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Understanding and Managing Atopic Dermatitis: Insights into Pathogenesis and Treatment Strategies

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Abstract

Background:

Atopic dermatitis (AD), also known as atopic eczema, is a common, chronic, non-infectious, relapsing-remitting inflammatory skin disease with increasing incidence globally. It results from a complex interaction of immune dysregulation, genetic mutations, and environmental factors, causing severe itchy skin lesions. AD affects 10-20% of children and 2-10% of adults in industrialized countries and often precedes other atopic diseases such as asthma.

Aim of the Study:

This study aims to summarize the current knowledge on atopic dermatitis, including its epidemiology, etiology, and treatment methods.

Materials and Methods:

A literature review was conducted using the PubMed database with keywords: "atopic dermatitis," "atopic eczema," "JAK inhibitors," "calcineurin inhibitors," and "AD systematic treatment."

Conclusion:

AD is a multifactorial disease involving epidermal barrier defects, genetic predispositions, and immune dysregulation. Effective management requires a combination of topical and systemic therapies. First-line treatments include emollients and topical corticosteroids, with

newer options like phosphodiesterase inhibitors, JAK inhibitors, and biologics offering promising results. This study provides a comprehensive overview of AD, emphasizing the need for a multifaceted treatment approach.

Keywords: Atopic dermatitis, immune dysregulation, JAK inhibitors, calcineurin inhibitors, atopic dermatitis treatment

INTRODUCTION

Atopic dermatitis (AD), commonly referred to as atopic eczema, is a prevalent, chronic, non-infectious, relapsing-remitting inflammatory skin disorder that has seen a rise in incidence in recent decades [1]. AD arises from a multifaceted interplay of immune system dysregulation, genetic mutations affecting the epidermis, and environmental influences, all of which contribute to significant pruritic skin lesions [2].

AD impacts approximately 10–20% of children in industrialized nations and 2–10% of adults [3]. Although it typically begins in childhood, around 25% of individuals with AD experience adult-onset disease [4]. Early-onset AD may initiate the "atopic march," a progression in which AD precedes the development of other atopic conditions such as asthma, eosinophilic esophagitis, and rhinoconjunctivitis [5]. Over half of the patients with moderate to severe AD develop asthma, compared to 8% of those without AD [6].

Characteristic symptoms include erythema, edema, lichenification, dyspigmentation, oozing, and xerosis. In infants, lesions often present as small bumps on the cheeks, whereas older children and adults frequently exhibit rashes on the knees, elbows, hands, or scalp. AD is marked by severe pruritus, especially nocturnal, often accompanied by skin pain and restricted daily activities [7–9]. The itching and unsightly lesions can lead to sleep disturbances and social embarrassment, increasing the prevalence of mental health disorders such as anxiety and depression, thus significantly impairing the quality of life for patients and

their families. Chronic sleep deprivation may also elevate the risk of cardiovascular, metabolic, and psychiatric conditions [10–12].

PATHOGENESIS

AD etiology is multifactorial and involves complex interactions between epidermal barrier defects, genetic disorders, innate and acquired immune dysregulation (including excessive T helper 2 (TH2 and TH22) cell activity), microbiome changes, and environmental factors [7].

Epidermal Barrier Defects. The skin microbiome plays a crucial role in the pathogenesis of AD [13]. The epidermis serves as a physical barrier, preventing microorganism penetration and retaining moisture and nutrients. It acts as the first line of immunological defense and comprises a complex ecosystem known as the skin microbiome. Barrier dysfunction in AD is characterized by reduced microbial diversity, dryness, altered lipid composition, and increased permeability, facilitating colonization by Staphylococcus aureus [14]. S. aureus, a gram-positive opportunistic bacterium, produces virulence factors such as superantigens (SAgs) like enterotoxins (SEA, SEB), toxic shock syndrome toxin 1 (TSST1), exotoxins, phenol-soluble modulins (PSMs), and proteases, all contributing to skin inflammation and barrier dysfunction in AD [13]. Dysregulated lipid metabolism, particularly reduced ceramides, leads to transepidermal water loss and increased penetration of irritants, allergens, and microbes. This barrier disruption results in chronic inflammation with epidermal hyperplasia and cellular infiltrates, including dendritic cells, eosinophils, and T-cells [1].

