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Novel systemic treatments in atopic dermatitis: Are there sex differences?

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ABSTRACT

Atopic dermatitis (AD) is a common inflammatory skin disease with a significant global disease burden. Several mechanisms underlie AD, such as epidermal barrier dysfunction and immune dysregulation, which have led to innovative systemic treatment options. Other inflammatory disorders, as well as innate and adaptive immune responses, have noted sex differences, but our article highlights a paucity of data on the impact of sex, gender, and gender identity on the pathophysiology and systemic treatments of AD.

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What is known about this subject in regard to women and their families?
- Atopic dermatitis (AD) is slightly more prevalent in women.
- The disability-adjusted life-years for patients with AD are higher than any other nonmalignant skin condition.
- Many new systemic therapies have been approved or are in the late stages of clinical development that will significantly improve the quality of life of patients with AD and their families.

What is new from this article as messages for women and their families?
- Female hormones have been shown to promote the development of type 2 immunity more than male hormones, providing a potential mechanism to explain the higher prevalence in women.
- Atopic dermatitis often flares immediately before menstruation and during pregnancy.
- Little is known about the pregnancy risks of newer systemic therapies for atopic dermatitis (e.g., dupilumab, tralokinumab, abrocitinib, upadacitinib, and baricitinib).

Introduction

Atopic dermatitis (AD) has the highest global disease burden in disability-adjusted life-years of any nonmalignant skin disorder (Laughter et al., 2021). Often widespread eczematous dermatitis and intense pruritus characterize this common, relapsing, inflammatory disease, as well a strong association with other atopic conditions, such as food allergy, asthma, and allergic rhinoconjunctivitis. The complex pathophysiology of AD includes epidermal barrier dysfunction, immune dysregulation, alteration of skin microbiome, and neuroimmune interactions (Kim et al., 2019; Stander, 2021; Weidinger et al., 2018). Systemic treatments that target these pathways have been heralded as a new treatment paradigm in AD.

The Global Burden of Disease study reported that 15% to 20% of children and up to 10% of adults have AD (Laughter et al., 2021). The global age-standardized prevalence varies globally, from China with 2% to Sweden with 7% (Laughter et al., 2021). This variability suggests that there are multiple factors that may influence AD development (Kim et al., 2020; Tackett et al., 2020; Torello, 2014). There are known sex differences in other atopic disorders, such as asthma (Holgate et al., 2015). Survey-based epidemiology studies on adult AD reveal a slight female predominance (Barbarot et al., 2018), but little is known regarding whether or how sex or gender affects AD pathophysiology or response to systemic treatments.

Sex is defined as the differential organization of chromosomes, reproductive organs, and gonadal hormone levels (Klein et al., 2016). The endogenous and exogenous concentrations, locations of gonadal hormones (estrogens such as 17-B-estradiol [E2], progestogens such as progesterone [P4], and androgens such as testosterone), and interactions with different organ systems differ between sexes. Sex is distinct from gender, which includes cultural and social characteristics attributed to being male, female, or nonbinary (World Health Organization, 2021). Gender and sex are related to but different from gender identity, which reflects a person's experience of gender. Sex, gender, and gender identity all contribute to health and impact immunity. All of the literature cited in this review describe the sex and not gender of study subjects; none of the studies cited in this review recruited transgender or nonbinary participants. This review will examine sex differences, when known, in the context of adaptive immunity, and specifically AD severity, pathophysiology, and systemic treatments.

Sex differences in innate and adaptive immunity

Sex differences have been reported in both innate and adaptive immune in vitro responses, but for the purposes of this review, we will highlight adaptive immunity. Effects of sex on innate immune response have been reviewed elsewhere (Klein et al., 2016). Sex differences in lymphocyte subpopulations have been noted. Female subjects have higher resting and activated CD4+ T lymphocyte (Abdullah et al., 2012; Lee et al., 1996) and CD19+ B lymphocyte counts (Abdullah et al., 2012; Furman et al., 2014) compared with male subjects. Polyclonal activation with phytohemagglutinin of peripheral blood mononuclear cells from female subjects results in greater interleukin (IL)-4 and IL-10 production than from male subjects (Giron-Gonzalez et al., 2000). In terms of antibody production, adult female subjects have higher total immunoglobulin (Ig) E, IgG, and IgM levels compared with male subjects (Abdullah et al., 2012; Furman et al., 2014). In contrast, cord blood IgE levels in male neonates were significantly higher than in female neonates in a small single-center study (Liu et al., 2003). These sex differences in adaptive immunity are thought to be mediated on both a genetic and acquired (i.e., hormonal differences) basis.

