

Approach to the Assessment and Management of Adult Patients With Atopic Dermatitis: A Consensus Document.

Section IV: Treatment Options for the Management of Atopic Dermatitis

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Abstract

The objectives of therapy for atopic dermatitis (AD) are to reduce skin inflammation and pruritus, restore skin barrier function, and improve quality of life (QoL). Treatments can be classified as moisturizing and basic care, topical therapy, phototherapy, and systemic therapy. In this review, we summarize the treatments for AD and recommendations for their use.

Keywords

atopic dermatitis, treatment options, topical, systemic, emerging therapy

There are many therapeutic options used in the management of atopic dermatitis (AD). However, the options for effective and targeted therapy for patients with moderate-to-severe disease have been more limited. The objectives of therapy are to reduce skin inflammation and pruritus, restore skin barrier function, and improve quality of life (QoL).

Treatments can be classified as moisturizing and basic care (emollients, cleansers, and other over-the-counter products), topical therapy, phototherapy, and systemic therapy, with recent guidelines placing topical therapy as first line.¹⁻³ Current guidelines also place phototherapy and/or systemic therapies as second line in patients refractory to topicals.¹⁻³

Moisturizing and Basic Care

The use of emollients is a cornerstone of AD therapy and prevention and is recommended in several guidelines.⁴⁻⁶ In addition, daily use is posited to have a steroid-sparing effect in patients with symptomatic AD and is strongly encouraged as maintenance therapy to reduce transepidermal water loss (TEWL), restore the epidermal barrier, and promote hydration.^{7,8} There are few head-to-head trials between specific moisturizers, with none demonstrating superiority of a specific product.⁹ There is a paucity of controlled studies evaluating the purported active ingredients in emollients (eg, plant extracts, colloidal oatmeal), with

several studies relying on biochemical markers rather than clinical outcomes to demonstrate efficacy.^{10-12,13}

Hydrophilic ointments and creams without added fragrances or preservatives are recommended over lipophilic emollients, as lipophilic products may cause irritation and should be applied to wet skin after bathing.¹⁴ At least 130 g/m²/wk of emollient should be recommended, which is approximately 250 g weekly for adults.¹⁵

Bathing and cleansing are important considerations for patients with AD. Not all experts agree on optimal bathing practices, and bathing has both positive and negative effects.¹⁶ Although bathing results in increased skin hydration and removes bacteria and irritants, water itself can be an irritant and impairs the epidermal barrier. While the evidence is scant, guidelines recommend daily bathing in lukewarm water for a maximum of 10 minutes, with avoidance of

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alkaline soaps and subsequent application of moisturizer.¹⁶ Bleach baths are commonly recommended as maintenance and preventative therapy, but evidence for their effectiveness in reducing disease severity and *Staphylococcus aureus* colonization is mixed.¹⁷ The general use of bleach baths is not recommended for patients with uncomplicated AD.

Topical Therapies

There are limited options for prescription topical therapy in AD. Until recently, topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) have been the only currently approved topical therapies for AD in Canada. Mayba and Gooderham¹⁸ provide a detailed overview of topical therapies for AD. In addition, the Eczema Society of Canada provides a concise summary chart of topical therapy formulations for health care providers (available at <https://eczemahelp.ca/wp-content/uploads/2016/11/ESC-Topical-Treatments-for-Atopic-Dermatitis-2016.pdf>), and the reader is referred to this patient support group for both patient and health care professional resources (www.eczemahelp.ca). Conventional and topical therapies are the mainstay of AD therapy and are sufficient in most patients, especially those with mild-to-moderate disease.

TCS are part of the first-line treatment for AD.^{6,7} The choice of TCS is dictated by potency, formulation, patient age, and body area to be treated.⁶ Potent and super-potent TCS should not be used in sensitive areas such as face, neck, skin folds, or genitals. Steroids are tapered slowly by some physicians once the clinical effect is obtained to avoid withdrawal rebound, despite limited evidence.⁶ Maintenance therapy with twice weekly TCS has been shown to prevent disease flares and is not associated with significant skin atrophy for up to 20 weeks.¹⁹⁻²¹ Wet wraps are a good option in patients with extensive AD and allow for TCS dilutions of as low as 1:20 hydrocortisone for 2 to 4 weeks without adverse effects.^{22,23} Lack of improvement during TCS treatment may be a sign of sensitization, and developing contact dermatitis and patch testing should be considered in these cases. Treatment noncompliance and steroid phobia are among the most common reasons for treatment failure with TCS; therefore, appropriate counselling is encouraged.²⁴⁻²⁶

TCI are second-line topical therapy for AD in patients who have not responded adequately to TCS, especially for those with frequent relapses of disease. TCI are especially useful as maintenance therapy; twice weekly tacrolimus has been shown to reduce relapses of AD.⁶ In moderate-to-severe patients over 16 years of age, 0.1% tacrolimus or 1% pimecrolimus is recommended.¹⁷ Head-to-head studies indicate that anti-inflammatory activity of 0.1% tacrolimus is superior to that of 1% pimecrolimus.^{27,28} Burning, stinging, and pruritus are the most common adverse events (AEs) encountered with TCI use.¹⁸ Again, these factors may impair treatment adherence in patients who are not counselled appropriately.