Genetic Factors. Children of parents with a history of allergic diseases have a significantly higher risk of developing AD. If one parent has AD, the risk triples, and if both parents are affected, the risk increases fivefold [1]. Numerous genes are implicated in the pathogenesis of AD. The first group includes genes whose mutations impair the epidermal barrier function. The second and third groups involve genes related to innate or adaptive immune response mechanisms, leading to overreactivity in the TLR system, excessive production of Th2 cytokines, or dysfunction in regulatory T lymphocytes. Genes encoding Th1, Th17, and Th22 cytokines play a fundamental role in the chronic phase of the disease. The fourth group comprises interleukin genes produced by keratinocytes under stress, such as IL-25, TSLP, and IL-33. The fifth group involves genes related to vitamin D metabolism and its receptor synthesis [15][16]. The filaggrin gene mutation is particularly notable, located on chromosome 1q21 in the epidermal differentiation gene complex (EDC) [17]. Filaggrin is a structural protein essential for the mechanical strength and integrity of the stratum corneum,

with its metabolites contributing to the natural moisturizing factor. Loss-of-function (LoF) mutations in the gene encoding filaggrin (FLG) are present in 10% to 40% of AD patients [18].

Immune System. Atopic eczema was initially considered a T-helper 2 (Th2) mediated condition with excessive IgE production in response to allergens. However, it is now recognized as a lifelong condition with variable clinical expression, involving epidermal barrier dysfunction, immune system anomalies, and microbiome alterations [19]. The clinical manifestation of AD results from the presence of T cells, IgE-binding antigen-presenting dendritic cells, and eosinophils [20]. TH2, TH22, and TH17 cells are the main drivers of the acute form of AD, while TH1, TH2, and TH22 cells are responsible for the chronic phase of the disease. TH17 cells are the source of Interleukin-17 (IL-17). Increased IL-17 and IL-22 expression are usually associated with acute and chronic AD lesions, with higher IL-22 expression commonly found in acute lesions [21]. The Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway plays a key role in the pathogenesis of AD. Cytokines such as IL-4, IL-5, IL-13, IL-31, IL-22, and thymic stromal lymphopoietin (TSLP) activate the JAK-STAT pathway, recruiting immune cells, keratinocytes, and peripheral sensory neurons involved in propagating inflammation and itch. AD is associated with increased signaling through all four JAKs (JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2)), unlike other autoimmune conditions such as psoriasis or alopecia areata, where typically one predominant JAK pathway is dysregulated [22].

Environmental Factors. Environmental factors such as increased exposure to airborne or food allergens, pollution, tobacco smoke, infections, use of antibiotics, breastfeeding duration, diet, cosmetics, pets, and strong detergents are significant contributors to the pathogenesis of AD [17].

DIAGNOSIS

The diagnosis of atopic dermatitis (AD) is primarily clinical, involving a detailed patient history with special attention to personal and family history of atopic disorders, along with a thorough physical examination. A skin biopsy is typically unnecessary [20]. The Hanifin-Rajka criteria serve as the "gold standard" for diagnosing AD [23]. Differential diagnoses include other dermatitis forms such as allergic or irritant contact dermatitis, childhood scabies, and early-stage cutaneous T-cell lymphoma in adults [20].

TREATMENT

Management of atopic dermatitis in both adults and children requires a multifaceted approach integrating pharmacological and non-pharmacological therapies [24]. Treatment objectives include reducing inflammation, preserving skin barrier integrity, alleviating pruritus, and preventing superinfections associated with stratum corneum degradation [25]. Effective and safe interventions are crucial for optimal management of atopic dermatitis, given its tendency for frequent relapses [26].

