in the parent protocols 2.Received study treatment in one the studies that have completed last patient last visit : R668-AD-0914, R668-AD-1026, R668-AD-1117, R668-AD-1021, R668-AD-1121, and R668-AD-1307 irrespective of duration of participation. 3.Underwent screening in R668-AD-1334 (Liberty AD SOLO 1) or R668-AD-1416 (Liberty AD SOLO 2), but could not be randomized due to randomization closure. •Willing and able to comply with all clinic visits and study-related procedures •Able to understand and complete study-related questionnaires •Provide signed informed consent
	24	≥18	all	•Chronic AD that had been present for at least 3 years before the screening visit; •Documented recent history (within 6 months before the screening visit) of inadequate response to a sufficient course of out-patient treatment with topical AD medication(s).

	No.	Age	gender	Inclusion Criteria
Injections	25	≥12	all	•12 years of age or older with a minimum body weight of 40 kg •Diagnosis of atopic dermatitis (AD) for at least 1 year and current status of moderate to severe disease (>= the following scores: BSA 10%, IGA 3, EASI 16, Pruritus NRS severity 4) •Recent history of inadequate response or inability to tolerate topical AD treatments or require systemic treatments for AD control
	26	≥18	all	• Chronic AD that has been present for at least 3 years before the screening visit; • ≥10% body surface area (BSA) of AD involvement at the screening and baseline visits; • Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks).
	27	≥18 and ≤75	all	•Subject has provided informed consent prior to initiation of any study specific activities/procedures. •Age greater than or equal to 18 to less than or equal to 75 years at screening. •Clinical diagnosis of chronic AD (also known as atopic eczema) for at least 2 years prior to screening and has confirmed AD (Hanifin and Rajka criteria for AD (Hanifin and Rajka, 1980). •AD that affects greater than or equal to' 10% body surface area as assessed by EASI at screening and on day 1. •An IGA score of greater than or equal to 3 at screening and on day 1. •An EASI score of greater than or equal to 16 at screening and on day 1. •Subject discontinued treatment with TCS, topical calcineurin inhibitors (TCI), prescription moisturizers, or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin for at least the 7 days immediately prior to the first dose of investigational product. •Documented recent history (within 12 months before the screening visit) of inadequate response totreatment with topical TCS or subjects for whom topical treatments are otherwise medically inadvisable (ie, because of important side effects or safety risks). •Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0 = clear to IGA 2 = mild) despite treatment with a daily regimen of TCS of medium or higher potency (with or without TCI as appropriate).
	28	≥19 and ≤65	all	• Patients with atopic dermatitis meeting the Hanifin and Rajka diagnostic criteria • Subacute and chronic patients with symptoms of atopic dermatitis lasting at least 6 months • Patients with moderate to severe atopic dermatitis (EASI score> 7) • Patients who are unable to use conventional therapy due to lack of improvement with conventional treatment methods or concerns about potential side effects • For those who are pregnant, those who are negative during the screening pregnancy test and who consent to contraception during the period of clinical trials • Patients who have voluntarily agreed in writing to participate in the trial

Table 3. Inclusion Criteria of Severity of Atopic dermatitis

	No.	Severity	Scoring Systems	SCORAD	BSA (%)	IGA	EASI	NRS
Internal medicine	1	Moderate to Severe	SCORAD	Unknown				
	2	Moderate to Severe						
	3	Moderate to Severe						
	4	Moderate to Severe						
	5	Moderate to Severe	BSA, IGA, EASI, NRS		Unknown	Unknown	Unknown	Unknown
	6	Moderate to Severe						
	7	Moderate to Severe						
	8	Moderate to Severe	BSA, IGA, EASI, NRS		≥10	≥3	≥16	≥4
	9	Unknown						
Dermatologic agents	10	Healthy person						
	11	Mild to Moderate	BSA, IGA, EASI		〉5	2 or 3		
	12	Mild to Moderate	BSA, IGA, EASI		〉5 and 〈30	2 or 3		
	13	Mild to Moderate	BSA, IGA, EASI		〉5	2 or 3		
	14	Mild to Moderate	SCORAD	≥40				
	15	Mild to Moderate	SCORAD	≥40				
	16	Mild to Moderate	EASI				unknown	
	17	Mild to Moderate						
Injections	18	Moderate to Severe	SCORAD	〉20				
	19	Moderate to Severe	SCORAD	〉20				
	20	Moderate to Severe	BAS		≥10			
	21	Moderate to Severe	SCORAD, BAS, IGA, EASI	≥25	≥10	≥3	≥12	
	22	Moderate to Severe	BSA		≥10			
	23	Moderate to Severe						
	24	Moderate to Severe						
	25	Moderate to Severe	BSA, IGA, EASI, NRS		≥10	≥3	≥16	≥4
	26	Moderate to Severe	BSA		≥10			
	27	Moderate to Severe	BSA, IGA, EASI		≥10	≥3	≥16	
	28	Moderate to Severe	EASI				〉7	

