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Biologic versus small molecule therapy for treating moderate to severe atopic dermatitis: clinical considerations

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Abstract

FDA approval of dupilumab for moderate-to-severe AD shifted the paradigm from use of broad, systemic immunosuppressants to a safer, targeted treatment and led to the emergence of newer interleukin (IL)-4/IL-13 directed biologics and small molecule therapies, namely Janus kinase (JAK) inhibitors. Tralokinumab and emerging (not yet approved) lebrikizumab, which both target IL-13, are alternative biologics to dupilumab. Emerging anti-IL-31 receptor nemolizumab is likely to be used second-line to other biologics, primarily for pruritus. Three JAK inhibitors are currently in use for treating AD, two of which, abrocitinib and upadacitinib, are FDA-approved. This review provides an in-depth, practical discussion on use of these biologics and JAK inhibitors that are approved or have completed phase 3 clinical trials in pediatric patients and adults, comparing the groups of medications based on available efficacy and safety data.

Keywords

abrocitinib; atopic dermatitis; baricitinib; biologics; cytokine signaling; dupilumab; eczema; interleukin-4; interleukin-13; Janus kinase inhibitor; lebrikizumab; nemolizumab; tralokinumab; upadacitinib

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Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disorder, with approximately 80% of cases starting in childhood and 20% in adulthood. Overall, 10–20% of children and 3–7% of adults in developed countries have AD. Based on a US study, 58% have mild disease, 35% moderate and 7% severe, with adolescents and adults more often moderate-to-severe than younger children.[1] AD is heterogenous in its age of onset, phenotypic differences based on ethnic background, risk of various cutaneous infections, including *Herpes simplex* virus (eczema herpeticum), trajectories in disease course, subsequent development of other atopic disorders (the *atopic march* with food allergy, allergic rhinitis and allergic asthma), and non-atopic comorbidities, particularly neuropsychiatric disorders (attention deficit-hyperactivity, anxiety, depression) and cardiovascular disease.[2] Meaningful subgrouping of AD patients to explain or predict these associations has yet to be defined. Substantial effort has been undertaken to better understand the complex immunologic mechanisms of AD, its heterogeneity, and its dynamic course with unpredictable flares.

The wide spectrum of AD severity defies a one-size-fits-all therapy and most available guidelines advise a stepwise therapeutic approach. Management comprises 3 main pillars: (i) identifying and avoiding possible provocation factors, among them irritants and allergic triggers; (ii) addressing epidermal barrier dysfunction, including moisturization; and (iii) initiating efficacious anti-inflammatory therapy, which both treats flares and provides long-term control. Given evidence that an imbalance of the skin microbiome (dysbiosis) with high colonization by *Staphylococcus aureus* contributes to worsening of inflammatory reactivity and disease chronicity, new strategies have been developed to reverse the microbiome imbalance.

Anti-inflammatory therapies for skin disorders are applied topically or administered systemically. According to guidelines, topical therapies are classically approved and used for mild-to-moderate AD, while systemic therapies are typically recommended only for moderate-to-severe AD (with topicals as adjunctive agents).[3, 4] This review focuses on biologics and systemic Janus kinase (JAK) inhibitors (JAKi, jakinibs) that are now FDA-approved or have completed phase 3 studies for pediatric and adult AD.

Biologics

In general, biologic therapies target one extracellular receptor subunit or cytokine, leading to more precise targeting than immunosuppressants and oral JAKi, leading to exceptional long-term safety and no required laboratory monitoring. Biologics are not metabolized by traditional cytochrome-based mechanisms or excreted renally, minimizing potential drug interactions. Limitations of biologics as a class include the need for frequent injections, conjunctivitis for interleukin (IL)-13 or IL-4/IL-13 blockade, the theoretical risk of anti-drug antibody formation with loss of efficacy over time, and difficulty in individualizing the dose. This review includes biologics that are approved or in late-stage development.

Dupilumab

In 2017, dupilumab became the first biologic therapy to receive approval from the U.S. Food & Drug Administration (FDA) for adults with moderate-to-severe AD and is the only approved biologic for pediatric patients (adolescents in 2019, children ≥ 6 years in 2020, and infants as young as 6 months old in June, 2022).[5] Dupilumab is a human IgG4 monoclonal antibody that binds the widely expressed IL-4 receptor α (IL-4Rα). Because IL-4Rα is present in both type 1 and type 2 IL-4 complex receptors, dupilumab mediates dual blockade of IL-4 and IL-13 signaling.[6–8] Current approvals or phase 3 studies for dupilumab include use for moderate-to-severe asthma characterized by an eosinophilic predominance, oral corticosteroid dependent asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, prurigo nodularis, hand dermatitis, chronic urticaria, and bullous pemphigoid.[5, 9–14]

Several phase 3 trials have demonstrated dupilumab's safety, tolerability, and efficacy for moderate-to-severe AD failing topical therapies or for whom topical therapies were inadvisable. (Table 1).[15–18] In SOLO 1 and SOLO 2, patients receiving 300mg dupilumab every two weeks achieved Investigator Global Assessment (IGA) of clear or almost clear (IGA 0/1) at 16 weeks, significantly more than placebo (36–38% versus 8–10%). Efficacy data were similar in patients receiving 300mg dupilumab every week (36–37%), supporting the recommendation of dosing every two weeks. Significant improvements were also observed in patient-reported symptoms, quality of life (QOL), use of rescue therapies, and symptoms of pre-existing anxiety or depression.[15]

The 52-week LIBERTY AD CHRONOS trial examined dupilumab plus topical corticosteroid (TCS) or topical calcineurin inhibitor (TCI) dual-therapy for adults. At week 16, 39% of patients on 300mg dupilumab every two weeks achieved IGA 0/1 vs 12% receiving placebo, while 69% of patients on dupilumab every two weeks achieved 75% improvement in the Eczema Area and Severity Index score (EASI-75) compared with 23% on placebo. This effect was durable at 52 weeks.[18] A second dual-therapy trial with TCS in patients resistant or intolerant to cyclosporine A reported similar efficacy data.[19]