TOPICAL AGENTS

Emollients. Emollients constitute fundamental therapy aimed at restoring the skin barrier integrity in atopic dermatitis (AD), addressing xerosis and alleviating itching. They play a pivotal role irrespective of AD severity, remedying impaired keratinization, decreased water binding, and abnormal lipid composition. Regular, daily application of emollients extends remission periods and reduces acute phase severity, often minimizing the need for steroids [18,19]. Emollients should be applied liberally and frequently, with adults advised to use at least 250g weekly. Optimal formulations exclude allergenic preservatives like parabens and emphasize physiological lipids (cholesterol, ceramides, free fatty acids), ideally in a 3:1:1 ratio of ceramides to cholesterol and saturated fatty acids. Moisturizers (humectants) and occlusive agents enhance efficacy by preventing water evaporation. Adequate skin cleansing is crucial to remove debris, sebum, and environmental pollutants, maintaining skin hydrolipidic balance essential for physiological homeostasis [18,19].

Topical corticosteroids (TCS). TCS are the first-line treatment for AD) exerting anti-inflammatory, anti-mitotic, and immunosuppressive effects [27]. The selection of appropriate strength, dosage, and duration of use poses significant challenges for both general practitioners and patients [24]. TCS are categorized by potency and potential side effects, including skin atrophy, stretch marks, rosacea, perioral dermatitis, telangiectasia, purpura, and other cutaneous and systemic reactions [28]. Additional adverse effects may include folliculitis, periocular dermatitis, delayed wound healing, hypopigmentation, hypertrichosis, masking or aggravation of dermatophyte infection, secondary infections, and contact dermatitis [28]. Topical glucocorticosteroids are particularly challenging to use on the face, intertriginous areas, scrotum, and the scalp of infants. In these regions, only low- or intermediate-potency steroids should be used for short durations [20]. For the face and eyelids, hydrocortisone 0.5% or 1% is generally safe. Higher-potency corticosteroids should be

avoided due to the risk of periorificial dermatitis, a steroid-induced form of rosacea. The body and limbs tolerate topical corticosteroids better than the face, with fewer adverse effects. Super-high-potency steroids should not be used for more than three weeks and should be tapered afterward to mitigate adverse effects. High- and medium-potency corticosteroids should be limited to a maximum of 12 weeks [27]. Wet compresses can enhance the efficacy of topical corticosteroids, but this should be done for short periods and under medical supervision [28].

Calcineurin inhibitors (TCIs). TCIs, such as pimecrolimus and tacrolimus, represent valuable topical anti-inflammatory therapies for atopic eczema, particularly suitable for use on the face and eyelids when mild topical corticosteroids are ineffective or potent corticosteroids are not preferred [24]. Pimecrolimus, derived from Streptomyces hygroscopicus var. Ascomyceticus, exhibits local anti-inflammatory effects with minimal systemic absorption [29]. Its potency is comparable to that of mild corticosteroid creams, while tacrolimus is considered moderate to strong in potency [30]. Pimecrolimus is well-tolerated for both short- and long-term use [31]. Topical calcineurin inhibitors do not heighten the risk of bacterial infections, but there is a slight elevation in viral infections, such as herpes simplex virus, with rates ranging from 10% to 20% [32]. The most common initial adverse effect of calcineurin inhibitors is a transient stinging or burning sensation, which typically diminishes within a few days [33]. Combination therapy using corticosteroids and calcineurin inhibitors is beneficial for managing flares and implementing proactive treatment for long-term control of atopic dermatitis. Proactive therapy involves intermittent, long-term application twice weekly in areas prone to relapse, following healing of visible lesions. This approach reduces recurrence rates and minimizes the need for glucocorticoids, thereby lowering the risk of side effects like skin atrophy [1,2].