Table 4. Exclusion Criteria of Clinical Trials

	No.	Exclusion Criteria
Internal medicine	1	•Too severe atopic dermatitis defined as the sum of scores is 80 and above by SCORAD index. •A history of liver disease; allergy to montelukast or cross-reacting medication; use of phenobarbital, phenytoin or rifampicin. •Patients on systemic steroids, immune-suppression or Korean herbal medicine during the previous 6 weeks.
	2	•Had investigational product permanently discontinued at any time during a previous baricitinib study. •Had temporary investigational product interruption continue at the final study visit of a previous baricitinib study and, in the opinion of the investigator, this poses an unacceptable risk for the participant s participation in the study
	3	•Are currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus), or a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or intravenous treatment for skin infections. •A history of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum in the past. •Participants who are currently experiencing a skin infection that requires treatment, or is currently being treated, with topical or systemic antibiotics. •Have any serious illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma). •Have been treated with the following therapies: ◦Monoclonal antibody for less than 5 half-lives prior to randomization. ◦Received prior treatment with any oral Janus kinase (JAK) inhibitor less than 4 weeks prior to randomization. ◦Received any parenteral corticosteroids administered by intramuscular or intravenous (IV) injection within 6 weeks prior to planned randomization or are anticipated to require parenteral injection of corticosteroids during the study. ◦Have had an intra-articular corticosteroid injection within 6 weeks prior to planned randomization. •Have high blood pressure characterized by a repeated systolic blood pressure >160 millimeters of mercury (mm Hg) or diastolic blood pressure >100 mm Hg. •Have had major surgery within the past eight weeks or are planning major surgery during the study. •Have experienced any of the following within 12 weeks of screening: venous thromboembolic event (VTE), myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure. •Have a history of recurrent (≥2) VTE or are considered at high risk of VTE as deemed by the investigator. •Have a history or presence of cardiovascular, respiratory, hepatic, chronic liver disease gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders or any other serious and/or unstable illness. •Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis. •Have specific laboratory abnormalities. •Have received certain treatments that are contraindicated. •Pregnant or breastfeeding.
	4	•Are currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus), or a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or intravenous treatment for skin infections. •A history of eczema herpeticum within 12 months, and/or a history of 2 or more episode of eczema herpeticum in the past. •Participants who are currently experiencing a skin infection that requires treatment, or is currently being treated, with topical or systemic antibiotics. •Have any serious illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma). •Have been treated with the following therapies: ◦Monoclonal antibody for less than 5 half-lives prior to randomization. ◦Received prior treatment with any oral Janus kinase (JAK) inhibitor. ◦Received any parenteral corticosteroids administered by intramuscular or intravenous (IV) injection within 2 weeks prior to study entry or within 6 weeks prior to planned randomization or are anticipated to require parenteral injection of corticosteroids during the study. ◦Have had an intra-articular corticosteroid injection within 2 weeks prior to study entry or within 6 weeks prior to planned randomization. •Have high blood pressure characterized by a repeated systolic blood pressure >160 millimeters of mercury (mm Hg) or diastolic blood pressure >100 mm Hg. •Have had major surgery within the past eight weeks or are planning major surgery during the study. •Have experienced any of the following within 12 weeks of screening: venous thromboembolic event (VTE), myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure.

	No.	Exclusion Criteria
Internal medicine	4	•Have a history of recurrent (≥ 2) VTE or are considered at high risk of VTE as deemed by the investigator. •Have a history or presence of cardiovascular, respiratory, hepatic, chronic liver disease gastrointestinal, endocrine, hematological, neurological, lymphoproliferative disease or neuropsychiatric disorders or any other serious and/or unstable illness. •Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection including herpes zoster, tuberculosis. •Have specific laboratory abnormalities. •Have received certain treatments that are contraindicated. •Pregnant or breastfeeding.
	5	•Prior exposure to any Janus kinase (JAK) inhibitor •Unable or unwilling to discontinue current AD treatments prior to the study •Requirement of prohibited medications during the study •Other active skin diseases or skin infections requiring systemic treatment or would interfere with appropriate assessment of atopic dermatitis lesions •Female subject who is pregnant, breastfeeding, or considering pregnancy during the study
	6	•Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study. •Currently have active forms of other inflammatory skin diseases, ie, not atopic dermatitis. •Have evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, Lupus) at the time of Day 0 that would interfere with evaluation of atopic dermatitis or response to treatment.
	7	•Discontinued from treatment (or rescue treatment period, if applicable) early in a qualifying Phase 3 study OR triggered discontinuation criteria at any point during the qualifying Phase 3 study OR meets exclusion criteria of the qualifying Phase 3 study. •Ongoing adverse event in the qualifying Phase 3 study which in the opinion of the investigator, or sponsor, is an ongoing safety concern OR the subject is currently triggering safety monitoring criteria in the qualifying Phase 3 study. •Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
	8	•Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study •Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, Q wave interval abnormalities, current or history of certain infections, cancer, lymphoproliferative disorders and other medical conditions at the discretion of the investigator •Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study •Other active nonAD inflammatory skin diseases or conditions affecting skin •Prior treatment with JAK inhibitors •Previous treatment with dupilumab •Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study
	9	• If you have other skin diseases or systemic diseases other than atopic dermatitis, they are excluded from the study. • Exclude patients who have been orally administered steroids and immunosuppressive agents up to one week before the subject interview (dermatologic agents are irrelevant). • Pregnant women who are breastfeeding or who do not have adequate contraception are excluded. • Excludes those who have clinically significant liver disease or LFT elevated more than twice the reference value. • Those who have participated in other clinical trials within one month before the start of the study are excluded. • Exclude individuals with irritable allergies to study-related drugs. • Exclude those who have digestive disorders after having a disease that may affect the absorption of the drug or surgery associated therewith. • Mentally retarded Excludes those who do not understand the agreement or are unable to follow the study due to emotional intellectual problems. • Exclude those who are deemed inappropriate by other clinical trial personnel.
Dermatologic agents	10	•Those who have a history of hypersensitivity or clinically significant hypersensitivity reactions to generic drugs (aspirin, antibiotics, etc.) •Those who have clinically significant liver, kidney, respiratory, endocrine, neurologic diseases or hematologic diseases, mental diseases, especially hemorrhagic diseases (hemophilia, von Willebrand disease, etc.), cardiovascular diseases (coronary artery disease, Congestive heart failure, arrhythmia, cerebrovascular disease, etc.) or who have a history of those diseases

