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Clinical Yardstick

Atopic Dermatitis Yardstick update

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Key Messages

- The pathophysiology of atopic dermatitis is complex and includes skin barrier and immune abnormalities with type 2 immune deviation central to a number of clinical phenotypes and underlying endotypes.
- Recognition of the persistent nature and systemic aspects of atopic dermatitis provides a rationale for treatment with systemic therapy including biologics and small molecules, including JAK inhibitors.
- Currently approved biologics for atopic dermatitis include dupilumab, a biologic that blocks interleukin (IL)-4 and IL-13 binding to IL-4 receptor alpha, and tralokinumab, a biologic targeting IL-13; more broadly acting JAK inhibitors include topical ruxolitinib for mild-to-moderate atopic dermatitis and oral abrocitinib and upadacitinib for moderate-to-severe atopic dermatitis.

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease recognized as a global health problem.[1,2] The Global Burden of Disease Study revealed that dermatitis including AD was the leading skin disease in terms of global burden of disease measured by disability-adjusted life years.[3] Recent epidemiologic studies in the United States found prevalence of up to 18% in school-aged children[4] and 7% in adults responding in the Atopic Dermatitis in America

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survey.[5] Among US adults with AD, 29% of the patients were classified as having moderate disease with 11% having severe disease with significant impact on quality of life.[6,7] Atopic comorbidities of AD including asthma and allergies are well recognized.[8] More recently, a number of non-atopic comorbidities including neuropsychiatric and cardiovascular disorders have been reported.[9-11] Since the publication of the Atopic Dermatitis Yardstick in early 2018, new therapies and new drug indications have been approved for AD. The authors provide an update on these therapies and their expert opinion in this evolving therapeutic landscape, recognizing that other treatments will likely be approved in the near future.

Rationale for Systemic Therapy in Atopic Dermatitis

Although AD has been thought of as a disease predominantly of children, often outgrown and treated with topical anti-inflammatory therapy in a reactive manner, AD can persist or have new onset in a significant number of adults.[12,13] The pathophysiology of AD is complex and characterized by skin barrier abnormalities and immune dysregulation.[14] The systemic nature of AD has become increasingly recognized with inflammatory changes that can be measured in a blood proteomic signature at an early age.[15] Recent studies point to systemic T cell activation with expansion of circulating T_H2 and T_H22 cells.[16] Furthermore, nonlesional AD skin is characterized by broad terminal differentiation defects in addition to immune abnormalities.[17] Although a number of clinical phenotypes and endotypes have been described, type 2 immunity seems to be central to all of them.[18] Type 2 immune deviation seems to define a distinct AD phenotype and endotype characterized by more severe disease with *Staphylococcus aureus* colonization, greater allergen sensitization, and barrier dysfunction.[19] Dysbiosis of the skin microbiome in patients with AD has been found to be related to altered epidermal lipids secondary to type 2 cytokine dysregulation.[20] Recognition of the systemic nature of AD has important translational implications providing a rationale for systemic treatments which can be narrow in their targeting or more broadly acting. In this update, we discuss both biologics and Janus kinase (JAK) inhibitors approved for treatment of AD.

Which Patients With Atopic Dermatitis Warrant Therapy With Systemic Therapy

Identifying appropriate patients with AD for treatment with systemic therapy has been discussed in several publications.[21-24] A multidisciplinary expert perspective provided a Delphi approach to addressing a number of key questions, including defining moderate-to-severe AD and treatment failure and recommended dupilumab as a first-line systemic treatment option.[21] The International Eczema Council provided an algorithm for evaluating patients with AD when considering systemic therapy,[22] the AD Yardstick added dupilumab to the stepwise management of AD,[23] and a review on managing severe AD included an annotated figure addressing both evaluation and treatment including with a biologic.[24] With the recent Food and Drug Administration (FDA) approval of JAK inhibitors, the authors provide rationale for treatment of moderate-to-severe AD with this class of systemic therapy.

Update on Dupilumab

Dupilumab in Adult Atopic Dermatitis

At the time the 2018 AD Yardstick was published, dupilumab, a fully human monoclonal antibody targeting interleukin-4 receptor alpha (IL-4Rα), was approved for adults with moderate-to-severe AD. Dupilumab interferes with signaling by 2 key type 2 cytokines IL-4 and IL-13.[25] Treatment of patients with AD with dupilumab has been found to suppress molecular markers of cutaneous and systemic type 2 inflammation and reverse epidermal abnormalities that coincided with clinical improvement.[26] The primary outcome of the pivotal phase 3 trials was an Investigator's Global Assessment (IGA) of 0 or 1 (clear or almost clear), and a reduction of 2 points or more in that score from baseline at week 16 was achieved by 36% to 38% of patients on dupilumab monotherapy at week 16 vs 8% to 10% on placebo ($P < .001$).[27] In addition, improvement of at least 75% in Eczema Area and Severity Index (EASI-75) from baseline to week 16 was reported in approximately 50% of patients on dupilumab. A number of other clinically relevant outcome measures including pruritus scores and patient-reported outcome (PRO) measures were also significantly improved in the patients treated with the biologic. Of note, median disease duration in patients enrolled in the phase 3 trials was approximately 26 years, median affected body surface area (BSA) was greater than 50%, and median EASI was approximately 30 (≥21.1 = severe AD). In addition, approximately 33% of patients had received systemic corticosteroids and approximately 30% had been treated with systemic immunosuppressives. A critical clinical concept that was not immediately appreciated was that a significant number of patients treated with dupilumab who did not achieve the primary end point of IGA 0/1 ("clear" or "almost clear") still had marked improvement as assessed by both investigator- and patient-reported validated measures compared with placebo: EASI (−48.9% vs −11.3%, $P < .001$), pruritus numerical rating scale (NRS) (−35.2% vs −9.1%, $P < .001$), affected BSA (−23.1% vs −4.5%, $P < .001$), Patient Oriented Eczema Measure score greater than or equal to 4-point improvement (57.4% vs 21.0%, $P < .001$), and Dermatology Life Quality Index (DLQI) score greater than or equal to 4-point improvement (59.3% vs 24.4%, $P < .001$).[28] Subsequent studies including a 52-week trial with dupilumab used together with topical corticosteroids (TCS)[29] and a second in adults with AD with inadequate response to or intolerance of cyclosporin A (CsA), or for whom CsA treatment was medically inadvisable[30] provided further evidence of both efficacy and safety found in monotherapy trials, including sustained benefit over an extended period of time.

