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Knowledge Gaps in the Treatment of Atopic Dermatitis

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ABSTRACT

Atopic dermatitis is a complex chronic inflammatory skin disorder with a rising global prevalence, affecting 2.6% of the population worldwide. Its multifactorial nature, influenced by genetic, environmental, and immunological factors, challenges effective treatment and management. This article highlights key knowledge gaps in atopic dermatitis treatment, including genetic predispositions, diagnostic dilemmas, pruritus management, and psychosocial impacts. It emphasizes the need for a personalized approach to atopic dermatitis care, leveraging advancements in genetic research, metabolomics, and biomarkers to enhance drug discovery and improve disease outcomes. Despite various therapeutic options, there remains an unmet need for treatments that effectively address atopic dermatitis' physical, psychological, and socioeconomic burdens. The role of psychosocial factors, treatment adherence, and the economic impact of atopic dermatitis are also explored. Current therapeutic approaches remain inadequate, underscoring the need for continued research into novel targeted therapies and improved patient care strategies.

Introduction

Atopic dermatitis is a chronic inflammatory condition characterized by recurring flares and remissions, with its global incidence rising steadily over the past decade[1]. Worldwide, the prevalence of atopic dermatitis is estimated to be around 2.6%, making it the skin disorder with the highest impact on disability-adjusted life years (DALYs)[2]. Among nonfatal diseases, atopic dermatitis ranks within the top 15, contributing 0.36% to the total DALYs burden out of 359 diseases and injuries assessed[3].

Due to a complex interplay between factors such as genotype, environmental triggers, alteration in microbiome signals, and responses of both innate and adaptive immune systems, the treatment becomes quite challenging due to its multifaceted influences[4]. It is a heterogenous skin disease with a variable disease course and morphology requires a more personalized treatment plan. The severity of the disease is assessed by evaluating objective signs, often overlooking subjective symptoms such as pruritus and psychological distress, which can be bothersome for the patients and decrease their quality of life[5]. Therapy should encompass achieving good disease control, addressing pruritus, and prioritizing the mental well-being of both patients and their caretakers for a comprehensive approach[3]. Mild forms of the disease are typically managed with appropriate skin care and topical therapies, while moderate to severe cases often necessitate systemic treatments. However, these therapies remain inadequate or unsatisfactory for many patients. The burden of atopic dermatitis is significant, particularly for children with moderate-to-severe cases and their caregivers. Systemic therapies' efficacy and side effect profiles vary, undermining clinicians' confidence in prescribing them.

Currently, there is no comprehensive and fully satisfactory treatment modality or protocol for atopic dermatitis, leaving significant unmet needs in its management. This review focuses on identifying and addressing the existing treatment gaps in atopic dermatitis.

Genetics

Approximately 80% of atopic dermatitis cases have a genetic predisposition, making the genome a significant focus of research for potential therapeutic targets. The loss of function in the Filaggrin gene has been identified as the strongest risk factor. At the same time, genome-wide association studies (GWAS) have uncovered various other genes that contribute to pathogenesis.[6]

Genome-wide association studies enable researchers to pinpoint genes linked to specific diseases or traits by examining a large population's entire DNA sequence (genome). This approach looks for even the slightest genetic variations, such as single nucleotide polymorphisms, insertions, or deletions, between individuals with the condition and those without. Additionally, genome-wide association studies has been used to explore how these genetic differences can influence a person's response to certain medications and their susceptibility to environmental factors like toxins.[7]

Researchers studying atopic dermatitis use large-scale genome-wide association studies across various populations, followed by fine mapping to pinpoint specific genetic markers. These markers undergo functional and epigenetic analysis to understand their role in the disease. The resulting insights will advance personalized medicine and drive drug discovery, leading to more targeted and effective treatments for atopic dermatitis.

Most loci identified by genome-wide association studies are located in intergenic regions, where their functional mechanisms remain elusive. Notably, the single nucleotide polymorphisms (SNPs) implicated are situated within the extensive intergenic region between EMSY a gene encoding a transcriptional regulator, and LRRC32, which encodes a transmembrane receptor on activated T-regulatory cells that influences TGF-beta activity[8,9]. These loci necessitate in-depth molecular studies within cells and tissues relevant to atopic dermatitis to understand their role in the disease better.[10]

Genome-wide association studies have identified numerous genes associated with atopic dermatitis, yet these genes are also present in unaffected individuals. The mechanisms underlying the phenotypic expression of the disease remain unclear and need further in-depth analysis.

Rare genetic variants have not been studied as extensively as common variants, despite their potential to exert moderate to significant effects on complex traits. Due to the high cost of whole-genome sequencing (WGS), whole-exome sequencing (WES) serves as a more practical alternative[8]. Whole-exome sequencing targets approximately 1% of the genome, focusing on coding and splice-site variants within annotated genes, making it particularly suitable for identifying genes associated with highly penetrant Mendelian disorders such as atopic dermatitis[9].

While genome-wide association studies examine numerous genetic variants for each trait, phenome-wide association studies (PheWAS) reverse this approach, analyzing multiple traits for their association with a single genetic variant[11]. This method can identify shared genetic factors and uncover novel associations, deepening our understanding of atopic dermatitis' complex genetic architecture, aiding drug discovery.