In pediatrics, three pivotal, 16-week, randomized, controlled trials[20–22] demonstrated efficacy and significant reduction in signs of inflammation, itch, and likelihood of skin infections,[23] each leading to their respective age-group approval (Table 1). In adolescents, 24% reached IGA 0/1 with dupilumab monotherapy vs 2% on placebo.[20] For ages 6 – 11 years, dupilumab plus concomitant TCS use led to IGA 0/1 for 30% using 300mg every 4 weeks (for patients < 30kg) vs 13% on placebo and IGA 0/1 for 39% using 200mg every 2 weeks (for patients ≥ 30kg) vs 10% on placebo.[21] In infants and children ages 6 months to < 6 years, 28% on dupilumab plus very low potency TCS reached IGA 0/1 vs 4% on placebo with monthly administration.[22]

Subcutaneous dosing options of 200mg and 300mg are available as pre-filled syringe and, for adolescents and adults, pre-filled pen. For adults, the recommended dose is 300mg every two weeks after a 600mg loading dose. For pediatrics, dosing is age- and weight-based: 300 mg every 2 weeks for ≥60 kg, 200 mg every 2 weeks for 30 to <60 kg, 300 mg every 4

weeks for 15 to <30 kg, and 200 mg every 4 weeks for 5 to <15 kg. An initial loading dose (double the weight-appropriate dose) should be administered for all patients ≥ 6 years.

Needle phobia and injection site pain can cause parents and patients to fear its initiation. Several tactics and tips can be helpful for clinicians and patients. First, for patients requiring loading doses, the initial injection can be given by a healthcare provider and the second by the parent/caregiver, allowing teaching in a supervised clinic setting and greater parental comfort with administering the injection. If too difficult to administer at home, providing access to monthly in-office administration can ensure treatment administration. To reduce pain, dupilumab should be given at room temperature (removed from the refrigerator for a minimum of 45 minutes, ideally a few hours, with stability at room temperature before administration up to 14 days). Pre-treatment topical anesthetic can be applied to the injection site until children become less frightened about the injection. During administration, parents can hold their child in a bear hug to soothe and limit movement. Use of distraction techniques before and during the injection, such as audio or visual media, toys or non-pharmacological vibratory or tactile devices (eg, Buzzy® or ShotBlocker®) can be helpful. The pen formulation has the familiarity of an epinephrine pen with no visible needle, and is both faster and easier to administer, including self-administer; however, some report more pain with its use, even when gently squeezing the injection site skin to prevent intramuscular delivery. The pen formulation is currently being tested in 6-to-11-year-olds.

Side effects have been reported, particularly injection site reactions and conjunctivitis in all age groups.[15, 18, 19] A systematic review analyzing more than 3300 patients on dupilumab reported 26.1% incidence of conjunctivitis overall.[24] In pediatric trials, up to 11% of adolescents were affected by conjunctivitis,[20] 21% of those 6–11 years of age,[21] and 5% 6 months - 5 years.[22] Given that increased occurrence of ocular surface disease from dupilumab has been restricted to AD cohorts in studies, the mechanism likely involves dupilumab-related reduction of goblet cells in an already compromised ocular barrier.[25] Of note, conjunctivitis is also seen in patients treated with tralokinumab[26] or lebrikizumab,[27] further linking goblet cell depletion to IL-13 inhibition. Most cases of conjunctivitis are mild and can be treated using artificial tears or antihistamine drops without disruption of dupilumab administration. More severe reactions warrant ophthalmology referral and anti-inflammatory medication. Increased AD severity and prior history of ocular inflammation are risk factors for development of medication-associated conjunctivitis[28, 29] *The prevalence of adverse reactions is higher than seen in clinical trials*.[30] In a review of real-world data, conjunctivitis was seen in up to 62% of patients treated with dupilumab.[31] Other side effects reported post-approval include persistent or new onset facial erythema[32–36] (reported in up to 20% of patients), psoriasiform dermatitis[37], and inflammatory arthritis.[38–40] Proposed mechanisms for facial erythema include unmasking of existing allergic contact dermatitis or psoriasis, topical steroid withdrawal[41], dupilumab-induced Malassezia hypersensitivity, or Demodex proliferation resulting in rosacea. Concomitant treatment of these adverse events often allows dupilumab continuation. Although alopecia areata has developed during dupilumab therapy, dupilumab improved alopecia areata in others. In both clinical trials and post-marketing data,[42] dupilumab temporarily induces eosinophilia, especially at 4–8 weeks after initiation, but has not been clinically relevant or requiring intervention, making

laboratory monitoring unnecessary. In our experience, dupilumab has high durability in real-life use, consistent with the minimal formation of neutralizing anti-drug antibodies.

Dupilumab administration to infants and children with AD and its approval for use in other diseases, including asthma and eosinophilic esophagitis, not only allows earlier initiation of systemic treatment as needed, but also has the potential to reduce the risk of or concurrently treat other atopic diseases. In younger children with AD, treatment coincides with childhood vaccine administrations. Consensus guidelines suggest that vaccines should be administered 4 weeks prior to dupilumab initiation, if possible.[43] Especially for children ≤6 years of age, who require routine administration of rotavirus, measles, mumps, and rubella (MMR), and varicella live vaccines, the risks of live vaccines are unknown and their administration during dupilumab use should be considered on a case-by-case basis. Dupilumab can be continued during administration of inactivated vaccines, including seasonal influenza injections and COVID 19 immunization. While adult studies have helped to reassure that dupilumab does not interfere with development of appropriate antibody titers, these studies were not performed in children; specific antibody levels can be measured to ensure serologic protection after vaccination if important.