Injection site reactions and conjunctivitis were more frequent in the dupilumab-treated patients than in the placebo groups. Pooled data from 3 adult monotherapy trials reported injection site reactions occurring in 10% of dupilumab-treated patients vs 5% in placebo-treated patients and conjunctivitis in 10% of dupilumab-treated patients vs 2% in placebo-treated patients. Although the conjunctivitis has not been fully explained, it was for the most part self-limited, and only 1 patient in the phase 3 monotherapy trials discontinued the study treatment.[27] A recent review of randomized placebo-controlled trials of dupilumab in AD, asthma, chronic rhinosinusitis with nasal polyps (CRSwNPs), and eosinophilic esophagitis (EoE) found that the incidence of conjunctivitis was more frequent with dupilumab treatment in most AD trials but very low and similar to that found in placebo-treated patients in the asthma, CRSwNP, and EoE trials.[31] Greater baseline AD disease severity and history of prior conjunctivitis were associated with increased conjunctivitis incidence. Of note, conjunctivitis was mostly mild to moderate in severity and most cases recovered or resolved while continuing on dupilumab. Common treatments included ophthalmic corticosteroids, antibiotics, and antihistamines or mast cell stabilizers. Several studies attempting to define the underlying pathomechanisms of conjunctivitis in patients with AD treated with dupilumab including the role of goblet cells and cytokine profile of tears are ongoing. A recent review of dupilumab-associated ocular manifestations and management, including a treatment algorithm, has been published.[32]

Face and neck erythema is another adverse effect that was not reported in the phase 3 clinical trials of dupilumab for AD. A number of disparate etiologies have been suggested including allergic contact dermatitis, *Malassezia* yeast infection, adverse drug reaction, rosacea, and psoriasis. In a systematic review, a total of 101 patients from 16 studies were reported to have dupilumab-associated facial or neck

erythema.[33] Of these 101 patients, 52% had baseline AD facial or neck involvement whereas 45% reported different cutaneous symptoms from preexisting AD. Patients were most frequently treated with TCS, topical calcineurin inhibitors, or topical antifungals. Of note, a recent prospective multicenter study of 162 patients with AD found that 85% reported preexisting facial dermatitis before dupilumab treatment, and of this subgroup, 88% reported improvement of their facial dermatitis with dupilumab therapy.[34]

As with any new systemic therapy, dupilumab trials were monitored for any signals of increased infections, though the mechanism of action targeting type 2 immunity suggested the potential to correct both immune and epidermal abnormalities.[26] Data from the large phase 3 trials were reassuring, but reflected only 16 weeks of exposure.[27] The 52-week trial provided further reassurance to clinicians,[29] and ongoing long-term open-extension studies continue to add to the safety profile of this biologic, most recently reporting 4-year safety data.[35] In a randomized, double-blinded, placebo-controlled study in adults with AD, dupilumab did not adversely affect antibody responses to vaccines (Tdap and quadrivalent meningococcal polysaccharide).[36] Recently published data from a blinded, placebo-controlled trial revealed that patients treated with dupilumab had decreased *S aureus* colonization and increased microbial diversity that correlated with clinical improvement of AD and biomarkers of type 2 immunity.[37] In addition, in an analysis of pooled data from 7 randomized, placebo-controlled dupilumab trials in 2932 adults with moderate-to-severe AD, serious infections were reduced with dupilumab, as were bacterial and other non-herpetic skin infections.[38] Although herpes viral infection rates overall were slightly higher with dupilumab than placebo, clinically important herpes viral infections (eczema herpeticum, herpes zoster) were less common with dupilumab. Systemic anti-infective medication use was lower in dupilumab-treated patients.

Expert opinion: Patients with AD starting treatment with dupilumab with a history of any preceding ocular signs or symptoms should be educated on recognizing early signs of ocular surface disease which may include sensation of dryness or grittiness. This can often be adequately treated with lubricating tears while continuing on dupilumab. In some patients, reducing the frequency of injections has allowed for maintaining control of the skin disease while minimizing ocular surface disease symptoms. Case reports of psoriasiform eruptions in patients treated with dupilumab have led to questions related to blocking type 2 immune responses with shift to a type 1 response.[39] However, it is important for clinicians to establish a diagnosis of AD, as patients with other inflammatory diseases including psoriasis have been erroneously treated with dupilumab. In addition, one of the authors of this Update has previously published on the Asian AD phenotype that combines features of AD and psoriasis with increased T_H17 polarization.[40] Note that real-world data from China did not report this problem.[41]

Dupilumab in Adolescent and Pediatric Atopic Dermatitis

A phase 3, randomized, double-blind, parallel-group monotherapy trial conducted in the United States and Canada enrolled 251 adolescent patients aged 12 to 17 years with moderate-to-severe AD.[42] Patients were stratified by severity and body weight to 16 weeks of treatment with 1 of the following 4 regimens: dupilumab 400 mg loading dose, 200 mg every 2 weeks (baseline weight < 60 kg); dupilumab 600 mg loading dose, 300 mg every 2 weeks (baseline weight ≥ 60 kg); dupilumab 600 mg loading dose, 300 mg every 4 weeks; or placebo (all patients received injections every 2 weeks to maintain study blinding). A significantly higher proportion of patients treated with both dupilumab regimens achieved EASI-75 and IGA 0 or 1 at week 16 vs placebo-treated patients. Efficacy of the every 2-week regimen was generally superior to that of the every 4-week regimen. The incidence of conjunctivitis in the dupilumab-treated patients was similar to that found in the adult trials. Self-reported comorbid type 2 diseases in this population included asthma (53.6%), food allergies (60.8%), and allergic rhinitis (65.6%). In a post hoc subgroup analysis of patients whose IGA was more than 1 at week 16, 80.5% of patients receiving dupilumab every 2 weeks vs 23.5% of those on placebo experienced clinically meaningful improvements in AD signs, symptoms, or quality of life at week 16.[43] Clinically meaningful improvement in one or more of 3 domains of signs, symptoms, and quality of life was defined as an improvement of greater than or equal to 50% in EASI, greater than or equal to 3 points in Peak Pruritus NRS (PPNRS), or greater than or equal to 6 points in the Children's DLQI from baseline. These data, similar to the adult AD experience, point to the limitations of using IGA as a primary outcome in AD.[28]