Phenome-wide association studies provide valuable insights into the multimorbidity associated with atopic diathesis and the potential pleiotropic effects of environmental factors[12]. This approach may help address key questions, such as differences in ethnic presentations, and elucidate the relationship between environmental exposures and phenotypic expression.

Metabolomics is a powerful tool that captures the phenotypic outcomes of various biological processes, such as environmental exposures, skin barrier function, and skin microbiota[13]. By examining the relationship between metabolite alterations and physiological or pathological changes, metabolomics offers valuable insights that can aid in identifying novel therapeutic targets.

Given the high genetic heritability of Atopic dermatitis, identifying causal genes is essential for developing

effective preventive and therapeutic strategies. Only 15% of risk variants have been identified through GWAS, and rare genetic variants account for an additional 12% of atopic dermatitis heritability. This underscores the importance of investigating the role of rare protein-coding variants in atopic dermatitis. With approximately 70% of heritability still unexplained, significant research is needed to understand individual risk factors fully which will pave the way for the development of new targeted therapies[14]. To explore these areas more thoroughly, additional studies are required to examine phenotype subgroups, less common and rare genetic variants, interactions between genes and the environment, gene-to-gene relationships, as well as epigenetic factors. Furthermore, integrating data from multi-omics technologies will be essential in advancing this research.

Diagnostic Dilemma

Atopic dermatitis is characterized by erythema, scaling, and pruritus, symptoms that are also common in other inflammatory skin conditions, including infections, allergic reactions, malignancies, and nutritional disorders. As the symptoms and signs of Atopic dermatitis can differ across various age groups and skin types, applying the same diagnostic criteria universally may lead to overestimation or underestimation of the disease in certain populations.

Accurately diagnosing atopic dermatitis with high specificity is essential in both clinical trials and practice, particularly given the expense of newer treatments, such as systemic biologic agents. Establishing precise diagnostic criteria ensures the reliability and reproducibility of studies by clearly defining a consistent and appropriate patient population[15].

Two studies assessing the Hanifin and Rajka diagnostic criteria found sensitivity ranging from 87.9% to 96.0% and specificity from 77.6% to 93.8%. Conversely, 19 validation studies of the UK diagnostic criteria showed a broader range, with sensitivity between 10% and 100% and specificity from 89.3% to 99.1%, making the UK criteria the most extensively validated. [16].While the Hanifin and Rajka (HR) diagnostic criteria and the United Kingdom Working Party (UK) criteria represent significant advancements, they are limited by usability issues and low sensitivity, respectively.[16]

Accurately diagnosing a history of atopic dermatitis in adults is challenging due to the overlapping symptoms with other skin conditions and the fluctuating nature of atopic dermatitis. Histopathological findings are not specific in the diagnostic evaluation of atopic dermatitis. As a result, clinicians mainly depend on clinical features to make a diagnosis. Potential biases in the original validation study, conducted by the same UK Working Party (UKWP) members who developed the criteria, may have influenced the results. Additionally, the UKWP criteria have not been specifically validated for an exclusively adult European population, which raises concerns about their applicability in this demographic. When applied to a unique cohort of psoriasis patients, the UKWP criteria identified a significant proportion of psoriasis cases, ranging from 19.7% to 47.7%, suggesting that these criteria may lead to overdiagnosis.[17]

Several severity scales, such as Scoring for atopic dermatitis (SCORAD), incorporate a combination of clinical signs like erythema, excoriation, and lichenification. Erythema is evaluated in these scales either directly, as seen in SCORAD and the Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score, or indirectly through the assessment of lesion extent, as in the Rajka and Langeland system and the Nottingham Eczema Severity Score (NESS)[18]. However, in many individuals with dark skin, erythema may not be visibly apparent and may present merely as skin darkening, potentially leading to misdiagnosis and an underestimation of the condition's severity.

Currently, no reliable biomarker exists to definitively distinguish this disease from other conditions. Historically, measurements of total or allergen-specific IgE levels, along with increases in tissue mast cells and peripheral eosinophil counts, have been assessed. However, these markers have shown inconsistent associations and are generally nonspecific[19,20].

Despite significant research efforts and the investigation of numerous biomarkers both skin and serum, including nitric oxide synthase 2/inducible nitric oxide synthase (NOS2/iNOS), matrix metalloproteinases (MMPs), human beta-defensin 2 (hBD-2), IL-36α, IL-36γ, CCL26, and CXCL9, the clinical application of these markers remains uncertain[21,22,23]. This is largely due to limitations such as small sample sizes and the lack of standardized detection methods. As a result, their routine use in clinical practice has yet to be established.

While various diagnostic criteria exist, relying solely on them can lead to misdiagnosis. Therefore, A comprehensive diagnostic tool is needed to accurately diagnose the condition. This tool should be tailored with age-specific modifications and encompass skin, serum, and genetic biomarkers, in addition to general severity assessment.