There are many endogenous and exogenous examples of differential gonadal hormone concentrations, which affect inflammatory responses (summarized by Kanda et al., 2019). Estrogen receptor a (ERa) is highly expressed on many T lymphocyte subtypes (Phiel et al., 2005), and high levels of estrogens are thought to promote a T_H2 and $T_{regulatory (reg)}$ phenotype. In human and mouse studies, periovulatory and pregnancy levels of E2 increased IL-4 and IL-10 production from murine ERa+CD4+ T lymphocytes (Lambert et al., 2005). In mice, pregnancy levels of E2 increased Foxp3 expression and CD25+ cell number, markers of T_{reg} (Tai et al., 2008). In vitro and in vivo, P4 has a significant pro-T_H2 effect (Straub, 2007). P4 increases the production of IL-4 by inducing a progesterone-inducible blocking factor that binds IL-4a/progesterone-inducible blocking factor heterodimer, leading to Janus kinase (JAK)/pathway activation (Kozma et al., 2006; Piccinni et al., 1995). P4 also promotes differentiation of fetal T lymphocytes into Foxp3+ T_{reg} in human cord blood (Lee et al., 2011).

Androgens have a contrasting effect on T lymphocytes. Testosterone treatment of dendritic cells and prostate stromal cells reduces in vitro production of IL-4 and IL-13 from cocultured T lymphocytes (Hepworth et al., 2010; Vignozzi et al., 2012). The Foxp3 promoter has an androgen response element, leading to androgen-mediated enhanced expression of Foxp3 in human T cells (Walecki et al., 2015). In summary, estrogens and progestogens promote T_H2 pathways and T_{reg} development, and androgens exert a similar effect on T_{reg} development but an opposite effect on T_H2 pathways.

Based on this, one might hypothesize that more type 2 immune targeted therapies (i.e., dupilumab, tralokinumab, lebrikizumab, and nemolizumab) could possibly be more effective in female than male patients with AD. There are no peer-reviewed publications evaluating the question of whether these drugs have greater clinical efficacy in female patients (after controlling for differences in pharmacokinetics). The effects of sex, and more specifically hormones, on the adaptive immune response clearly warrants further investigation. The fact that AD affects both sexes with only a slight female predominance could indicate that sex and the associated hormonal differences are not key drivers of AD immunopathology. The effect of gender or gender identity on immune responsiveness has not been studied.

Sex differences in the pathophysiology of atopic dermatitis

Next, we next sought to determine the impact of sex and gender on the pathophysiology of AD, with a particular focus on epidermal barrier function, immune dysregulation, and skin dysbiosis. Reduced expression of filaggrin (through loss-of-function *FLG* variants or other mechanisms), increased protease/antiprotease activity, reduced expression of tight junction proteins (claudins -1, -4, and -23), and abnormal lipid composition and organization are all thought to contribute to the epidermal barrier defects observed in subjects with AD (Stander, 2021).

Contrasting data exist on the influence of sex on epidermal barrier defects. Loss-of-function *FLG* variants predispose to AD arguably by inducing skin barrier defects; in a parent-of-origin study in European families with AD, children of *FLG*-carrier mothers had a 1.5-fold increased risk of AD compared with *FLG*-carrier fathers, but this was only found when the mother was sensitized to common allergens (Esparza-Gordillo et al., 2015). This suggests that a maternal *FLG*-variant may have effects on early life development, potentially by affecting conditions during pregnancy that confer a greater risk for AD development than paternal transmission of *FLG* mutation.

In adults without AD, basal transepidermal water loss is higher in men than women, but in a study of children with AD, no sex differences were found in basal transepidermal water loss (Hon et al., 2020). In a mouse model of AD with tape stripping, castration of male mice or antagonism of the androgen receptor enhanced skin barrier recovery after tape stripping (Kao et al., 2001). We were unable to find studies that identified sex differences in filaggrin expression, protease/antiprotease activity, or tight junction expression/function in subjects with AD.

Skin dysbiosis, characterized by an abundance of *Staphylococcus aureus*, is thought to be a contributing factor to AD development and severity (Paller et al., 2019). The 16S rRNA sequencing of the AD skin microbiome is notable for reduced bacterial diversity, which is a function of disease severity and is characterized not just by the increased expression of *S. aureus*, but also the reductions of the genera *Streptococcus*, *Corynebacterium*, and *Propionibacterium* (Kong et al., 2012). There is a paucity of data examining the role of sex or gender in skin microbiota; however, cross-sectional studies have recently found that prepubertal younger children have less lipophilic microbes, such as *Corynebacterium, Cutibacterium,* and *Malassezia*, compared with postpubertal young adults (Oh et al., 2012; Park et al., 2021). It would be interesting to test whether these pubertal changes in skin microbiome may in any way help promote AD remission which we think can occur in up to 70% of childhood onset cases.