Dupilumab with TCS was subsequently studied in children aged 6 to 11 years with severe AD. In a double-blind phase 3 trial, 367 patients were randomized 1:1:1 to 300 mg dupilumab every 4 weeks, dupilumab every 2 weeks (100 mg every 2 weeks, baseline weight < 30 kg; 200 mg every 2 weeks, baseline weight ≥ 30 kg), or placebo with concomitant medium-potency TCS.[44] At 16 weeks, both the every 4-week and every 2-week dupilumab plus TCS regimens resulted in clinically meaningful and statistically significant improvement in signs, symptoms, and QOL vs placebo plus TCS in all prespecified end points. For every 4-week, every 2-week, and placebo regimens, 32.8%, 29.5%, and 11.4% of patients achieved IGA scores of 0 or 1; 69.7%, 67.2%, and 26.8% achieved EASI-75; and 50.8%, 58.3%, and 12.3% achieved greater than or equal to 4-point reduction in worst itch score, respectively. Optimal dupilumab doses for efficacy and safety were 300 mg every 4 weeks in children less than 30 kg and 200 mg every 2 weeks in children more than or equal to 30 kg. Conjunctivitis and injection site reactions were more common with dupilumab plus TCS than with placebo plus TCS.

LIBERTY AD PRE−SCHOOL was a phase 2/3 trial of children aged 6 months to younger than 6 years with moderate-to-severe AD. In the phase 2 trial, dupilumab pharmacokinetics and safety in patients with severe AD were evaluated.[45] This included an initial cohort of children aged older or equal to 2 years to younger than 6 years followed by a younger cohort aged older or equal to 6 months to younger than 2 years. Pharmacokinetic sampling, safety monitoring, and efficacy assessments were performed during the 4-week period after a single subcutaneous injection of dupilumab, in 2 sequential dosing groups (3 mg/kg and then 6 mg/kg). Treatment with low−to−medium potency TCS was allowed. A total of 40 patients were enrolled (20/age cohort, 10/dose level within a cohort) between December 20, 2017, and July 22, 2019. Within each age cohort, pharmacokinetic exposures after a single injection of dupilumab increased in a greater than dose−proportional manner. At week 3, treatment with 3 and 6 mg/kg dupilumab reduced scores of mean EASI by 44.6% and 49.7% (older cohort) and 42.7% and 38.8% (younger cohort) and mean PPNRS scores by 22.9% and 44.7% (older cohort) and 11.1% and 18.2% (younger cohort), respectively. At week 4, improvements in most efficacy outcomes diminished in both age groups, particularly with the lower dose. The safety profile was comparable with that found in adults, adolescents, and children. Single−dose dupilumab was generally well tolerated and substantially reduced clinical signs/symptoms of AD. Slightly better responses were found in older than younger children. The pharmacokinetics of dupilumab were nonlinear, consistent with previous studies in adults and adolescents. Data from the phase 3 trial were just recently published.[46] Patients were randomly assigned to subcutaneous placebo or dupilumab (weight ≥5 kg to <15 kg: 200 mg; ≥15 kg to <30 kg: 300 mg) every 4 weeks plus low-potency TCS (hydrocortisone acetate 1% cream) for 16 weeks. The primary end point at week 16 was the proportion of patients with an IGA score 0 to 1 (clear or almost clear). The key secondary end point (co-primary end point for the EU and EU reference market) at week

16 was the proportion of patients with EASI-75. There were 162 patients randomly assigned to receive dupilumab (n = 83) or placebo (n = 79) plus topical corticosteroids. Baseline demographics revealed that 77% of the children had severe disease (IGA 4, EASI 34, SCORing Atopic Dermatitis 72). Self-reported atopic comorbidities included 68% food allergies, 44% allergic rhinitis, 41% asthma, and 4% allergic conjunctivitis. Prior systemic therapy for AD included corticosteroids in 19%, CsA 11%, methotrexate 7%, azathioprine 1%, and mycophenolate 1%. There were 11 patients under 2 years of age, and 6 of those patients were treated with dupilumab. At week 16, significantly more patients in the dupilumab group than in the placebo group had IGA 0 to 1 (23 [28%] vs 3 [4%], difference 24% [95% confidence interval (CI), 13–34]; $P < .001$) and EASI-75 (44 [53%] vs 8 [11%], difference 42% [95% CI 29–55]; $P < .001$). Overall prevalence of adverse events was similar in the dupilumab group (53 [64%] of 83 patients) and placebo group (58 [74%] of 78 patients). Conjunctivitis incidence was higher in the dupilumab group (4 [5%]) than the placebo group (0). No dupilumab-related adverse events were serious or led to treatment discontinuation.

Expert opinion: Data on immunization with live viral vaccines in patients on dupilumab are lacking. A Canadian expert group representing pediatrics, dermatology, infectious diseases, and hematology-oncology developed recommendations based on a modified Delphi process including the following 7 statements with evidence summary[47]: (1) Based on available data, dupilumab does not seem to affect the development of protective antibody titers to inactivated vaccines. (2) Dupilumab treatment does not need to be interrupted for administration of inactivated vaccines. (3) For patients on dupilumab treatment, seasonal inactivated influenza vaccination should continue as recommended. (4) Based on available data, live attenuated vaccines should be avoided while on dupilumab. However, such vaccines can be considered on a case-to-case basis weighing the risk of infection vs the risks of vaccination. (5) When live attenuated vaccines are required, they should be given at least 4 weeks before initiation of dupilumab treatment, if possible. However, such vaccines can be considered on a case-to-case basis weighing the risk of infection vs the risks of vaccination. (6) While on dupilumab, measurement of specific antibody levels can be considered to ensure serologic protection after vaccination on dupilumab therapy. (7) There is no evidence to suggest that immunization while on dupilumab causes an exacerbation of AD.