Ultraviolet phototherapy. Ultraviolet (UV) phototherapy represents a viable option for treating atopic dermatitis when initial therapies prove ineffective [2]. UV radiation is categorized into UVA (320-400 nm), UVB (290-320 nm), and UVC (200-290 nm), with UVA further divided into UVA1 (340-400 nm) and UVA2 (320-340 nm) [34]. Phototherapy options for atopic dermatitis include broadband UVB (BB-UVB, 290-320 nm), narrowband UVB (NB-UVB, 311-313 nm), psoralen ultraviolet A (PUVA) therapy, and UVA1 cold light therapy [34]. Narrowband UVB phototherapy, specifically, is considered a second-line treatment for moderate to severe atopic dermatitis due to its reduced side effects compared to other UV therapies [34]. Phototherapy mechanisms involve decreased expression of pro-inflammatory cytokines, inhibition of Langerhans cell activity, and suppression of T

lymphocyte-mediated immune responses [34]. Despite its efficacy, phototherapy may be challenging for routine use due to tolerability issues, feasibility concerns, and logistical burdens [14]. Safety precautions, such as wearing protective eyewear and standing independently in a lighting cabinet, are crucial before considering phototherapy for children [24]. Combining phototherapy with topical calcineurin inhibitors or systemic immunosuppressive agents is generally discouraged due to potential interactions and increased risks [20].

Topical phosphodiesterase inhibitors. Topical phosphodiesterase inhibitors represent a nonsteroidal treatment approach targeting phosphodiesterase-4 (PDE-4), an intracellular enzyme pivotal in inflammation by degrading cyclic adenosine monophosphate (cAMP) [23]. Elevated PDE-4 activity in circulating immune cells of atopic dermatitis (AD) patients correlates with increased levels of proinflammatory cytokines and chemokines such as IL-2, IL-4, and IL-31, which exacerbate AD symptoms [23]. Crisaborole, a topical PDE-4 inhibitor, mitigates inflammation by reducing cytokine production through its inhibition of PDE-4 [23]. Crisaborole offers a promising alternative for AD treatment, especially in cases refractory to conventional therapies [35]. However, its use may be limited by application site discomfort, potentially restricting its broader application [35].

Topical JAK Inhibitors. Topical JAK inhibitors (JAKi) encompass small molecules designed to selectively target specific JAK receptors—JAK1, JAK2, JAK3, and TYK2—or combinations thereof [22]. Formulations such as delgocitinib, ruxolitinib, and tofacitinib are currently available [18]. Ruxolitinib, a topical cream containing a JAK1/JAK2 inhibitor, has gained approval for managing mild-to-moderate atopic dermatitis in patients aged 12 years and older, supported by robust safety and efficacy profiles [22]. Research continues to explore the potential applications of various JAK inhibitors in chronic hand eczema and broader atopic dermatitis treatment paradigms. Ruxolitinib demonstrates efficacy in alleviating pruritus and exhibits favorable tolerability, with nasopharyngitis being the most commonly reported adverse event during treatment [22].

SYSTEMIC AGENTS

Corticosteroids. Corticosteriods should be reserved for exceptional cases and short durations (from a few days to three weeks) to manage acute flares [14, 19]. Despite their potent anti-inflammatory effects, systemic corticosteroids do not address barrier defects or innate immunity issues and may lead to adverse effects. Moreover, discontinuation often results in a rebound effect.

Other immunosuppressants. Systemic immunosuppressants agents such as cyclosporine, methotrexate, azathioprine, and mycophenolate are used for systemic immunosuppression in atopic dermatitis. Their variable efficacy and associated safety risks, including the need for frequent laboratory monitoring, limit their broader use [36]. Cyclosporine is approved for short- to medium-term treatment of severe atopic dermatitis, with caution against prolonged use due to potential complications like hypertension and renal insufficiency [14, 20]. Azathioprine and mycophenolate mofetil are alternatives when cyclosporine is ineffective or unsuitable [20].

