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SYSTEMIC MANAGEMENT OF ATOPIC DERMATITIS: NEW AND EMERGING THERAPIES

1. ATOPIC DERMATITIS

Atopic dermatitis, also known as atopic eczema (hereafter referred to as eczema) is the most common chronic inflammatory skin disease worldwide and, together with associated allergies, asthma, allergic rhinitis (with or without nasal polyposis), and eosinophilic esophagitis, atopic disorders represent a growing source of patient morbidity and health care cost globally.[1,2] The incidence of eczema spans all age groups, but in over 80% of cases it manifests during infancy or early childhood; interestingly, there is now recognition that a significant number of patients suffer from adult-onset, chronic-persistent, and/or late-relapsing disease.[1,3,4] Eczema is a complex disease with extreme heterogeneity, including highly variable penetrance, clinical phenotypic presentations (ethnicity, age and temporal factors), and natural history across the lifespan. The term endotype has been introduced to describe potential variance in therapeutic responsiveness and etiology, particularly with respect to genetic and immunologic profiling, as well as environmental triggering.[1,4–6] Notably, the range of treatment options available for patients with atopic disorders is changing rapidly, especially for eczema.[7] In this review, we provide a brief overview of targeted systemic therapeutic options for patients with eczema and atopy (**Table 1**).

2. WHO QUALIFIES FOR SYSTEMIC THERAPY?

A detailed approach to the management of eczema is beyond the scope of this review; however, our group has published a systematic review and quality assessment of existing guidelines for reference.[8] Management options range from skin-directed (topical corticosteroids, calcineurin inhibitors, PDE4 inhibitors, as well as phototherapy) to systemic agents, based on extent, severity, and type of disease.[1,5,8] Notably, assessment of disease is challenging, as highly-detailed full body skin examinations are required for validated disease assessment, including the primary outcome measure, the Eczema Area and Severity Index (EASI).[9] A stepwise approach to management of refractory or more severe disease generally focuses on systemic agents to induce itch remission rapidly, a core factor to drive improvement in quality of life. Objectively, a current target for eczema control is an EASI of <7; however, patient reported outcomes for itch and quality of life, such as the Dermatology Life Quality Index (DLQI), should strongly influence this target.[1,8, 9, 53] The importance of these subjective measures is highlighted when considering the temporal instability of the disease and the barriers to accessing specialized care and objective measures during flares. For individuals with refractory or extensive eczema affecting more than ten percent corporeal surface area, or special sites such as the hands or face, antimetabolite immunosuppressive agents have long been used, despite being off-label.[1,5,8,10,11] Therapeutic switches for ensuring safety of continuous immunomodulation for long-term maintenance of remission are now preferred management, as targeted therapies are considered to minimize the risk of adverse effects across the lifespan.[1,5,8,11] Patients and providers alike are increasingly seeking direct access to targeted agents when able. Broadly, targeted agents approved for eczema are categorized into biologics (monoclonal antibodies) and small molecule inhibitors.

3. WHAT TRADITIONAL IMMUNOSUPPRESSANTS ARE USED FOR ECZEMA?

Traditional immunosuppressive antimetabolites remain in frequent use despite being off- label in Canada in large part due to health system cost considerations.[5,8,11] Selection of these agents is based on individualized efficacy and safety considerations, while adhering to international management guidelines and requirements for screening and monitoring. Usage varies according to expertise, access to monitoring, as well as regional or national health system factors.

Cyclosporine is an effective small molecule calcineurin inhibitor that prevents IL-2 transcription resulting in reduced effector T cell function. Cyclosporine has long been approved by the European Medicines Agency (but not the FDA or Health Canada for refractory eczema.[11,12] It has been considered a first-line agent for adults with severe disease in European guidelines due its rapid onset; patients can achieve 51% and 72% improvement of eczema at week 2 and 12, respectively.[13] However, cyclosporine

should be administered in 3–6-month intervals for a maximum of 2 years to minimize side effects such as hypertension, nephrotoxicity and risk of malignancy or infection.[11,14,15] Unfortunately, relapse and rebound is common following cyclosporine discontinuation; therefore, careful tapering and/or switching to maintenance therapies is needed.[11,14]