Controlling Pruritus

Atopic dermatitis is often referred to as the "itch that rashes" because the itching begins first, leading to skin rashes due to scratching. Chronic pruritus is the most distressing symptom of atopic dermatitis, causing significant sleep disturbances and a decreased quality of life[24]. Patients with apparent clinical improvement often complain of pruritus, underscoring the importance of addressing subjective symptoms. Therefore, the quality of life does not proportionately correlate with the observable clinical features of the patient. It was found that in a study about 91% of patients suffered from pruritus and had either associated symptoms such as pain (59%) or heat sensation (53%)[24].

Patients' descriptions of pruritus are subjective and may include sensations such as itching, burning, tingling, or stinging. Due to this subjectivity, accurately assessing pruritus in clinical practice can be challenging. Currently, there are no serologic or tissue markers available to objectively determine the nature or severity of itch[25].

Although validated tools like the Visual Analog Scale (VAS) and Numeric Rating Scale (NRS) are commonly used, they have limitations as they rely on patient-reported outcomes. These self-reported scores often do not align well with objective measures of scratching behavior, such as those obtained through actigraphy[26].

Itch despite being a frequently reported symptom, it is not routinely evaluated by many clinicians. Patients often feel that healthcare providers do not take their pruritus seriously, which can lead to insufficient treatment and low patient satisfaction[27,28]. Therefore, healthcare providers should routinely assess patients' itch and consider adjusting or switching treatments if the patient continues to report worsening or lack of significant improvement in pruritus[29], even when there is a noticeable improvement in objective signs and symptoms.

Stress is a common trigger for flares that worsen pruritus. Psychological stress disrupts permeability barrier homeostasis by increasing endogenous glucocorticoids. Insomniac psychological stress further impairs barrier function and stratum corneum integrity, reducing epidermal cell proliferation, differentiation, and corneodesmosome density due to protein degradation like desmoglein1. Psychological stress also inhibits epidermal lipid synthesis, decreasing lamellar bodies and weakening the barrier and stratum corneum.[30]

The close connection between the psyche and skin is well established, with psychogenic and emotional factors known to amplify the perception of itch. However, the precise mechanisms behind this interaction require further investigation to determine whether they could serve as therapeutic targets.

There is no single receptor for itch or pain; both are transmitted by unmyelinated C fibers in the epidermis and dermal-epidermal junctions. They travel through the dorsal root ganglia and ascend via the contralateral spinothalamic tract to the thalamus, where they are then processed in the cingulate and other cortical areas, including the parietal lobes, allowing us to experience the discomfort of pain and itch[31]. Therefore, evaluating whether pain medications can be modified to develop treatments for itch is important, given the shared pathways in pain management.

Understanding the neurological mechanisms linking itch, scratching, sleep disturbances, and systemic inflammation is crucial. Clinical psychologists play a key role[32], using habit reversal techniques where patients recognize scratching and replace it with alternative behaviors. Patients track scratching episodes and share progress with a therapist or support group, with social reinforcement encouraging adherence to these new behaviors[33]. Sleep disturbances which is often secondary to pruritus in children, whether acute or chronic, have been correlated with various cognitive, mood, and behavioral issues, as well as lower academic performance.

Despite the wide range of available treatments, the response is often delayed and does not attain satisfactory results. Also, only a very few studies evaluate drug-free remission periods specifically for pruritus; most research tends to focus on overall clinical improvement instead.

Interleukin 31 is crucial in pruritus for various dermatological conditions. Nemolizumab, an IL-31 receptor A antagonist, showed over 50% improvement in pruritus in a recent trial. Tralokinumab and lebrikizumab, which target IL-13, are in trials for atopic dermatitis, while Tezepelumab, an anti-TSLP monoclonal antibody, is also being explored for the condition[34,35]. Despite many such drugs being in development, there is an urgent need to accelerate clinical trials to address the critical treatment gap in managing pruritus.

For all patients, it's essential to focus on barrier repair, sleep assessment, and patient education. In severe cases of atopic dermatitis flares, managing systemic inflammation with targeted monoclonal antibodies or immunosuppressants may be required[29]. It's also important to evaluate whether the patient is experiencing underlying psychological stress which can impact pruritus, often overlooked during outpatient visits. A study by Weishaar et al. revealed that emotional responses like aggression and depression were more common in dermatology patients than in those suffering from systemic pruritus[36]. This emphasizes the need for a psychologist's input when pruritus remains unmanageable despite escalated treatment.

Educating patients on proper skin care practices is essential but can be time-consuming especially in resource-limited settings, particularly in developing countries where outpatient visit times are constrained. To address this, providing educational leaflets and pamphlets in the patient's vernacular language or creating a freely accessible website can help deliver crucial information effectively.

While pharmaceutical companies continue to develop a range of targeted therapies, there is still no FDA-approved drug specifically for controlling pruritus. This may be due to the complex and multifactorial pathogenesis of itch, which differs across conditions like inflammatory or systemic-associated pruritus. Although the peripheral mechanisms vary significantly between diseases, the central perception of itch may involve shared pathways. Further research is needed to determine whether therapeutic strategies should focus more on targeting central neural processes rather than solely blocking peripheral interleukins or chemokines. Therefore, there is an increasing need to delve deeper into the pathomechanisms of itch to develop new, targeted therapies with fewer side effects.