Long-term data is available for adolescents from a phase 3 open-label extension; 43% on 300mg of dupilumab every 2 or 4 weeks reached IGA 0/1 by 52 weeks. Of these, 29% maintained IGA 0/1 for 12 consecutive weeks (weeks 40 – 52) and discontinued dupilumab. After a mean of 18 weeks, 43% remained clear/almost clear using TCS alone.[44] Long-term safety was maintained. Additional post-approval studies showed IL-4/IL-13 blockade to repair the skin barrier, reduce skin infections and *S. aureus* colonization, and improve comorbidities.[45–47]

Tralokinumab

Tralokinumab was approved in the US and Europe for adults with moderate-to-severe AD in 2021. It is a human IgG4 monoclonal antibody that neutralizes cytokine IL-13 and interrupts activation of the IL-13Rα1 and, to a lesser extent, IL-13Rα2 receptor subunits.[48, 49] Growing evidence suggests that IL-13, found in greater amounts in AD skin than IL-4, is the central cytokine involved in AD pathogenesis, causing disruption of the skin barrier, keratinocyte-mediated amplification of the inflammatory response, and activation of the neuronal itch response.[50–53] The recommended dose for adults with moderate-to-severe AD is 300mg SC every two weeks after the 600mg loading dose (Table 1).

ECZTRA 1 and ECZTRA 2 studied tralokinumab monotherapy in adults over 52 weeks. At 16 weeks, tralokinumab 300mg every two weeks was superior to placebo in achieving IGA 0/1 (15.8% vs. 7.1% and 22.2% vs. 10.9%, respectively) and EASI-75 (25.0% vs. 12.7% and 33.2% vs. 11.4%, respectively). In the second phase, patients with good response were re-randomized to tralokinumab every two weeks, tralokinumab every four weeks, or placebo. At 52 weeks, durable responses occurred in 51%−60% of patients on tralokinumab every two weeks and 39%−51% of patients treated every four weeks. Of patients re-randomized to placebo, 21%−47% met IGA or EASI endpoints at 52 weeks, suggesting persistent treatment effect.[54] A network meta-analysis confirmed the efficacy of tralokinumab, but found it slightly lower than dupilumab at 16 weeks.[55] During the first 16 weeks of the ECZTRA

6 study, significantly more adolescents with moderate-to-severe AD receiving tralokinumab 150mg or 300mg achieved IGA 0/1 and EASI-75 without rescue than placebo-treated adolescents. Conjunctivitis occurred in 3–4% on tralokinumab vs. 2% on placebo.[56]

The 32-week, phase 3 ECZTRA 3 trial evaluated tralokinumab plus TCS versus placebo plus TCS in adults. At week 16, tralokinumab responders were re-randomized to receive tralokinumab every two weeks or every four weeks thereafter. Both regimens achieved IGA 0/1 or EASI-75 after 16 weeks compared to placebo (39% vs 26% for every two weeks and 56% vs 37% every four weeks, respectively). Similar trends were observed with concomitant TCS use in the ECZTRA 7 trial of adults who previously used cyclosporine.[57] Because biologics are frequently prescribed with topical agents, pragmatic dual-therapy trials may better reflect expected outcomes in clinical practice.[54, 58, 59]

Overall, tralokinumab is well-tolerated, with conjunctivitis occurring in up to 13.1% in phase 3 trials.[54, 57, 58] A review estimated an overall prevalence of 7.5%, possibly lower than reported for dupilumab.[60] Patients on dual therapy with TCS had slightly higher rates of headache[57, 58], injection site reaction, and upper respiratory tract infection (URI)[58] compared to placebo. Tralokinumab is not currently under development for other type 2 diseases.

Lebrikizumab

Lebrikizumab also targets IL-13, disrupting formation of the IL-13Rα1/IL-4Rα complex and downstream signal transduction.[61] In two recent phase 3 trials, lebrikizumab 250mg every two weeks demonstrated efficacy at 16 weeks, achieving IGA 0/1 (33–43%) and EASI-75 (51%−59%) compared to placebo (11–13% and 16–18%, respectively) (Table 1). Improvements in itch, sleep loss, and quality of life were also reported.[62, 63] A 16-week dual-therapy trial with TCS reported significant improvements in IGA and EASI-75.[64] Lebrikizumab's safety profile is similar to tralokinumab, with up to 7.5% incidence of conjunctivitis in phase 3 trials.

Nemolizumab

Nemolizumab is an investigational human monoclonal antibody that antagonizes the receptor for IL-31, a cytokine associated with pruritus.[65, 66] IL-31 receptors are expressed on cutaneous sensory neurons and, when activated, promote itch signals.[67] A phase 3 trial of Japanese patients on 60mg nemolizumab every four weeks plus TCS/TCI showed 43% reduction in pruritus per visual analogue scale (VAS) compared to 21% for patients on placebo at 16 weeks (Table 1). Percent improvement in EASI scores from baseline was 46% on nemolizumab group versus 33% on placebo. Injection site reactions (8%) and elevated creatine phosphokinase (CPK) levels (3%) occurred.[68] One study noted increased dose-dependent occurrence of predominantly mild asthma events.[69] Studies of 30mg nemolizumab with TCS are ongoing.

JAK inhibitors (JAKi or jakinibs)

JAK-STAT signaling (particularly JAK1) is downstream of activation of type 2 cytokines (IL-4, IL-13, IL-31) (Figure 1).[70, 71] JAKi in murine models impaired IL-4– and IL-13–

dependent T_H2 cell differentiation, improved skin barrier function, and decreased pruritus. Clinical trials have similarly shown reduction in inflammation and itch.[72–74] First-generation JAKi (such as tofacitinib and baricitinib) interfere with more than 50 cytokines and thus affect numerous tissues. JAKi to treat AD now include second-generation inhibitors, which potentially have a narrower range of inhibition (JAK1 selectivity) and thus may have a better safety profile and higher efficacy than first-generation JAKi. Three systemic JAKi are approved for treatment of AD: baricitinib (European Medicines Agency (EMA)-approved for AD but currently only FDA-approved for alopecia areata) and second-generation JAKi abrocitinib and upadacitinib (both JAK1-selective; both FDA- and EMA-approved). Upadacitinib is also FDA-approved for moderate-to-severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic ankylosing spondyloarthritis, and ulcerative colitis, and baricitinib for rheumatoid arthritis.

