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Review Article

A Clinician's Guide to Counseling about Prescription Medication Risks in Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic inflammatory skin condition that can cause intense itching and recurrent eczematous lesions. It affects one in five children worldwide and often persists into adulthood, requiring management of both acute flares as well as more proactive strategies. With the emergence of new and more powerful therapeutics in the last decade, the safety and efficacy of these treatments have been under increased scrutiny. Accordingly, the complexity for selection of an appropriate medication has greatly increased. This review aims to clearly outline the risks of medications so that clinicians can communicate them to their patients more effectively. This review will focus on the most commonly used therapies and selected therapies in late-stage development including topical corticosteroids, topical calcineurin inhibitors, Janus kinase inhibitors, and biologics.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition that can cause intense itching and recurrent eczematous lesions.[1] It affects one in five children worldwide and often persists into adulthood.[2] Although there is no existing cure for AD, new therapeutic agents have been launched and many more are in development. Newer medications must adhere to more stringent modern guidelines and thus are often more thoroughly evaluated than medications from decades ago.[3] This produces a vast amount of information for a physician to interpret before recommending the most appropriate treatment to patients. Importantly, it also creates an imbalance between older medications with less rigorous evidence and reporting, and newer therapies that are much more standardized: this can make it nearly impossible to compare risks and benefits. With a complex and ever-changing breadth of prescription medications for AD, it is more important than ever for clinicians to understand the safety and efficacy of new treatments for AD in a timely manner. This review will focus on the most commonly used therapies (Table 1) and selected therapies in late-stage development including various topical therapies (Table 2), Janus kinase (JAK) inhibitors (Table 3), and biologics (Table 4).

TOPICAL AGENTS

TOPICAL CORTICOSTEROIDS

Topical corticosteroids (TCS) serve as first-line treatments for AD flares.[4] Although many patients find TCS effective in managing their AD, widespread concerns about the safety of TCS have contributed to poor adherence and subsequent worsening of AD and quality of life.[5] Chronic, long-term use of TCS can also cause adverse effects such as atrophy, acne, telangiectasia, striae and purpura, focal hypertrichosis, hypopigmentation, and perioral dermatitis.[6,7] They also may result in subclinical barrier disruption, such that there may be increases in percutaneous absorptions and systemic adverse events. TCS also has the potential for systemic side effects such as adrenal suppression, poor growth, hypertension, hyperglycemia, insulin resistance, and cataracts.[6]

A recent systematic review regarding the safety of topical corticosteroids in atopic eczema by Axon et. al. (2021) may shed light on the incidence of TCS-associated adverse events and allow clinicians to accurately counsel patients on medication risks of AD agents. When comparing once daily TCS to twice daily application, no cases of skin thinning were observed in a 3-week randomized controlled trial

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Table 1. Conventional Therapies for Atopic Dermatitis and Side Effects to Monitor in Patients

Treatment	Side Effects	Lab Monitoring and Other Notes
Topical Corticosteroids	Chronic, long-term use of TCS can cause adverse effects such as atrophy, acne, telangiectasia, striae, purpura, focal hypertrichosis, hypopigmentation, and perioral dermatitis. Systemic adverse events can include adrenal suppression, poor growth, hypertension, hyperglycemia, insulin resistance, and cataracts. Topical steroid withdrawal: burning pain, severe itch, and desquamation after cessation of TCS. Presents as "red sleeve," "headlight sign," or "elephant wrinkles." Associated with sensitive areas (face/genitals), use of TCS without periodic breaks, and/or use of TCS with escalating potency.	Unsupervised use of TCS can result in local and systemic adverse events. Duration of treatment should be limited to a maximum of 2 to 4 weeks of continuous use, regardless of potency. Guidelines to limit adverse events include use of lower-potency steroids, morning-only applications, alternate-day treatment, and decreasing the extent of occlusion.
Topical Calcineurin Inhibitors	Burning pain (32.1%) and pruritus (12.8%). NOTE: No evidence of increased cancer risk in children with atopic dermatitis using topical tacrolimus 0.03% or 0.1% ointment across a 10-year period.	The long-term safety of topical calcineurin inhibitors has not yet been established. Therefore, continuous and long-term topical use of calcineurin inhibitors should be avoided or entirely limited to areas of atopic dermatitis.
Cyclosporine	Use is recommended for a maximum of 2 years due to its immunosuppressive nature. Adverse effects include infection, nephrotoxicity, hypertension, hepatotoxicity, paresthesia, tremors, headaches, nausea, diarrhea, myalgias, electrolyte imbalance, hyperlipidemia, gingival hyperplasia, and hypertrichosis.	Weeks 2, 4, 6, 8, 10, 12: blood pressure and renal function Weeks 4, 8, 12: electrolytes, complete blood counts, liver function tests, lipid panels, and uric acid >Week 12: monthly monitoring of above Contraindicated: live vaccines
Methotrexate	Infections, liver and bone marrow toxicity, nausea, fatigue, headache, pulmonary toxicities, and drug interactions.	Week 1: complete blood count and liver functions Dose increase, after 1-2 weeks: complete blood count and liver function Maintenance dose: complete blood counts and liver function tests every 3-6 months. Annually: renal function (x1-2/year) Hepatoxicity should be screened for at cumulative doses of 3.5 to 4.0 grams. Initial screening method: non-invasive vibration controlled transient elastography. Gold method: biopsy. Contraindicated: live vaccines
Azathioprine	Infection, gastrointestinal disturbances, liver dysfunction, and leukopenia. In patients with inflammatory bowel disease, AZA can increase the risk of non-melanoma skin cancer and lymphoma	Month 1, 2: complete blood counts, renal function tests, and liver function tests (x2/month) Month 3-6: complete blood counts, renal function tests, and liver function tests (x1/monthly) >Month 7: complete blood counts, renal function tests, and liver function tests (every other month) Contraindicated: live vaccines