Epidermal barrier disruption and skin microbiome are thought to contribute to the immune dysregulation observed in patients with AD. AD lesions consist of CD4+ T lymphocytes, eosinophils, and dendritic cell subsets, which are key drivers of inflammation (Weidinger et al., 2018). Release of alarmins from epidermal barrier disruption or innate receptor stimulation (IL-33, IL-25, and TSLP) activate innate lymphoid 2 cells and initiate a T_H2 response characterized by the production of IL-4, IL-5, and IL-13, as well as IL-31. Downstream signaling of these cytokines is mediated by JAK/STAT pathways. TSLP specifically increases OX40 ligand, which binds to OX40 ligand receptor on naive T cells, stimulating production of IL-4 and IL-13. IL-4 and IL-13 promote IgE class switching (Weidinger et al., 2018). The in vitro and in vivo data summarized earlier in this review allow for us to hypothesize that sex differences, in part mediated by either endogenous or exogenous hormones, could amplify or abrogate several steps in this inflammatory cascade.

Sex differences in the severity of atopic dermatitis

There are many examples where sex steroid levels are altered exogenously, including administration of oral contraceptives, gender-affirming hormonal therapy, and gonadotropin-releasing hormone modulators. Menarche and pregnancy are physiological states where sex steroids change endogenously. AD worsens during the premenstrual phase of menses in 33% to 64% of subjects and during pregnancy in 52% to 61% of subjects (Kemmet et al., 1991; Ricci et al., 2012; Weatherhead et al., 2007). Although there are other biological variables that might explain this observation, this does suggest that an increase or decrease in estrogens and progestogens may contribute to AD mechanisms. We were unable to find literature that addressed whether AD severity changed in response to the use of exogenous sex steroid or sex steroid modulators.

In summary, sex and gender are understudied variables in AD and in clinical immunology in general. In a study evaluating how often scientific papers reported the sex of animal or human subjects, immunology ranked the lowest of 10 biological disciplines (Beery et al., 2011). We commend funding agencies and journals that encourage increased focus on sex and gender as key biological variables to consider.

New systemic atopic dermatitis treatments

For this review, we limited our discussion to new systemic AD treatments that have completed pivotal phase 3 trials, biologics targeting type 2 immunity, and oral JAK inhibitors (JAKi). Dupilumab is a Food and Drug Administration (FDA)– and European Medicines Agency (EMA)–approved fully humanized monoclonal antibody targeting the IL-4 receptor alpha subunit, which effectively blocks signaling of IL-4 and -13. Tralokinumab, (approved by the European Medicines Agency in the second quarter of 2021) and lebrikizumab (recently granted FDA Fast-track status) are biologics that target IL-13. Nemolizumab targets the IL-31 receptor and is not yet approved for the treatment of AD in any country. Three JAKi are awaiting FDA safety review: Abrocitinib (approved in the United Kingdom and Japan), baricitinib (approved in the European Union, Japan, and Australia), and upadacitinib, (just approved in the European Union).

A phase 3 assessment of the safety and efficacy of dupilumab began with two identical clinical trials (SOLO 1 and 2) in adults with moderate to severe AD. Significantly more dupilumab-treated patients achieved disease improvement, as measured by the Investigator Global Assessment (IGA), Eczema Area and Severity Index (EASI)-75, and Peak Pruritis Numerical rating scaled (NRS), with reduced frequency of patient-reported AD symptoms (including itch and sleep loss), improvement in quality-of-life (QoL) measures, and reduced symptoms of anxiety and depression (Simpson et al., 2016). A subsequent trial (CHRONOS) used the same dosing scheme but allowed for the use of concomitant topical corticosteroids (TCS) to reflect real-world disease management, and replicated all endpoints (Blauvelt et al., 2017). Adults treated for up to 3 years had sustained treatment responses (Beck et al., 2020).

Phase 3 clinical trials in adolescents and children showed similar rates of overall efficacy in dupilumab-treated groups (Paller et al., 2020; Simpson et al., 2020). AD exacerbations, asthma, and allergic rhinitis flares were abated with normalization of epidermal proteins, reduced scratching, and improved antimicrobial responses, as noted by fewer bacterial skin and herpes virus infections (Guttman-Yassky et al., 2019). The adverse effects of dupilumab included injection site reactions and a range of ocular complaints (including sicca, conjunctivitis, and blepharitis; Beck et al., 2020; Blauveltet al., 2017; Paller et al., 2020; Simpson et al., 2016; 2020).

