Treatment for Itch in Atopic Dermatitis

Subjects: Agriculture, Dairy & Animal Science | Allergy

Contributor: Mitsutoshi Tominaga

This entry briefly describes the recent drugs for the treatment of atopic itch.

Atopic dermatitis Itch

1. Background

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder with a complex pathophysiology and clinical heterogeneity in the age of its onset, morphology, and the distribution and severity of lesions [1][2]. The prevalence of AD is approximately 4% in adults and 10% in children, with 50% developing persistent skin disease as adults [3]. The pathophysiology of AD involves complex interactions between epidermal barrier disruption, skin microbiome dysbiosis, and altered type 2 immune responses [2][4].

2. Treatment for Itch in AD

Despite numerous and extensive studies of the pathophysiology of itch in AD, currently available systemic treatments have limited potency and restricted use due to safety concerns. Newly emerging biologic agents may become superior AD treatments, and their efficacy and safety are now being investigated in systematic reviews and meta-analyses. At the time of writing, dupilumab was the only biologic therapy being extensively investigated, and although other drugs were promising, available data were insufficient. Longer follow-ups and larger population studies are required to obtain reliable biologic safety profiles [5]. Recently developed biologic agents related to type 2 inflammation for the treatment of itch in AD are summarized in **Table 1**.

Table 1. Therapeutic potential of the biologic agent-type 2 inflammation-related regulation of itch in atopic dermatitis.

Mediator	Mechanism	Drug	Status	Clinical Effects	References
IL-4, IL-13	Anti-IL-4Rα	Dupilumab	Approved for moderate-to-severe AD (FDA)	Improvement in pruritus NRS by ≥4 points; IGA, EASI, SCORAD, DLQI	[6][7][8][9]

Mediator	Mechanism	Drug	Status	Clinical Effects	References
IL-13	Anti-IL-13	Lebrikizumab	Phase 2b	Improvement in pruritus NRS by ≥4 points; EASI, IGA, BSA, POEM	[10]
		Tralokinumab	Phase 3	Improvement in pruritus NRS by ≥4 points; IGA, BSA, EASI, SCORAD, POEM	[11][12]
IL-31	Anti-IL-31	BMS-981164	Phase 1	Data not yet released	https://clinicaltrials.gov/ct2/show/NCT01614756 (accessed on 15 September 2021)
	Anti-IL-31Rα	Nemolizumab	Phase 3	Improvement in pruritus VAS by 40–60%	[13][14][15][16]
JAK	JAK1/JAK2 inhibitor	Baricitinib	Approved for AD in Japan and the EU; undergoing phase 3 trials in other countries	Improvement in pruritus NRS by ≥4 points; IGA, EASI, SCORAD, skin pain, POEM, DLQI	[17][18] https://clinicaltrials.gov/ct2/results?cond=Atopic+Dermatitis&term=baricitinib&cntry=&state=&city=&dist= (accessed on 15 September 2021)
	JAK1, JAK2, JAK3, and a tyrosine kinase 2 inhibitor	Delgocitinib 0.5% (topical)	Approved for AD in Japan; undergoing phase 3 trials in other countries	Improvement in pruritus NRS points; IGA, EASI, BSA	[19][20] https://clinicaltrials.gov/ct2/show/NCT04949841?term=delgocitinib&cond=Atopic+Dermatitis&draw=2&rank=6 (accessed on 15 September 2021)
	JAK1/3 inhibitor	Tofacitinib 2% (topical)	Phase 2a	Improvement in ISI; EASI, PGA, BSA	[21]
	JAK1 inhibitor	Abrocitinib (oral)	Phase 3	Improvement in pruritus NRS by ≥4	[22][23]