Unlike cyclosporine, methotrexate works slowly, and patients often take as long as 8-12 weeks before responding optimally; however, methotrexate is generally considered a safer option for long-term maintenance.[5,11,14] This antifolate antimetabolite inhibits synthesis of DNA and RNA.[16–19] Up to 60% of patients can achieve improvement of disease whilst on methotrexate as part of a monotherapy or combination therapy regimen.[20,21] Methotrexate usage must be weighed against its teratogenic and hepatic adverse effects.[11,14] Mycophenolate mofetil and azathioprine are less commonly used systemic immunosuppressants for eczema patients but may be used as adjuncts or when cyclosporine and/or methotrexate are contraindicated.[11,14,20,22] While systemic glucocorticoids are a recognized rescue therapy for moderate-to-severe eczema, their usage is restricted to short-term management of acute flares due to their unfavorable safety profile with prolonged treatment.[11,14] Importantly, the cumulative risk of rescue corticosteroids must be considered across the lifespan.

4. WHAT TARGETED AGENTS ARE USED, AND WHEN?

A rapid pace of translational discovery has led to landmark shifts in the management of eczema over the last six years: there are now four on-label therapies with demonstrated efficacy in AD and that are safe for long-term maintenance of remission (**Table 2**). Patients and providers are thus seeking improved health trajectories across the lifespan, with increasing awareness of ameliorated outcomes, due to the capacity for targeted agents to selectively modulate branches of the immune system without broad immunosuppression, or while minimizing off-target effects to other organs. Health systems are recognizing these novel agents and balancing econometric evaluations against budget impact analyses.

a. Targeted Biologics: Monoclonal Antibodies

Biologics for eczema are proliferating; notably, these selective agents are injections. As the first targeted agent approved for eczema, dupilumab is licensed for use across the greatest number of atopic conditions and has the widest age range of regulatory approvals (**Table 2**).[23–25] This fully humanized monoclonal antibody targets the alpha subunit of IL-4 receptor (IL-4R)[26] blocking type 2 (IL-4 and IL-13) signaling, and significant skin clearance has been established in 3 pivotal trials for adults.[27,28] It has also been approved for children aged 6 to 11 years with uncontrolled eczema (**Tables 1 and 3**).[29,30] The FDA also accepted dupilumab for priority review for approval in children between the ages of 6 months and 5 years.[31] A phase 2/3 trial in this patient population found that 53% of such patients were able to achieve EASI75 at week 16 with dupilumab, versus 11% with placebo.[32] With a signal for conjunctivitis but otherwise minimal adverse effects, given its consistent safety profile for patients 6 years and older, dupilumab's strengths include efficacy over a range of other moderate-to-severe allergic diseases such as uncontrolled asthma and nasal polyps that may influence its selection in patients with these co-morbidities (**Table 1**).[33]

Tralokinumab is another selective and high-affinity human monoclonal antibody against IL-13, the dominant Th2 cytokine in skin. It was approved by Health Canada for adults with moderate-to-severe eczema in late 2021;[34,35] public reimbursement in Canada is pending.[31,32] In clinical trials, the majority of tralokinumab responders maintained their response through week 52 and there is some evidence for improved long-term response rates.[34–36] In pivotal trials, EASI75 at week 52 was maintained by 60% of treatment responders who continued tralokinumab (vs. 33% who transitioned from tralokinumab to placebo), after the week 16 primary endpoint in ECZTRA 1, and 56% who continued tralokinumab (vs. 21% who transitioned to placebo) in ECZTRA 2. Tralokinumab does not have any notable contraindications or additional safety monitoring requirements associated with its use for patients prior, during, or post initiation (**Table 3**).[36]

Of note, a recent Canadian literature review and expert clinical framework notes that exposure to dupilumab during pregnancy poses little risk to mother and fetus, with negligible absorption of dupilumab by infants who are breastfed by women taking dupilumab.[33]

b. Targeted Small Molecule Inhibitors: JAK1 Inhibitors (JAKi)