Antihistamines are often used as a blanket treatment for various types of itch, including itch associated with atopic dermatitis. While they are effective for conditions like urticaria, they tend to be less beneficial for other forms of pruritus. In atopic dermatitis, the itch-relief from first-generation antihistamines is primarily due to their sedative effects rather than actual reduction in overall itch[37]. Antihistamines may provide relief from histamine-induced itching, but they are less effective in addressing the multiple factors that contribute to itch in atopic dermatitis. Moreover, using antihistamines in high doses can lead to side effects like daytime sleepiness, weight

gain, dry mouth, urinary retention, and dizziness. Although newer-generation antihistamines have been developed with fewer side effects, more robust studies are needed to determine their efficacy in reducing pruritus in atopic dermatitis patients.

Itch is the most reported symptom in dermatology and can stem from a variety of causes, including dermatologic, systemic (e.g. renal, hepatobiliary, endocrine), paraneoplastic, neuropathic, psychogenic origins or systemic drugs[38]. Currently, there are no validated treatment algorithms or diagnostic tests to differentiate between these causes of itch. Therefore, even after a thorough clinical examination, detailed history, dose adjustments, and escalation of treatment for atopic pruritus, significant improvement may not always be achieved. In such cases, it is essential to rule out underlying systemic diseases and psychogenic factors coexisting with atopic dermatitis. A biopsy should be considered to exclude chronic dermatologic conditions such as pityriasis rubra pilaris, mycosis fungoides, psoriasis when conventional atopic dermatitis treatments fail to alleviate pruritus[39].

Psychological and Psychiatric Effects

From embryonic development onward, the skin and psyche are deeply interconnected with the body's physiological state, a relationship that persists throughout life, regardless of age. A disruption in the balance of either the psyche or the skin has a direct impact on the other, highlighting their interconnected nature. Chronic skin diseases, especially those acquired in early childhood, disrupt both physical and psychological homeostasis, with the psyche influencing skin conditions and dermatological symptoms leaving lasting effects on mental well-being.

It is the brain, not the skin, that experiences the sensation of itching. The itch is a neuronal projection of a centrally generated sensation, either localized to specific areas of the skin (localized pruritus) or spread across larger portions of the body (generalized pruritus)[40]. Since different types of itch are perceived in atopic dermatitis, with distinct molecular and/or structural foundations, pinpointing the precise molecular, structural, and neurophysiological differences has proven to be an exceptionally challenging task[41]. Currently, there is no strong evidence for the existence of a specific 'itch center' in the brain[42].

The relationship between stress and itch in patients with atopic dermatitis is both complex and significant, involving elements of the neuro-endocrino-immunocutaneous system (NEICS) and the hypothalamo-pituitary-adrenal (HPA) axis[40]. Future research could explore new therapies that target stress-related pathways, such as Corticotrophin releasing hormone receptors or inhibitors of 11-hydroxysteroid dehydrogenase 1 (11-HSD1), to alleviate flares and pruritus[43,44,45].

The vicious itch-scratch cycle in atopic dermatitis causes significant stress, which can in turn worsen the condition. Further investigation is needed to fully understand this causal link. Various studies have found that personality traits influence the subjective perception of itch. The Lethargic personality style was linked to a higher overall itchy quality of life score (ItchyQoL), while both overcontrolled and under controlled personality style were associated with a greater symptomatic impact from chronic pruritus[45]. Patients commonly experienced itching during depressive episodes, with the symptoms disappearing once the depression subsided. However, recurrent itching tended to accompany the return of depressive episodes.

Atopic dermatitis has a significant impact on both patients and their partners, placing a heavy burden on their lives and negatively affecting their sexual well-being which has to be addressed[46,47].

Children diagnosed with atopic dermatitis face an elevated risk of developing mental health comorbidities, including depression, anxiety, academic challenges, ADHD, conduct disorder, and autism. These additional challenges significantly burden caregivers, making patient care more demanding[48]. As dermatological lesions are visible, individuals often develop social anxiety is especially pronounced in school-aged children and teenagers facing discrimination and stigmatization[49].

To help manage the psychological impact of atopic dermatitis, it is important to incorporate mindfulness and relaxation strategies. Instructing patients in relaxation methods like deep breathing exercises and mindfulness meditation can effectively alleviate stress, which frequently worsens symptoms.

Combining clinics offers a cost-effective approach to managing dermatologic diseases and psychosocial comorbidities by reducing diagnostic errors, ineffective treatments, unnecessary referrals, and excessive consultations. Despite the well-established connection between psychological comorbidities, the involvement of psychologists or psychiatrists in treatment remains limited[50]. The intricate two-way relationship between itch and psychological factors highlights the importance of a multidisciplinary approach in managing itch and related conditions within clinical practice.

The multidisciplinary team, must ideally include specialists such as psychiatrists, psychologists, and residents, in consultations and management discussions to optimize care[51,52]. The burden of disease is greater among parents of older children, as well as among male and younger parents[53]. Caregivers should also be assessed to ensure they are mentally equipped to provide adequate support, especially in case of children[54,55]. In many regions, seeking psychological help carries a stigma, so positioning psychologists within the dermatology department or on adjacent floors could encourage patients to view these services as a standard part of their dermatological care, making them more likely to utilize them.