	No.	Exclusion Criteria
Dermatologic agents	10	•Those who had clinical symptoms suspected of acute infectious disease within 2 weeks before the scheduled date of the first administration, or whose temperature measured by the screening test (eardrum) was 38.0 ° C or higher •Those who have taken any prescription drugs, herbal medicines, crude drugs within 2 weeks before the scheduled date of administration of the medicines for clinical trials , or over-the-counter medicines or vitamin preparations within 1 week. •Those who have a history of substance abuse, or positive urine screening tests (cannabinoid, opiates, amphetamine, cocaine, barbiturate, benzodiazepine) •Those who have a history of smoking within 3 months (However, if they quit smoking three months before the first scheduled medication, they are eligible for selection) •Those who have been found to be positive in serological tests (HBs antigen, hepatitis C virus antibody and HIV antibody) •Those who drink continuously (above 21 units / week, 1 unit = 10 g of pure alcohol) •Those who have been taking medicines by participating in other clinical trials or bioequivalence studies within 3 months prior to the date of first dosing •Those who have been bleeding, blood drawings or blood donation of 400mL or more within 8 weeks before the scheduled date of administration of the drug for clinical trials •Those who have vital signs measured at sitting position after the break for more than 3 minutes, ◦Low blood pressure (systolic blood pressure 〈90 mmHg, diastolic blood pressure 〈50 mmHg) ◦High blood pressure (systolic blood pressure greater than 150 mmHg, diastolic blood pressure greater than 100 mmHg) •Test subjects who are deemed unsuitable for participating in clinical trials due to clinical laboratory tests, ECG results, or other reasons
	11	•Who has skin diseases other than atopic dermatitis or scar in the affected area which can affect the study, determined by the study investigators. •Who has clinically significant medical history or diseases involving liver, kidney, neurological system, psychical disorder that can affect study results. •Who has used systemic steroids, antibiotics, immunosuppressants, or received photochemical therapy within 28 days before study drug administration. •Who has used topical steroids, immunosuppressants or antibiotics to treat atopic dermatitis within 14 days before study drug administration. •Who has used or is expected to inevitably use prohibited concomitant medications during the study. •Women who is pregnant /breast-feeding, or who has childbearing potential and does not use available contraceptives. •Who has dosed other study medications within 30 days before screening. •Who is determined ineligible for study participation by investigators for any other reasons.
	12	•Who has skin diseases other than atopic dermatitis or scar in the affected area which can affect the study, determined by the study investigators. •Who has clinically significant medical history or diseases involving liver, kidney, neurological system, psychical disorder that can affect study results. •Who has used systemic steroids, antibiotics, immunosuppressants, or received phototherapy within 28 days before study drug administration. •Who has used topical steroids, topical calcineurin inhibitors or antibiotics to treat atopic dermatitis within 14 days before study drug administration. •Who has used or is expected to inevitably use prohibited concomitant medications during the study. •Women who is pregnant /breast-feeding, or who has childbearing potential and does not use available contraceptives. •Who has dosed other study medications within 30 days before screening. •Who is determined ineligible for study participation by investigators for any other reasons.
	13	•Who has skin diseases other than atopic dermatitis or scar in the affected area which can affect the study, determined by the study investigators. •Who has clinically significant medical history or diseases involving liver, kidney, neurological system, psychial disorder that can affect study results. •Who has used systemic steroids, antibiotics, immunosuppressants, or received photochemical therapy within 28 days before study drug administration. •Who has used topical steroids, immunosuppressants or antibiotics to treat atopic dermatitis within 14 days before study drug administration. •Who has used or is expected to inevitably use prohibited concomitant medications during the study. •Women who is pregnant /breast-feeding, or who has childbearing potential and does not use available contraceptives. •Who has dosed other study medications within 30 days before screening. •Who is determined ineligible for study participation by investigators for any other reasons.
	14	•Participants have oozing in the lesion •Users of following medications prior to trial periods ① Oral steroids, immunosuppressants and antibiotics within 4 weeks prior to this trial ② Topical steroids, immunosuppressants and antibiotics within 2 weeks prior to this trial ③ Light therapy within 2 weeks prior to this trial ④ Other medications thought to be inappropriate by researchers •Participants have severe burn or wide wound •Participants have oozing or ulcer in the lesion •Allergic reactions to Angelica gigas, Siebold et Zuccarini, sesame oil and lard •Participants have skin disease except atopic dermatitis •Participants have severe renal function disease (sCr 〉 2.0 mg/dL) •Participants have severe liver function disease (ALT, AST, ALP ≥ 2.5 × normal limits)

	No.	Exclusion Criteria
Dermatologic agents	14	•Participants have uncontrolled chronic diseases •Pregnancy, lactation •Participation in another clinical trial within one month of enrolment •Underlying disease or history of severe disease, abnormal state (paralysis; mental retardation other emotional or mental problems; diseases that can affect the absorption of drugs; no enough time to participate in this trial; visual disturbance and hearing impairment; inability to understand written consent or engage in this study) •Judgment by experts that the potential subject's participation is inappropriate.
	15	•Those who have serious skin diseases other than atopic dermatitis •The subjects were clinically diagnosed with bacterial viruses or fungi, If you have salty atopic dermatitis •Persons with intractable chronic diseases such as hypertension, chronic active hepatitis, diabetes mellitus •Pregnant or lactating women or those who are pregnant during the clinical trial •Those who received oral steroids or oral antibiotics, systemic photochemotherapy and other immunosuppressive agents within 4 weeks of the start of the study •Persons with liver function or renal impairment •Those with a history of substance abuse •The person who showed hypersensitivity to the raw material preparation of CP001 •Those who participated as subjects in other clinical studies within 60 days of the start of the test
	16	Unknown
	17	• Concurrent skin diseases (infections) • Immunocompromised • Recently received phototherapy or systemic therapy
injections	18	Unknown
	19	•Subjects who have systemic infection at the baseline visit •Subjects who have asthma at the baseline visit •Treatment with oral corticosteroids, oral antibiotics, whole body photochemotherapy, immunosuppressive drug within 4 weeks before the baseline visit •Treatment with topical steroids, antibiotics within 2 weeks before the baseline visit •Subjects who already took or need to take the medicine which is prohibited to take during the clinical study. •Pregnant, breast-feeding women or women who plan to become pregnant during this study. (Females of Childbearing Potential must have a negative urine pregnancy test at Screening and Baseline) •Subjects who currently participate in other clinical trial or participated in other clinical trial within 30 days •Creatinine value ≥ 2 Upper limit of the normal range at screening test •AST/ALT value ≥ 2 Upper limit of the normal range at screening test •Any other condition which the investigator judges would make patient unsuitable for study participation
	20	•Patients under the age of 13 year. •Patients who are unable to agree on their own (emergency patients, patients with mental disability, patients with limited capacity to consent due to stroke or delirium caused by diabetes). •Patients with severe disease whose expected survival duration is less than 3 months. •Pregnancy or planned pregnancy within 1 year •Skin condition not appropriate for blood sampling and transfusion •The standardized clinical severity scoring system for atopic dermatitis (SCORAD) values <25 (Mild atopic dermatitis)
	21	•Subjects with medical history or surgery/procedure history •Subjects with diseases at the time of participation in this study (systemic infection, other serious skin disorders, pigmentation or extensive scarring in atopic dermatitis symptom region) •Subjects who need prohibited medication during clinical period •Pregnant, breast-feeding women or women who plan to become pregnant during this study •Subjects who currently participate in other clinical trial or participated in other clinical trial within 4 weeks •Any other condition which the investigator judges would make patient unsuitable for study participation