Tralokinumab and lebrikizumab are biologic drugs that target IL-13. Two identical, year-long, phase 3 clinical trials (ECZTRA1 and 2) evaluated the efficacy and safety of tralokinumab in adults with moderate to severe AD (Wollenberg et al., 2021). Significantly more tralokinumab-treated adults achieved an IGA score of 0 or 1 and improvements in SCORing Atopic Dermatitis (SCORAD) patient-reported AD symptoms (including itch and sleep loss) and QoL. The most prevalent side effects included upper respiratory infections and conjunctivitis. An earlier phase 2b trial that allowed for concomitant TCS use revealed similar results (Wollenberg et al., 2019). Phase 2b clinical trials of lebrikizumab in adult patients revealed dose-dependent efficacy, notably with no significant increase in conjunctivitis rates (Guttman-Yassky et al., 2020). Lebrikizumab phase 3 trials have not been reported yet. These data suggest that IL-13 inhibition alone may be sufficient for clinical improvement in some adults with AD, possibly with lower rates of ocular side effects.

Nemolizumab is an IL-31 receptor A antagonist, a cytokine implicated in the pathogenesis of pruritus. A Japanese phase 3 trial was recently published, enrolling patients age ≥13 years and allowing concomitant TCS usage (Kabashima et al., 2020). At 16 weeks, pruritus was significantly reduced (visual analogue score [VAS]) in patients treated with nemolizumab 60 mg, with QoL, sleep, and EASI scores trending in the same direction, but these did not achieve statistical significance. Equivalent percentages of patients in the treatment and placebo groups reported worsening of AD without significant additional adverse events reported. These studies highlight the role of IL-31 in AD pruritus, but assessment of AD signs did not reach statistically significant levels of improvement.

JAKi are a less selective, anti-inflammatory treatment approach and have been shown to be highly effective as oral treatments for the management of AD. JAKs are a group of cytoplasmic tyrosine kinases, which regulate the downstream signaling pathway for many cytokines and growth factors. Many AD-relevant cytokines signal through JAK1, including IL-4, IL-13, and IL-31.

Baricitinib is an oral JAK1/2 inhibitor recently approved to treat adults with moderate to severe AD in the European Union (2 and 4 mg/day). Two identical phase 3 studies, BREEZE-AD1 and BREEZE-AD2, indicated that 4 mg baricitinib improved AD severity, QoL, itch, and sleep compared with a placebo, with the 2-mg dose showing significance with the primary endpoints but variable response to the secondary endpoints (Simpson et al., 2020). Malignancy rates were not different from placebo at week 16, but long-term follow-up studies are needed to adequately address risk for malignancy.

Previous rheumatoid arthritis trials have demonstrated rare cases of venous thromboembolism, but none were reported in these AD trials. BREEZE-AD3 was an extension of these trials conducted to determine the long-term safety of this medication class, which showed sustained efficacy through 68 weeks (Silverberg et al., 2021). Infections, most commonly eczema herpeticum, cellulitis, and pneumonia, were the most common adverse events. Increased rates of eczema herpeticum appeared to be strongly linked to AD severity, suggesting that prolonged therapy and improvements in lesions may offset these initial increases. Asymptomatic elevations in creatine phosphokinase were noted, possibly due to the importance of JAK1 in myoblast differentiation. Importantly, no increased risks of cardiovascular events, thromboembolic events, or malignancy were reported above background rates. Notably, rates of conjunctivitis in the baricitinib-treated groups were lower than that observed in the placebo groups (Silverberg et al., 2021). A subsequent trial, BREEZE-AD7, revealed added clinical benefit of simultaneous TCS usage with 4 mg of baricitinib, despite previous inadequate disease control with TCS alone (Reich et al., 2020).

JAK2 is involved in hematopoiesis; thus, a selective JAK1 inhibitor may theoretically have a lower risk for cytopenia. Upadacitinib, a selective JAK1 inhibitor (15 and 30 mg doses) was studied in two pivotal phase 3 trials, Measure Up 1 and 2, in adolescents and adult with AD (age 12-75 years). This study showed clinically meaningful improvements in disease severity (proportion of patients achieving EASI-75, EASI-90, and EASI-100; proportion of patients achieving vIGA-AD response compared with placebo), itch (≥4-point improvement in Worst Pruritus-NRS from baseline), skin pain (AD Symptom Scale skin pain, AD Total Symptom Scale-7), QoL (Dermatology Life Quality Index [DLQI] improvement of ≥4 and DLQI score of 0 or 1), sleep (AD-Impact Scale sleep domain), anxiety and depression (Hospital Anxiety and Depression Scale-A and -D <8). Herpes zoster, acne, upper respiratory infections, nasopharyngitis, headache, asymptomatic elevation in creatine phosphokinase levels, and worsening of AD were the notable adverse events (Guttman-Yassky et al., 2021).