Overall oral JAKi can be used in children 12 years and older (upadacitinib) and adults 18 years and older (abrocitinib, upadacitinib and barictinib) who have moderate-to-severe atopic dermatitis that has been refractory to systemic and topical therapy or who are candidates for systemic therapy (Table 2 for pivotal trials). Caution should be used in those greater than 65 years of age, with increased risk for cardiovascular disease, smokers or long-term former smokers, with increased risk for thrombosis, and with increased risk for cancer unless there is no suitable alternative. JAKi should be used with caution in combination with other immunosuppressants, strong CYP3A4 inhibitors (such as clarithromycin and ketoconazole, particularly relevant for upadacitinib), and CYP2C19 metabolizers or strong inhibitors (particularly relevant for abrocitinib). Examples of strong CYP2C19 inhibitors are azole antifungals (eg fluconazole), selective serotonin receptor inhibitors (eg fluoxetine and fluvoxamine), tricyclic antidepressants (eg amitriptyline), proton-pump inhibitors (eg lansoprazole) and gemfibrozil. Abrocitinib is contraindicated with concomitant use of antiplatelet therapy (except for low-dose aspirin < 81mg daily) during the first three months of treatment due to risk of thrombocytopenia. Although not tested in clinical trials, relative indications for considering JAKi preferentially may be for short-term use, including seasonal AD flares, and if concomitant alopecia areata or vitiligo. JAKi provide more rapid improvement in both signs and symptoms of AD than biologics, given their broader suppression of immune activation, including of the itch-related IL-31 pathway, making them a good choice for rapid control, especially in biologic-resistant patients. JAK inhibitor dosing and frequency of these oral drugs can be varied and tailored to an individual patient’s needs more easily than biologics. They also have a shorter half-life with more rapid clearance than biologics and no associated risk of anti-drug antibodies. In contrast to available biologics, which require no laboratory monitoring, JAKi require monitoring for tuberculosis and abnormalities of blood counts and lipids at baseline and during the treatment course. In addition, all JAKi for AD have an increased risk of herpes infections, particularly herpes zoster and serious infections. The boxed warning on all JAKi was based on the ORAL Surveillance study (NCT02092467), which evaluated the safety of tofacitinib in patients who were 50 years of age or older and had at least one additional cardiovascular risk factor.[75] While these events have rarely occurred with more selective JAKi for AD, they remain theoretical risks and limit their use primarily to otherwise healthy patients without significant risk factors.

Baricitinib

The JAK1/2 selective inhibitor baricitinib was the first JAKi approved (in Europe) for systemic treatment of AD (Table 2). BREEZE-AD1, AD2, AD4, and AD7 showed that >50% of patients administered baricitinib 4mg daily, as monotherapy or in combination with TCS, achieved primary endpoints IGA 0/1 and EASI-75 at week 16 compared to placebo.[76] Notably, itch relief occurred by week 1 of treatment at the 4mg dosage.[77, 78] Nasopharyngitis, URIs, CPK elevations, and headache were the most frequently reported adverse events. In Breeze-AD3, a 52-week double-blind extension study of 2 randomized clinical trials, baricitinib 4mg and 2mg demonstrated sustained long-term efficacy in adults.[79]

Abrocitinib

Abrocitinib is FDA-approved for adults unresponsive to other systemic therapy at a starting dose of 100mg, with the option to advance to 200mg if response in inadequate. JAK1-selective inhibitor abrocitinib in phase 3 JADE trials (Mono-1 and 2) demonstrated IGA 0/1 responses in affected adults and adolescents at 200mg, 100mg and placebo of Mono-1 44%/Mono-2 38%, 24%/28%, and 8%/9%, respectively (Table 2).[80, 81] Like baricitinib, abrocitinib was effective in improving sleeping patterns and overall quality of life in adolescents and adults.[82] The most frequent dose-related, drug-related side effect of abrocitinib is nausea. Others, typically mild, are headaches, dizziness, nasopharyngitis, URI symptoms, vomiting, CPK increase (without rhabdomyolysis), folliculitis and acne, and herpes zoster infection. Severe treatment-related events included eczema herpeticum, herpangina and pneumonia, acute pancreatitis, and chronic inflammatory bowel disease; occasional patients receiving 200mg abrocitinib had thrombocytopenia. Transient and usually mild elevations in serum aminotransferase were not linked to clinically apparent acute liver injury.[83] In a 12-week head-to-head comparison of abrocitinib to dupilumab 300mg every 2 weeks in adults, both the 100mg and 200mg doses of abrocitinib (FDA-approved as starting dose) was similar in efficacy but the 200mg dose was superior in Worst Itch NRS ≥4 points at 2 weeks.[73] JADE-TEEN, a phase 3 trial for 12–17 year olds, showed that abrocitinib plus TCS greatly improved signs and symptoms of AD compared to TCS alone; >70% of treated teens showed improved sleep and Patient-Oriented Eczema Measure (POEM) score.[82, 84] Of note, the plasma concentration of abrocitinib is greatly increased by co-administration with inhibitors of cytochrome P450 (CYP2C19/fluvoxamine; CYP2C9 and CYP3A/systemic azole antifungals and macrolide family antibiotics) and is reduced by CYP inducers, such as rifampin.[85]