(RCT) with 94 adults. No significant differences in telangiectasia, folliculitis, or burning/itching/stinging were observed between once or twice daily TCS application across 4 RCTs involving 740 adolescents/adults over a 4 to 16 week time period.[5] However, a small proportion of patients on TCS did experience skin thinning and transient biochemical adrenal suppression (cortisol). An analysis of two RCTs of 2 to 4 weeks comparing TCS vs. emollient/vehicle demon-

strated a pooled incidence (n=305) of 2% for skin thinning, while a meta-analysis of 4 RCTs comparing TCS vs. topical calcineurin inhibitors (TCI) (n=2068) demonstrated an incidence of 0.4% for skin thinning with TCS use. A meta-analysis of 11 uncontrolled observation studies (up to 4 weeks of treatment) reported biochemical adrenal suppression (cortisol levels) in 20/522 children (3.8%) with any potency TCS. However, no clinical symptoms or signs of adrenal suppression were observed, and cortisol levels returned to normal after TCS were discontinued.[5]

Some patients on long-term TCS therapy may be concerned with topical steroid withdrawal (TSW), a condition denoted by burning pain, severe itch, and skin desquamation after cessation of TCS. A systematic review of TSW in AD patients by Hajar et. al. suggests TSW is associated with TCS use in sensitive areas (face/genitals), continued use without periodic breaks and/or with escalating potency.[8] Although a diagnostic criteria for TSW does not currently exist, suggestions of red skin, "red sleeve," "headlight sign," and "elephant wrinkles" have been proposed by Sheary et. al. after a retrospective cohort study of 55 patients.[9] Thus, patients with TSW may present with rebound eruptions to the upper or lower limbs ending at the margin of the dorsal and palmar border ("red sleeve," n=22/55); an erythematous face with a clear nose and perioral skin ("headlight sign," n=29/55); and thickened skin with reduced elasticity on the anterior knees or extensor elbows ("elephant wrinkles," n=31/55).[9]

TOPICAL CALCINEURIN INHIBITORS

Topical calcineurin inhibitors (TCI) serve as second-line treatments for AD flares, particularly in delicate areas such as the face, neck, eyelids, skin folds, and genitalia. Although TCI treatment has been demonstrated to be effective in managing AD, the FDA assigned a 'black box' warning to TCIs in 2005, indicating serious or life-threatening risks, due to insufficient data regarding long-term safety and risk of cancer. These 'black box' warnings have made TCI prescriptions for patients in need incredibly challenging. However, these warnings may be retracted given a recent large study (APPLES) by Paller et. al. that found no evidence of increased cancer risk in children with AD (n=7954) using topical tacrolimus 0.03% or 0.1% ointment across a 10-year period.[10] Six incident cancers were identified in the study, but their incidence closely matched the expected rate in age- and sex-matched populations from countries represented in the study. Each incident presented with unique etiologies, and the timing of their diagnosis was not associated with tacrolimus or enrollment in APPLES. A meta-analysis of 14 RCTs indicates that adverse events from treatment with TCIs include burning pain (32.1%) and pruritus (12.8%).[11]