A third pivotal trial evaluated upadacitinib with concomitant TCS and observed similar efficacy to monotherapy with upadacitinib, suggesting little additional benefit of dual-therapy unlike other biologics (Reich et al., 2021). The Heads Up trial (Blauvelt et al., 2021) compared the safety and efficacy of upadacitinib (30 mg) and dupilumab (300 mg q2weeks) and found statistically significant improvements in EASI-75 and EASI-100. The rates of eczema herpeticum and herpes zoster were higher for patients who received upadacitinib, whereas rates of conjunctivitis and injection-site reactions were higher in dupilumab patients.

Abrocitinib, which is also a JAK1 selective inhibitor, demonstrated in a phase 3 monotherapy trial (JADE – MONO 1) rapid and significant improvement in the signs (IGA, EASI75) and symptoms (peak pruritus [PP]-NRS, Pruritus and Symptoms Assessment for Atopic Dermatitis) in adolescent and adult patients with moderate to severe disease after only 12 weeks of treatment (Simpson et al., 2020). Notably, the benefit observed with abrocitinib did not plateau by the 12-week timepoint, suggesting that greater improvement might be seen with longer treatment durations. Itch improvement was unusually rapid, with a PP-NRS response observed as early as 2 weeks into treatment for both doses (100 mg and 200 mg per day). Although the study was not designed to compare to the two doses, the higher dose gave numerically greater efficacy than the lower dose.

In the phase 3 JADE COMPARE trial, adults with moderate to severe AD were randomized to abrocitinib at 100 or 200 mg per day dosing, approved dupilumab dosing, or placebo (Bieber et al., 2021). Abrocitinib 200 mg was superior to dupilumab in itch response at 2 weeks (4-point improvement in PP-NRS) and had numerically greater efficacy at 12 and 16 weeks as measured by IGA and EASI-75. No serious thromboembolic, major cardiovascular events, malignancies, or serious systemic infections were noted, but abrocitinib appeared to have a dose effect on thrombocytopenia, nausea, and acne, which were not observed in dupilumab-treated patients (Bieber et al., 2021).

Despite these very promising phase 3 studies in both the biologics and JAKi, which demonstrated clear efficacy for the treatment of patients with moderate to severe AD, no study has published a peer-reviewed paper evaluating whether clinical responses varied as a function of sex (controlling for pharmacokinetics). Enrollment of most studies skewed male, with randomization strategies resulting in roughly equal percentages of male and female subjects in each treatment arm (Table 1). We hope that the analysis of sex on response to these targeted therapies will be addressed in future publications.

As noted earlier, pregnancy often leads to AD exacerbation. The safety and efficacy of dupilumab has not been studied in pregnant women. Since dupilumab is a recombinant IgG4 monoclonal antibody, the intrauterine exposure from mid-gestation on is likely