Upadacitinib

Upadacitinib in the phase 3 Measure Up 1 and 2 clinical trials demonstrated efficacy and safety through 16 weeks, which was maintained through week 52 in adults and adolescents (Table 2).[72, 86] IGA 0/1 scores and Worst Itch NRS score improvement of ≥4 were achieved at 16 weeks in 40–60% (vs 5–12% for placebo), with dose-dependent efficacy (15mg vs 30mg). Meaningful improvements also occurred at week 16 for quality of life, anxiety and depression, and sleep.[86] The most frequently reported treatment-emergent adverse event with upadacitinib is acne, but other changes (except lack of nausea) resemble those of

abrocitinib: cough, headache, urinary tract infection, URI, nasopharyngitis, and transient elevation in CPK levels. Infections included herpes zoster, eczema herpeticum, herpangina, and one case each of pneumonia and tuberculosis. Non-melanoma skin cancer occurred within 3 months of initiation in a few subjects.[86] A 260-week follow-up study is ongoing.[86] In head-to-head comparison of upadacitinib (30mg daily) to dupilumab (300mg every 2 weeks), upadacitinib performed superiorly at 16 weeks for skin clearance (EASI-75) and itch relief (Worst Itch NRS ≥4).[87] Rates of serious infection including eczema herpeticum and herpes zoster were higher for patients who received upadacitinib, whereas the rate of conjunctivitis was higher for patients who received dupilumab. The 15mg dose of upadacitinib is FDA-approved for initiation in adults and adolescents ≥40kg with 30mg dose escalation allowed for failure to improve adequately. Of note, strong cytochrome P450 (CYP3A) inhibition from antifungals and macrolides (as for abrocitinib), can greatly increase levels of upadacitinib, whereas broad inducers of CYP (such as rifampin) can decrease levels, although without clinical adverse events.[88]

Given the potential risks of systemic JAKi, topicals are an appealing alternative to oral administration. Although outside of the scope of this review, it should be noted that two topical JAKi, delgocitinib (pan-JAK) and ruxolitinib (JAK1/2 inhibitor), are currently available for mild-to-moderate AD.[89, 90] [89, 91] Delgocitinib is only approved and available in Japan, whereas ruxolitinib is U.S. FDA-approved. Packaging limits delgocitinib to 5g per application and ruxolitinib 1.5% cream to 20% body surface area because of concerns regarding systemic absorption.[92–96]

In summary, several biologics are now FDA-approved or emerging that offer therapy that targets specific cytokines or receptors recognized to be central to the pathogenesis of AD. These biologics are all injected subcutaneously with a frequency of once every two weeks or less. JAKi target a broader array of immune signaling and thus carry greater safety risks, despite their high potential efficacy (Table 3). As JAKi are small molecular inhibitors, they are able to be administered orally, allowing for greater dosing flexibility. As with biologics for psoriasis during the past 20 years, it is possible that biologics in the future will achieve greater efficacy and/or a requirement for less frequent administration than currently available IL4R- and IL-13-targeting biologics. Second-generation JAKi are more selective than first-generation JAKi, potentially leading to greater efficacy and safety. Regardless, patients may not respond to currently available biologics or small molecule therapy as single agents. Combining a biologic, such as dupilumab, with a broader systemic agent, such as methotrexate or a JAKi, may control AD in patients who do not improve on a single agent alone or during flares. The safety, feasibility, and cost effectiveness of combination therapy needs to be better studied in a carefully selected patient population. Finally, given the cost and potential risks of both biologics and JAKi, future discovery of biomarkers that predict response to specific biologics and JAKi could optimize patient-specific treatment choice.

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Abbreviations:

AD	atopic dermatitis
CPK	creatine phosphokinase
CYP	cytochrome P
EASI	Eczema Area and Severity Index score
FDA	Food & Drug Administration
IL	interleukin
IGA	Investigator Global Assessment
JAK	Janus kinase
JAKi, jakinibs	JAK inhibitors
MMR	measles, mumps, and rubella
POEM	Patient-Oriented Eczema Measure
TCS	topical corticosteroid
TCI	topical calcineurin inhibitor
URI	upper respiratory tract infection

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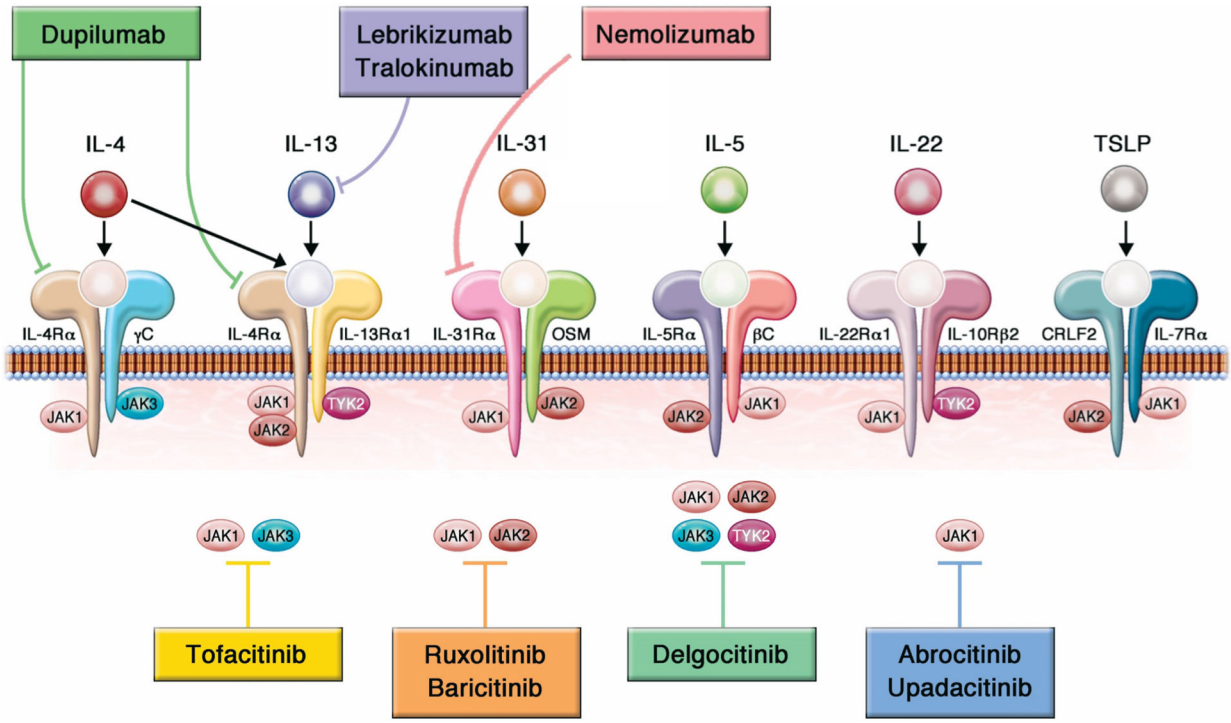

Figure 1.