Importantly, these medications have been given a black box warning in several countries due to concerns regarding the theoretical risk of lymphoma associated with the use of TCI. Prospective studies do not appear to support this finding, and documented positive associations are likely marginal and confounded by disease severity.²⁹⁻³⁴ Interestingly, AD misdiagnosed as cutaneous T-cell lymphoma (CTCL) is likely to have led to misclassification bias. CTCL is therefore an important differential diagnosis to rule out during patient assessment.^{30,31}

Crisaborole, a topical phosphodiesterase 4 (PDE4) inhibitor, has recently been approved by Health Canada for the treatment of mild-to-moderate AD in patients 2 years of age or older.

Other topical therapies are used off-label in AD, and their routine use is neither supported by evidence nor recommended. These include antihistamines, cannabinoid or opioid receptor antagonists, topical anaesthetics, and capsaicin.

Phototherapy

Narrowband ultraviolet B (nbUVB, 311 nm) is a first-line phototherapy option in AD and has been demonstrated to have a steroid-sparing effect.^{35,36} It is most efficient in combination with TCS, moisturizers, and salt baths.³⁷ Typically, 2 or 3 treatments per week are used for 6 to 12 weeks or longer.³ Long-term use of nbUVB has not previously been shown to increase the risk of cutaneous malignancy in longitudinal case-controlled studies.³⁸

As an alternative, medium-dose UVA1 (340-400 nm) may be useful in patients with acute and severe skin inflammation due to a lower erythemogenic effect and comparable efficacy.^{6,39} Availability of and accessibility to phototherapy vary regionally but should be considered wherever available.

Systemic Therapies

Systemic therapies should be considered for patients with moderate-to-severe AD who fail first-line therapies. These may be classified into 3 main groups: systemic corticosteroids, conventional systemic therapies, and biologic therapy. Gooderham et al⁴⁰ summarize the available systemic treatment options, and the reader is referred to this publication for a comparative analysis of systemic treatment options.

There is not a standard definition for AD treatment failure. Due to the range of potency and dosage of TCS, it is difficult to generalize the time to treatment failure postinitiation. Studies have demonstrated that acute treatment of moderate-to-severe AD with high-potency TCS can reduce disease burden in 3 days with continual improvement for 3 weeks.² An American steering committee of AD experts published 4 types of treatment failure in AD: (1) inadequate clinical improvement, (2) failure to achieve stable long-term disease control, (3) failure to relieve impairment (ie, failure to improve QoL), and (4) unacceptable AEs.²

A Canadian working group of expert dermatologists recently recommended a simplified classification of adult patients with AD according to the effectiveness of their first-line topical treatments: (1) patients whose AD is adequately controlled with topical treatments and (2) patients with moderate-to-severe AD whose disease is not adequately controlled by topical therapies or in whom topical treatments are not appropriate.¹ Inadequate disease control is defined as absence of clinically meaningful improvement within 4 to 8 weeks of therapy initiation with TCS or TCI of at least moderate potency or disease flare within 1 week of discontinuation.¹

Many systemic therapies have little reliable evidence for their efficacy in AD. Furthermore, many are not indicated for AD in several countries. However, these are widely used therapeutic options for patients refractory to topical therapies and do provide benefit to patients with moderate-to-severe AD. A summary of the practical utilization of the available systemic therapies for AD is found in Table 1.