Mediator	Mechanism	Drug	Status	Clinical Effects	References
				points; IGA, EASI	
		Upadacitinib (oral)	Phase 3	Improvement in pruritus NRS by ≥4 points; IGA, EASI	[24][25][26]
PDE4	PDE4 inhibitor	Crisaborole 2% (topical)	Approved for mild-to-moderate AD (FDA) [32]	Improvement in the severity pruritus scale & NRS points; IGA, AD signs, DLQI	[27][28][29]
TSLP	Anti-TSLPR	Tezepelumab	Phase 2a	Improvement [33] in pruritus NRS points & the 5-D itch scale; EASI, IGA, SCORAD (Numerical improvement *)	[6][7] [30]
#IL-33	Anti-IL-33	Etokimab	Phase 2a proof-of-concept study	Improvement [35][36][37] in pruritus scores; EASI, SCORAD, IGA, DLQI	[31]

* No significant difference; # Proof-of-concept study; NRS = Numerical Rating Scale; FDA = Food and Drug Administration; IGA = Investigator Global Assessment; EASI = Eczema Area and Severity Index; SCORAD= SCORing Atopic Dermatitis; DLQI= Dermatology Life Quality Index; VAS = Visual Analog Score; ISI = Itch Severity Item; BSA = Body Surface Area; POEM = Patient-Oriented Eczema Measure.

nd IL-13
ected on
pendent
ne genes
ms were
and 2)
ncluding
oL [8][34].

ls [35][36].
rticularly
need for
ekly with
ervations

for AEs are advised [9][38]. Dupilumab was the first biologic to be approved by the US Food and Drug Administration (FDA) as the first-line treatment for moderate-to-severe AD in patients aged 6 years and older in the USA and it has also been approved for use in patients aged 12 years and older in the EU [4][32].

The mechanism of action of dupilumab does not only involve the IL-4/IL-13 pathways. Mack et al. performed the high-dimensional immune profiling of patients with AD and found deficiencies in specific subsets of natural killer (NK) cells. NK cell defects were reversed after the blockade of type 2 cytokines in patients with AD. A treatment with dupilumab was associated with the significant recovery of NK cells, as confirmed by clinical flow cytometry, together with improved clinical scores and inflammatory cytokine levels. These findings suggest that NK cells play an immunoregulatory role in type 2 inflammation in AD, possibly via the IL-4 pathway [39].

2.2. Anti-IL-13

Anti-IL-13 interrupts type 2 immune signaling by directly binding to soluble IL-13 [1][40]. Agents for anti-IL-13 activity include lebrikizumab, which selectively hinders the establishment of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex [10], and tralokinumab, which specifically binds to IL-13, thereby preventing any interplay with the IL-13 receptor and subsequent downstream IL-13 signaling [11].

A phase 2b placebo-controlled randomized clinical trial (RCT) on patients with moderate-to-severe AD demonstrated that a 16-week treatment with lebrikizumab significantly improved pruritus NRS by ≥4 points, clinical scores, and QoL in a dose-dependent manner with good safety [10]. In two parallel 16-week phase 3 (ECZTRA1 and 2) trials on moderate-to-severe AD adults, tralokinumab monotherapy was more effective than a control treatment after 16 weeks (improvement in pruritus NRS by ≥4 points, sleep interference, QoL, and clinical signs), and was tolerated well at 52 weeks [12]. An additional phase 3 (ECZTRA3) trial on these patients demonstrated that the combination of tralokinumab and topical corticosteroids (TCS) as needed was effective and achieved similar favorable outcomes and AEs to those in ECZTRA1 and 2 [11].

2.3. Anti-IL-31 Signaling

2.3.1. Anti-IL-31

An agent targeting IL-31 for clinical use (BMS-981164) was examined in a phase I study between 2012 and 2015 [41]; however, the findings obtained were not released until now (https://clinicaltrials.gov/ct2/show/NCT01614756, accessed on 15 September 2021).

2.3.2. Anti-IL-31RA

Nemolizumab is a subcutaneously administered humanized mAb against IL-31Rα, which is involved in itch in AD [41]. Among IL-31 strategies to alleviate pruritus, only nemolizumab has successfully completed late-stage clinical studies. This drug binds to IL-31Rα in cells such as neurons, blocking the binding of IL-31, which inhibits IL-31 signaling [32]. Moreover, nemolizumab has been investigated for the refinement of sleep, daily functioning, and QoL disruptions in patients with AD [14].