A. JAK-STAT pathway, ultimately leading to regulation of gene transcription in the nucleus. B. Cytokine binding and activation of a variety of receptors leads to signaling through the JAK-STAT pathway to cause inflammation. Modified figure reprinted with permission from Chovatiya and Paller. J Allergy Clin Immunol 2021;148:927–940.

Table 1.

Biologics for Atopic Dermatitis (Currently Approved or Completed Phase 3 Clinical Trials)

Biologic	Study Type	Trial Identifier	Subject Number	Duration (weeks)	Dose (%)	Age (years)	Primary Endpoints Achieved	Secondary Endpoints Achieved	Notable Adverse Events
Dupilumab	Phase 3 (monotherapy)	SOLO 1, NCT02277743	671	16 wks	300mg Q1W, Q2W	≥18	IGA 0/1	EASI 50/75/90, %EASI, BSA, SCORAD, PP-NRS 4, POEM, DLQI, HADS	Injection-site reactions, conjunctivitis
	Phase 3 (monotherapy)	SOLO 2, NCT02277769	708	16 wks	300mg Q1W, Q2W	≥18	IGA 0/1	EASI 50/75/90, %EASI, BSA, SCORAD, PP-NRS 4, POEM, DLQI, HADS	Injection-site reactions, conjunctivitis
	Phase 3 (+/−TCS)	LIBERTY AD CHRONOS, NCT02260986	740	52 wks	300mg Q1W, Q2W	≥18	IGA 0/1, EASI 75	%EASI, BSA, SCORAD, PP-NRS 4, POEM, DLQI, HADS	Injection site reactions, conjunctivitis
	Phase 3 (+TCS)	LIBERTY AD CAFÉ, NCT02755649	325	16 wks	300mg Q1W, Q2W	≥18	EASI 75	IGA 0/1, EASI 50/90, %EASI, BSA, SCORAD, PP-NRS 4, POEM, DLQI, HADS	Injection site reactions, conjunctivitis
	Phase 3 (monotherapy)	SOLOCONTINUE, NCT02395133	422	36 wks	300mg Q1W, Q2W, Q4W, Q8W	≥18	%EASI, EASI 75	IGA 0/1, %EASI, EASI 50, PP-NRS 3	Injection site reactions, conjunctivitis
	Phase 3 (monotherapy)	NCT03912259	165	16 wks	300mg	≥18	IGA 0/1	IGA 0/1, EASI 75, PP-NRS 4, BSA, DLQI, POEM	Conjunctivitis, nasopharyngitis, upper respiratory infection
	Phase 3 (monotherapy)	NCT03054428	251	16 wks	300mg Q2W, Q4W 200mg Q2W	12–17	IGA 0/1	EASI 50/75/90, %PP-NRS, PP-NRS 3, PP-NRS-4, SCORAD, CDLQI, POEM, HADS	Injection site pain, conjunctivitis
	Phase 3 (+TCS)	NCT03345914	367	16 wks	300mg Q4W, 200mg Q2W, 100mg Q2W	6 – 11	IGA 0/1	EASI 50/75/90, %EASI, %PP-NRS, PROMISanxiety/ depression, SCORAD, CDLQI, POEM, DFI	Injection site pain, conjunctivitis
	Phase 3 (+TCS)	NCT03346434	162	16 wks	200mg Q4W	6 mo – 5 yrs	IGA 0/1	EASI 50/75/90, %EASI, %PP-NRS, PP-NRS 4, SCORAD, CDLQI, POEM,	Injection site pain, conjunctivitis
Tralokinumab	Phase 3 (monotherapy)	ECZTRA 1, NCT03131648	802	52 wks (16 wks initial + 36 wks maintenance)	300mg Q2W, Q4W	≥18	IGA 0/1, EASI 75	EASI 50/90, SCORAD 50/75, PP-NRS 4, DLQI	Conjunctivitis, nasopharyngitis, upper respiratory infection