	No.	Exclusion Criteria
	22	•Active dermatologic conditions that may confound the diagnosis of AD. •Use of tanning beds or phototherapy within 6 weeks prior to randomisation. •Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomisation. •Treatment with TCS and/or TCI within 2 weeks prior to randomisation. •Active skin infection within 1 week prior to randomisation. •Clinically significant infection within 4 weeks prior to randomisation. •A helminth parasitic infection within 6 months prior to the date informed consent is obtained. •Tuberculosis requiring treatment within the 12 months prior to screening. •Known primary immunodeficiency disorder. •Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥2.0 times the ULN (upper limit of normal) at screening. •Positive hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody or hepatitis C virus antibody serology at screening. •History of anaphylaxis following any biologic therapy.
	23	•Patients who, during their participation in a previous dupilumab clinical trial, developed a serious adverse event (SAE) deemed related to dupilumab*, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient. •Patients who, during their participation in a previous dupilumab clinical trial, developed an AE that was deemed related to dupilumab* and led to study treatment discontinuation, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient. •Conditions in the previous dupilumab study consistent with protocol-defined criteria for permanent study drug discontinuation, if deemed related to dupilumab* or led to investigator - or sponsor-initiated withdrawal of patient from the study (eg, non-compliance, inability to complete study assessments, etc.). *Note for exclusion criteria # 1, 2, and 3: In studies that are still blinded, conditions deemed related to the study treatment will be considered related to dupilumab. •Treatment with an investigational drug, other than dupilumab, within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit •Pregnant or breastfeeding women, or planning to become pregnant or breastfeed during the patient's participation in this study
injections	24	•Participation in a prior Dupilumab clinical trial; •Important side effects of topical medication (e.g. intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects), as assessed by the investigator or treating physician; •Having used any of the following treatments within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, was likely to require such treatment(s) during the first 2 weeks of study treatment: 1.Immunosuppressive/immunomodulating drugs (e.g, systemic steroids, cyclosporine, mycophenolate-mofetil, Janus kinase inhibitors, interferon-gamma [IFN-γ], azathioprine, methotrexate, etc.); 2.Phototherapy for AD; •Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit; •History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening; •Positive hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at the screening visit; •Active or acute infection requiring systemic treatment within 2 weeks before baseline visit; •Known or suspected history of immunosuppression; •Pregnant or breastfeeding women, or planning to become pregnant or breastfeed during the participant's participation in this study.
	25	•Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study •Prior treatment with JAK inhibitors •Other active nonAD inflammatory skin diseases or conditions affecting skin •Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, Q wave interval abnormalities, current or history of certain infections, cancer, lymphoproliferative disorders and other medical conditions at the discretion of the investigator •Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use contraception
	26	•Participation in a prior Dupilumab clinical study. •Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit; •Having used any of the following treatments within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment: ○Immunosuppressive/ immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)

	No.	Exclusion Criteria
	26	◦ Phototherapy for AD •Regular use (more than 2 visits per week) of a tanning booth/ parlor within 4 weeks of the screening visit; •Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit; •History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening; •Positive with hepatitis B surface antigen (HBsAg) or hepatitis C antibody at the screening visit; •Active chronic or acute infection requiring systemic treatment within 2 weeks before the baseline visit; •Known or suspected history of immunosuppression; •Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study; •Women unwilling to use adequate birth control, if of reproductive potential and sexually active. Note: The information listed above is not intended to contain all considerations relevant to a participant's potential participation in this clinical trial therefore not all inclusion/ exclusion criteria are listed.
injections	27	•Active dermatologic conditions, which might confound the diagnosis of AD or would interfere with the assessment of treatment, such as scabies, seborrheic dermatitis, cutaneous lymphoma, ichthyosis, psoriasis, allergic contact dermatitis, or irritant contact dermatitis. •History of a clinically significant infection within 28 days prior to day 1 that, in the opinion of the investigator or medical monitor, might compromise the safety of the subject in the study, interfere with evaluation of the investigational product, or reduce the subject's ability to participate in the study. Clinically significant infections are defined as either of the following: 1) a systemic infection; or 2) a serious skin infection requiring parenteral antibiotic, antiviral, or antifungal medication. •Diagnosis of a helminth parasitic infection within 6 months prior to screening that had not been treated with or had failed to respond to standard of care therapy. •Documented medical history of chronic alcohol or drug abuse within 12 months prior to screening. •History of anaphylaxis following any biologic therapy. •Evidence of active liver disease at screening, including jaundice or aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase greater than twice the upper limit of normal (ULN). •Diagnosis and/or treatment of tuberculosis within the 12 months prior to screening. •Positive hepatitis B surface antigen or hepatitis C antibody serology. Subjects with a history of hepatitis B vaccination without a history of hepatitis B are allowed to enroll in the study. •Positive human immunodeficiency virus (HIV) test at screening or the subject is taking antiretroviral medications, as determined by medical history, prior medications, and/or the subject's verbal report. •Other Medical Conditions〉 •History of malignancy, except for basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy ≥ 12 months prior to screening or other malignancies treated with apparent success with curative therapy ≥ 5 years prior to screening. •History or evidence of severe depression, schizophrenia, previous suicide attempts, or suicidal ideation. Prior/Concomitant Therapy: •Subjects who are unwilling to abstain from the use of TCS, TCI, prescription moisturizers, or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin from screening through week 16 (applies only to Part A subjects) •Subjects who have had side effects of topical medications including intolerance to treatment, hypersensitivity reactions, significant skin atrophy, or systemic effects as assessed by the investigator or by the subject's treating physician (applies only to Part B subjects) •More than or equal to 30% of the total lesional surface is located on areas of thin skin that cannot be safely treated with medium or higher potency TCS (eg, face, neck, intertriginous areas, areas of skin atrophy) (applies only to Part B subjects) •Receipt of any approved biologic agent (eg, dupilumab) within 4 months prior to screening •Have used immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon (IFN)-gamma, Janus kinase inhibitors, azathioprine, methotrexate) within 4 weeks prior to screening, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment. •Have had phototherapy for AD in the 2 months prior to day 1, and subjects unwilling to avoid phototherapy during the first 16 weeks of the study •If on allergen-specific immunotherapy, subjects must be on a maintenance dose and schedule for ≥ 28 days prior to screening. Allergen-specific immunotherapy is defined as SC immunotherapy to aeroallergens and/o venom (Hymenoptera) as well as sublingual immunotherapy to aeroallergens •Vaccination with a live or attenuated vaccine within 28 days prior to day 1. Receipt of inactive/killed vaccinations (eg, inactive influenza) is allowed, provided the vaccinations are not administered within 7 days before or after any study visit. Note that receipt of the Th2 cytokine inhibitor suplatast within 15 days prior to screening is allowed. •Major surgery within 8 weeks prior to screening or planned inpatient surgery or hospitalization during the study period •Currently receiving treatment in another investigational device or drug study, or less than 6 months since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