In an RCT, double-blind phase I/Ib study, the administration of nemolizumab as a single subcutaneous dose improved the pruritus visual analog score (VAS) score to approximately 50% by week 4, in contrast to 20% by a control treatment. It improved sleep comfort and decreased the need to use hydrocortisone butyrate. Furthermore, there were no serious AEs or discontinuation due to AEs [15].

In a phase 2 trial, nemolizumab significantly improved the pruritus VAS score (43.7%) vs. control (20.9%), which was inadequately controlled by topical treatments in moderate-to-severe AD patients. The incidence and types of AEs in the nemolizumab group were similar to those in the placebo group, except for exacerbations in AD and peripheral edema, which were more prevalent in those receiving nemolizumab [13]. In a phase 2B 24-week RCT study, nemolizumab achieved improvements in pruritus NRS by ≥4 points, the NRS-sleep scale, Investigator Global Assessment (IGA) response, EASI score, and SCORAD [16].

In a 16-week double-blind phase 3 trial, moderate-to-severe pruritus AD patients with an inadequate response to topical agents showed greater improvements in the pruritus VAS score with the subcutaneous administration of nemolizumab plus topical agents (42.8%) than with placebo plus topical agents (21.4%). Injection-site reactions

were more common in the nemolizumab group than in the placebo group. Longer and larger trials to establish the long-lasting impact and safety of nemolizumab for AD are needed [14].

2.4. JAK Inhibitors

The JAK and signal transducer and activator of transcription (JAK-STAT) pathway is used by cytokines as an intracellular signaling pathway. The phosphorylation, dimerization, and translocation of specific STAT proteins occur in the nucleus after the activation of JAK proteins, and each JAK protein then communicates with numerous cytokine receptors involved in inflammatory diseases [42]. The JAK-STAT pathway has been reported to encompass several tyrosine kinase proteins that interact with the common γ-chain of cytokine receptors and generate cytokine-mediated responses, and is essential for T helper 2 cell differentiation [32][43].

Baricitinib, an oral selective JAK1/JAK2 inhibitor, was the first oral JAK inhibitor to progress to phase 3 clinical trials for AD [44]. In two multicenter, double-blind, phase III monotherapy trials (BREEZE-AD1 and BREEZE-AD2) on moderate-to-severe AD adults, baricitinib attenuated the clinical signs of AD within 16 weeks with the prompt amelioration of itch. AEs were similar between the baricitinib and control groups [17]. In another phase 3 RCT (BREEZE-AD7), moderate-to-severe AD adults with an inadequate response to TCS therapy who received 4 mg of baricitinib plus TCS showed significant improvements in pruritus NRS by ≥4 points, the signs and symptoms of AD, sleep, skin pain, and QoL. The safety profile was similar to that reported in previous studies on baricitinib for AD [18]. Baricitinib has been approved for AD in Japan and the EU, and is being investigated in phase 3 trials in other countries (https://clinicaltrials.gov/ct2/results?cond=Atopic+Dermatitis&term=baricitinib&cntry=&state=&city=&dist=, accessed on 15 September 2021).

Delgocitinib (formerly JTE-052) is a novel, small-molecule JAK inhibitor that is being developed in Japan. It exerts inhibitory effects on JAK1, JAK2, JAK3, and tyrosine kinase 2 [45]. In a phase 3 RCT, double-blind open-label study, 0.5% delgocitinib ointment improved pruritus NRS points (daytime and nighttime) as well as clinical signs and symptoms with good safety for up to 28 weeks in Japanese adults with moderate-to-severe AD [19]. A long-term study of the safety and efficacy of this ointment revealed that it was tolerated well and effectively improved pruritus NRS points up to 52 weeks [20]. Delgocitinib has been approved for the treatment of AD in Japan. It is being investigated in phase 3 trials elsewhere (https://clinicaltrials.gov/ct2/show/NCT04949841?term=delgocitinib&cond=Atopic+Dermatitis&draw=2&rank=6, accessed on 15 September 2021).