Environmental Factors

Atopic dermatitis is a complex condition influenced by a combination of genetic and environmental factors. Gaining insight into how genes interact with one another and with environmental triggers, such as allergens or

pollutants, is essential for a deeper understanding of the disease. Various epidemiological studies have shown a higher prevalence of the disease in urban or developed countries compared to rural or developing areas, indicating that environmental factors may play a role in disease manifestation. However, the precise mechanism has yet to be determined[56].

Identifying triggers can be challenging, as symptoms may not manifest immediately after exposure to a topical irritant or allergen. This delayed response complicates the process of pinpointing the specific allergen responsible.

Airborne allergens are among the most challenging and poorly understood triggers for eczema. While people are not necessarily allergic to substances like pollen, dust mites, pet dander, cockroaches, or mold, these allergens can exacerbate eczema by producing protease enzymes that break down proteins in the skin, leading to a weakened skin barrier and increased susceptibility to flare-ups. Although measures such as deep cleaning the home and using air purifiers are recommended, their effectiveness in controlling airborne allergens is limited. Moreover, these practices can be both time-consuming and financially burdensome for patients and caregivers already facing significant challenges. The expense of buying hypoallergenic products and adhering to special diets further increases the financial burden on patients.

Although commercially available patch tests provide a range of allergens, they represent only a small fraction of the millions of potential allergens. Only about half of the patients successfully identify the causative allergen through these commercial tests[57].

Gene profiling has identified a set of biomarkers that distinguish allergic contact dermatitis from irritant contact dermatitis[58]. This discovery can be used to screen patients, reducing the need for unnecessary patch testing and follow-up visits, thereby minimizing patient burden.

Ideally, usage or open patch test should be conducted, but this is often not feasible due to the resource-intensive nature of the procedure, particularly in developing countries. Requiring patients to make significant life decisions, such as changing their occupation or place of residence, based on patch tests that frequently yield false positives, can be detrimental exacerbating financial constraints. Reliable methods for allergen detection remain limited.

While it may seem straightforward for a physician to advise patients to avoid allergens, in practice, this can be extremely challenging. Allergens are often ubiquitous, making them difficult to avoid, or they may be related to the patient's occupation, such as in the case of masons who are exposed to potassium dichromate in cement or protective rubber gloves.

Myths and Misinformation

The World Health Organization has highlighted the "infodemic"- an overwhelming surge of information combined with the rapid spread of false or misleading news, images, and videos as a major threat to global health[59]. Atopic dermatitis is a common skin disorder with a complex multifactorial etiology, which is particularly vulnerable to such misinformation.

Misinformation often circulates around several key topics, including so-called "simple cures" for atopic dermatitis, as well as misunderstandings related to diet, chemicals, dust, vaccines, red skin syndrome, and alternative therapies. Given the profound impact of atopic dermatitis on quality of life, patients and their families are especially susceptible to these falsehoods[60].

In recent years, YouTube has emerged as a notable source of medical information for health care consumers. However, a study evaluating the 100 most viewed videos on atopic dermatitis revealed concerning results: nearly two-thirds of the videos were of poor scientific quality, one-third contained potentially harmful content, and half were misleading[61]

It was found that approximately three-fourths of children underwent dietary restrictions, with about one-third of these patients reporting noticeable improvements following dietary modifications[62]. Most dietary information was sourced from media, books, or magazines (51%), with friends (32%) being the next most common source, followed by general practitioners (27%), and district nurses or health visitors (18%)[63].

The main dietary changes involved cutting out eggs, dairy products, and food additives, while adding soy and goat's milk. Fewer than 10% of patients reported any improvement from these mostly unsupervised diets. Harmful practices included drinking unboiled, unpasteurized goat's milk regularly, feeding unmodified goat's milk to a 4-month-old infant, and following highly restrictive diets [63].

Many parents observed that, even though exclusion diets did not yield any benefits, they hesitated to reintroduce certain foods due to concerns about exacerbating their child's dermatitis. Furthermore, both parents and children reported that the dietary restrictions often became more burdensome than the dermatitis itself, especially when the child started school and socializing at friends' homes.[63]

Despite the lack of evidence supporting the widespread use of dietary interventions for atopic dermatitis, numerous reports and reviews have highlighted the potential risks associated with this practice. These risks include failure to thrive and deficiencies in vitamins and minerals. Additionally, the cost of inappropriate special diets, such as gluten-free diets, can impose a significant financial burden on families[63]. Several reports indicated cases of Kwashiorkor-like protein-energy malnutrition, cardiac arrest, and septic shock, likely resulting from overly restrictive diets.[64,65,66]

Many individuals opt for herbal remedies due to their perceived naturalness, cultural beliefs, or dissatisfaction with conventional treatments. Herbal options include topical applications (such as creams, oils, or compresses) and oral supplements (such as teas, capsules, or tinctures). While some herbal remedies may offer symptomatic relief, their efficacy varies widely. The lack of standardized dosages, inconsistent quality, and limited

scientific evidence present significant challenges. Additionally, herbal treatments may not effectively address the underlying inflammatory processes in atopic dermatitis.