Current Dupilumab Dosing in Atopic Dermatitis

Dupilumab is approved in the United States for patients aged older or equal to 6 months with moderate-to-severe AD uncontrolled by topical prescription medicines or when those medications are not advised (Table 1). Injections can be self-administered, and currently, there is no requirement for any laboratory monitoring. For patients 12 years and older, dupilumab can also be administered by a prefilled pen. The approved dosing regimen in adults 18 years and older is a 600 mg loading dose subcutaneously followed by 300 mg subcutaneously every 2 weeks. In patients 6 months to 17 years, dosing is weight based as per Table 1. Depending on weight, the dosing interval may be every 2 weeks vs every 4 weeks. In addition, for patients in the age range older or equal to 6 months to younger than 6 years, there is no loading dose.

There are limited data on treatment regimens other than every 2-week dosing. In one study, patients who stopped dupilumab treatment before restarting open-label therapy had quick recapture of disease control and no adverse events.[48] However, patients could develop clinically relevant antidrug antibodies (ADAs) with repeated stopping and restarting a biologic, and 2 patients with hypersensitivity reactions on dupilumab in the phase 3 trials had high titers of ADA.[27] A study of adult patients with AD responding to either every 2-week or every 1-week dupilumab treatment who were rerandomized to receive dupilumab every 4 weeks or every 8 weeks found worsening eczema control assessed by EASI for the group, suggesting that most adult patients with AD benefit from continuing on every 2-week dosing regimen.[49] Note that results could be different in a younger population. In addition, patients with AD with comorbidities including asthma and rhinosinusitis seem to respond to treatment with dupilumab and those without these concomitant diseases.[50] Real-world data suggest that dupilumab persistence (95% CI) at 6 and 12 months was 91.9% (90.7%-93.2%) and 77.3% (75.0%-79.7%), respectively.[51]

Expert opinion: A current clinical challenge is to identify patients who would maintain disease control with less frequent dosing. This may be especially relevant given indication for dupilumab in a younger AD population. It may be reasonable (though off-label) to taper dupilumab to an every 3- or 4-week dosing regimen in a patient who has been clear/almost clear for at least 6 to 12 months, while monitoring for relapse.

Tralokinumab

IL-13 is a cytokine predominantly produced by T_H2 and type 2 innate lymphoid cells (ILC2s), but also, to a lesser extent, by mast cells, basophils, eosinophils, natural killer cells, macrophages, dendritic cells, and monocytes.[52] IL-13 plays a pivotal role in the production and maintenance of the T_H2 inflammatory reaction and in the dysfunction of the epidermal barrier.[53,54] The overexpression of IL-13 leads to the down-regulation of key proteins of the epidermis (such as filaggrin, loricrin, and involucrin) and of its lipids causing dysfunction of the epidermal barrier. IL-13–mediated tissue inflammation promotes fibrotic skin remodeling and skin thickening through the recruitment of fibroblasts and a subsequent increase in collagen deposition. IL-13 also decreases the expression of antimicrobial peptides and leads to an increased susceptibility to skin infections, particularly from *S aureus*. At the same time, IL-13 sensitizes neurons considered to be pruritogenic and seems to be directly linked to pruritus.[55]

Given the importance of IL-13 in epidermal hyperplasia and fibrosis, it likely plays a more important role in local skin inflammation than IL-4.[56-58] Two selective IL-13 inhibitors (lebrikizumab and tralokinumab) have undergone clinical trials. Tralokinumab was approved by the FDA on December 28, 2021, for the treatment of moderate-to-severe AD in adult patients (≥18 years) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. A recent study also found tralokinumab monotherapy had superior efficacy to placebo for all primary and key secondary end points in pediatric patients aged 12 to 17 years with moderate-to-severe AD. Most of the responders at week 16 maintained efficacy at week 52 without any use of TCS, and a substantial proportion of patients in the open-label phase achieved progressive control at week 52, with the proportion of IGA 0/1 and EASI-75 responders increasing over time. Tralokinumab was well tolerated in 52 weeks in this pediatric population, with a safety profile consistent with that found in adults.[59]

Tralokinumab is a human immunoglobulin (Ig)G4 monoclonal antibody that specifically binds to human IL-13 in an epitope that overlaps with the binding site of the IL-13 receptor α1 and α2 subunits (IL-13Rα1 and IL-13Rα2). Although it prevents binding to both IL-13Rα1 and IL-13Rα2, the binding affinity of IL–13 to the IL–13Rα2 is higher than that for tralokinumab; therefore, unbound IL–13 can still bind to the IL–13Rα2. IL-13Rα2, however, has no significant cytoplasmic domain and does not seem to function as a signal mediator. It is believed to act as a decoy receptor that internalizes the IL-13 found in excessive circulating levels.[60]

Tralokinumab inhibits the bioactivity of IL-13 including the release of proinflammatory cytokines, chemokines, and IgE.

Table 1
Comparison of Approved Systemic Medications for Moderate-to-Severe AD

Medication	Dupilumab	Tralokinumab	Abrocitinib	Upadacitinib
Mechanism	MoAb vs IL-4 receptor alpha	MoAb vs IL-13	JAK1 inhibition	JAK1 inhibition
Age indicated	≥6 mo	≥18 y	≥12 y	≥12 y
Dosage and route	≥18 y 600 mg 300 q 2 wk 6 mo-17 y, weight-based dosing ≥60 kg 600 mg × 1 300 mg q2w 30 kg to <60 kg 400 mg × 1 200 mg q2w 15 kg to <30 kg 600 mg × 1 300 mg q4w ≥6 mo to <6 y 15 kg to <30 kg 300 mg q4w (no loading dose) 5 kg to <15 kg 200 mg q4w (no loading dose)	600 mg 300 mg q 2 wk (SQ) After 16 wk, option to decrease to 300 q 4 wk if clear/almost clear	100 mg OD Option to uptitrate to 200 mg OD after 12 wk if inadequate response 50 mg dose in pts with moderate renal impairment or treated with inhibitors of CYP2C19 or poor metabolizers of CYP2C19	15 mg OD in pts weighing ≥40 kg Uptitrate to 30 mg OD if inadequate response in patients <65 y
	200 and 300 mg syringes, and autoinjectable pens SUBQ	150 mg syringes SUBQ	100 and 200 mg tabs PO	15 and 30 mg tabs PO
Adverse reactions	Conjunctivitis, injection site reactions	Conjunctivitis, injection site reactions	Infections, mortality, thrombosis malignancy, MACE	Infections, mortality, thrombosis malignancy, MACE
Lab monitoring	None	None	TB, CBC (baseline and after 4 wk and with increased dose), CMP, hepatitis B and C, pregnancy, lipid panel after 4 wk Avoid if absolute lymphocyte count < 500 cells/mm^3, absolute neutrophil count < 1000 cells/mm^3, Hb < 8 g/dL, platelets < 150,000/mm^3	TB, CBC (baseline and after 4 wk and with increased dose), CMP, hepatitis B and C, pregnancy, lipid panel after 12 wk Avoid if absolute lymphocyte count < 500 cells/mm^3, absolute neutrophil count < 1000 cells/mm^3, Hb < 8 g/dL.
Drug-drug interaction			CYP450 (2C19)	CYP450 (3A4)
Immunization	As per product insert: Patients should be up to date with all immunizations before initiating therapy. Avoid use of live vaccines in patients treated with dupilumab.	As per product insert: Complete all age-appropriate immunizations before initiating therapy; avoid administering live vaccines during therapy. Limited data regarding co-administration with nonlive vaccines suggest similar antibody responses in tralokinumab-treated and placebo-treated patients.	Update immunizations before starting therapy, consider H zoster vaccine for pts aged ≥19 y No live vaccines	Update immunizations before starting therapy, consider H zoster vaccine for pts aged ≥19 y No live vaccines