Systemic Corticosteroids

Systemic corticosteroids are approved by the US Food and Drug Administration (FDA) and Health Canada for patients with moderate-to-severe AD; however, there is a paucity of safety and efficacy data to support their long-term use in adult AD. Therefore, they are not recommended by the American Academy of Dermatology except for acute severe exacerbations and as a bridge therapy to other systemic, steroid-sparing treatments.³ In addition, a recent consensus statement by the International Eczema Council advises against the routine use of systemic corticosteroids for AD, noting that their use should be reserved for special circumstances and limited to short-term use.⁴¹

In adults, the evidence for prednisolone in treating severe AD is poor, with evidence of disease exacerbation following treatment discontinuation.^{42,43} Current literature supports the use of systemic corticosteroids only in short courses as a bridge to steroid-sparing immunosuppressants, given their poor tolerance, safety profile, and risk of severe rebound upon cessation of treatment.^{2,44}

Methotrexate

Methotrexate (MTX) is commonly used off-label in the treatment of moderate-to-severe AD in part due to its low cost. However, the evidence for MTX in the treatment of AD is scant.^{43,45} Small prospective studies and a few head-to-head trials show moderate efficacy in treating AD with moderate onset of response, good tolerability, and few adverse effects.⁴⁶⁻⁴⁹ The use of MTX should therefore be considered for use in patients with stable moderate-to-severe disease.

Cyclosporine A

Cyclosporine A (CsA) is considered the most efficacious non-biologic, steroid-sparing immunosuppressant for AD.^{2,43,50}

Amongst all of the oral immunosuppressants used off-label in AD, cyclosporine has the most robust efficacy and safety data shown in randomized controlled trials (RCTs), with a clinical improvement in AD severity of between 53% and 95% after short-term treatment.^{2,40} However, relapse rates are high upon discontinuation, and end-organ toxicity is a major concern in the long-term use of this therapy.⁴³ Therefore, CsA should be reserved for use as a short-term rescue therapy, particularly in patients experiencing acute disease flares or those with unstable disease. CsA should not be used for more than 1 year in the treatment of AD.

Azathioprine

Azathioprine (AZA) is used off-label in AD, with moderate treatment efficacy supported by a number of mostly older clinical studies, including a few small RCTs.^{48,51,52} In addition, AZA shows improvement in outcomes such as patient-reported itch and Dermatology Life Quality Index (DLQI).⁵¹ Importantly, AZA showed equivalent efficacy to MTX in a small head-to-head trial but with lower overall tolerability.⁴⁸

Common side effects such as gastrointestinal (GI) symptoms as well as serious AEs including end-organ toxicity, myelosuppression, and carcinogenicity are important considerations for use of this therapy in AD. Thiopurine methyltransferase (TPMT) activity or genotype should be measured (if available) prior to treatment initiation to determine dosing and to minimize the risk of myelosuppression.^{50,51}

Mycophenolate

Mycophenolate mofetil (MMF) and mycophenolate sodium are less commonly used, off-label systemic therapies in the treatment of AD. The available efficacy data for the treatment of AD are limited to small case series and case studies, showing moderate efficacy and good tolerability.^{2,53,54} Importantly, mycophenolate sodium was shown in a head-to-head trial against CsA to be equivalently effective as a maintenance therapy following a 6-week CsA therapy regimen, with a relatively longer time to relapse following treatment discontinuation.⁵⁴

MMF has a relatively slower onset of action compared to other immunosuppressants used in the treatment of AD.^{2,54} However, its relatively favourable tolerability and safety profile make it a reasonable maintenance therapy option.

Dupilumab

Dupilumab is the first biologic approved by Health Canada, the FDA, and the European Medicines Agency (EMA) for the treatment of moderate-to-severe AD. Dupilumab selectively inhibits type 2 cytokines interleukin (IL)-4 and IL-13.⁵⁵ Four phase III RCTs in over 2500 patients with AD have demonstrated significant clinical efficacy with respect to both objective and subjective measures of treatment efficacy.⁵⁵⁻⁵⁷ Clinical improvements appear to be rapid and sustained, with

Table 1. Overview of Available Systemic Therapies for the Treatment of AD.