Rigorous clinical trials comparing herbal remedies to standard treatments are limited. Safety concerns include allergic reactions, interactions with medications, exacerbation of existing conditions, and contamination, which can lead to secondary infections. Dermatologists must remain vigilant about the misleading information circulating within communities and be prepared to counter it with accurate, evidence-based guidance.

Treatment Adherence

Patients' beliefs about their condition and medications can influence adherence, especially for patients with chronic relapsing and remitting conditions with no cure. They need to be counselled regarding the nature of the disease which is crucial for compliance.

Understanding patient preferences, lifestyle, and financial capacity is essential for effective treatment planning. Actively involving patients in their treatment decisions can significantly enhance adherence, especially when factors such as convenience, ease of application, and the impact on daily life are considered. Consistent patient education regarding their condition, available treatments, and the significance of adherence is essential for achieving successful outcomes. It is also important to clearly explain the rationale behind each treatment, addressing any misconceptions or fears that patients may have.

Providing patients with a clear, written treatment plan is another key element of effective care. Such plans should include detailed instructions on medication application, frequency, and duration, as well as highlighting potential side effects and strategies to manage them. Patients should also be informed about the potential adverse effects they may experience when starting the drug, the time it may take for the drug to take effect when to seek medical advice in the event of adverse reactions, and the appropriate steps to take in such situations. Patients should be counselled on the fact that some treatments, particularly those for pruritus, may take time to show effects, which can help prevent premature discontinuation of therapy[67]. Additionally, patients often find time-consuming treatments like wet wraps to be inconvenient and tedious. As a result, many prefer systemic medications, even though topical treatments generally have far fewer side effects.

Incorporating behavioural strategies can further support treatment adherence. Techniques such as linking medication application to existing daily routines, like brushing teeth, can make adherence easier. Positive reinforcement, such as rewarding adherence with small incentives for children, and sharing success stories from other patients can also be motivating.

The emotional aspects of atopic dermatitis should not be overlooked, as anxiety, depression, and stress can significantly impact adherence. Encouraging patients to adopt coping strategies and stress management techniques can support overall treatment success. Additionally, the relationship between the patient and healthcare provider, as well as the broader healthcare system, plays a vital role in adherence. Evidence suggests that the more chronic conditions a person has, along with the number of medications they are taking, can significantly affect their ability to adhere to treatment.

Scheduling follow-up appointments soon after treatment initiation is crucial for assessing progress, adjusting therapy as needed, and reinforcing adherence. Early visits ensure that patients remain on track with their treatment plans, addressing any issues promptly to avoid setbacks.

Constant warnings about the 'dangers' of topical corticosteroids from family, friends, and online sources can shape how patients or parents view the safety of topical corticosteroids, which may result in them not following the prescribed treatment[68]. Topical steroid phobia is a widespread concern, with global prevalence rates ranging from 31% to 95.7%. This fear is consistent across different patient races, ethnicities, and dermatological conditions[69]. A person's educational background, particularly higher literacy levels and greater access to online resources has been linked to an increased prevalence of steroid phobia. Female patients, caregivers, and individuals who have experienced side effects from topical corticosteroids are especially likely to develop steroid phobia. Factors contributing to this include insufficient education, fear of side effects, multiple medications, exposure to misinformation, negative experiences with topical steroids, and frequent changes in healthcare providers[70]. Healthcare professionals, such as pharmacists, general practitioners, and non-physician clinicians, tend to exhibit steroid phobia more frequently than dermatologists[71].

To effectively address steroid phobia and improve adherence to topical corticosteroid treatment, healthcare providers should implement targeted interventions. Successful strategies include patient education through educational videos[72], personalized oral education tailored to individual concerns, and demonstrations of topical steroid application. Since steroid phobia can cause poor adherence, leading to persistent disease[73] and potentially necessitating systemic treatments, providers must screen for steroid phobia, particularly in at-risk populations. Individualized educational interventions based on screening outcomes can significantly enhance patient understanding and treatment compliance.[74]

Literature Gaps

Most clinical trials focus on comparing new treatments against placebo or vehicle controls. However, head-to-head comparisons between various treatments are scarce. Although the FDA requires placebo-controlled studies for drug licensing, these studies do not necessarily assist clinicians and policymakers in making informed decisions[75].

In a comprehensive network meta-analysis conducted by Wilkes et al, they identified randomized controlled trials (RCTs) evaluating treatments for atopic eczema. These trials compared pimecrolimus, tacrolimus, or topical corticosteroids with other interventions or

vehicle/emollient controls. Surprisingly, 50% of these trials were vehicle-controlled studies. The frequent use of vehicle controls in trials assessing the efficacy of pimecrolimus or tacrolimus even after their efficacy had been well-established raises legitimate concerns about usefulness of such studies for medical advancements[76].