CRISABOROLE AND DIFAMILAST, PHOSPHODIESTERASE 4 INHIBITORS

Phosphodiesterase 4 (PDE4) inhibitors can be used to treat AD by preventing the degradation of cyclic adenosine monophosphate and subsequently reducing the expression of proinflammatory cytokines. Two identically designed phase 3 randomized, double-blind, vehicle-controlled trials (RDBVCTs) with mild-to-moderate AD patients (≥2 years old, n=503, 513) demonstrated that patients treated twice daily with crisaborole 2% ointment, relative to vehicle control, achieved a 2-grade or greater improvement in Investigator's Static Global Assessment (ISGA) score to clear (0)/almost clear(1) in proportions of 32.8% and 31.4% vs. 24.4% and 18%, respectively.[12] Adverse events were limited to application site pain (4.4% with crisaborole 2% ointment vs. 1.2% with vehicle control). In a subsequent phase 4 open-label study involving infants (3 to <24 months, n=137) with mild-to-moderate AD, 30.2% of patients treated with crisaborole 2% ointment twice daily achieved ISGA 0/1.[13] Treatment-emergent adverse events were limited to application site pain (3.6%) and erythema (2.9%).

Another PDE4 inhibitor, Difamilast (OPA-15406), demonstrates potential for treating mild-to-moderate AD. In a phase 2 RDBVCT with children/adults (≥10 years old) treated twice daily with vehicle control, difamilast 0.3%, or difamilast 1%, patients demonstrated a dose-dependent improvement in AD. By week 4, 2.7%, 14.6%, and 20.9% of patients given vehicle control, difamilast 0.3%, and difamilast 1%, respectively, achieved an IGA 0/1 with at least a 2-grade reduction from baseline score. The most common treatment-emergent adverse event was worsening of AD in patients treated with difamilast 0.3% and 1% (8 of 41, 20% and 2 of 43, 5% respectively).[14] In a phase 3 RDBVCT with children/adolescents (2-14 years old) in Japan, patients treated twice daily with difamilast 1% vs. vehicle control achieved IGA 0/1 (47.1% vs. 18.1%) and EASI-75 (57.7% vs. 18.1%) by week 4.[15] Adverse events related to treatment were limited to worsened AD (1%), folliculitis (1%), and impetigo (2%). A similar phase 3 RDBVCT was conducted with adult patients (15-70 years old) in Japan, in which patients treated twice daily with difamilast 1% vs. vehicle control achieved IGA 0/1 (38.5% vs. 12.6%) and EASI-75 (42.9% vs. 13.2%) by week 4.[16] The most frequent adverse event was worsening of AD in 0.5% of patients in the difamilast 1% group and 6% of patients in the vehicle group.

RUXOLITINIB, TOPICAL JAK 1/2 INHIBITOR

Ruxolitinib is a selective inhibitor of JAK1 and JAK2 that can be formulated in water-containing vehicles for topical applications. In a phase 2 RDBPCT with mild-to-moderate AD adult patients (18-70 years old), patients treated twice daily with ruxolitinib 1.5% cream vs. vehicle control achieved at least a 4-point reduction in itch Numerical Rating Scale (NRS) (62.5% vs. 11.1% by week 4 and 57.9% vs. 14.3% by week 8).[17] Subsequently, in two parallel phase 3 RDBPCTs (TruE-AD1 and TruE-AD2) with pediatric and adult patients (≥12 years old), patients treated with ruxolitinib 1.5% cream achieved IGA 0/1 (53.8% and 51.3% vs. 15.1% and 7.6% in vehicle control group), EASI-75 (62.1% and 61.8% vs. 24.6% and 14.4% in vehicle control group), and NRS4 (52.2% and 50.7% vs. 15.4% and 16.3% in vehicle control group) by week 8. Treatment-emergent adverse events from both trials were limited to nasopharyngitis