Product	Drug Class/Target	Indicated for AD	Clinical Efficacy in AD	Safety	Laboratory Monitoring ⁴⁴	Additional Notes
Systemic corticosteroids	Steroid hormone	Yes	Small head-to-head RCT vs cyclosporine, N = 38 ⁴² Small placebo-controlled studies in pediatric AD, N = <30 ^{1,71-73} May not achieve stable remission in patients with severe AD ⁴³	Low tolerability and risk of severe rebound upon cessation of treatment ^{2,42,43}	Long-term treatment may require blood pressure monitoring, ophthalmologic examination, HPA axis suppression testing, bone density evaluation, blood counts and glycemia ^{45,74}	Use only in short courses as a bridge to steroid-sparing immunosuppressants
MTX	Immunosuppressant (folic acid inhibitor)	No	Moderate efficacy demonstrated in small prospective studies and head-to-head trials ⁴⁶⁻⁴⁹	Relatively well tolerated Possible AEs associated with MTX treatment can be mitigated with proper dosage titration ⁴³	Baseline only: - Hepatitis B and C - HIV if indicated - Pulmonary function tests if indicated Baseline and follow-up monitoring: - Tuberculosis - Renal and liver function - CBC, differential, platelets - HCG as indicated	Use in patients with stable disease
CsA	Immunosuppressant (broad spectrum)	No	53% to 95% mean clinical improvement in AD severity reported ² Rapid onset of response compared to MTX ⁴⁹ High relapse rates upon discontinuation (80% by 2 months)	Multiple toxicities associated with long-term or high-dose therapy, including nephrotoxicity and carcinogenicity ⁴³	Baseline only: - Urinalysis - HIV if indicated Baseline and follow-up monitoring: - Tuberculosis - Renal and liver function - Lipids - Blood pressure - CBC, differential, platelets - Mg ⁺ , K ⁺ , uric acid - HCG if indicated	Use only as short-term rescue treatment Not recommended for more than 1 year

(continued)

Table 1. (continued)

Product	Drug Class/Target	Indicated for AD	Clinical Efficacy in AD	Safety	Laboratory Monitoring ⁴⁴	Additional Notes
AZA	Immunosuppressant (purine analog)	No	Moderate efficacy demonstrated in several small studies and head-to-head trials ^{43,47} Improvements in pruritus and QoL reported ⁵¹	Dose-dependent side effects, including GI symptoms, hepatotoxicity and myelotoxicity ⁵² Chronic leukopenia incidence 5% to 25% and acute bone marrow failure may occur rarely ⁵²	Baseline only: - TPMT enzyme levels - Hepatitis B and C - HIV if indicated Baseline and follow-up monitoring: - Tuberculosis - Renal and liver function - CBC, differential, platelets - HCG if indicated	TPMT-based dosing reduces predicted toxicity while maintaining drug efficacy ^{51,75}
Mycophenolate	Immunosuppressant (nucleic acid synthesis inhibitor)	No	Moderate efficacy demonstrated in a few small studies ^{2,53,54} As effective as CsA as maintenance therapy ⁵⁴ Slower onset of action compared to other immunosuppressants ^{2,54}	Well tolerated, good safety profile Most commonly reported AEs include mild headaches, GI symptoms, and fatigue ⁵³	Baseline only: - Renal function - HIV if indicated Baseline and follow-up monitoring: - Tuberculosis - Liver function - CBC, differential, platelets - HCG if indicated	Appropriate as maintenance therapy
Dupilumab	Biologic (IL-4/IL-13 inhibitor)	Yes	Excellent efficacy demonstrated in several large phase III RCTs ⁵⁵⁻⁵⁷ Concomitant use of TCS furthers clinical improvement ^{56,57} Rapid onset of action ⁵⁵⁻⁵⁷	Well tolerated, good safety profile Most commonly reported AEs include injection site reactions and conjunctivitis ⁵⁵⁻⁵⁷ No laboratory monitoring	None	Use for the long-term treatment in patients who are inadequately controlled by topicals

Abbreviations: AD, atopic dermatitis; AE, adverse event; AZA, azathioprine; CBC, complete blood count; CsA, cyclosporine A; GI, gastrointestinal; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; K⁺, potassium; Mg⁺, magnesium; MTX, methotrexate; QoL, quality of life; RCT, randomized controlled trial; TCS, topical corticosteroid; TPMT, thiopurine methyltransferase.

Table 2. Systemic Therapies in Development for AD.

Product (Company)	Target	Program Status	Efficacy in Adult AD	Safety Signals	Additional Notes
Biologics					
Tralokinumab (LEO Pharma) ^{60,76}	IL-13	Phase III	Significant EASI-50 at 12 weeks for high-dose regimen with concomitant TCS	Most frequent AEs included nasopharyngitis, URTI, and headache with active arms similar to placebo	
Lebrikizumab (Hoffman-La Roche) ⁶²	IL-13	Phase II	Significant EASI-50 at 12 weeks for highest dose-frequency regimen with concomitant TCS	AEs were similar between treatment arms and placebo and mostly mild or moderate	
Nemolizumab (Chugai-Galderma) ⁶³	IL-31	Phase II	Significant pruritus reduction but no significant improvement in EASI scores at 12 weeks	The limited size and length of the trial preclude conclusions regarding adverse events	
Fezakinumab (Pfizer) ⁶⁴	IL-22	Phase II	Significant improvement in SCORAD scores in severe AD subgroup at 12 weeks	Tolerated well with no significant safety signals	
Secukinumab (Novartis) ⁷⁷ (NCT02594098)	IL-17A	Phase II	Has not been determined	Has not been determined in AD	Approved for the treatment of moderate to severe PsO, PsA, AS
Small molecules					
Baricitinib (Eli Lilly-Incyte) ⁶⁵	JAK1/2	Phase II	EASI-50 significantly reduced in high dose with concomitant TCS	No new safety signals consistent with data from other studies in RA, PsO, and alopecia areata	
Upadacitinib (Abbvie) ⁶⁸	JAK1	Phase II	EASI-90 significantly reduced at 16 weeks	No new safety signals detected	Upadacitinib achieved breakthrough therapy status by the FDA