Tofacitinib citrate, an oral small-molecule JAK1/3 inhibitor that was initially approved to treat rheumatoid arthritis, acts by blocking Th2 cytokine signaling (IL-4, -5, and -13). Tofacitinib is presently being examined for its potential as a treatment for AD [32]. The efficacy of topical tofacitinib was evaluated in 69 adults with mild-to-moderate AD in a phase 2a, double-blind RCT. Tofacitinib 2% ointment showed significantly higher efficacy than a control treatment for improvements in the Itch Severity Item score and clinical signs, with the early onset of effects and tolerable AEs [21].

Oral selective JAK1 inhibitors, such as abrocitinib and upadacitinib, have been shown to alleviate itch and clinical manifestations in patients with moderate-to-severe AD. Two phase 3 RCTs demonstrated that abrocitinib monotherapy for 12 weeks was effective and tolerated well, e.g., improvements in pruritus NRS by ≥4 points, EASI, and IGA responses [22][23]. Upadacitinib has been approved for moderate-to-severe active rheumatoid arthritis, and may disrupt JAK1 signaling followed by the Th2 cytokines involved, thereby alleviating chronic itch [24][25]. In a phase 2B dose-ranging RCT, 30 mg of upadacitinib was shown to improve pruritus NRS by ≥4 points as well as clinical manifestations [24]. The combination of upadacitinib and TCS in a phase 3 double-blind AD study achieved similar clinical outcomes [25] and was tolerated well [26].

2.5. A Phosphodiesterase 4 (PDE4) Inhibitor

PDE4 inhibitors decrease cyclic adenosine monophosphate concentrations, which reduces the production of proinflammatory cytokines involved in AD. Crisaborole 2% ointment was the first nonsteroidal PDE4 inhibitor used to treat mild-to-moderate AD [1]. Two pivotal phase 3 28-day, double-blind RCTs of crisaborole 2% in mild-to-moderate AD adults showed the earlier achievement and greater proportion of itch improvements (measured by the severity of pruritus scale and IGA scores) [27]. Moreover, a post hoc analysis revealed the significantly earlier achievement of itch management by crisaborole than by a control treatment [28].

Another study reported that crisaborole reversed the biomarker profiles of skin inflammation (e.g., Th2 and Th17/Th22 axes) and improved barrier function (e.g., immune cell infiltration and epidermal hyperplasia/proliferation) with good clinical efficacy (pruritus NRS and clinical signs), thereby supporting the therapeutic benefits of targeting PDE4 in AD patients [29]. Crisaborole 2% ointment was approved by the FDA for the treatment of mild-to-moderate AD in infants aged 3 months and older.

2.6. Anti-TSLP

Tezepelumab (AMG 157) is a human anti-TSLP monoclonal immunoglobulin G2λ that specifically binds to human TSLP and inhibits interactions with its receptor [46]. In a double-blind, placebo-controlled study, a treatment with tezepelumab attenuated allergen-induced bronchoconstriction and indexes of airway inflammation before and after an allergen challenge in mild allergic asthma patients [46]. A phase 2 clinical trial conducted among patients receiving long-acting beta-agonists and medium-to-high doses of inhaled glucocorticoids showed lower rates of clinical asthma exacerbation by tezepelumab than by a placebo. The incidence of AEs was similar among trial groups [47].

A phase 2a study on tezepelumab- or placebo plus TCS-treated moderate-to-severe AD adults reported slight improvements (clinical signs and pruritus) from the control following 12 weeks of treatment, and greater responses at 16 weeks. In tezepelumab vs. placebo groups, pruritus NRS were 33.54 vs. 25.41 (p = 0.258), EASI50 responses were 64.7% vs. 48.2% (p = 0.091), and SCORAD50 were 41% vs. 29.4% (p = 0.219), respectively [30]. Overall, these findings suggest that targeting TSLP is beneficial for the treatment of asthma, but may not be as effective at attenuating dermatitis-related itch.