Table 2. New Topical Therapies for Atopic Dermatitis

Treatment	Target	Dosage	Main Outcomes	Adverse Events
Crisaborole	PDE4	2% ointment twice daily	≥2 y.o. (n=503, 513): IGA 0/1 (32.8%, 31.4%) ≤2 y.o. (n=137): ISGA 0/1 (30.2%)	≥2 y.o. (n=1016): application site pain (4.4%) 3-24 m.o: application site pain (3.6%), erythema (2.9%)
Difamilast (OPA-15406)	PDE4	1% ointment twice daily	≥10 y.o. (n=43): IGA 0/1 (20.9%) [Japan] ≥15 y.o. (n=182): IGA 0/1 (47%), EASI75 (58%) ≤15 y.o. (n=85): IGA 0/1 (39%), EASI75 (43%)	≥10 y.o.: worsening AD (5%) [Japan] ≥15 y.o.: worsening AD (1%), folliculitis (1%), impetigo (2%) ≤15 y.o.: worsening AD (0.5%)
Ruxolitinib	JAK 1/2	1.5% ointment twice daily	≥12 y.o. (n=253, 228): IGA 0/1 (54%, 51%), EASI75 (62%, 62%), and itch NRS≥4 (52%, 51%)	≥12 y.o.: nasopharyngitis (2.6%), upper respiratory tract infection (2.4%), headache (2.2%), and application site burning (<1%)
Delgocitinib	JAK 1/2/3 and TYK 2	0.5% ointment twice daily	≥16 y.o. (n=106): face and neck IGA 0/1 (23%), overall IGA (22.8%), mEASI75 (26.4%), significant reductions in itch NRS	≥16 y.o.: nasopharyngitis (19.5%), Kaposi's varicelliform eruption (3.9%), and acne (3.2%).

Abbreviations: EASI, Eczema Area and Severity index; mEASI, modified EASI; EASI75, improvement of greater than or equal to 75% in EASI; IGA, Investigator Global Assessment; ISGA, Investigator's Static Global Assessment; IGA or ISGA 0/1, clear/almost clear with greater than or equal to 2 grade improvement; JAK, Janus kinase; NRS, numerical rating scale; itch NRS≥4, improvement of at least 4 points in numerical rating scale; PDE4, phosphodiesterase 4; TYK, tyrosine kinase; y.o., year old.

(n=13/499, 2.6%), upper respiratory tract infection (n=12/499, 2.4%), headache (n=11/499, 2.2%), and application site burning (<1%).[18] Although long-term safety of ruxolitinib is still under evaluation, investigators of TRuE-AD1 and TRuE-AD2 noted that the mean plasma concentrations of ruxolitinib remained below 15% of the WB IC_{50} for JAK2 inhibition, and no clinically meaningful changes occurred in hematologic parameters.[18] Furthermore, the low bioavailability of JAK inhibitors from topical ruxolitinib application allows targeted treatment of AD skin lesions with minimal safety issues, in contrast to oral JAK inhibitors.

SYSTEMIC AGENTS

CYCLOSPORINE, IL-2 INHIBITOR

Cyclosporine A (CsA) is a calcineurin inhibitor of IL-2 and T-cell activation that is commonly used as a first-line, short-term therapy for adults and children with moderate-to-severe AD refractory to standard therapy. According to a meta-analysis of 602 patients in 2006, CsA can demonstrate a relative effectiveness of 55% within the first 6-7 weeks of therapy.[19] Subsequent reviews of CsA have further confirmed its effectiveness to range from 53% to 95% in different clinical severity scores after short-term treatment (10 days to 8 weeks).[20] However, due to its immunosuppressive nature, the use of CsA is recommended for a maximum of 2 years. If used intermittently, the cumulative dose is much lower and CsA may be used for longer periods of time. Adverse events commonly associated with CsA include infection, nephrotoxicity, hypertension, hepatotoxicity, paresthesia, tremors, headaches, nausea, diarrhea, myalgias, electrolyte imbalance, hyperlipidemia, gingival hyperplasia, and hypertrichosis.[20] For patient safety, regular examinations of blood pressure and renal function are recommended every two weeks, whereas electrolytes, complete blood counts, liver function tests, lipid panels, and uric acid values should be monitored every four weeks. However, after 12 weeks on cyclosporine, patients can be switched to monthly monitoring. Special attention should be paid to renal function in patients on long-term CsA therapy. Furthermore, when seeking immunizations, alternatives to live vaccines should be first explored, as CsA's immunosuppressive nature may cause illness from live vaccines.[21-23]