Biologic agents are appealing options for long-term maintenance due to their favorable safety profiles; however, their pharmacodynamics are slower than oral targeted agents. Patients suffering from moderate-to-severe eczema frequently require rapid rescue and remission of disease, as demonstrated by the prevalent use of systemic corticosteroids despite their broad adverse effect profiles. A new class of agents, the small molecule inhibitors of Janus kinases

(JAKi), control disease rapidly by interrupting signal transduction downstream of cytokine receptors;[1] JAKi are already used in rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis (**Tables 1,2**).[37,38] The JAKi of interest for eczema in North America (upadacitinib and abrocitinib) are oral small molecule inhibitors with predominant selectivity for JAK1.[5] JAK1 inhibitors are highly effective at blocking signaling downstream of the type 2 cytokines that contribute to eczema pathophysiology; they also interrupt signaling downstream of other cytokine families, including interferons, the gp130 receptor group, IL-10-related, and common gamma chain cytokines.[39,40] While serious adverse effects of special interest have been highlighted in patients with rheumatoid arthritis under combination treatment with the less selective JAK inhibitor (JAK1/3) tofacitinib, leading to blanket inclusion of black box warnings for the JAK class across all diseases, this data has not been extrapolated to selective JAK1 inhibition in patients with eczema.[41,42] Notably, a wide range of topical and oral inhibitors of JAK and related kinases are under active development for a wide range of dermatologic conditions, including vitiligo and alopecia areata, which are common underlying comorbid conditions in patients with severe eczema. [43]

Upadacitinib was the first approved JAKi for moderate-to-severe eczema in adults and adolescents (>12 years).[44,45] In phase 3 studies, patients treated with upadacitinib achieve rapid control as early as week 4, with 70% EASI75 and IGA-AD scores by Week 16 compared to placebo (**Table 4**).[46–48] Notably, patients experienced rapid improvements in itch beginning as early as 1-2 days following the first dose. At higher dosing (30 mg) upadacitinib achieved higher skin clearance compared to dupilumab after four months, with 60.6% versus 38.7% achieving 90% improvement in the EASI.[49] Routine blood work is recommended pre-treatment with monitoring at 3 months and as per care required (**Table 3**).[38] Non-live vaccination prior to therapy, followed by booster vaccination after two months is recommended, with stronger recommendations in patients who are at a greater risk for developing shingles, including patients of Asian ethnicity. Shared decision-making is needed to review timing and options for therapy modifications during vaccinations.[38] Upadacitinib should be prescribed with caution in patients with infection, hematologic disorders, history of clotting, and liver or kidney impairment, and is contraindicated during pregnancy and breastfeeding.[38]

Abrocitinib is a comparable JAK1 inhibitor recently approved by Health Canada, with small differences in adverse effect profiles including a slightly lower signal for acne.[50,51] Patients receiving abrocitinib also showed significantly greater improvements in their EASI75 and Investigator Global Assessment- Atopic Dermatitis (IGA-AD) scores compared with the placebo group across three pivotal registration studies (**Table 5**).[26,50] Unlike dupilumab and tralokinumab, upadacitinib and abrocitinib require additional safety considerations prior to and post initiation of therapy (**Table 3**).[37]

5. CHOOSING THE BEST SYSTEMIC ECZEMA THERAPY

The systemic therapy that best suits an individual's unique eczema presentation depends on multiple patient-specific factors, including age, underlying comorbidities, disease- and risk-factors, endotype variables and personal preferences, in addition to health system considerations related to reimbursement and access. However, only select therapeutic agents (cyclosporine, upadacitinib, abrocitinib, prednisone) have kinetics that are useful in achieving very rapid remission of eczema, while others (dupilumab, tralokinumab, methotrexate) have slower onset of action but also possess multiple years of data demonstrating durability of response over time with favorable safety profiles. In addition, restricted options are available for certain populations, including children and women of childbearing potential. For patients with health-related quality of life affected by comorbid atopic conditions like asthma and/or chronic rhinosinusitis with nasal polyps (CRSwNP), dupilumab remains advantageous (**Table 3**). Although tralokinumab may not be as efficacious as dupilumab at the time points considered here, it remains a viable alternative with fewer safety concerns than the JAK inhibitors and targets the key mediator in skin.[10,52] As more molecules progress through clinical development, including additional IL-13 inhibitors and biologics targeting OX40 or ligand co-stimulatory signaling, further research is required to determine how to personalize management approaches with the idealized aim to identify therapeutic approaches that may alter the natural history of disease.