	No.	Exclusion Criteria
injections	27	Other Exclusions: •Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 14 weeks after the last dose of investigational product. (Females of childbearing potential should only be enrolled in the study after a negative highly sensitive serum pregnancy test). •Female subjects of childbearing potential who are sexually active with unsterilized male partners unwilling to use 1 highly effective method of contraception during treatment and for an additional 14 weeks after the last dose of investigational product. Cessation of contraception after this point must be discussed with a responsible physician. Females of childbearing potential are defined as those who are not surgically sterile (ie, had bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause). A highly effective method of contraception is defined as one that resulted in a low failure rate (ie, 〈 1% per year) when used consistently and correctly. Refer to Appendix 5 for additional contraceptive information. •Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 14 weeks after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information. •Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 14 weeks after the last dose of investigational product. •Male subjects unwilling to abstain from donating sperm during treatment and for an additional 14 weeks after the last dose of investigational product. •Subject has known sensitivity to any of the products or components to be administered during dosing. •History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
	28	• Patients with uncontrolled comorbidities such as moderate infections, bleeding • HBV, HCV, HIV and VDRL positive • In hypertensive patients whose blood pressure is not controlled to 140 mmHg or DBP 90 mmHg in spite of the administration of antihypertensive agents during screening • An uncontrolled diabetic patient with an HbA1c value of 8.0 or greater as measured at screening • Screening requires the use of a second-line modulator or systemic steroid with high-dose inhaled steroids, or an uncontrolled asthma patient • Patients with skin autoimmune diseases including psoriasis and systemic autoimmune diseases (such as lupus erythematosus, rheumatoid arthritis, and severe workouts) • Within 4 weeks prior to screening, patients with systemic corticosteroids, systemic immunosuppressants / immune response modifiers, high-frequency topical corticosteroids (WHO Groups I-III), local immunomodulators and biological agents • Patients with a dose of corticosteroids (WHO Group IV, V), systemic photochemotherapy and systemic antibiotics within 2 weeks before screening • Patients with antihistamine dosage for oral or injections within 1 week prior to participation in the trial • Concomitant contraindications Patient who has been treated with medication during the test period • Pregnant or lactating women • Women who are not willing to use appropriate contraception during the trial • Patients participating in other clinical trials or participating in other clinical trials within the past 30 days • Patients who were judged to be inappropriate by other researchers

환 된 경우를 만성 아토피 피부염의 기준으로 하여 피험자를 선정하였다.

두 번째로 아토피 피부염의 중증도에 대한 선정기준을 정리한 것은 다음과 같다. 건강한 성인 남성을 대상으로 한 1건의 임상시험은 해당 사항이 없었으며 1건의 임상시험은 아토피 환자를 대상으로 한 임상시험이었으나 공개된 자료에는 정확한 기준이 나와 있지 않았다. 나머지 26개의 임상시험 중 7개는 경증과 중등증(Mild to Moderate)의 아토피 피부염을 대상으로 임상시험을 진행하였으며 19개는 중등증과 중증(Moderate to Severe) 아토피 피부염을 대상으로 진행하였다. 특징적인 것은 국소 도포제로 시행한 임상시험의 경우 모두 경증과 중등증 아토피 피부염만을 대상으로 임상시험을 진행하였고 경구약과 주사제의 경우 대부분 중등증과 중증 아토피 피부염을 대상으로 하였다.

피험자 선정을 위해 아토피의 중증도를 평가하는 도구로는 SCORAD index를 단독으로 이용한 경우가 5개, BSA를 단독으로 이용한 경우가 3개, EASI를 단독으로 이용한 경우가 1개, BSA와 IGA 두 가지를 이용한 경우가 3개, EASI, IGA, BSA를 모두 이용한 경우가 1개, EASI, IGA, SCORAD, BSA를 이용한 경우가 1개였으며 EASI, IGA, BSA, 가려움증에 대한 NRS를 이용한 경우가 3개 있었다. 나머지는 공개된 자료에 선정 당시 중증도를 평가하는 도구가 기재되어있지 않았다(Table 3).

6. 제외기준

피험자 제외기준은 일반적인 임상시험과 마찬가지로 전신 질환, 조절되지 않는 고혈압, 감염이 있는 자, 간수치가 일정 수준보다 높은 자, 임신부, 수유부 등을 제외하는 기준들을 볼 수 있었다(Table 4).

이 중 아토피 피부염의 치료 목적으로 사용되는 스테로이드, 면역억제제 등의 약물과 광화학요법에 대한 기준을 정리하여 알아보았다.

28개의 임상시험 중 기존 아토피 피부염 치료 시행에 따라 피험자 제외기준이 설정되어 있는 임상시험은 19개였다. 총 14개의 연구에서는 경구로 스테로이드, 면역억제제, 항생제를 복용한 경우를 제외기준에 포함 시켰다. 구체적인 복용 시기는 임상시험 시작전 4주 이내에 복용한 경우를 제외기준에 포함시킨 연구가 11개로 가장 많은 것으로 나타났다. 이어 1개의 임상시험에서는 6주, 1개의 임상시험에서는 8주를 기준으로 하였으며 나머지 1개의 임상시험은 정확한 기간은 알 수 없었다. 14개의 임상시험을 제외한 나머지 임상시험 중 1개의 임상시험에서는 항생제는 제외기준에 포함시키지 않았으나 일주일전까지 경구로 스테로이드나 면역억제제를 투여한 사람은 제외기준에 포함 시켰다.

다음으로 광화학치료를 받은 환자를 제외기준에 포함시키는 임상시험들이 12개가 있었다. 경구 약물과 마찬가지로 4주 이내에 광화학치료를 받은 환자들을 제외기준에 포함시킨 임상시험이 총 8개로 가장 많았다. 2개의 임상시험에서는 2주 이내에 광화학치료를 받은 경우를 제외기준에 포함 시켰다. 1개의 임상시험에서는 6주 이내에 광화학치료를 시행하였거나 태닝을 한 경우를 제외기준에 포함 시켰고 1개의 임상시험에서는 정확한 기간은 나와 있지 않았다.