METHOTREXATE, DIHYDROFOLATE REDUCTASE INHIBITOR

Methotrexate (MTX) is a dihydrofolate reductase inhibitor that interrupts nucleic acid synthesis and T-cell function, thereby decreasing inflammation and immune reactivity. In a 24-week study with a median dose of 15 mg/wk of MTX, patients improved 52% from baseline. Patients are recommended to start on a low dose of MTX and gradually escalated to a minimum effective dose to mitigate gastrointestinal side effects; doses can range 7.5-25 mg/week for adults and 10-20 mg/m^2/week in children. Common adverse events associated with MTX include infections, liver and bone marrow toxicity, nausea, fatigue, headache, pulmonary toxicities, and drug interactions. Laboratory monitoring such as complete blood counts and liver function tests should be performed 1 week after the initial dose, and 1-2 weeks after every dose increase. Once on main-

tenance dosing, complete blood counts and liver function tests can occur every 3-6 months. Hepatoxicity should be screened for at cumulative doses of 3.5 to 4.0 grams. While the gold standard for evaluating hepatoxicity is liver biopsy, recent guidelines suggest non-invasive vibration controlled transient elastography such as Fibroscan for initial screening. Other laboratory monitoring should also include renal function 1-2 times annually. Lastly, when seeking immunizations, alternatives to live vaccines should be recommended if possible, as MTX's immunosuppressive nature may cause illness from live vaccines.[23]

AZATHIOPRINE

Azathioprine (AZA) is a purine-mimic antimetabolite that inhibits lymphocyte proliferation. The currently recommended dosage for adults is 50 mg/day for 1-2 weeks and 1-4 mg/kg/day in children.[24] In two separate RDBPCTs, AZA demonstrated an improvement of 26% and 37% in Six Area, Six Sign, AD scores after 3 months.[25,26] Prior to prescription, baseline thiopurine methyltransferase (TMTP) activation should be measured to limit myelotoxicity from AZA.[25,27] Common adverse events associated with AZA include infection, gastrointestinal disturbances, liver dysfunction, and leukopenia.[26] In patients with inflammatory bowel disease, AZA can increase the risk of non-melanoma skin cancer and lymphoma.[28,29] Complete blood counts, renal function tests, and liver function tests are recommendedevery 2 weeks for 2 months, then monthly for 4 months, and then every other month.[24] When seeking immunizations, alternatives to live vaccines should be first explored, as AZA's immunosuppressive nature may cause illness from live vaccines

JAK INHIBITORS

BARICITINIB, JAK 1/2 INHIBITOR

Baricitinib is an oral selective JAK1/2 inhibitor approved by the FDA for the treatment of rheumatoid arthritis and alopecia areta. However, clinical trials have been conducted for the application of baricitinib to moderate-to-severe AD. In two similar 16-week phase 3 RDPCT with adult moderate-to-severe AD patients (BREEZE-AD1 and BREEZE-AD2), patients given placebo, 1, 2, or 4 mg baricitinib once daily demonstrated a dose-dependent improvement in lesions and pruritus.[30,31] However, due to serious adverse events such as deep vein thrombosis and pulmonary embolism at 4 mg once daily dosing in rheumatoid arthritis studies, the FDA limited the maximum daily dose of baricitinib to 2 mg.[32] By week 16 of a subsequent phase 3 RDPCT with adult moderate-to-severe AD patients (BREEZE-AD5) given placebo, 1, or 2 mg baricitinib, patients on 2 mg baricitinib relative to placebo achieved IGA 0/1 (24% vs. 5%), EASI-75 (30% vs. 8%), and ⩾4-point improvement in itch NRS (25% vs. 5%).[33] Common adverse events included elevated creatinine phosphokinase (5.7%), headaches (8.9%), and herpes simplex infections (5.3%).[30,31,33] Laboratory monitoring such as complete blood counts should be performed every four weeks for the first three months, then every three months to monitor bone marrow toxicity.[34] Liver function tests should also be done at baseline, every four weeks for the initial twelve weeks, and then every three months thereafter. Similarly, renal function tests should be performed every three months.[34] Lipid panels should also be ordered at baseline and at 12 weeks after initiation, followed by management per standard guidelines.[34] Additionally, live vaccines are contraindicated in patients using baricitinib, and immunization status should be current before starting the drug.[34] Although these trials demonstrate the efficacy of baricitinib in treating moderate-to-severe AD, more studies must be conducted to understand its long-term safety, effectiveness, and potential use in children and adolescents.