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		Children								Adolescent and Adult							
MOA	Rx	Children 6 months-5 years				Children 6-11 years				Adolescents 12-17 years				Adults			
		AD	Asthma	CRS wNP	EoE	AD	Asthma	CRS wNP	EoE	AD	Asthma	CRS wNP	EoE	Eczema	Asthma	CRS wNP	EoE
Anti-IL-4R alpha (IL4/IL13)	Dupilumab[1]	Pending*				✓! @	✓! @			✓! @	✓! @#		Pending	✓! @	✓! @#	✓! @#	@
Anti-IL-13	Tralokinumab[2]													✓! @			
Anti-JAK1	Upadacitinib[3]									✓! @				✓! @			✓**
Anti-JAK1	Abrocitinib[4]													✓!			

Table 1. New systemic therapies approved for patients with Atopic Dermatitis (Eczema), considering other atopic disorders, as of April 2022.
CRSwNP (chronic rhinosinusitis with nasal polyposis)
! Approved by Health Canada as of April 2022
@ Approved by U.S. FDA
 # Approved as add-on maintenance treatment only
** Accepted for Priority Review by the U.S. FDA5*
*** Approved for moderate-to-severe ulcerative colitis, active psoriatic arthritis, and moderately to severely active rheumatoid arthritis*

Mechanism of Action	Therapeutic Name	Phase 2	Phase 3	FDA Approval	Health Canada Approval	Phase 4
Anti-IL-4R alpha (IL4/IL13)	Dupilumab	✓ !@# [1]	✓ !@# [2]	✓	✓	✓ !@# [3]
Anti-IL-13	Tralokinumab	✓ ! [4]	✓ !@ [5]	✓	✓	
	Lebrikizumab	✓ ! [6]	✓ !@ [7]			
Anti-IL-31	Nemolizumab	✓ !@ [8]	✓ !@ [9]			
Anti-JAK1	Upadacitinib	✓ ! [10]	✓ !@ [11]	✓	✓	
	Abrocitinib	✓ ! [12]	✓ !@ [13]	✓		
Non-Specific Anti-JAK1/2	Baricitinib	✓ ! [14]	✓ !@# [15]			

Table 2. New and emerging therapies in clinical development for the treatment of Atopic Dermatitis (Eczema) as of April 2022.[5]

Green *(Approved for use);* **Orange** *(Clinical development ongoing - Not approved);* **Yellow** *(Not filing for approval in North America)*

Disease Severity: M (moderate); MS (moderate-to-severe); S (severe)

Study Population: ! (Adult); @ (Adolescent); # (Children)

*Study status "Completed" unless labelled with any of the following: $ (Active, not recruiting); ^ (Active, recruiting); * (Terminated)*

[1] *Dupilumab Phase 2 Clinical Trials: NCT02407756[@#MS], NCT01859988[!MS], NCT02210780[!], NCT01639040[!MS], NCT01979016[!MS], NCT01548404[!MS], NCT03346434[#MS]*

[2] *Dupilumab Phase 3 Clinical Trials: NCT03346434[#MS], NCT01949311[$!MS], NCT02277769[!MS], NCT03912259[!MS], NCT02277743[!MS], NCT02260986[!MS], NCT02755649[!MS], NCT02395133[!MS], NCT03054428[@MS], NCT04678882[$@#MS], NCT03345914[#MS]*

[3] *Dupilumab Phase 4 Clinical Trials: NCT03293030[^!MS], NCT03667014[$!MS], NCT03389893[*!MS], NCT04358224[^!MS], NCT04447417[!@MS], NCT05203380[^@MS], NCT04823130[^!MS], NCT04033367[!MS], NCT04718870[#MS], NCT05265234[^!MS]*