Biological Treatment. Dupilumab, a fully human monoclonal IgG4 antibody, blocks IL-4 and IL-13 signaling by binding to the shared α-subunit of the IL-4 receptor, thereby inhibiting the Th2 response crucial in AD pathogenesis [37]. It effectively inhibits Th2-associated chemokines and reduces expression of hyperplasia-related and IL-17/IL-22-modulated genes. Dupilumab is approved for moderate-to-severe AD in adults, adolescents, and children when topical therapies are inadequate or inappropriate. It is used concomitantly with daily emollients and may be combined with topical corticosteroids as needed [18]. Common adverse events include conjunctivitis, nasopharyngitis, upper respiratory tract infections, sinusitis, blepharitis, local reactions at injection sites, and herpes simplex virus infections [37]. Conjunctivitis is the most common adverse event, typically mild to moderate and self-limiting; artificial tears may be recommended at treatment initiation. Dupilumab is generally considered a safe and effective biologic therapy with minimal adverse effects. Omalizumab, another monoclonal antibody targeting free IgE via recombinant technology, inhibits its binding to receptors on mast cells and basophils. Further studies are needed to explore its potential in AD treatment due to its favorable safety profile [39]. Amlitelimab, targeting OX40 ligand in the immune system, shows promise in alleviating AD symptoms beyond placebo effects. This novel treatment warrants further investigation in larger clinical trials [40].

JAK Inhibitors. Upadacitinib, a selective JAK1 inhibitor, suppresses downstream cytokine signaling, making it immunosuppressive [24]. Metabolized primarily by CYP3A4, its plasma levels are influenced by strong CYP3A4 inhibitors or inducers. Upadacitinib achieves rapid onset of action with a significant reduction in AD severity in 70-80% of patients within 16 weeks of oral administration. However, JAK inhibitors can cause cytopenia and elevated lipid levels, necessitating regular blood tests. Common adverse effects include upper respiratory tract infections, acne, and an increased risk of infections such as herpes simplex and shingles.

CONCLUSION

The pathogenesis of AD involves a combination of genetic predisposition, immune dysregulation, epidermal barrier dysfunction, and environmental influences. The clinical manifestation of AD varies widely, from mild to severe forms, with significant impacts on patients' quality of life due to chronic itching, sleep disturbances, and potential mental health comorbidities. Effective management of AD necessitates a comprehensive approach integrating both pharmacological and non-pharmacological therapies. Topical treatments such as emollients, corticosteroids, calcineurin inhibitors, and emerging therapies like JAK inhibitors provide targeted relief by addressing inflammation and restoring skin barrier function. Systemic agents like corticosteroids, immunosuppressants, and biologics such as dupilumab and omalizumab offer additional options for severe cases resistant to topical therapies. Advancements in understanding AD pathophysiology have paved the way for novel therapeutic strategies targeting specific immune pathways, such as IL-4/IL-13 signaling inhibition and JAK-STAT pathway modulation.

Author's contribution

Conceptualization, Wiktoria Julia Krzesłowska and Kamila Szewczyk; methodology, Weronika Hołownia, Kamila Szewczyk, Paulina Pytel; software, Szymon Wiśniewski, Bartłomiej Szewczyk; check, Weronika Hołownia, Szymon Wiśniewski; formal analysis, Wiktoria Julia Krzesłowska and Paulina Pytel; investigation, Bartlomiej Szewczyk; resources, Szymon Wiśniewski, Bartłomiej Szewczyk, Weronika Hołownia; data curation, Weronika Hołownia, Szymon Wiśniewski; writing - rough preparation, Kamila Szewczyk; writing - review and editing, Kamila Szewczyk; project administration, Wiktoria Julia Krzesłowska, Bartłomiej Szewczyk.visualization, Kamila Szewczyk, Weronika Hołownia; supervision, Kamila Szewczyk, Paulina Pytel;All authors have read and agreed with the published version of the manuscript.

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