Abbreviations: CBC, complete blood cell count; CMP, comprehensive metabolic panel; CYP, cytochrome P450; Hb, hemoglobin; IL, interleukin; JAK, Janus kinase; Lab, laboratory; MACE, major adverse cardiovascular event; MoAb, monoclonal antibody; OD, once a day; PO, orally; pts, patients; q, every; q2w, every 2 weeks; q4w, every 4 weeks; SQ, subcutaneously; SUBQ, subcutaneously; tabs, tablets; TB, tuberculosis.

Tralokinumab was associated with decreased concentrations of T_H2 and T_H22 immunity biomarkers in the blood, such as thymus and activation-regulated chemokine (TARC/CCL17), periostin, IL-22, lactate dehydrogenase (LDH), and serum IgE. It decreased the expression of keratin 16 and Ki-67 in AD skin and up-regulated protein expression of loricrin.[61] Tralokinumab also suppressed expression of genes in the T_H2 pathway, including CCL17, CCL18, and CCL26, and markers of T_H17- and T_H22-regulated genes in lesional skin.[62]

Thus, neutralizing IL-13 cytokine with tralokinumab modulates type 2 immunity.[61] In addition, tralokinumab treatment shifts skin barrier markers toward a nonlesional profile.[62] Tralokinumab treatment shifts skin natural moisturizing factors and lipid parameters from a lesional to a nonlesional skin profile in adolescents with AD. The drug substantially increased natural moisturizing factor content and improved lipid composition by increasing proportion of EOS-ceramides and other ceramides with long-chain fatty acids, decreasing sphingomyelins and lysophosphatidylcholines with short-chain fatty acids thus improving the skin barrier.[63]

Early Efficacy, Sustainability, Durability, and Progressive Improvement

Tralokinumab studied in 3 phase III clinical trials reached its primary end points at week 16 (ECZTRA 1 and 2 in monotherapy and ECZTRA 3 with concomitant TCS), with response maintained over time.[64,65] Tralokinumab combined with TCS was found to have early and sustained efficacy and safety in a 12-week, phase IIb trial in moderate-to-severe AD. These are the first pivotal phase III trials revealing that by specifically targeting IL-13 alone, patients can achieve significant improvements in AD signs and symptoms and quality of life and maintain these improvements over time without the requirement for TCS. These trials provide evidence that tralokinumab offers a long-term, well-tolerated treatment option for patients with moderate-to-severe AD.[64]

Patients with IGA 0/1 or EASI-75 response at week 16 were found to have sustained responses at week 52 and week 32 in ECZTRA 1, 2 and ECZTRA 3, respectively. Findings are similar in efficacy and safety in patients with moderate-to-severe AD across the North American and non-North American trial populations. Thus, tralokinumab was well tolerated in ethnically diverse North American populations, suggesting no special treatment considerations may be required for this subpopulation.[66] Importantly, this analysis reveals that additional patients achieved the clinical response targets preferred by regulatory authorities (IGA 0/1 or EASI-75) beyond week 16, indicating that response rates progressively improve over time with continued tralokinumab therapy.[67]

More than 50% of patients who achieved clinical responses at week 16 with tralokinumab every 2 weeks maintained that response to week 52 without any rescue medication, including TCS, and 39% to 51% of patients-maintained response when receiving tralokinumab every 4 weeks. Unexpectedly, a proportion (21% to 47%) of tralokinumab responders at week 16 who were rerandomized to placebo-maintained responses at week 52. Retained response over 36 weeks without active maintenance treatment or TCS suggests that tralokinumab could induce sustained diminution of symptoms with interruption of therapy and skin normalization for some patients. It has previously been found that IL-13 expression is much lower in nonlesional than lesional AD skin.[53,57,68] It is therefore possible that after a period of clear or almost clear skin achieved with tralokinumab every 2 weeks, IL-13–mediated inflammation in the skin may have been extinguished, altering the natural disease course. Support for reversal of IL-13–associated skin abnormalities with tralokinumab was provided by the observed greater reduction in skin colonization with *S aureus*, which was consistent with observations in the phase II study.[69] In addition to decreasing *S aureus* colonization, fewer skin infections requiring systemic treatment and a lower frequency of eczema herpeticum were found with tralokinumab. These findings may be due to the effect of tralokinumab on improving skin barrier integrity.

Patient-Reported Outcomes

The range of both clinician- and patient-reported outcomes reveals progressive and sustained improvements using tralokinumab every 2-week and every 4-week treatment regimens, maintaining an EASI-75 response at week 32. Furthermore, the improvements in EASI-90 response rates and DLQI were similar between the every 2-week and every 4-week treatment arms during weeks 16 to 32.