Table 1
Systemic treatments (type 2 biologics and Janus kinase inhibitors) in AD

Trial	N	Age, year	% female	Randomization	Duration	Concomitant TCS	Primary endpoints	Secondary endpoints
Dupilumab **MOA: IL-4 receptor antagonist**								
SOLO1	671	18+	41.9	1:1:1 300 mg qw: 300 mg q2w: placebo	16 weeks	No	Proportion of patients with IGA score 0 or 1 and reduction from baseline of ≥2 points	Improvement from baseline of ≥75% on EASI; improvement of ≥4 points at weeks 2, 4, and 16, or of ≥3 points at week 16 in weekly average of peak scores for pruritis; mean percent change from baseline on EASI score, SCORAD score, and GISS; mean percent change from baseline to week 2 on Pruritis-NRS; proportion of patients with EASI-50 or EASI-90, mean change from baseline on Pruritis-NRS; percent body-surface area affected; DLQI score; POEM score; HADS score
SOLO2	708	18+	42.4	1:1:1 300 mg qw: 300 mg q2w: placebo	16 weeks	No	Same as SOLO1	Same as SOLO1
CHRONOS	740	18+	39.7	3:1:3 300 mg qw: 300 mg q2w: placebo	52 weeks	Yes	Percent patients achieving IGA 0 or 1 and ≥2-point improvement from baseline; EASI-75 from baseline to week 16	Proportion of patients achieving IGA 0 or 1 and ≥2-point reduction from baseline at week 52; EASI-75 at week 52; PP-NRS improvement (reduction) of ≥4 points (baseline to weeks 2, 4, 16, 24, 52), and ≥3 points (baseline to weeks 16 and 52), PP-NRS percentage change (baseline to weeks 16 and 52); percentage change (baseline to weeks 16 and 52) in scores for EASI, SCORAD, GISS, PP-NRS (also to week 2), change (baseline to weeks 16 and 52) in PP-NRS score; percent body surface area affected; POEM; HADS; DLQI; proportion of topical medication-free days; incidence rate of flares through week 52
LIBERTY AD ADOL	251	12–17	41	1:1:1 300 mg q4w: weight-based regimen q2w (200 mg baseline weight <60 kg; 300 mg baseline weight ≥60 kg): placebo	16 weeks	No	Proportion of patients with IGA score of 0 or 1 at week 16; ≥75% improvement in EASI (EASI-75) from baseline to week 16	Percent changes from baseline in EASI and PP-NRS at week 16; proportion of patients with 3- or 4-point or more improvement from baseline in PP-NRS, EASI-50, or EASI-90 at week 16; percent change in SCORAD; change in Children's DLQI, POEM, HADS, effect on comorbid asthma control using Juniper Asthma Control Questionnaire, and allergic rhinitis using Total Nasal Symptoms Score
LIBERTY AD PEDS	367	6–11	50.1	1:1:1 300 mg q4w: weight-based regimen q2w (100 mg q2w, baseline weight <30 kg; 200 mg q2w, baseline weight ≥30 kg): placebo	16 weeks	Yes	Proportion of patients with IGA score of 0 or 1 at week 16; ≥75% improvement in EASI (EASI-75) from baseline to week 16 (EU only)	Percent change in EASI and weekly average of PP-NRS from baseline to week 16
EXPLORE	54	18+	44.4	1:1 200 mg qw: placebo	16 weeks	No	Mean percent change in EASI scores from baseline to week 16	PP-NRS scores and proportions of patients achieving reduction of ≥50%, ≥75%, and ≥90% from baseline in EASI and SCORAD scores at week 16; mean percent change from baseline to week 16 in total SCORAD score, POEM score, total GISS, and GISS components
Tralokinumab **MOA: IL-13 antagonist**								
ECZTRA1	802	18+	40.9	3:1 300 mg q2w: placebo; at week 16 those who met IGA of 0 or 1 or EASI-75 rerandomized 2:2:1 300 mg q2w: 300 mg q4w: placebo for 36 weeks maintenance treatment; those who achieved clinical response on placebo continued placebo q2w; those not achieving clinical response were transferred to open-label 300 mg q2w with optional TCS	52 weeks	No	IGA score of 0 or 1 at week 16; EASI-75 at week 16	Reduction of weekly average daily WP-NRS of ≥4 points; change in SCORAD; change in DLQI, EASI-50, EASI-90, and POEM

Table 1 (*continued*)

Trial	N	Age, year	% female	Randomization	Duration	Concomitant TCS	Primary endpoints	Secondary endpoints
ECZTRA2	794	18+	40.4	3:1 300 mg q2w: placebo	52 weeks	No	IGA score of 0 or 1 at week 16; EASI-75 at week 16	Reduction of weekly average daily WP-NRS of ≥4 points; change in SCORAD; change in DLQI, EASI-50, EASI-90, and POEM
Phase 2b trial	204	18–75	46.1	1:1:1:1 45 mg q2w: 150 mg q2w: 300 mg q2w: placebo	12 weeks	Yes	Change in EASI score from baseline to week 12; percentage of participants achieving IGA response of 0 or 1 with reduction of ≥2 from baseline to week 12	Change from baseline in EASI and SCORAD scores by visit up to week 22; percent with reduction of ≥50% in EASI score and reduction of ≥50% in SCORAD score at week 12; percent achieving IGA response by visit up to week 22; change in Pruritis-NRS and DLQI from baseline to week 12

Lebrikizumab
MOA: IL-13 antagonist

Trial	N	Age, year	% female	Randomization	Duration	Concomitant TCS	Primary endpoints	Secondary endpoints
Phase 2b Trial	280	18+	59.3	2:3:3:3 placebo q2w: 125 mg q4w: 250 mg q4w: 250 mg q2w	16 weeks	No	Percent change from baseline in EASI to week 16	Proportion of patients achieving IGA of 0 or 1; proportion with at least 50%, 75%, and 90% improvement in EASI; percent change from baseline on Pruritis-NRS, proportion with ≥4-point improvement in Pruritis-NRS; percent change from baseline in total BSA involvement; change in POEM; change in DLQI