[4] *Tralokinumab Phase 2 Clinical Trials: NCT04556461[$!MS], NCT02347176[!MS]*

[5] *Tralokinumab Phase 3 Clinical Trials: NCT05194540[^!@MS], NCT03587805[$!@MS], NCT03761537[!MS], NCT04587453[!MS], NCT03363854[!MS], NCT03526861[@MS], NCT03160885[!MS], NCT03131648[!MS]*

[6] *Lebrikizumab Phase 2 Clinical Trials: NCT02465606[!MS], NCT03443024[!MS], NCT02340234[!MS]*

[7] *Lebrikizumab Phase 3 Clinical Trials: NCT04250350[$@MS], NCT04178967[$!@MS], NCT04146363[$!@MS], NCT04250337[!@MS], NCT04626297[^!MS], NCT04392154[^!@MS], NCT05149313[^!@MS], NCT04760314[$!@MS]*

[8] *Nemolizumab Phase 2 Clinical Trials: NCT04921345[^#MS], NCT03921411[@MS], NCT01986933[!M,MS,S], NCT03100344[!MS], NCT04365387[^!@MS]*

[9] *Nemolizumab Phase 3 Clinical Trials: NCT03985943[$!@MS], NCT03989349[$!@MS], NCT03989206[^!@MS]*

[10] *Upadacitinib Phase 2 Clinical Trials: NCT02925117[!MS]*

[11] *Upadacitinib Phase 3 Clinical Trials: NCT03738397[!MS], NCT04195698[$!MS], NCT03569293[$!@MS], NCT03568318[$!@MS], NCT03607422[$!@MS], NCT03661138[$!@MS]*

[12] *Abrocitinib Phase 2 Clinical Trials: NCT03915496[!MS], NCT02780167[!MS]*

[13] *Abrocitinib Phase 3 Clinical Trials: NCT04345367[!MS], NCT03720470[!MS], NCT03796676[@MS], NCT03575871[!@MS], NCT03349060[!@MS], NCT03422822[$!@MS]*

[14] *Baricitinib Phase 2 Clinical Trials: NCT02576938[!MS]*

[15] *Baricitinib Phase 3 Clinical Trials: NCT03952559[^@#MS], NCT03559270[$!MS], NCT03435081[!MS], NCT03334422[!MS], NCT03334435[$!MS], NCT03733301[!MS], NCT03428100[$!MS], NCT03334396[!MS]*