다음으로 국소 스테로이드(Topical Corticosteroids, TCS)를 환부에 도포한 경우에 대해서는 6개의 임상시험에서 제외기준에 포함 시켜 경구 약물에 비해서는 제외기준에 해당하는 경우가 상대적으로 적은 것으로 나타났다. 1개의 연구에서는 4주 이내에 국소 스테로이드를 사용한 경우를 제외기준에 포함 시켰고 5개의 연구에서는 2주 이내에 사용한 경우에만 제외기준에 포함 시켜 경구 약물보다는 제외기준이 다소 완만하게 나타났다.

3개의 연구에서는 임상시험 시작에 앞서 투여된 약물에 대해서는 제외기준이 없었으나 시험 기간 내에 기존의 아토피 치료 약물을 중단할 수 없는 경우에는 제외기준에 포함 시켰다.

7. 유효성 평가 도구

임상시험의 1차 유효성 평가 도구로 쓰인 지표의 경우 가장 많이 쓰인 것은 IGA(Investigator's global assessment) score였다. 총 11개의 연구에서 IGA score로 사용하였으며 투여 후에 IGA 0점(clear), 1점(almost clear)인 경우를 유효한 것으로 보았다.

다음으로 많이 TEAEs(Treatment emergent adverse events)를 1차 평가 도구로 기재한 연구가 5개였다. 다음은 SCORAD(SCORing of Atopic Dermtaitis) index를 평가도구로 사용한 연구가 3개 있었다. EASI(Eczema Area and Severity Index) score를 단독으로 1차 유효성 평가도구로 선정한 연구도 5개 있었다. 3개의 연구에서는 EASI score와 IGA score 모두를 1차 유효성 평가도구로 사용하였으며 1개의 연구에서는 objective SCORAD index를 1차 유효성 평가 도구로 사용하였다(Table 5). 보조 평가도구로는 삶의 질 측정(DLQI, EQ-5D, HUI3), 가려움증에 대한 NRS(Numeral Rating Scale), 혈중 Total IgE, IL-17, IL-22, IFN-γ ,Eosinophil count 등과 연고사용량에 대한 설문조사 등이 사용되었다.

Table 5. Primary Efficacy Evaluation

No.		
1	Internal medicine	SCORAD Index
2		IGA score
3		IGA score
4		IGA score
5		EASI, IGA score
6		TEAEs
7		TEAes
8		EASI, IGA score
9		SCORAD Index
10	Dermatologic agents	TEAEs
11		IGA score
12		IGA score
13		IGA score
14		EASI
15		oSCORAD
16		IGA score
17		IGA score
18	Injections	TEAEs
19		SCORAD Index
20		EASI
21		EASI
22		EASI, IGA score
23		TEAEs
24		IGA score
25		EASI
26		IGA score
27		IGA score
28		EASI

Ⅳ. 고 찰

아토피 피부염은 환자와 환자의 가족으로 하여금 신체적인 고통뿐 아니라 정신적인 고통을 유발할 수 있는 만성질환이다. 그러나 아직 그 원인조차 다양한 가설이 존재하기는 하나 정확하게 밝혀지지는 않은 실정이다[7]. 이에 치료법도 아직 명확하게 설정된 것이 없으며 증상 경감을 위해 항히스타민제, 국소 스테로이드 등의 투여를 하는 것이 일반적으로 행해지고 있는 치료법이라 할 수 있다. 그러나 일반적으로 이러한 치료법으로 아토피 피부염을 완치시키는 것은 거의 어려운 것으로 알려져 있으며 다양한 부작용 또한 일으키는 것으로 알려져 있다[8,9].

국민건강보험공단과 대한아토피피부염학회의 보도자료에 따르면 2010년부터 2015년까지 연간 평균 110만 명의 환자가 아토피 피부염으로 진료를 받은 것으로 나타났으며 뿐만 아니라 아토피 환자 중 10명 중 1명이 ADHD, 우울증 등의 정신질환을 앓을 정도로 환자의 삶의 질을 심하게 저해하는 것으로 나타났다. 이에 경구약과 국소도포제, 주사제뿐만 아니라 보습제, 크림 등 아토피 피부염 의약품 및 의약외품 개발을 위한 다양한 연구 및 임상시험이 이루어지고 있다[4,10].

아토피 피부염 치료제 개발을 위하여 식약처에서

승인받아 시행하였거나 시행 중인 임상시험은 총 43건으로 검색이 되었으며 이중 동일한 약물로 임상시험 단계 및 대상자를 달리하여 시행을 하였거나 기존 임상시험의 연장선상으로 추가 승인을 받은 임상시험을 제외하면 총 25종의 의약품이 임상시험을 허가받은 것을 알 수 있었다.

특히 본 연구에서 14개의 임상시험, 8개의 의약품이 임상 3상 단계를 진행 중이거나 종료되었으나 '식약처 의약품통합정보시스템'의 의약품 등 정보검색 페이지에서(https://nedrug.mfds.go.kr/searchDrug) 검색결과 10년간 아토피 치료제로 의약품 시판 허가를 받은 신약은 2018년 3월 30일에 허가를 받은 수입의약품인 '듀피젠트프리필드주300밀리그램(성분명: 두필루맙)'을 제외하고는 없는 것으로 나타나 아직까지 국내의 아토피 치료 신약 개발은 쉽지 않은 것으로 나타났다. 특히 한약의 경우 식약처에서 승인받은 임상시험은 7개에 해당하였고 이중 연구 계획서가 공개되어있는 것은 3개로 나타나 양약에 비해서는 상대적으로 연구가 적은 것으로 나타났다.

또 임상시험 설계에 있어서 기존 의약품을 양성 대조군으로 사용하는 경우는 공개된 자료에는 없었으며 시험 의약품의 Vehicle이나 Vitamin C 등의 위약을 대조군으로 설정하고 있음을 알 수 있었다. 또한 중재군을 3개 이상으로 설정하여 용량에 따른 효과를 확인하는 임상시험도 14건이 있었다.