The UK National Institute for Health and Care Research (NIHR) has funded two significant head-to-head comparison trials. The first, the Treatment of Severe Atopic Eczema Trial (TREAT), compared ciclosporin and methotrexate in children. It found that while ciclosporin offers a quicker initial response, methotrexate provides better long-term disease control after therapy cessation. The second trial is a randomized, assessor-blind study that assessed the most effective systemic treatments for adults with atopic eczema, comparing ciclosporin, methotrexate, dupilumab, and a JAK inhibitor. While clinical trials offer valuable insights, their widespread implementation faces limitations due to the substantial costs, time commitments, and labour-intensive processes involved[77,78].

This is where network meta-analyses prove valuable. They allow for the comparison of multiple interventions, helping to estimate the ranking and hierarchy of these treatments. Additionally, they provide more precise estimates of relative effectiveness by integrating both direct and indirect comparisons, offering a comprehensive overview that surpasses the accuracy of individual studies[79].

While randomized controlled trials are regarded as the gold standard for treatment comparisons, they generally provide only a short-term perspective. This limitation is particularly significant when evaluating disease control in chronic conditions like atopic dermatitis and when assessing the long-term safety of medications[80].

To address these limitations, post-marketing open-label studies were introduced to assess adverse effects. These studies are typically sponsored by the pharmaceutical companies, feature strict inclusion criteria, and lack control group comparisons. However, a study by Spelsberg et al. revealed that these trials contribute minimally to the identification of adverse effects. This is largely due to small sample sizes and the fact that many participating physicians are required to maintain confidentiality about all data, including adverse drug reactions, in accordance with the sponsor's guidelines[81].

Several national treatment registries have been established, especially for patients starting or changing systemic therapies, under the international TREAT (Treatment of Atopic Eczema) Registry Taskforce. These initiatives have resulted in an international consensus on core outcomes for systemic therapy registries. The main emphasis is on gathering prospective data to evaluate the long-term effectiveness, safety, and cost-efficiency of systemic treatments, while also enabling comparisons between existing and newer medications[82].

HOME (Harmonizing outcomes measurement for Eczema) was established in 2008 by Professors Hywel Williams and Jochen Schmitt to unite the eczema research community in standardizing outcome measures through the creation of a core outcome set to be included in all eczema clinical trials. This initiative aims to standardize the assessment of atopic dermatitis in terms of severity, disease burden, and adverse events, thereby facilitating meta-analyses by ensuring consistent outcome measurement[83]. Despite these efforts, many studies do not adhere to this standard, making it challenging for clinicians to make meaningful comparisons.

Although children constitute a significant portion of atopic dermatitis patients, there are relatively few studies focusing on this population. This scarcity is partly due to the higher resource demands and stringent regulatory controls required for conducting paediatric research. Furthermore, in trials that include both children and adults, the number of paediatric participants is often too small to yield statistically significant results that can be effectively translated into clinical practice.

Navigating Treatment Options

With a diverse array of topical and systemic treatments now available, there are currently over 70 new drugs in development[84]. This vast array of options can make selecting the appropriate treatment a complex challenge for physicians. Factors such as the patient's age, disease severity, symptoms, comorbidities, and purchasing power must all be considered, underscoring the growing importance of personalized treatment approaches.

A crucial aspect of clinical decision-making is incorporating the patient's perspective. To achieve this, many clinicians discuss the individual disease burden and potential impacts on health-related quality of life (HRQoL). Additionally, reaching a consensus on specific treatment goals greatly aids in effective therapeutic management. In a cross-sectional study conducted by Augustin et al. in Germany, patient priorities in treatment goals were identified. The goals most rated as 'quite important' or 'very important' were 'being free of itching' (96.0%), 'achieving better skin quickly' (97.8%), and 'healing all skin defects' (85.7%)[85].

BIOMAP (biomarkers for atopic dermatitis and psoriasis) investigates the causes and mechanisms of atopic dermatitis and psoriasis by identifying key biomarkers linked to disease outcomes. Leveraging advancements in translational medicine, the project aims to enhance drug discovery and improve disease management by integrating clinical, genetic, and epidemiological insights with molecular analysis and bioinformatics. It examines the largest dataset of over 50,000 patients, using advanced molecular techniques to identify biomarkers contributing to variations in disease outcomes. This marks a major step toward personalized medicine[86].

Several websites have been introduced to assist clinicians and patients in selecting appropriate treatments based on a target-to-treat approach, in which specific disease activity targets guide treatment decisions. For instance, Eczematherapies.com ranks various available systemic treatments according to their impact on quality of life, pruritus, and clinical signs[87].

Despite the wide range of available treatments, none offer complete clinical resolution or fully alleviate pruritus, and the effectiveness of a drug can vary

significantly between individuals, likely due to genetic differences. However, as we continue to advance in the development of more precise, targeted therapies, the underlying mechanisms will become clearer. In the future, it is conceivable that blood tests could be developed to predict a patient's response to specific drugs, allowing for more personalized and effective treatment strategies.

Skin and Gut Microbiome

Numerous studies have explored the gut microbiome and its potential role in disease pathogenesis through the "gut-skin axis." Microbiota plays a pivotal role in modulating itch, especially in the context of atopic dermatitis. Research indicates that children with atopic dermatitis exhibit significantly lower diversity in both their gut and skin microbiomes compared to healthy individuals[88,89]. An imbalance in microbial communities, known as dysbiosis, in both the gut and skin has been linked to disease exacerbation[89].