PROs are beneficial to patients because AD symptom relief is a key treatment concern for patients. Tralokinumab with or without TCS was found to have early and clinically meaningful improvements vs placebo in several PROs. In a study of 1596 and 380 patients randomized in ECZTRA 1 and 2 and ECZTRA 3, respectively, early separation from placebo was observed in percentage improvement in worst average daily pruritus NRS score (week 1, ECZTRA 1 and 2; week 2, ECZTRA 3) and from day 2 in ECZTRA 1 and 2 daily data. More tralokinumab-treated patients achieved clinically meaningful improvements (=4 points) in NRS by week 2 (ECZTRA 1 and 2) or week 3 (ECZTRA 3) vs placebo. Improvements in eczema-related sleep NRS were found within 2 weeks (week 1, ECZTRA 1 and 2; week 2, ECZTRA 3), supported by similar improvements in other sleep measures. Meaningful changes in DLQI were observed from week 2 (ECZTRA 1 and 2).[70]

Tralokinumab is for subcutaneous use supplied as a single-dose, prefilled, latex-free syringe with a needle guard in a siliconized type 1 clear glass syringe. Each prefilled syringe delivers 150 mg tralokinumab/1 mL, and the inactive ingredients are acetic acid (0.3 mg), polysorbate 80 (0.1 mg), sodium acetate trihydrate (6 mg), sodium chloride (5 mg), and water. Dosing is 600 mg (four 150 mg injections) as initial dose followed by 300 mg every 2 weeks (Table 1). Different from dupilumab is the option of reducing frequency of injections to 300 mg every 4 weeks that may be considered for patients below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment. Similar to dupilumab, before tralokinumab initiation, it is recommended to complete all age-appropriate vaccinations and to avoid use of live vaccines during the treatment.

Safety Profile

Tralokinumab exhibited good safety profiles, with adverse effects usually being comparable between the control and treatment groups. Adverse reactions include upper respiratory tract infections, conjunctivitis, injection site reactions, and eosinophilia. Conjunctivitis, including allergic conjunctivitis, was reported in 7.5% of subjects treated with tralokinumab 300 mg every other week and in 3.1% of subjects treated with placebo in the initial treatment period of up to 16 weeks in the pool of 5 trials.[71] In most cases, conjunctivitis resolved at the end of the initial treatment period. Conjunctivitis led to discontinuation of treatment in 2 subjects. Similar incidence of conjunctivitis was reported during the maintenance treatment period of the monotherapy trials; 8.9% of subjects treated with tralokinumab 300 mg every 2 weeks and 6.3% of subjects treated with tralokinumab 300 mg every 4 weeks. Tralokinumab-treated subjects had a greater mean initial increase from baseline in eosinophil count compared with placebo with the mean and median increase from baseline to week 4 of 190 and 100 cells/mcL, respectively. This increase in eosinophils declined to baseline level with continued treatment. Marked eosinophilia (>5000 cells/mcL) in the initial treatment period of up to 16 weeks was reported in 1.2% in the tralokinumab-treated subjects and 0.3% in the placebo. Across all trial periods, the ADA incidence for subjects who received tralokinumab was 4.6%; 0.9% had persistent ADA and 1.0% had neutralizing antibodies. However, no clinically meaningful differences in the pharmacokinetics, safety, or efficacy of tralokinumab were observed in patients who tested positive for anti-tralokinumab antibody (including neutralizing antibodies).

Expert opinion: Noteworthy observations from the tralokinumab clinical trials include the following: Early clinically meaningful improvement in pruritus reported within 1 to 2 weeks with some patients reporting as early as day 2. Sustained and maintained efficacy was found with tralokinumab with or without TCS. Response rates progressively improved over time beyond week 16. A subset of tralokinumab responders at week 16, likely those with more intermittent or moderate rather than severe disease, can be maintained not only on every 4-week dosing, but even longer. Patients to consider initiating tralokinumab treatment could be patients who failed dupilumab before starting oral JAK inhibitors or immunosuppressants, patients who have facial dermatitis and/or significant conjunctivitis before dupilumab or worsening of these symptoms after initiating dupilumab, and who report rare or unusual adverse effects after starting dupilumab, such as for example, joint pain, vasculitis, severe headache, or dizziness.

Janus Kinase Inhibitors

Ruxolitinib

Topical ruxolitinib 1.5% cream is the first topical therapy in the JAK inhibitor family to be approved in United States for AD. It is currently approved for mild-to-moderate AD in patients 12 years and older with affected areas up to 20% of BSA. The approval was based on the Topical Ruxolitinib Evaluation in AD (TRuE-AD) trials, which consisted of 2 phase 3 identical double-blind, randomized,

vehicle-controlled trials that enrolled a total of 1249 subjects with mild-to-moderate AD.[72] The subjects were 12 years and older with an IGA score of 2 to 3 and a BSA involvement of 3% to 20%. The subjects were randomized 2:2:1 to twice-daily application with ruxolitinib 0.75% cream, ruxolitinib 1.5% cream, or vehicle cream for 8 weeks. The primary end point was the success of IGA score of 0 to 1 and greater than or equal to 2 grade at week 8. Secondary end points include EASI-75 and 4-point reduction in itch NRS score (NRS-4). Treatment success at week 8 for ruxolitinib 0.75% vs ruxolitinib 1.5% vs vehicle in both trials was as follows: IGA: 39% to 50% vs 51% to 54% vs 8% to 15%; EASI-75: 52% to 56% vs 62% to 62% vs 14% to 25%; NRS-4: 40% to 43% vs 51% to 52% vs 15% to 16%. Adverse events that were greater than or equal to 1% and greater in ruxolitinib-treated groups than vehicle were nasopharyngitis, bronchitis, ear infection, increased eosinophil count, urticaria, diarrhea, folliculitis, tonsillitis, and rhinorrhea. Adverse events that occurred less than 1% of subjects in the ruxolitinib-treated groups but none in the vehicle group were neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, staphylococcal infection, and acneiform dermatitis. As with other JAK inhibitors, topical ruxolitinib 1.5% cream carry a boxed warning of serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis.