UPADACITINIB AND ABROCITINIB, SELECTIVE JAK1 INHIBITORS

Upadacitinib is a JAK1 inhibitor approved by the FDA for the treatment of atopic dermatitis in adults and children 12 years of age and older. Clinical trials have been conducted for the application of upadacitinib to moderate-to-severe AD. In a phase 2 RDBPCT with adult AD patients given placebo, 7.5, 15, or 30-mg once daily upadacitinib demonstrated a dose-dependent improvement in pruritus and sleep.[35,36] By week 16, EASI-75 was achieved in 9.8%, 28.6%, 52.4%, and 69.0% of patients, respectively. Two similar phase 3 RDBPCT with adolescents/adults (Measure Up 1 and Measure Up 2) on 30 mg daily compared to placebo demonstrated achievements of IGA 0/1 (62% and 52% vs. 8% and 5%) and EASI-75 (80% and 73% vs. 16% and 13) by week 16.[37] Common adverse events included acne (14.3%), elevated CPK (9.5%), headache (9.5%). Recommended lab monitoring includes complete blood counts and liver function tests at baseline and periodically thereafter. Lipid panel examination is also recommended at 12 weeks, followed by clinical management per standard guidelines. Although these trials demonstrate the efficacy of upadacitinib in treating moderate-to-severe AD, more studies must be conducted to understand its long-term safety, effectiveness, and potential use in children.

Another selective JAK1 inhibitor, abrocitinib, demonstrates short-term efficacy in treating moderate-to-severe AD in adolescents and adults, and has recently been approved for atopic dermatitis in adult patients. In two phase 3 RDBCTs (JADE MONO-1 and JADE MONO-2), adolescent/adult patients (⩾ 12 years old) were treated with placebo, 100 mg, or 200 mg abrocitinib. Although both 100 mg and 200 mg abrocitinib provided significant therapeutic relief of AD relative to placebo, a dose-dependent response was observed. By week 12 in JADE MONO-1 and JADE MONO-2, patients treated with 200 mg abrocitinib compared to placebo achieved an IGA 0/1 (44% and 38.1% vs. 8% and 9.1%), EASI-75 (63% and 61% vs. 12% and 10.4%), and ⩾4-point improvement in itch NRS (57% and 55.3% vs. 15% and 11.5%). Common adverse events included nausea (20% and 14.2%) and headaches (10% and 7.7%). Laboratory monitoring including complete blood counts and lipid pan-

Table 3. New JAK Inhibitors for Atopic Dermatitis

Treatment	Target	Dosage	Main Outcomes	Treatment-emergent adverse events (TEAEs)
Baricitinib	JAK 1/2	2 mg once daily	≥18 y.o. (n=124): IGA 0/1 (24%), EASI75 (30%), itch NRS≥4 (25%)	≥18 y.o.: elevated CPK (6%), headache (9%), and herpes simplex infections (5%)
Upadicitinib	JAK 1	30 mg once daily	≥12 y.o. (n=286, 282): IGA 0/1 (52%, 62%), EASI75 (80%, 73%)	≥12 y.o.: acne (11%, 12%), elevated CPK (9.5%), headache (9.5%)
Abrocitinib	JAK 1	200 mg once daily	≥12 y.o. (n =154, 155): IGA 0/1 (44%, 38%), EASI75 (63%, 61%), and itch NRS≥4 (57%, 55%)	≥12 y.o.: nausea (20%, 14%), headaches (10%, 7.7%).

Abbreviations: EASI, Eczema Area and Severity index; EASI75, improvement of greater than or equal to 75% in EASI; IGA, Investigator Global Assessment; IGA 0/1, clear/almost clear with greater than or equal to 2 grade improvement; JAK, Janus kinase; NRS, numerical rating scale; itch NRS≥4, improvement of at least 4 points in numerical rating scale for itch; y.o., year old.

els should be performed at baseline and every 4 weeks thereafter.

BIOLOGICS

DUPILUMAB, INHIBITION OF IL-4/13 SIGNALING BY IL-4R

Dupilumab, a monoclonal antibody approved by the FDA for moderate-to-severe AD in patients aged 6 months and older, inhibits IL-4 and IL-13 signaling through targeting of IL-4R. Phase 3 RDBPCTs demonstrated that adult subjects (⩾ 18 years old) dosed on dupilumab 300 mg every two weeks (after 600mg loading dose) achieved the primary end point of IGA0/1 significantly more than those in the control group: 38% (SOLO 1) and 36% (SOLO 2) with dupilumab vs. 10% and 8% with placebo. Subjects also demonstrated EASI-75, itch NRS greater than or equal to 4 and improved quality of life measures compared to placebo.[38] Subsequent studies with adults (CHRONOS) have further demonstrated long term (52-week) safety and efficacy with comparable improvements between 300 mg once weekly and 300 mg every two weeks. As a result, the current recommendation for dupilumab is 300 mg every two weeks in adults.