2.7. Anti-IL-33

A previous study evaluated the efficacy of vaccination against IL-33 in a house dust mite (HDM)-induced airway inflammation mouse model. The inhibition of HDM-induced airway hyperresponsiveness and inflammation and the production of inflammatory cytokines were observed after the vaccination against IL-33 [48]. In a 6-week placebo-controlled phase 2a study, a single dose of etokimab, an anti–IL-33 biologic, was administered to desensitize peanut-allergic adults. The findings obtained revealed the safety of etokimab, and that a single dose of etokimab may desensitize peanut-allergic individuals and attenuate atopy-related AEs [49]. Chen et al. investigated the efficacy of etokimab in a proof-of-concept clinical study among moderate-to-severe AD. A single intravenous dose of 300 mg of etokimab achieved improvements in 5D itch scores, EASI, SCORAD, IGA, and DLQI 29 days after drug administration and was generally tolerated [31]. The inhibition of IL-33 appears to be effective for alleviating allergic disease symptoms, including AD; however, further studies on its efficacy are needed.

References

1. Puar, N.; Chovatiya, R.; Paller, A.S. New treatments in atopic dermatitis. Ann. Allergy Asthma Immunol. 2021, 126, 21–31.
2. Czarnowicki, T.; He, H.; Krueger, J.G.; Guttman-Yassky, E. Atopic dermatitis endotypes and implications for targeted therapeutics. J. Allergy Clin. Immunol. 2019, 143, 1–11.
3. Leung, D.Y.; Guttman-Yassky, E. Assessing the current treatment of atopic dermatitis: Unmet needs. J. Allergy Clin. Immunol. 2017, 139, S47–S48.
4. Langan, S.M.; Irvine, A.D.; Weidinger, S. Atopic dermatitis. Lancet 2020, 396, 345–360.
5. Snast, I.; Reiter, O.; Hodak, E.; Friedland, R.; Mimouni, D.; Leshem, Y.A. Are Biologics Efficacious in Atopic Dermatitis? A Systematic Review and Meta-Analysis. Am. J. Clin. Dermatol. 2018, 19, 145–165.
6. Beck, L.A.; Thaci, D.; Hamilton, J.D.; Graham, N.M.; Bieber, T.; Rocklin, R.; Ming, J.E.; Ren, H.; Kao, R.; Simpson, E.; et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N. Engl. J. Med. 2014, 371, 130–139.
7. Paller, A.S.; Bansal, A.; Simpson, E.L.; Boguniewicz, M.; Blauvelt, A.; Siegfried, E.C.; Guttman-Yassky, E.; Hultsch, T.; Chen, Z.; Mina-Osorio, P.; et al. Clinically Meaningful Responses to Dupilumab in Adolescents with Uncontrolled Moderate-to-Severe Atopic Dermatitis: Post-hoc Analyses from a Randomized Clinical Trial. Am. J. Clin. Dermatol. 2020, 21, 119–131.
8. Simpson, E.L.; Bieber, T.; Guttman-Yassky, E.; Beck, L.A.; Blauvelt, A.; Cork, M.J.; Silverberg, J.I.; Deleuran, M.; Kataoka, Y.; Lacour, J.P.; et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N. Engl. J. Med. 2016, 375, 2335–2348.