임상시험 피험자 모집에 있어서 특징적인 점은 첫 번째로 나이에 있어서 미성년자를 포함시킨 경우가 많았다는 점이다. 성인이 아닌 미성년자를 포함 시킨 임상시험도 28개의 임상시험 중 11건에 해당하는 것으로 나타났다. 일반적으로 미성년자를 대상으로 한 임상시험의 경우 연구 윤리적인 문제 등에 있어서 성인보다 까다로울 뿐만 아니라 약물의 용량 결정 등 연구설계에 있어서도 여러 어려움이 따른다[10]. 그러나 그럼에도 불구하고 아토피 피부염의 경우 유아기 및 아동 청소년에서 다발 하는 질환[3]이라는 특성상 많은 연구에서 성인을 제외한 미성년자만을 대상으로 임상시험이 진행되거나 혹은 성인뿐만 아니라 미성년자도 선정기준에 포함하여 진행하는 것을 알 수 있었다. 그러나 성인만을 대상으로 한 임상시험도 17개에 해당하여 약물의 특성 및 예상되는 부작용 등의 여러 요인에 따라 적절한 피험자 연령 설정이 필요할 것으로 사료된다. 특히 미성년자를 포함하여 임상시험 진행 시에 설계 단계에서부터 약물 투여 용량 결정 및 피험자에 대한 보호 등이 더 철저하게 고려되어야 할 것으로 사료된다.

또한 임상시험의 대상이 되는 질환인 아토피 피부염의 이환 기간, 중증도에 대해서도 각기 다른 기준을 설정하고 있었는데 만성질환의 일종인 아토피 피부염[1]의 특성상 아급성, 만성 아토피 피부염을 대상으로 하는 경우가 많음을 알 수 있었다. 급성, 아급성, 만성을 나누는 기준은 임상시험을 진행하는 기관에 따라 서로 다르게 설정하는 것으로 보이나 대부분 급성과 아급성을 구분하는 기준은 6개월, 아급성과 만성을 구분하는 기준은 1년으로 설정하고 있는 것으로 보인다.

다음으로 시험 대상으로 잡은 아토피 피부염의 중증도를 평가하는 기준 역시 임상시험마다 다소의 차이가 있는 것으로 나타났다. 일반적으로 임상에서는 SCORAD index나 EASI score를 아토피 피부염의 중증도를 평가하는 도구로 많이 사용하고 있고 유효성도 가장 많이 입증되어 있으나[12] 임상적으로 경증, 중등증, 중증을 구분하는 명확한 기준이 정해져 있지는 않다. 이는 임상시험들에서도 마찬가지인 것으로 나타났으며 임상시험 대상자 선정을 위해 사용하는 평가 기준도 각각의 시험마다 다소 다른 것으로 나타났다. 측정 도구로는 SCORAD index, EASI, IGA, BSA, NRS 등을 단독으로 사용하거나 2개에서 4개까지 기준을 중복하여 사용하는 경우들도 있었다.

먼저 SCORAD를 기준으로 중증도를 평가하는 경우 2개의 임상시험에서는 20을 초과하는 경우를 중등증에서 중증 아토피 피부염으로 평가하였고 1개의 임상시험에서는 25점 이상을 중등증에서 중증 아토피 피부염으로 평가하였다. 또 다른 연구에서는 40점 이

하를 경증에서 중증증 아토피 피부염으로 평가하였다.

EASI score가 중증도 평가 도구로 정확한 기준이 제시되어있는 임상시험은 총 5개 였는데 모두 중등증과 중증을 기준으로 한 임상시험이었다. 이 중 3개의 시험에서는 16점 이상인 경우를 중등증과 중증으로 보았고 1개의 임상시험에서는 12점, 1개의 임상시험에서는 7점을 중등증과 중증 아토피 피부염의 기준으로 설정하여 다소 차이가 크게 나타났다.

다음으로 BSA의 경우는 대부분의 임상시험에서 기준이 일치하는 것을 알 수 있었다. BSA를 중증도 평가 도구로 활용하여 피험자를 설정한 임상시험 중 중증도의 기준이 중등증에서 중증인 임상시험 7개 모두에서 기준점수를 BSA 10% 이상인 것으로 보았으며 기준이 경도에서 중등증인 시험인 경우에는 5%를 초과하는 경우를 대상으로 보았다.

IGA 같은 경우에는 인체의 4부위별 홍반, 부종, 찰상 등의 증후를 0점에서 3점으로 평가하는 시험자의 전반적 평가로 식약처에서 2009년 발간한 생약(한약) 제제의 아토피 피부염에 대한 임상시험 가이드라인에서는 임상시험의 유효성 평가 도구로 권고하고 있는 평가 도구이다. 그러나 여러 연구 및 임상시험에서 IGA 평가도 연구자마다 측정하는 방법 및 점수가 다소 차이가 있는 것으로 나타났다[13]. IGA가 평가기준으로 제시되어있는 7개의 임상시험에서는 모두 2점을 경증, 3점을 중등증, 4점을 중증의 기준으로 보는 것으로 나타났다.

마지막으로 가려움증에 대한 환자의 주관적인 점수인 NRS를 피험자 선정에 사용하는 경우도 2개의 임상시험이 있었고 모두 중등증과 중증 환자에 대한 임상시험이었는데 4점 이상을 중등증과 중증으로 설정하였다.

다음으로 제외기준 같은 경우에는 윤리적 문제, 약물과의 상호작용 등의 이유로 각각의 임상시험마다 다양한 기준이 설정되어있었다. 이중 특히 아토피 피부염의 증상 호전과 관련성이 높은 경구 스테로이드, 국소 스테로이드, 광화학요법 등에 대해서 규제를 하는 경우가 많았다. 이는 약물의 투여 경로에 따라 제한하는 것에 다소 차이가 있었는데 경구약의 경우 경구로 스테로이드, 항생제, 면역억제제 등을 투여 받은 경우와 전신 광화학요법 대부분 제외기준에 포함시켰으나 국소 스테로이드 도포에 대한 제외기준을 둔 경우는 확인할 수 없었다. 반면 국소 도포제에 대한 연구에서는 정확한 제외기준이 나와있지 않은 1개의 연구를 제외하고 모든 연구에서 경구 스테로이드제, 항생제, 면역억제제를 복용한 경우를 제외했을 뿐만아니라 4개의 연구에서 국소도포제를 사용한 경우도 제외기준에 포함 시켰다. 주사제의 경우 11개중 7개의 연구에서 경구로 스테로이드를 복용한 경우와 광화학요법을 받은 경우를 제외기준에 포함 시켰으며 2개의 연구에서 국소 스테로이드를 도포한 경우를 기준에 포함 시켰다. 임상시험 시작 전 최종 투약 기간의 경우 임상시험마다 다소 차이가 있었으나 대부분의 연구에서 경구 스테로이드 및 광화학요법은 4주, 국소 스테로이드의 경우에는 2주를 기준으로 설정하였다. 즉, 상대적으로 경구 스테로이드나 국소 스테로이드, 광화학요법등의 기존 치료가 임상시험 약물의 작용에 영향을 미칠 것으로 사료 되어 Wash-out기간을 설정할 경우 경구 약물은 4주, 국소 도포제는 일반적으로 2주, 광화학요법은 대부분 4주를 기준으로 보는 것으로 나타났다.