In similar trials (LIBERTY AD) with adolescents aged 12 to 17 years old, subjects given weight-based dosing of dupilumab (⩾60 kg: 300 mg; <60 kg: 200 mg) every two weeks achieved similar improvements: IGA 0/1 (24.4% vs. 2.4%), EASI-75 (41.5% vs. 8.2%), and itch NRS improvement ⩾ 4 pts (36.6% vs. 4.8%) relative to placebo.[39]

In a separate trial (LIBERTY AD PEDS) for children aged 6 to 11 years old, subjects given topical corticosteroids and weight-based dosing of dupilumab (⩾30 kg: 400 mg loading dose + 200 mg every 2 weeks; <30 kg: loading dose 600 mg + 300 mg every 4 weeks) demonstrated similar improvements: IGA 0/1 (29.5% vs. 11.5%), EASI-75 (67.2% vs. 26.8%), and itch NRS improvement ⩾ 4 pts (58.3% vs. 12.3%).[40] Common adverse reactions in AD patients on dupilumab included mild injection site reactions, conjunctivitis, and transient, mild-to-moderate eosinophilia. In a small number of patients taking dupilumab, new or exacerbated facial erythema that do not respond to topical anti-inflammatory medication has also been observed.

In another trial (LIBERTY AD PRE-SCHOOL) for infants and toddlers aged 6 months to 6 years, subjects given topical corticosteroids and weight-based dosing of dupilumab (5-<15 kg: 200 mg every 4 weeks; ⩾15-30 kg: 300 mg every 4 weeks) demonstrated remarkable improvement in AD: IGA 0/1 (28% vs. 4%) and EASI-75 (53% vs. 11%) by week 16 when compared against topical steroid alone.[39] Common adverse events consisted of nasopharyngitis (8% vs. 9%), upper respiratory tract infection (6% vs. 8%), conjunctivitis (5% vs 0%), herpes viral infections (6% vs. 5%), and injection site reactions (2% vs. 3%) when comparing dupilumab vs. placebo respectively.[39]

LEBRIKIZUMAB AND TRALOKINUMAB, IL-13 INHIBITORS

Lebrikizumab is a high-affinity, monoclonal IL-13 antibody that inhibits heterodimerization of IL-13Rα with IL-4Rα and subsequent signaling through the IL-4 receptor. In a 16-week phase 2b dose-ranging RDBPCT with adults subjects (⩾ 18 years old), lebrikizumab injections significantly improved measures of clinical manifestations of atopic dermatitis, pruritus, and quality of life in a dose-dependent manner when compared to placebo.[40] With 250 mg every 2 weeks (after 500-mg loading dose at baseline and week 2), subjects demonstrated notable improvements comparable to placebo: IGA 0/1 (44.6% vs. 15.3%), EASI-75 (60.6% vs. 24.3%), and itch NRS improvement greater than or equal to 4 (70% vs. 27.3%). Common adverse reactions reported in subjects treated with lebrikizumab included nasopharyngitis (12% vs. 3.8%), conjunctivitis (5.3% vs. 1.9%), and injection site pain (2.7% vs. 0%) compared to placebo.

Tralokinumab, a human IgG_4 monoclonal antibody, also binds to IL-13, preventing its binding to both IL-13Rα1 and IL-13Rα2. Phase 3 RDBPCTs demonstrated that adult subjects (⩾ 18 years old) dosed on tralokinumab 300 mg every two weeks (after double-dose loading) achieved the primary end point of IGA0/1 significantly more than those in the control group, comparing 15.8% (ECZTRA1) and 22.2% (ECZTRA2) with tralokinumab vs. 7.1% and 10.9% with

placebo.[41] Subjects also demonstrated improved EASI-75 (25% and 33% vs. 12.7% and 11.4% for placebo) and pruritus NRS improvement greater than or equal to 4 (20% and 25% vs. 10.3% and 9.5% for placebo). Common adverse reactions reported in subjects treated with tralokinumab included conjunctivitis (7.1% and 3% vs. 2% and 1.5% for placebo) and upper respiratory tract infections (mainly reported as the common cold) (23.1% and 8.3% vs. 6.8% and 2.9% for placebo).