9. Deleuran, M.; Thaci, D.; Beck, L.A.; de Bruin-Weller, M.; Blauvelt, A.; Forman, S.; Bissonnette, R.; Reich, K.; Soong, W.; Hussain, I.; et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J. Am. Acad. Dermatol. 2020, 82, 377–388.
10. Guttman-Yassky, E.; Blauvelt, A.; Eichenfield, L.F.; Paller, A.S.; Armstrong, A.W.; Drew, J.; Gopalan, R.; Simpson, E.L. Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults with Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial. JAMA Dermatol. 2020, 156, 411–420.
11. Silverberg, J.I.; Toth, D.; Bieber, T.; Alexis, A.F.; Elewski, B.E.; Pink, A.E.; Hijnen, D.; Jensen, T.N.; Bang, B.; Olsen, C.K.; et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: Results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br. J. Dermatol. 2021, 184, 450–463.
12. Wollenberg, A.; Blauvelt, A.; Guttman-Yassky, E.; Worm, M.; Lynde, C.; Lacour, J.P.; Spelman, L.; Katoh, N.; Saeki, H.; Poulin, Y.; et al. Tralokinumab for moderate-to-severe atopic dermatitis: Results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br. J. Dermatol. 2021, 184, 437–449.
13. Ruzicka, T.; Hanifin, J.M.; Furue, M.; Pulka, G.; Mlynarczyk, I.; Wollenberg, A.; Galus, R.; Etoh, T.; Mihara, R.; Yoshida, H.; et al. Anti-Interleukin-31 Receptor A Antibody for Atopic Dermatitis. N. Engl. J. Med. 2017, 376, 826–835.
14. Kabashima, K.; Matsumura, T.; Komazaki, H.; Kawashima, M.; Nemolizumab, J.P.S.G. Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus. N. Engl. J. Med. 2020, 383, 141–150.
15. Nemoto, O.; Furue, M.; Nakagawa, H.; Shiramoto, M.; Hanada, R.; Matsuki, S.; Imayama, S.; Kato, M.; Hasebe, I.; Taira, K.; et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. Br. J. Dermatol. 2016, 174, 296–304.
16. Silverberg, J.I.; Pinter, A.; Pulka, G.; Poulin, Y.; Bouaziz, J.D.; Wollenberg, A.; Murrell, D.F.; Alexis, A.; Lindsey, L.; Ahmad, F.; et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. J. Allergy Clin. Immunol. 2020, 145, 173–182.
17. Simpson, E.L.; Lacour, J.P.; Spelman, L.; Galimberti, R.; Eichenfield, L.F.; Bissonnette, R.; King, B.A.; Thyssen, J.P.; Silverberg, J.I.; Bieber, T.; et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: Results from two randomized monotherapy phase III trials. Br. J. Dermatol. 2020, 183, 242–255.

18. Reich, K.; Kabashima, K.; Peris, K.; Silverberg, J.I.; Eichenfield, L.F.; Bieber, T.; Kaszuba, A.; Kolodsick, J.; Yang, F.E.; Gamalo, M.; et al. Efficacy and Safety of Baricitinib Combined with Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020, 156, 1333–1343.
19. Nakagawa, H.; Nemoto, O.; Igarashi, A.; Saeki, H.; Kaino, H.; Nagata, T. Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: A phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study. J. Am. Acad. Dermatol. 2020, 82, 823–831.
20. Nakagawa, H.; Nemoto, O.; Igarashi, A.; Saeki, H.; Murata, R.; Kaino, H.; Nagata, T. Long-term safety and efficacy of delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with atopic dermatitis. J. Dermatol. 2020, 47, 114–120.
21. Bissonnette, R.; Papp, K.A.; Poulin, Y.; Gooderham, M.; Raman, M.; Mallbris, L.; Wang, C.; Purohit, V.; Mamolo, C.; Papacharalambous, J.; et al. Topical tofacitinib for atopic dermatitis: A phase IIa randomized trial. Br. J. Dermatol. 2016, 175, 902–911.
22. Silverberg, J.I.; Simpson, E.L.; Thyssen, J.P.; Gooderham, M.; Chan, G.; Feeney, C.; Biswas, P.; Valdez, H.; DiBonaventura, M.; Nduaka, C.; et al. Efficacy and Safety of Abrocitinib in Patients with Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2020, 156, 863–873.
23. Simpson, E.L.; Sinclair, R.; Forman, S.; Wollenberg, A.; Aschoff, R.; Cork, M.; Bieber, T.; Thyssen, J.P.; Yosipovitch, G.; Flohr, C.; et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): A multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020, 396, 255–266.
24. Guttman-Yassky, E.; Thaci, D.; Pangan, A.L.; Hong, H.C.; Papp, K.A.; Reich, K.; Beck, L.A.; Mohamed, M.F.; Othman, A.A.; Anderson, J.K.; et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J. Allergy Clin. Immunol. 2020, 145, 877–884.
25. Silverberg, J.I.; de Bruin-Weller, M.; Bieber, T.; Soong, W.; Kabashima, K.; Costanzo, A.; Rosmarin, D.; Lynde, C.; Liu, J.; Gamelli, A.; et al. Upadacitinib plus topical corticosteroids in atopic dermatitis: Week-52 AD Up study results. J. Allergy Clin. Immunol. 2021.
26. Reich, K.; Teixeira, H.D.; de Bruin-Weller, M.; Bieber, T.; Soong, W.; Kabashima, K.; Werfel, T.; Zeng, J.; Huang, X.; Hu, X.; et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): Results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021, 397, 2169–2181.
27. Paller, A.S.; Tom, W.L.; Lebwohl, M.G.; Blumenthal, R.L.; Boguniewicz, M.; Call, R.S.; Eichenfield, L.F.; Forsha, D.W.; Rees, W.C.; Simpson, E.L.; et al. Efficacy and safety of crisaborole ointment, a

novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J. Am. Acad. Dermatol. 2016, 75, 494–503.e6.

28. Yosipovitch, G.; Gold, L.F.; Lebwohl, M.G.; Silverberg, J.I.; Tallman, A.M.; Zane, L.T. Early Relief of Pruritus in Atopic Dermatitis with Crisaborole Ointment, A Non-steroidal, Phosphodiesterase 4 Inhibitor. Acta Derm.-Venereol. 2018, 98, 484–489.
29. Bissonnette, R.; Pavel, A.B.; Diaz, A.; Werth, J.L.; Zang, C.; Vranic, I.; Purohit, V.S.; Zielinski, M.A.; Vlahos, B.; Estrada, Y.D.; et al. Crisaborole and atopic dermatitis skin biomarkers: An intrapatient randomized trial. J. Allergy Clin. Immunol. 2019, 144, 1274–1289.
30. Simpson, E.L.; Parnes, J.R.; She, D.; Crouch, S.; Rees, W.; Mo, M.; van der Merwe, R. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial. J. Am. Acad. Dermatol. 2019, 80, 1013–1021.
31. Chen, Y.L.; Gutowska-Owsiak, D.; Hardman, C.S.; Westmoreland, M.; MacKenzie, T.; Cifuentes, L.; Waithe, D.; Lloyd-Lavery, A.; Marquette, A.; Londei, M.; et al. Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. Sci. Transl. Med. 2019, 11, eaax2945.
32. Cabanillas, B.; Brehler, A.C.; Novak, N. Atopic dermatitis phenotypes and the need for personalized medicine. Curr. Opin. Allergy Clin. Immunol. 2017, 17, 309–315.
33. Hamilton, J.D.; Suarez-Farinas, M.; Dhingra, N.; Cardinale, I.; Li, X.; Kostic, A.; Ming, J.E.; Radin, A.R.; Krueger, J.G.; Graham, N.; et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J. Allergy Clin. Immunol. 2014, 134, 1293–1300.
34. Iannone, M.; Tonini, G.; Janowska, A.; Dini, V.; Romanelli, M. Definition of treatment goals in terms of clinician-reported disease severity and patient-reported outcomes in moderate-to-severe adult atopic dermatitis: A systematic review. Curr. Med. Res. Opin. 2021, 37, 1295–1301.
35. Ariens, L.F.M.; van der Schaft, J.; Bakker, D.S.; Balak, D.; Romeijn, M.L.E.; Kouwenhoven, T.; Kamsteeg, M.; Giovannone, B.; Drylewicz, J.; van Amerongen, C.C.A.; et al. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry. Allergy 2020, 75, 116–126.
36. Abraham, S.; Haufe, E.; Harder, I.; Heratizadeh, A.; Kleinheinz, A.; Wollenberg, A.; Weisshaar, E.; Augustin, M.; Wiemers, F.; Zink, A.; et al. Implementation of dupilumab in routine care of atopic eczema: Results from the German national registry TREATgermany. Br. J. Dermatol. 2020, 183, 382–384.
37. Bansal, A.; Simpson, E.L.; Paller, A.S.; Siegfried, E.C.; Blauvelt, A.; de Bruin-Weller, M.; Corren, J.; Sher, L.; Guttman-Yassky, E.; Chen, Z.; et al. Conjunctivitis in Dupilumab Clinical Trials for

Adolescents with Atopic Dermatitis or Asthma. Am. J. Clin. Dermatol. 2021, 22, 101–115.