Expert opinion: There are few direct comparative studies between topical JAK inhibitors vs currently available topical treatments such as TCS and TCI. In a phase 2 trial, both ruxolitinib 1.5% cream and triamcinolone 0.1% cream attained nearly equal efficacy in EASI improvement at week 12 (84.9% vs 86.8%). However, the anti-itch effect was 3 times greater for ruxolitinib 1.5% cream and 2 times greater for triamcinolone 0.1% cream vs placebo, suggesting that ruxolitinib 1.5% cream may have a slight advantage in patients with significant pruritus.[73] The current indication for topical ruxolitinib 1.5% cream is limited to 20% or less of BSA in patients with mild-to-moderate AD because of potential systemic absorption. However, clinicians may need to treat with this medication off-label in patients with more severe disease with greater BSA involvement. A recent open-label study enrolled 41 adolescents and adults with mild-to-severe AD involving 25% BSA and higher.[74] Patients applied ruxolitinib 1.5% cream twice a day for 28 days to all AD lesions. At 28 days, if there was no safety concern, subjects continued the medication for another 28 days. The mean BSA of the cohort was 31.2% (range: 25% to 90%) and mean EASI score was 20.8. A total of 6 subjects had treatment-emergent adverse effects related to the treatment: 1 subject had neutropenia, 3 subjects had elevated transaminase levels, 1 had dyspnea, and 1 had hemoglobin decrease. One subject had lower extremity abscess, but this was considered unrelated to the treatment. Regarding the pharmacokinetic data, the mean *Css* (concentration at steady state) during the 28-day period was 104 nM, which is significantly higher than 35.7 nM in the TRuE-AD studies discussed previously.[75] However, both are still significantly below 281 nM, which is the half-maximal inhibitory concentration for thrombopoietin-stimulated phosphorylation of STAT3, an indication of bone marrow suppression. The *Css* for subjects with BSA 25% to 39% vs greater than or equal to 40% was 30.9 vs 274 nM, respectively, further supporting higher amount of medication application correlates with an increased plasma concentration of ruxolitinib. The proportion of subjects achieving EASI-75 at days 28 and 56 were 79.5% and 94.6%, respectively. Although the study is reassuring that adverse effects were mild to moderate and plasma concentration of ruxolitinib was well below the bone marrow suppression level, long-term controlled studies are needed to confirm the safety of ruxolitinib cream in patients with more severe AD with higher BSA involvement.

Abrocitinib

A number of phase 3 clinical trials were performed with abrocitinib in adolescents 12 years and older and adult patients with moderate-to-severe AD, who had prior inadequate response or contraindication to topical treatments. These included the monotherapy trials JADE Mono 1 and 2 studies with daily oral abrocitinib 100, 200 mg vs placebo.[76] Patients were assigned 2:2:1 to 100 mg abrocitinib, 200 mg abrocitinib, or placebo daily for 12 weeks. The co-primary end points were the proportion of patients who had achieved an IGA of 0/1 and EASI-75 met at week 12. Additional studies evaluated abrocitinib 200 and 100 mg vs dupilumab 300 mg every other week in the JADE compared with phase 3 study. The primary end point was similar to the monotherapy studies, with secondary end points at week 2 of itch NRS response and IGA of 0/1 and EASI-75 at week 16. Although the 200 mg (but not the 100 mg abrocitinib) was superior to dupilumab in terms of itch response at week 2, most of the other end points did not reveal significance when comparing abrocitinib and dupilumab. Nausea was the most common adverse event reported by 11.1% of patients with acne noted in 6.6% with the 200 mg dose. Of note, topical treatments were allowed during the study, perhaps attenuating the differences between abrocitinib and dupilumab.[77] Although differences were found early in the treatment, dupilumab largely caught up in terms of efficacy toward week 16. Nevertheless, in JADE extend, 80% and 67.7% prior dupilumab nonresponders (as evaluated by ≥ 75% in EASI) achieved greater than or equal to EASI-75% responses with abrocitinib 200 mg and 100 mg and greater than or equal to 4-point improvement in PPNRS in 77.3% and 37.8%, respectively. Most common AEs in abrocitinib-treated patients were nasopharyngitis, nausea, acne, and headaches. Conjunctivitis was not a frequent occurrence on abrocitinib as compared with dupilumab.[78] This study reveals the benefit of abrocitinib in dupilumab nonresponders. More recently, Reich et al[79] evaluated data from JADE COMPARE trial applying stringent efficacy end points. At week 16, 48.9%, 38.0%, and 38.8% of the abrocitinib 200 mg, 100 mg, and dupilumab groups, respectively, achieved greater than or equal to 90% improvement from baseline in EASI vs 11.3% placebo; 14.9%, 12.6%, and 6.5% achieved IGA 0 (clear) vs 4.8% placebo; 29.7%, 21.6%, and 24.0% achieved DLQI 0/1 (no/minimal impact on quality of life) vs 10.6% placebo; and 57.1%, 44.5%, and 46.1% achieved Night Time Itch Scale severity 0/1 (no/minimal night-time itch) vs 31.9% placebo. Kaplan-Meier median time to greater than or equal to 90% improvement from baseline in EASI was 59, 113, and 114 days in the abrocitinib 200 mg, 100 mg, and dupilumab groups, respectively, and was not evaluable for placebo; median time to PPNRS 0/1 (no/very minimal itch) was 86 and 116 days for abrocitinib 200 mg and dupilumab groups, respectively, and was not evaluable for abrocitinib 100 mg and placebo groups.

Expert commentary: Although JAK inhibitors have a box warning and their use needs to be monitored, there is a benefit to their use in patients who do not want an injectable therapy and want an oral medication that allows flexibility of dosing and in patients who failed or could not sustain response on dupilumab or other biologics, including those patients who have adverse effects on dupilumab (eg, conjunctivitis, occurrence or exacerbation of facial rashes, or arthralgias). Furthermore, patients with more moderate disease who do not want to be on a systemic medication continuously may be able to take an oral JAK inhibitor more intermittently, rather than stop and restart a biologic, which could be problematic (eg, development of ADA). Because JAK1 inhibition with abrocitinib targets more than one cytokine pathway, one can also postulate that JAK inhibitors may likely be able to control most AD subtypes, which reveal skewing of more than just the T_H2 pathway. However, careful monitoring needs to be instituted and particular caution should be exercised in patients older than 65 years of age (Table 1). Note the recent FDA approval of

abrocitinib 100 mg daily for patients 12 years and older with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. If an inadequate response is not achieved with abrocitinib 100 mg orally once daily after 12 weeks, consider increasing dosage to 200 mg orally once daily. Discontinue therapy if inadequate response is seen after dosage increase to 200 mg once daily.