NEMOLIZUMAB, IL-31 INHIBITOR

Nemolizumab is a monoclonal antibody that targets IL-31Rα, a receptor known to play a role in the pathogenesis of atopic dermatitis. A 12-week Phase 2 RDBPCT with adult subjects given a weight-based dosing of nemolizumab 0.5 mg/kg every 4 weeks demonstrated a reduction in pruritus visual analogue scale score by 59.8% vs. 20.9% in placebo.[42] Subsequently, with a 52-week extension period of nemolizumab treatment, subjects on 0.5 mg/kg nemolizumab every 4 weeks demonstrated improvements in work productivity and decreased pruritus-associated sleep disturbances up to week 64.[43] Common adverse reactions in AD patients included creatinine phosphokinase (CPK) elevation (5.6% on 0.5 mg/kg, 17.3% on 2.0 mg/kg) and peripheral edema of the lower extremities for varied durations (5.6% on 0.5 mg/kg, 11.5% on 2.0 mg/kg).[42]

CONCLUSION

The safety and efficacy of new therapies continue to be the primary focus for improving the care of patients with atopic dermatitis. Many of the aforementioned therapies for atopic dermatitis come with side effects, but strategies do exist to further mitigate their severity. Topical corticosteroids are associated with a number of side effects both local and more widespread, but their risk can be decreased by educating patients about appropriate use of the medication, such as its quantity, target areas, and duration of application, including taking breaks. Calcineurin inhibitors and PDE-4 inhibitors both carry the risk of transient burning and pain, but this side effect can be managed by adding a low potency topical steroid in the first few days as needed. Oral agents such as cyclosporine, azathiaprine, and methotrexate present an increased risk of immunosuppression and consequent infections, so frequent blood monitoring must be diligently performed. In contrast, dupilumab presents one of the safest profiles for use in AD, while the newer JAK inhibitors, IL-13 and IL-31 inhibitors, appear to present moderate risk. Indeed, a contributing factor to adverse events may be inadequate anticipatory guidance at the time of the visit. By providing informative handouts or demonstrating proper medication use, it is possible to minimize the frequency and severity of some side effects. Though many agents in Phase 2 or 3 clinical trials have demonstrated short-term efficacy with a tolerable or minimal side effect profile, additional research is required to understand long-term safety and expand such therapies to a broader patient population.

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Table 4. New Biologics for Atopic Dermatitis

Treatment	Target	Dosage	Main Outcomes	Adverse Events
Dupilumab	IL-4Rα	Age and weight-dependent	≥18 y.o. (n=465): IGA0/1 (36%, 38%), EASI75 (44%, 51%), itch NRS≥4 (36%, 41%) 12-<18 y.o. (n=82): IGA 0/1 (24%), EASI75 (42%), itch NRS≥4 (37%) 6-<12 y.o (+TCS) (n=122): IGA 0/1 (30%), EASI75 (67%), itch NRS≥4 (58%) 6 mo-<6 y.o. (+TCS) (n=162): IGA 0/1 (28%), EASI75 (53%).	≥ 18 y.o.: Mild injection site reactions (8%, 14%); conjunctivitis (4%, 5%); transient eosinophilia 12-<18 y.o.: mild injection site reactions (9%), conjunctivitis (10%), 6-<12 y.o.: mild injection site reactions (11%), conjunctivitis (15%); 6 mo-<6 y.o.: nasopharyngitis (8%), upper respiratory tract infections (6%), conjunctivitis (5%), herpes viral infections (6%), injection site reactions (2%)
Lebrikizumab	IL-13	LD: 500 mg (repeated on wk 2) 250 mg once every two weeks	≥18 y.o. (n=75): IGA0/1 (45%), EASI75 (61%), itch NRS-4 (70%)	≥18 y.o.: nasopharyngitis (12%), conjunctivitis (5%), injection site pain (3%)
Tralokinumab	IL-13	LD: 600 mg 300 mg once every two weeks	≥18 y.o. (n=601, 591): IGA0/1 (16%, 22%), EASI75 (25%, 33%), itch NRS≥4 (20%, 25%)	≥18 y.o.: conjunctivitis (3%, 7%), upper respiratory tract infections (mainly reported as common cold) (8%, 23%)
Nemolizumab	IL-31	0.5 mg/kg once every four weeks	≥18 y.o. (n=54): ≥ 2 pt improvement in IGA (38%), percentage change in EASI (-42.3%), percent change in pruritus visual-analogue scale (-59.8%)	≥18 y.o.: elevated CPK (5.6%), lower extremity peripheral edema (5.6%)

Abbreviations: EASI, Eczema Area and Severity index; EASI75, improvement of greater than or equal to 75% in EASI; IGA, Investigator Global Assessment; IGA 0/1, clear/almost clear with greater than or equal to 2 grade improvement; IL-4Rα, interleukin-4 receptor alpha; IL-13, interleukin-13; IL-31, interleukin 31; LD, loading dose; NRS, numerical rating scale; itch NRS≥4, improvement of at least 4 points in numerical rating scale; +TCS, topical steroids; y.o., year old.

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