Nemolizumab
MOA: IL-31 receptor antagonist

Trial	N	Age, year	% female	Randomization	Duration	Concomitant TCS	Primary endpoints	Secondary endpoints
JapicCTI- 173740	215	13+	34.4	2:1 60 mg q4w: placebo	16 weeks	Yes	Percent change in weekly mean VAS score for pruritis from baseline to week 16	Time course of percent change in daily VAS score for pruritis up to week 4; percent change in EASI score from baseline to week 16; percent patients with score ≤4 on DLQI; percent patients with ≥4 point decrease from baseline in DLQI; percent patients with score ≤7 on Insomnia Severity Index

Baricitinib
MOA: JAK1/2 inhibitor

Trial	N	Age, year	% female	Randomization	Duration	Concomitant TCS	Primary endpoints	Secondary endpoints
BREEZE-AD1	624	18+	37.3	2:1:1:1 placebo: 1 mg: 2 mg: 4 mg	16 weeks	No	Superiority of baricitinib 4 mg or 2 mg over placebo tested via proportion of patients achieving vIGA-AD score of 0 or 1 with a ≥2-point improvement from baseline at week 16	Proportion of patients treated with 1 mg achieving vIGA-AD 0 or 1; proportion of patients treated with baricitinib achieving 75% and 90% improvement in EASI score; percentage change from baseline in total EASI score; 75% improvement in SCORAD; mean change from baseline in Skin Pain-NRS at 16 weeks; proportion of patients achieving ≥4-point improvement in Itch-NRS at weeks 1, 2, 4, and 16; mean change from baseline in item-2 score of AD Sleep Scale at weeks 1 and 16
BREEZE-AD2	615	18+	38.0	2:1:1:1 placebo: 1 mg: 2 mg: 4 mg	16 weeks	No	Same as BREEZE-AD1	Same as BREEZE-AD1
BREEZE-AD3	124	18+	43.5	Responders/partial responders continued regimen from BREEZE-AD1/2; patients initially randomized to placebo or 1 mg were 1:1 randomized to get 4 mg or 2 mg, baricitinib as rescue therapy for AD exacerbation; nonresponders receiving placebo, 1 mg or 2 mg rerandomized 1:1 2 mg:4 mg; nonresponders receiving 4 mg stayed on 4 mg	68 weeks	No	Proportion of patients achieving vIGA-AD score of 0 or 1 at weeks 16, 36, and 52	Proportion of patients achieving EASI-75 and ≥4-point improvement in Itch-NRS
BREEZE-AD5	440	18+	49.1	1:1:1 placebo: 1 mg: 2 mg	16 weeks	No	Proportion of patients achieving ≥75% reduction in EASI at week 16	Itch-NRS, Skin Pain-NRS, AD Sleep Scale from baseline to week 16; treatment-emergent adverse events and serious adverse events

Table 1 (continued)

Trial	N	Age, year	% female	Randomization	Duration	Concomitant TCS	Primary endpoints	Secondary endpoints
BREEZE-AD7	329	18+	34.4	1:1:1 2 mg: 4 mg: placebo	16 weeks	Yes	Proportion of patients achieving vIGA-AD score of 0 or 1, with a ≥2-point improvement from baseline at week 16	Proportion of patients achieving 75% and 90% improvement in EASI at week 16; 75% improvement in SCORAD at week 16; ≥4-point improvement on Itch-NRS among patients with baseline score ≥4 on day 2 and weeks 1, 2, 4, and 16; percent change from baseline in total EASI at week 16; mean percent change in Skin Pain-NRS at week 16 and item 2 on AD Symptom Score at weeks 1 and 16
Upadacitinib **MOA: JAK1 inhibitor** Measure Up 1	847	12–75	46.2	1:1:1 15 mg: 30 mg: placebo	16 weeks	No	Proportion of patients achieving EASI-75; proportion of patients achieving vIGA-AD response of 0 or 1 with ≥2-point reduction from baseline at week 16	Proportion with ≥4-point improvement in WP-NRS from baseline at weeks 1 and 16 (given baseline ≥4); proportion achieving EASI-90, EASI-75 at week 2; proportion with ≥4-point improvement in WP-NRS at day 2 for 30 mg group and day 3 for 15 mg group; proportion with AD flare; proportion with improvement in ADerm-IS sleep domain score from baseline to week 16; proportion with improvement in ADerm-SS skin pain score; proportion with improvement in ADerm-SS 7-item total symptom score at week 16; ADerm-IS emotional state domain score improvement; ADerm-IS daily activities domain score improvement; proportion achieving EASI-100
Measure Up 2	836	12–75	43.7	1:1:1 15 mg: 30 mg: placebo	16 weeks	No	Same as Measure Up 1	Same as Measure Up 1
AD Up	901	12–75	39.3	1:1:1 15 mg: 30 mg: placebo	16 weeks	Yes	Proportion achieving EASI-75 at week 16; proportion achieving vIGA-AD response (score of 0 or 1 with ≥2 grades of improvement from baseline) at week 16	Proportion achieving ≥4-point improvement in WP-NRS score from baseline at weeks 1, 4, and 16 (given score of ≥4 at baseline); proportion achieving EASI-90 at weeks 4 and 16; proportion achieving EASI-75 at weeks 2 and 4; proportion in 30 mg group achieving EASI-100 at week 16
Abrocitinib **MOA: JAK1 inhibitor** JADE-MONO1	387	12+	43	2:2:1 100 mg: 200 mg: placebo	12 weeks	No	Proportion achieving IGA response (score of 0 or 1 with ≥2-grade improvement from baseline); proportion achieving EASI-75 at week 12	Proportion achieving PP-NRS response (≥4-point improvement from baseline) at weeks 2, 4, and 12; least squares mean change from baseline in PSAAD total score at week 12; proportion achieving IGA response at weeks 2, 4, and 8; proportion achieving EASI-75 at weeks 2, 4, and 8; proportion achieving EASI-50 and EASI-90 at all timepoints; proportion achieving PP-NRS response at week 8; time to PP-NRS response; proportion achieving improvement of ≥75% in SCORAD
JADE-COMPARE	838	18+	51.1	2:2:2:1 200 mg abrocitinib: 100 mg abrocitinib: 300 mg dupilumab q2w: placebo	12 weeks	Yes	IGA response (score of 0 or 1 with improvement of ≥2 from baseline); EASI-75 at week 12	Itch response (improvement of ≥4-points on PP-NRS at week 2; IGA and EASI-75 response at week 16