Abbreviations: AD, atopic dermatitis; AE, adverse event; AS, ankylosing spondylitis; FDA, Food and Drug Administration; EASI, Eczema Area and Severity Index; EASI-50, EASI-90, the proportion of patients with an improvement on the EASI of at least 50% (EASI-50) or at least 90% (EASI-90); IL, interleukin; JAK, Janus kinase; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroid; URTI, upper respiratory tract infection.

clinical efficacy observed as early as 2 weeks and for as long as 52 weeks.^{55,56} Furthermore, the concomitant use of TCS appears to further improve clinical outcomes and, importantly, reflects the practical management of AD in real-world practice.^{56,57} Dupilumab does not appear to be associated with any major safety signals and does not require laboratory monitoring.⁵⁵⁻⁵⁷

A recent multidisciplinary consensus of AD experts recommended that dupilumab be used as a first-line systemic treatment in adults with moderate-to-severe AD who are uncontrolled with topical therapies.² This recommendation is based on the strong efficacy and safety data for dupilumab in comparison to the safety profiles of conventional systemic therapies that are not approved for use in AD.²

Emerging Therapies

Many of the conventional systemic immunosuppressants are nontargeted and have drug-specific risks associated with broad suppression of the immune system.⁵⁸⁻⁶⁰ Only in the past year has a new class of targeted systemic therapy

been approved for AD, and its efficacy underscores our understanding of the crucial role of type 2 inflammation in the pathogenesis of disease. The therapeutic pipeline has expanded greatly with this new knowledge of the underlying molecular basis of disease, and most therapies in development aim to target various points in this pathway. Emerging therapies for AD can be categorized into biologic therapies and small molecules, and a summary of the promising candidates in development for AD is represented in Table 2.

Emerging Biologic Therapies

A number of biologic agents are in various stages of development as treatments for AD. Tralokinumab and lebrikizumab are human monoclonal antibodies targeting IL-13, a type 2 cytokine important in mediating inflammation and epidermal barrier function. Both candidates show clinical efficacy in moderate-sized RCTs, with mostly mild to moderate safety signals.^{61,62} Nemolizumab targets the IL-31 receptor, which is thought to be a primary driver of itch. Accordingly, clinical

trial results show significant improvements in pruritus in patients with AD but not in Eczema Area and Severity Index (EASI) scores.⁶³ Fezakinumab targets IL-22, which is thought to play a role in barrier function and may be an important target in specific AD populations. Clinical trial results show clinical improvement only in the severe AD subgroup with good tolerability and safety.⁶⁴ Finally, secukinumab is approved for the treatment of moderate to severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis and is in development for the treatment of AD. The efficacy and safety of this molecule have not been determined for AD.

Emerging Small Molecules

Several promising small molecules are in development for the treatment of AD, the most promising of which target the Janus kinase (JAK) family of signalling molecules. JAK signalling lies downstream of multiple cytokine signalling cascades, including the type 2 inflammatory pathway. Baricitinib, PF-04965842, and upadacitinib target the JAK pathway and have shown significant clinical efficacy at 16 weeks, showing promise in the effective treatment of moderate-to-severe AD.⁶⁵⁻⁶⁸

There is a wide range of additional targets in clinical development for AD, including thymic stromal lymphopoietin (TSLP)/OX40 ligand, neurokinin 1 (NK1), the κ opioid receptor, and histamine H4.

Several groups have published guidelines or recommendations on the treatment and management of moderate-to-severe AD in adults.^{1-3,5,6,10,16,45,69,70} Publications before 2017 are outdated, as the availability of novel topical and biologic therapies has changed the treatment paradigm for adult patients with moderate-to-severe disease. However, published guidelines are largely in agreement on the patient management journey from assessment to therapy and their selection criteria for systemic therapy.¹⁻³ Our recommendations are largely in agreement with published treatment algorithms and have been updated to reflect current therapy options as well as to provide practical recommendations for assessment and management.

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