마지막으로 임상시험의 효과를 평가하는 유효성 평가 도구의 경우 11개의 연구에서 IGA score로 사용하였으며 3개의 연구에서는 EASI와 IGA를 모두 사용하여 IGA를 1차 유효성 평가도구에 포함시킨 연구는 총 14개였다. 투여 후에 IGA 0점(clear), 1점(almost clear)인 피험자의 비율을 확인하였다. 이는 식약처에서 설정한 가이드라인과도 일치하는 결과였다. 기타 EASI 및 SCORAD, oSCORAD를 단독 혹은 다른 지표와 결합하여 1차 유효성 평가도구로 사용한 연구들도 있었으며 보조 유효성 평가도구로 IGA, EASI, SCORAD, oSCORAD에 더하여 혈액검사(Total IgE, IL-17, IL-22, IFN-γ ,Eosinophil count 등), 삶의

질 측정(DLQI, EQ-5D, HUI3), 가려움증에 대한 NRS, 연고사용량에 대한 설문조사 등도 활용이 되었다.

식약처에서 허가받은 아토피 피부염 치료목적의 의약품에 대한 여러 임상시험의 연구계획서를 정리한 결과 많은 제약사와 병원 등을 통해서 다양한 임상시험이 이뤄지고 있음을 알 수 있었다. 그러나 신약 허가를 받은 의약품은 많지 않아 앞으로도 신약개발을 위해서는 지속적으로 임상시험이 이뤄져야 할 것으로 생각된다. 한 편 시행되는 임상시험들의 구체적인 설계는 각 시험마다 다소 차이가 있는 것으로 나타났다. 특히 약물 투약 기간, 시험대상자의 연령 등은 각각의 임상시험 약물의 특성에 따라 서로 다르게 설정해야 할 것으로 생각된다. 다만 병용 약물에 있어 임상시험 약물의 작용에 영향을 줄 수 있는 기존 아토피 치료제에 대해서는 어느 정도 기준이 필요할 것으로 생각된다. 본 논문의 결과를 기준으로 하였을 때 경구 약물은 시험시작 직전 4주 이내에 복용한 경우에는 어느 정도 영향이 있을 것으로 생각을 하는 것이 적절할 것으로 생각되며 국소 도포제의 경우에는 2주 이내에 사용한 경우에는 임상 시험에 영향을 줄 가능성이 있기 때문에 Wash-out 기간을 설정하는 것이 필요할 것으로 생각된다.

또한 각각의 임상시험에서 다소의 차이가 있었던 유효성 평가도구 역시 본 논문의 결과 및 식약처의 가이드라인을 고려할 때 1차 유효성 평가도구는 IGA score를 기준으로 하는 것이 적절할 것으로 사료되며 기타 지표들을 보조 유효성 평가도구로 다양하게 활용하는 것이 적절할 것으로 생각된다.

이와같이 본 연구에서 정리한 자료를 바탕으로 추후 한약 의약품 임상시험 설계에 있어서 피험자 선정 기준, 제외기준, 대조군 설정 및 유효성 평가 도구 설정 등에 참고할 수 있으리라 생각된다.

V. 결 론

국내에서 식약처의 승인을 받고 시행되었거나 시행중인 아토피 피부염 의약품의 임상시험 계획서 28개를 정리한 결과는 다음과 같다.

1. 임상시험 약물은 경구약, 주사제, 국소 도포제 등 다양한 제형으로 개발이 되고 있었으며 각각 비슷한 비율로 나타났다. 상대적으로 한약의 경우 임상시험이 미진한 것으로 나타났다.
2. 대조군 평가 시험에서 대조군에 대한 처리는 대부분 Vehicle을 이용한 위약 시험이 이루어지고 있었다.
3. 임상시험 형태는 대부분의 시험에서 한 중재군이 하나의 치료만 받는 평행설계의 형태를 취하고 있었다.
4. 피험자의 연령은 미성년자를 포함한 연구도 28개 중 11개에 해당하여 미성년자를 대상으로 하는 임상시험도 상당 부분을 차지하는 것으로 나타났다.
5. 피험자 선정에 있어서 아토피 피부염 이환 시기의 경우 6개월 이상인 아급성 만성이나 1년 이상인 만성 아토피 피부염을 기준으로 하는 경우가 많았다.
6. 피험자 선정에 있어서 아토피 피부염 중증도의 경우 경증과 중등증 아토피 피부염을 대상으로 한 경우와 중등증과 중증 아토피 피부염을 대상으로 한 임상시험으로 나누어볼 수 있었는데 평가 기준에는 SCORAD index, EASI, IGA, BSA, NRS등이 다양하게 사용되었다.
7. 피험자 선정 시 아토피 피부염 치료 목적으로 사용된 약품에 대한 규제나 Wash-out 기간의 경우 경구약 임상시험의 경우 경구 스테로이드나 면역억제제에 대해서는 제한을 두고 있었으나 국소 스테로이드에 대해서는 비교적 제외기준이 적었으며 국소 도포제의 경우 경구 약물과 국소 도포제 모두를 규제하는 경우가 많았다. 주사제의 경우 각각의 임상시험마다 규제를 하는 경우도 있었고 하지 않는 경우도 있었다. 경구 약물의 경우 시험시작 4주전, 국소 도포제의 경우 시험 시작 2주 전을 기준으로

하는 경우가 많았다.

8. 임상시험 1차 유효성 평가 도구로서 가장 많이 활용된 것은 IGA였으며 SCORAD index, EASI, NRS 등도 활용되었다.

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