Treatment-related changes in skin and gut bacterial diversity suggest that atopic dermatitis therapies increase microbial diversity, which precedes improvements in disease symptoms[90]. Several studies have revealed differences in the gut microbiome between patients with atopic dermatitis and healthy controls. Individuals with atopic dermatitis often exhibit elevated levels of organisms like Faecalibacterium prausnitzii, Clostridium, and Escherichia coli, with the risk and severity of the condition correlating with the diversity and abundance of specific bacteria, highlighting the need for large-scale gut microbiome studies to confirm these associations[91,92]. However, further epidemiological across diverse geographical regions and ethnic groups are needed to better understand each microbial species' contribution.

The inflammation in atopic dermatitis is primarily driven by the Th2 cytokine pathway, with IL-4 and IL-13 playing key roles. Animal models have shown that probiotics may help regulate the Th1/Th2 balance and enhance Treg activity through interactions with dendritic cells. This effect still needs to be confirmed in adult populations[93].

An individual's health can be influenced by the composition of their gut microbiota, which is largely shaped by dietary habits, lifestyle choices, antibiotic use, and stress levels[94]. Recent research, utilizing advanced molecular sequencing, is focusing on the potential therapeutic strategies for targeting gut microbiota, particularly through probiotics, prebiotics, and faecal microbiota transplantation, as adjuvant treatments for atopic dermatitis[94,95,96].

Economic Burden

Atopic dermatitis is a substantial economic burden encompassing direct and indirect medical costs related to quality of life, productivity loss, and psychosocial factors impacting patients, families, and the healthcare system. The annual cost of atopic dermatitis in the United States is estimated at a conservative $5.297 billion[97].

Atopic dermatitis affects around 20% of European adults in moderate-to-severe forms, with total annual costs reaching up to €20,695 per person, driven largely by work productivity losses and direct medical expenses[98]. Various reviews highlighted that uncontrolled atopic dermatitis significantly increases these costs, alongside substantial personal and societal impacts[99]. Effective treatment and management are essential to reduce the burden of moderate-to-severe atopic dermatitis on patients and healthcare systems.

The direct medical costs of atopic dermatitis encompass expenses associated with healthcare resource utilization (HCRU), including outpatient visits, hospitalizations, and prescription medications. Indirect costs of atopic dermatitis, such as lost productivity due to frequent medical consultations and travel, are also considerable. The chronic nature of atopic dermatitis exacerbates this financial strain, as ongoing treatment and management are required[100].

Prolonged treatment periods can elevate the risk of infections and other adverse events, requiring frequent laboratory monitoring and leading to substantial drug-related expenses. The psychological and social impacts of the disease further amplify its economic burden. Patients often experience social stigma, anxiety, and depression due to visible symptoms, leading to reduced work productivity and social isolation.

According to Ellis et al., comorbid conditions such as allergic rhinitis, asthma, and otitis media are common among atopic dermatitis patients, increasing healthcare utilization and costs. These conditions contribute to absenteeism and further reduce productivity, compounding the economic impact[101].

A comprehensive approach to understanding and addressing the economic burden of atopic dermatitis begins with thorough cost-of-illness studies tailored to specific regions. These studies should assess the financial impact on individuals, families, and society, providing critical data to policymakers for making healthcare policies and resource allocation. Applying these findings can facilitate the creation of evidence-based policies designed to alleviate the economic burden associated with the disease[102].

Supportive services for caregivers are also essential, which includes personal care and emotional support, significantly adds to the overall burden. Providing access to psychological support, social workers, and occupational therapy can help alleviate the pressures faced by caregivers. Additionally, education and practical advice from dermatology specialist nurses can empower patients and caregivers with knowledge on atopic dermatitis management[103].

A holistic approach to managing atopic dermatitis should consider not only the medical costs but also the out-of-pocket expenses incurred by patients, such as the cost of moisturizers, hygiene products, and even cleaning expenses. Addressing these everyday costs is crucial in easing the financial burden on families.

Improving access to care is another key factor in reducing the impact of atopic dermatitis. Establishing conveniently located dermatology services within communities and exploring out-of-hours services can make it easier for patients to receive the care they need, accommodating

their schedules and improving overall treatment outcomes[103].

Conclusion

Significant progress has been made in understanding the pathogenesis of atopic dermatitis and in developing targeted treatments, yet there remains a considerable journey ahead to reduce the burden of this disease. Despite the well-documented psychological comorbidities associated with atopic dermatitis, they are often inadequately addressed in clinical practice. Policymakers must recognize this gap when allocating healthcare resources.

As research advances, the identification of biomarkers will soon allow for more precise, individualized treatment options, moving away from the current "hit or miss" approach. This shift will not only save time but also reduce costs for patients. To achieve this, there is a pressing need for increased funding for large-scale research and patient registries, with a particular focus on the pediatric population.

Substantial gaps in our understanding of atopic dermatitis persist, highlighting the need for collaboration between molecular research specialists and healthcare professionals to bridge these gaps and alleviate the overall disease burden.

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