Biologic	Study Type	Trial Identifier	Subject Number	Duration (weeks)	Dose (%)	Age (years)	Primary Endpoints Achieved	Secondary Endpoints Achieved	Notable Adverse Events
	Phase 3 (monotherapy)	ECZTRA 2, NCT03160885	794	52 weeks (16 wks initial + 36 wks maintenance)	300mg Q2W, Q4W	≥18	IGA 0/1, EASI 75	EASI 50/90, SCORAD 50/75, PP-NRS 4, DLQI, IGA *(maintenance), EASI 75 (maintenance)*	Conjunctivitis, upper respiratory infection
	Phase 3 (+TCS)	ECZTRA 3, NCT03363854	380	32 weeks (16 wks initial + 16 wks continuation)	300mg Q2W, Q4W	≥18	IGA 0/1, EASI 75	EASI 50/90, SCORAD 50/75, PP-NRS 4, DLQI, TCS use	Conjunctivitis, upper respiratory infection, oral herpes, headache
	Phase 3 (+TCS)	ECZTRA 7, NCT03761537	277	26 weeks	300mg Q2W	≥18	EASI 75	IGA 0/1, SCORAD, DLQI	Injection site pain, conjunctivitis, headache
	Phase 3 (monotherapy)	NCT03526861	289	52 wks (16 wks initial + 36 wks maintenance)	150mg Q2W, Q4W, 300 mg Q2W, Q4W	12–17	IGA 0/1, EASI 75	EASI 50/90, %PP-NRS,PP-NRS 4,SCORAD, CDLQI,POEM	Injection site pain, conjunctivitis, headache, upper respiratory infection
Lebrikizumab	Phase 3 (monotherapy)	ADvocate 1, NCT04146363	424	52 weeks (16 wks induction + 36 wks maintenance)	250mg Q2W, Q4W	≥12	IGA 0/1, EASI 75	%EASI, EASI 90, SCORAD, BSA, %PP-NRS, PP-NRS 4, sleep loss, DLQI, CDLQI, POEM	Conjunctivitis
	Phase 3 (monotherapy)	ADvocate 2, NCT04178967	445	52 weeks (16 wks induction + 36 wks maintenance)	250mg Q2W, Q4W	≥12	IGA 0/1, EASI 75	%EASI, EASI 90, SCORAD, BSA, %PP-NRS, PP-NRS 4, sleep loss, DLQI, POEM	Conjunctivitis
	Phase 3 (+TCS)	ADhere, NCT04250337	228	16 weeks	250mg Q2W	12–17	IGA 0/1, EASI 75	%EASI, EASI 90, SCORAD, BSA, %PP-NRS, PP-NRS 4, sleep loss, DLQI, POEM	Conjunctivitis, headache
Nemolizumab	Phase 3 (+TCS/ TCI)	JapicCTI-173740	215	68 weeks (16 wks + 52 wks OLE)	60mg Q4W	≥13	%VAS pruritus	Conclusions limited: no adjustment for multiple comparisons	Injection site reactions, cytokine abnormalities, increased creatinine kinase

Table 2.

JAK Inhibitors for Atopic Dermatitis (Currently Approved or Completed Phase 3 Clinical Trials)

Biologic	Study Type	Trial Identifier	Subject Number	Duration (weeks)	Dose (%)	Age (years)	Primary Endpoints Achieved	Key Secondary Endpoints Achieved	Notable Adverse Events
Abrocitinib(JAK1)	Phase 3 (monotherapy)	JADE MONO-1, NCT 03349060	387	12 wks	200mg, 100mg	12+	IGA 0/1, EASI-75	PP-NRS4, %PSAAD	Nausea, vomiting, elevated CPK, headache, herpes simplex, folliculitis, nasopharyngitis transient thrombocytopenia
	Phase 3 (monotherapy)	JADE MONO-2, NCT 03575871	391	12 wks	200mg, 100mg	12+	IGA 0/1, EASI-75	PP-NRS4, %PSAAD	
	Phase 3 (monotherapy)	JADE-REGIMEN, NCT 03627767	1,233	52 wks	200mg, 100mg	12+	Flare, loss of EASI-50, IGA	IGA 0/1	
	Phase 3 (+TCS)	JADE-TEEN,NCT 03796676	285	12 wks	200mg, 100mg	12–17	IGA 0/1, EASI-75	PP_NRS4, %PSAAD	
	Phase 3 (+TCS)	JADE EXTEND, NCT 03422822	3154	Variable	200mg, 100mg	12	Safety multiple	IGA, EASI-50,75,90, iNRS, Pt-GA, BSA, DLQI, POEM	
	Phase 3 (+TCS vs DUPI 300 q2wks)	JADECOMPARE, NCT 03720470	838	16 wks	200mg, 100mg	>18	IGA 0/1 wk 12, EASI-75 wk 12	PP-NRS4 vs placebo, DUPI, IGA 0/1 vs placebo, DUPI, EASI-75 vs placebo, DUPI *	
Baricitinib	Phase 3 (monotherapy)	BREEZE-AD1,NCT03334396	624	16 wks	4mg, 2mg, 1mg	>18	vIGA-AD 0/1	vIGA-AD 0/1, %EASI, EASI-75, 90, SCORAD-75, i-NRS, %skin pain-NRS, Item 2-ADSS	Headache, herpes simplex, increased CPK
	Phase 3 (monotherapy)	BREEZE-AD2,NCT03334422	615	16 wks	4mg, 2mg, 1mg	>18	vIGA-AD 0/1	vIGA-AD 0/1, %EASI, EASI-75, 90, SCORAD-75, i-NRS, %skin pain-NRS, Item 2-ADSS	Headache, increased CPK
	Phase 3 (+TCS)	BREEZE-AD3, NCT03334435	1645	52 wks	4mg, 2mg	>18	VIGA-AD 0/1 (wks 16, 32,52)	IGA- 0/1/2, IGA 0/1 (non-responders), EASI-75, i-NRS, Skin-pain NRS4, Item2-ADSS1.5	No change from Breeze, 1, 2
	Phase 3 (+TCS)	BREEZE-AD4, NCT03428100	463	16 wks	4mg, 2mg, 1mg	>18	EASI-75	%EASI, EASI-90, vIGA 0/1, SCORAD-75, iNRS, %skinpain-NRS, Item2-ADSS	Headache, influenza, nasopharyngitis
	Phase 3 (monotherapy)	BREEZE-AD5, NCT03435081	440	16 wks	2mg, 1mg	>18	EASI-75	EASI-90, vIGA, i-NRS, % skin-pain-NRS, % item2-ADSS, SCORAD 75	Herpes simplex, diarrhea, nasopharyngitis, upper respiratory infection, nausea