38. Wollenberg, A.; Beck, L.A.; Blauvelt, A.; Simpson, E.L.; Chen, Z.; Chen, Q.; Shumel, B.; Khokhar, F.A.; Hultsch, T.; Rizova, E.; et al. Laboratory safety of dupilumab in moderate-to-severe atopic dermatitis: Results from three phase III trials (LIBERTY AD SOLO 1, LIBERTY AD SOLO 2, LIBERTY AD CHRONOS). Br. J. Dermatol. 2020, 182, 1120–1135.
39. Mack, M.R.; Brestoff, J.R.; Berrien-Elliott, M.M.; Trier, A.M.; Yang, T.B.; McCullen, M.; Collins, P.L.; Niu, H.; Bodet, N.D.; Wagner, J.A.; et al. Blood natural killer cell deficiency reveals an immunotherapy strategy for atopic dermatitis. Sci. Transl. Med. 2020, 12, eaay1005.
40. Erickson, S.; Heul, A.V.; Kim, B.S. New and emerging treatments for inflammatory itch. Ann. Allergy Asthma Immunol. Off. Publ. Am. Coll. Allergy Asthma Immunol. 2021, 126, 13–20.
41. Kabashima, K.; Irie, H. Interleukin-31 as a Clinical Target for Pruritus Treatment. Front. Med. 2021, 8, 638325.
42. Damsky, W.; King, B.A. JAK inhibitors in dermatology: The promise of a new drug class. J. Am. Acad. Dermatol. 2017, 76, 736–744.
43. Deleanu, D.; Nedelea, I. Biological therapies for atopic dermatitis: An update. Exp. Ther. Med. 2019, 17, 1061–1067.
44. Schwartz, D.M.; Kanno, Y.; Villarino, A.; Ward, M.; Gadina, M.; O'Shea, J.J. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat. Rev. Drug Discov. 2017, 17, 78.
45. Tanimoto, A.; Ogawa, Y.; Oki, C.; Kimoto, Y.; Nozawa, K.; Amano, W.; Noji, S.; Shiozaki, M.; Matsuo, A.; Shinozaki, Y.; et al. Pharmacological properties of JTE-052: A novel potent JAK inhibitor that suppresses various inflammatory responses in vitro and in vivo. Inflamm. Res. Off. J. Eur. Histamine Res. Soc. 2015, 64, 41–51.
46. Gauvreau, G.M.; O'Byrne, P.M.; Boulet, L.P.; Wang, Y.; Cockcroft, D.; Bigler, J.; FitzGerald, J.M.; Boedigheimer, M.; Davis, B.E.; Dias, C.; et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. N. Engl. J. Med. 2014, 370, 2102–2110.
47. Corren, J.; Parnes, J.R.; Wang, L.; Mo, M.; Roseti, S.L.; Griffiths, J.M.; van der Merwe, R. Tezepelumab in Adults with Uncontrolled Asthma. N. Engl. J. Med. 2017, 377, 936–946.
48. Lei, Y.; Boinapally, V.; Zoltowska, A.; Adner, M.; Hellman, L.; Nilsson, G. Vaccination against IL-33 Inhibits Airway Hyperresponsiveness and Inflammation in a House Dust Mite Model of Asthma. PLoS ONE 2015, 10, e0133774.
49. Chinthrajah, S.; Cao, S.; Liu, C.; Lyu, S.C.; Sindher, S.B.; Long, A.; Sampath, V.; Petroni, D.; Londei, M.; Nadeau, K.C. Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. JCI Insight 2019, 4, e131347.