Upadacitinib

Multiple phase 3 clinical trials of upadacitinib were performed in patients with moderate-to-severe AD. Measure Up 1 and Measure Up 2 were identically designed, multicenter, double-blind, placebo-controlled, randomized clinical trials including adolescents (aged 12-17 years) and adults (aged 18-75 years) with moderate-to-severe AD who had prior inadequate response or contraindication to prescription topical therapies.[80] Patients were randomly assigned (1:1:1) to receive oral upadacitinib 15 mg, 30 mg, or placebo once-daily monotherapy for 16 weeks, that is no prescription topical therapy allowed. In addition, AD Up was a similarly designed multicenter, double-blind, placebo-controlled, randomized clinical trials of upadacitinib 15 mg, 30 mg, or placebo once daily in combination with TCS for 16 weeks.[81] Co-primary end points of EASI-75 and vIGA-AD0/1 response at week 16 and all secondary end points were met in all 3 studies.[80,81] Patients treated with upadacitinib had rapid clinical responses across all 3 studies.

Another phase 3, randomized, multicenter trial (Heads Up) compared oral upadacitinib 30 mg once daily with dupilumab 600 mg loading dose followed by 300 mg every other week in adults (18-75 years) with moderate-to-severe AD. The results revealed that 71% of patients treated with upadacitinib achieved the primary end point of EASI-75 compared with 61% of patients treated with dupilumab at week 16 ($P = .006$). In addition, upadacitinib had superiority vs dupilumab for all ranked secondary end points, including early improvements in itch and skin clearance.[82] Furthermore, patients treated with upadacitinib had much faster clinical responses than those with dupilumab. Yet, over time, the efficacy of dupilumab caught up to upadacitinib for several end points, for example, EASI-75 and PPNRS4 responses. Patients treated with upadacitinib had notably high rates of achieving robust clinical end points, such as EASI-90 and EASI-100 and achieving PPNRS scores of 0/1. For these more robust end points, upadacitinib had greater efficacy compared with dupilumab at all time points evaluated. The most frequently associated adverse events found with oral JAK inhibitor use in patients with AD included upper respiratory infections, headache, nausea, diarrhea, and elevated blood creatinine phosphokinase levels. For upadacitinib, a nonspecific acneiform eruption was frequently observed. Herpes simplex infections were observed with abrocitinib and baricitinib. Overall, JAK inhibitors did not lead to higher rates of discontinuation because of adverse events compared with placebo in patients with AD.

Expert opinion: The US FDA applied black box warnings to all oral JAK inhibitors for major adverse cardiovascular events, venous thromboembolism, malignancy, and serious infections based on safety concerns regarding use of tofacitinib in rheumatoid arthritis (RA) in a noninferiority trial compared with tumor necrosis factor-alpha inhibitors in adults aged 50 years or older with at least one cardiovascular risk factor. Even in patients with RA, these adverse events are still rare. Furthermore, these rare but serious adverse events occur less frequently with abrocitinib and upadacitinib in AD than RA. Regardless, use of JAK inhibitors in patients with risk factors for these serious adverse events should be carefully weighed in treatment discussions (Table 1).

Oral JAK inhibitors are indicated for patients with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. This would include treatment with systemic immunosuppressives such as cyclosporin or methotrexate not approved for AD in the United States, but also systemic steroids, which although approved are strongly discouraged for chronic use including chronic intermittent treatment in the AD Yardstick or AAD Guidelines.[83]

To minimize risk of adverse events, it is recommended to use the lowest possible dose to achieve and maintain clinical response. Two different approaches can be used to accomplish this goal. According to the US FDA recommendations, lower doses of abrocitinib 100 mg or upadacitinib 15 mg should be used as starting doses. If patients do not achieve satisfactory clinical response, the dose can be increased to abrocitinib 200 mg or upadacitinib 30 mg. Once patients achieve satisfactory clinical response, the dose can be lowered to use the lowest possible maintenance dose. An alternative (currently off-label in the United States) approach would be to start patients at higher doses of abrocitinib 200 mg or upadacitinib 30 mg to achieve a rapid clinical response and then taper to lower doses of abrocitinib 100 mg or upadacitinib 15 mg for maintenance. This approach is supported by data from the JADE-REGIMEN study that induced clinical responses using abrocitinib 200 mg monotherapy and sustained clinical responses in a large proportion of patients who were randomized to receive abrocitinib 100 mg maintenance dosing.[84] Although use of upadacitinib was not formally studied using this approach, it is likely that the results of JADE-REGIMEN are generalizable to upadacitinib at a high level. This approach may be particularly useful in patients who have very severe disease at baseline and those who require very rapid clinical responses.

In the United States and Canada, recombinant zoster vaccine is approved for adults 19 years and older who have weakened immune systems because of disease or therapy.[85] As such, we recommend that all patients aged 19 years or older be vaccinated with recombinant zoster vaccine before initiating oral JAK inhibitors.

There is currently a dearth of evidence to identify optimal management strategies for the acneiform eruption of upadacitinib. However, in our anecdotal experience, the acne is generally not a major concern for patients, often spontaneously improves with continued use of upadacitinib, and can be mitigated by reducing the dose of upadacitinib and conventional acne therapies, including topical antibiotics and retinoids.

In a systematic review and meta-analysis of randomized clinical trials of 12 to 16 weeks of duration for systemic or biologic monotherapy (no concomitant prescription topical therapy allowed) in moderate-to-severe AD, upadacitinib 30 mg followed by abrocitinib 200 mg led to highest clinical responses (IGA clear or almost clear, EASI-75, and 4-point improvement in PPNRS).[86] Upadacitinib 15 mg daily was associated with considerably higher clinical responses than dupilumab at week 16, whereas abrocitinib 100 mg daily was associated with similar clinical responses to dupilumab 600 mg loading dose and 300 mg every other week. Baricitinib 4 mg and 2 mg daily (note: baricitinib is currently not approved in the United States for AD) and tralokinumab 300 mg every 2 weeks were associated with lower rates of clinical response than dupilumab in this network meta-analysis, though head-to-head trials are lacking for these agents. All 3 oral JAK inhibitors (abrocitinib, baricitinib, and upadacitinib) were associated with higher rates of clinical response than dupilumab at week 2.

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