Biologic	Study Type	Trial Identifier	Subject Number	Duration (weeks)	Dose (%)	Age (years)	Primary Endpoints Achieved	Key Secondary Endpoints Achieved	Notable Adverse Events
	Phase 3 (monotherapy)	BREEZE-AD6, NCT03559270	374	16 wks	4mg, 2mg	>18	EASI-75	IGA- 0/1, BSA<3%, Itch-NRS4	Headache, herpes simplex, upper respiratory infection
	Phase 3 (+TCS)	BREEZE-AD7, NCT03733301	329	16 wks	4mg, 2mg	>18	vIGA-AD 0/1	EASI-75,90, SCORAD-75, i-NRS, %skin pain-NRS, %item 2-ADSS	
Upadacitinib	Phase 3 (monotherapy)	Measure UP 1, NCT03569293	847	16 wks	30mg, 15mg	12–75	EASI-75, vIGA 0/1	EASI 90/100, worst itch-NRS4, POEM4, DLQI4, DLQI 0/1	Acne, headache, nasopharyngitis, herpes zoster, increased CPK, upper respiratory infection
	Phase 3 (monotherapy)	Measure Up 2, NCT03607422	836	16 wks	30mg, 15mg	12–75	EASI-75, vIGA 0/1	EASI 90/100, worst itch-NRS4, POEM4, DLQI4, DLQI 0/1	Acne, headache, nasopharyngitis, herpes zoster, increased CPK, upper respiratory infection
	Phase 3 (+TCS)	AD Up, NCT03568318	300	16 wks	30mg, 15mg	12–75	EASI-75, vIGA 0/1	EASI90/100, worst itch-NRS4	Acne, headache, nasopharyngitis, herpes zoster, increased CPK, upper respiratory infection, eczema herpeticum
	Phase 3 (monotherapy vs.DUPI 300 q2 wks)	Heads Up, NCT 03738397	692	16 wks	30mg	18–75	EASI-75	EASI 90/100, worst itch-NRS4, % worst itch-NRS 30 mg dose superior to DUPI	Rates of acne, serious infection, eczema herpeticum, herpes zoster, and laboratory-related adverse events were higher for upadacitinib Rates of conjunctivitis and injection-site reactions were higher for DUPI

*200mg (not 100mg) of ABRO was superior to DUPI for itch scores only (not IGA or EASI-75).

Table 3.

Benefits and Risks of Biologics vs JAK Inhibitors

Medication	Benefits	Risks	Convenience/Desirability	Comments
Biologics	More precise targeting than immunosuppressants and oral JAK inhibitors No lab monitoring required	Associated pain, risk of injection site reaction	Requires refrigeration and special shipping	All AD biologics administered subcutaneously
Dupilumab	High efficacy for inflammation and itch No increased risk of systemic infection Fewer skin infections Excellent safety to date Requires no lab monitoring Available for 6 months and older with AD	Conjunctivitis Red face syndrome reported in real-life experience, but not trials Rare arthritis Rare psoriasiform dermatitis	Given every 2–4 wks Pain with injection	Longest duration of experience in AD Only new systemic medication shown to be efficacious for other atopic disorders and thus can have potential benefits on other atopic conditions
Tralokinumab	Moderate efficacy for inflammation and itch No increased risk of systemic infection or herpes Fewer skin infections High safety to date Requires no lab monitoring	Excellent safety- Conjunctivitis is adverse event but may be less than with dupilumab	Given every 2–4 wks Usually 2 syringes per dose Pain with injection	Although no head-to-head trials, phase 3 trial results suggest lower efficacy short-term than dupilumab or lebrikizumab Efficacy improves with time Only available for adults
Lebrikizumab	High efficacy for inflammation and itch No increased risk of systemic infection or herpes Fewer skin infections High safety to date Requires no lab monitoring	Conjunctivitis is adverse event	Given every 2–4 wks Pain with injection	Not yet FDA-approved
Nemolizumab	High efficacy for itch in some studies	High creatine kinase levels Possible worsening or new onset asthma	Given every 4 wks	Not yet FDA-approved Lower efficacy for inflammation than other biologics Role in treating AD is unclear, given availability of other biologics with greater anti-inflammatory efficacy Only published phase 3 study from Japan and 60mg dosing (vs 30mg in ongoing studies)
JAK Inhibitors	Small molecule inhibitors with rapid clearance	Require lab monitoring All with boxed warning based on tofacitinib data (malignancy, thrombosis, cardiovascular issues, serious infections, death)	Oral Easy to stop and start (eg, for short-term/seasonal use) Multiple doses available to tailor to patient needs	Broader range of effects, which means potential value for other concomitant non-atopic disorders (eg alopecia areata and vitiligo), but also higher risk for side effects
Baricitinib	Currently FDA-approved for adults with alopecia areata (4mg) More modest efficacy than other JAK inhibitors, but also fewer tolerability issues	Boxed warning Not as targeted as JAK1 selective medications but less adverse events than other JAKi in trials Headache, nasopharyngitis, increased infections, including herpetic	Daily administration Does not require refrigeration	Not FDA-approved for AD (approved in Europe)
Abrocitinib	High efficacy suggests use for severe AD Flexibility in dosing – start at 100mg daily and can increase to 200mg daily	Boxed warning Nausea/vomiting, headache, nasopharyngitis, infections, including herpes simplex and zoster, acne Abnormal platelet counts, increased	Daily administration Easy to stop and start Does not require refrigeration	12-week head-to-head trial in adults suggests that only 200mg dose is more efficacious than dupilumab 300mg every 2 wks for itch (and not for IGA 0/1/EASI-75)

Medication	Benefits	Risks	Convenience/Desirability	Comments
		transaminases, high creatine kinase, hyperlipidemia		
Upadacitinib	High efficacy suggests use for severe AD Flexibility in dosing – start at 15mg daily and can increase to 30mg daily	Boxed warning Acne, headache, nasopharyngitis, infections, including herpes simplex and zoster Abnormal blood counts, increased transaminases, high creatine kinase, hyperlipidemia	Daily administration Easy to stop and start Does not require refrigeration	16-week head-to-head trial in adults suggests that 30mg dose is more efficacious than dupilumab 300mg every 2 wks