	Dupilumab (Dupixent®)[1]	Tralokinumab (Adtralza®)[2]	Upadacitinib (Rinvoq®)[3]	Abrocitinib (Cibinqo®)[4]
Patient Population per Health Canada	6 years and older	18 years and older	12 years and older	18 years and older
Indications	Moderate-to-severe AD, asthma, severe chronic rhinosinusitis with nasal polyposis	Moderate-to-severe AD	Moderate-to-severe AD, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis	Moderate-to-severe AD
Contraindications	Hypersensitivity to dupilumab	Hypersensitivity to tralokinumab	Hypersensitivity to upadacitinib	Antiplatelet therapies except for low-dose aspirin during the first 3 months of treatment
Relative Contraindications and/or Black Box Warnings	Pregnancy	Pregnancy	Pregnancy; Breastfeeding; Active serious infection, hematologic disorders, severe renal and/or hepatic impairment, malignancy, thrombosis	Pregnancy; Breastfeeding; Active serious infection, hematologic disorders, severe renal and/or hepatic impairment, malignancy, thrombosis, major adverse cardiovascular events
Route of Administration	Subcutaneous Injection	Subcutaneous Injection	Oral	Oral
Mode of Action	Anti-IL-4R alpha (IL4/IL13)	Anti-IL-13	JAK1 Inhibitor	JAK1 Inhibitor
Adverse Events (based on product monograph, >1%)	a) Injection site reactions (9.7% dupilumab, 5.5% placebo) b) Conjunctivitis (9.7% dupilumab, 3.2% placebo) c) Oral herpes (3.6% dupilumab, 1.6% placebo)	a) Upper respiratory tract infections (ECZTRA 1/2: 23.8% 300 mg, 20.2% placebo; ECZTRA 3: 29.0% 300 mg, 15.1% placebo) b) Injection site reactions (ECZTRA 1 & 2: 7.3% 300 mg, 4.0% placebo; ECZTRA 3: 10.7% 300 mg, 0.8% placebo) c) Conjunctivitis (ECZTRA 1 & 2: 5.1% 300 mg, 1.8% placebo; ECZTRA 3: 11.1% 300 mg, 3.2% placebo)	a) Upper respiratory tract infection (25.4% 30 mg, 22.6% 15 mg, 16.5% placebo) b) Acne (15.1% 30 mg, 9.6% 15 mg, 2.2% placebo) c) Herpes simplex (8.4% 30 mg, 4.1% 15 mg, 1.7% placebo)	a) Nasopharyngitis (8.7% 200 mg, 12.4% 100 mg, 7.9% placebo) b) Nausea (14.5% 200 mg, 6.0% 100 mg, 2.1% placebo) c) Headache (7.8% 200 mg, 6.0% 100 mg, 3.5% placebo) d) Herpes simplex (4.2% 200 mg, 3.3% 100 mg, 1.8% placebo)
Serious Adverse Events of Special Intertest (based on product monograph)	N/A	N/A	Malignancy (0 patient on placebo, 2 on 15 mg, 7 on 30 mg) Serious Infections (5 patients on placebo, 26 on 15 mg, 30 on 30 mg) Thrombosis (2 patient on placebo, 1 on 15 mg, 1 on 30 mg)	Malignancy (0 patients on placebo, 4 on 100 mg, 2 on 200 mg) Serious Infections (2 patients on placebo, 18 on 100 mg, 16 on 200 mg) Thrombosis (0 patients on placebo, 0 on 100 mg, 5 on 200 mg) Major Adverse Cardiovascular Events (0 patients on placebo, 1 on 100 mg, 2 on 200 mg)
Recommended screening and monitoring Blood Work	N/A	N/A	Screening: HepB, HepC, TB, LFT, CBC, lipid panel Monitoring: CBC, LFT, lipid panel	Screening: HepB, HepC, TB, LFT, CBC, lipid panel Monitoring: CBC, LFT, lipid panel

Table 3. Comparison of targeted systemics approved in Canada for moderate-to-severe atopic dermatitis (AD) as of April 2022.

	MEASURE Up 1[6]		Measure Up 2[7]		AD Up[8]		HEADS UP[9]
Treatment (upadacitinib versus placebo)	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1	% of patients to achieve EASI75	% of patients to achieve vIGA of 0 or 1	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1	% of patients to achieve EASI75
15 mg	70%	48%	60%	39%	65%	40%	
30 mg	80%	62%	73%	52%	77%	59%	71%
Placebo	16%	8%	13%	5%	26%	11%	
Dupilumab 300 mg							61%

Table 4: Summary of primary endpoint results from the Measure Up 1 and 2, AD Up, and HEADS UP upadacitinib Atopic Dermatitis trials.
EASI75 (at least 75% improvement from baseline in Eczema Area and Severity Index)
IGA (Investigator Global Assessment)

	JADE MONO-1		JADE MONO-2		JADE COMPARE	
Treatment (abrocitinib versus placebo)	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1 & 2-point reduction	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1 & 2-point reduction	% of patients to achieve EASI75	% of patients to achieve IGA of 0 or 1 & 2-point reduction
100 mg	40%	24%	44%	28%	58%	36%
200 mg	62%	44%	61%	38%	70%	48%
Placebo	12%	8%	10%	9%	27%	14%
Dupilumab 300 mg					58%	36%

Table 5: Summary of primary endpoint results from the JADE MONO-1, JADE MONO-2, and JADE COMPARE abrocitinib atopic dermatitis trials.[10]
EASI75 (at least 75% improvement from baseline in Eczema Area and Severity Index)
IGA (Investigator Global Assessment)

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