AD, atopic dermatitis; ADerm-IS, Atopic Dermatitis-Impact Scale; ADerm-SS, Atopic Dermatitis-Symptom Scale; BSA, body-surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EU, European Union; GISS, generic impact scoring system; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator Global Assessment; IL, interleukin; JAK, Janus kinase; MOA, mechanism of action; NRS, numerical rating scale; POEM, Patient Oriented Eczema Measure; PP, peak pruritis; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; q2w, every 2 weeks; q4w, every 4 weeks; qw, weekly; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroid; VAS, visual analogue score; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis; WP, worst pruritis

Size of trial, sex-specific enrollment patterns, duration of trial, and primary and secondary outcomes are highlighted in these highlighted phase 3 trials

to be quite high (Koren et al., 2018). Based on an appraisal of the current literature, clinicians are advised to avoid the use of dupilumab in woman planning pregnancy, who are pregnant, or who are breastfeeding (Heilskov et al., 2020). Three case reports of patients with AD who have received dupilumab during pregnancy have been published (Kage et al., 2020; Lobo et al., 2021; Mian et al., 2020). No adverse events were reported for the mother or infant.

More definitive answers will likely come from the observational pregnancy-monitoring study enrolling woman from North America to evaluate outcomes of planned or unexpected pregnancies (NCT04173442; Regeneron Pharmaceuticals and Sanofi), which began enrollment in 2018 and is expected to be completed early 2026. This study will hopefully clarify the safety and efficacy of dupilumab treatment in pregnant woman with AD and/or asthma and their neonates. Little is known about the risks of tralokinumab, lebrikizumab, or nemolizumab during pregnancy or breastfeeding.

There is greater concern with the administration of oral JAKi during pregnancy. In 2016, the European League Against Rheumatism task force recommended avoiding the JAKi tofacitinib during pregnancy and lactation due to insufficient data, high breast-milk concentration, and evidence for teratogenicity in animal studies (Gotestam Skorpen et al., 2016). No case reports of baricitinib, upadacitinib, or abrocitinib usage during pregnancy or breastfeeding could be found. Additional studies aimed at investigating the effects of systemic AD therapies during conception, pregnancy, and lactation are still needed.

Conclusion

What is the role of sex on AD pathophysiology and response to treatment? The question is more important than ever given the potential effects of sex and endogenous or exogenous sex hormones on AD immune pathways and the rich pipeline of both targeted and less targeted systemic treatments. To effectively address the impact of sex and/or gender on the natural history, phenotypes/endotypes of AD, and response to treatments, large observational studies will be needed that can be sufficiently powered to control for key confounders, such as race, ethnicity, socioeconomic status, access to health care, age of AD onset, and be inclusive of our diverse gender landscape, as well as unique situations where endogenous and exogenous hormonal levels fluctuate.

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