Atopic Dermatitis: Mechanism and Topical Treatment Strategies

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Abstract. Atopic dermatitis is a chronic inflammatory skin disease with a complex pathogenesis relating to immunology, genetic inheritance, and environmental conditions. Various treatments are applied to relieve the symptoms of AD. One of the most common types of medication applied is topical treatments. The review examines the mechanisms of action and pathways for topical corticosteroids, non-steroid topical calcineurin inhibitors, and phosphodiesterase 4 inhibitors based on a wide range of research and studies targeting AD. The three treatment strategies are compared under different disease conditions. The review suggests that to maximize the effectiveness and minimize side effects, the application of each type of medication should be carefully considered depending on the severity of AD conditions and the individual's physical condition.

Keywords: atopic dermatitis, topical corticosteroids, topical calcineurin Inhibitors, phosphodiesterase 4 inhibitor

1. Introduction
Atopic dermatitis (AD) is one of the most common skin diseases with associated phenotypes varying, including but not limited to monotonous eczematous lesions on the face, neck, and skin folds, and nummular eczema [1]. The disease is highly observable among young children between 1 and 5 years of age, who, together with females and people from resource-rich countries, constitute the major patient groups of AD. With increasing knowledge of the complex background of AD from genetics, immunological, and environmental aspects in combination with the continuous improvements in diagnostic and therapeutic methods targeting the disease, current research has brought in large numbers of new insights on AD's pathological pathway and ways to relieve the symptoms. Because of the complexity of the disease being heterogeneous, a more in-depth understanding of the genetic and immunological mechanisms is significant for the development of effective treatment strategies [2]. Despite the fact that many works of literature and previous research have focused on drug treatment effectiveness, there is a lack of analysis that highlights comparisons between different drug treatments in terms of their effectiveness under different conditions. This paper will examine the three most widely applied AD medical treatment types. The research method applied in this paper is primary and secondary research on various sources, including database resources, theoretical concepts, and experimental results. This paper will highlight the different mechanisms of action of these types of drugs in affected AD patients' bodies. This paper will also present a detailed analytical comparison between different treatments. By summarizing and analyzing the mechanisms and limitations of treatment strategies, the paper contributes more comprehensive insights into the different cases of the application of topical drugs.
in treating AD. By mentioning the physiological mechanisms of AD, it raises awareness of the significance of AD among potential readers. This paper also offers new directions for future clinical studies on AD, which can effectively increase the life quality of numerous AD patients worldwide.

2. Factors affecting AD

2.1. Immunological factors
A large proportion of AD patients are found to have innate immune system defects that lead to a more sensitive, skewed Th2 response to environmental agents [3]. According to recent research, the acute and subacute lesions of AD exhibit overexpression of Th2 cytokines. Clinical studies using a monoclonal antibody that blocks the IL-4/IL-3 receptor have recently demonstrated the impact of the key Th2 cytokine on AD. There is sufficient evidence to suggest that the disorder involves multiple immune pathways.

The interleukins (IL) 4, 5, and 13 are found on chromosome 5q31-33, which belong to the Th2-type cytokines [4]. The Th2-type cytokine is closely associated with the promotion of the number of antibodies to immunoglobulin E (IgE) and the eosinophilic response in atopy, along with the release of an anti-inflammatory, interleukin-10 (IL-10) [5]. Another involved immune cell is the Th22 cell. With a primary function of protecting epithelial barrier organs such as the skin and lungs while modulating inflamed and injured tissues, Th22 cells mount an immune response when activated. In AD, Th2 and Th22 cells are transported to the lesion area on the skin where they release Th2 and Th22 cytokines, respectively [6].

Interleukin 4 (IL-4) in Th2-type cytokines activates the massive secretion of IgE by the plasma cells. The secreted IgE binds to receptors that are located on mast cells, basophil cells, and macrophage cells. This sensitizes these cells to the allergen, causing a consequent allergic reaction. TNF-a, a type of Th2-cytokine, activates a large number of infiltrating cells such as monocytes and macrophage cells. It, therefore, stimulates the secretion of various chemokines and innate immunity molecules by the keratinocytes [7]. The secreted IgE binds to receptors that are located on mast cells, basophil cells, and macrophage cells. By sensitizing these cells through binding, an allergic response occurs. A high number of infiltrating cells such as monocytes and macrophages are activated by TNF-a in Th2 cytokines. Therefore, it induces keratinocytes to secrete various chemokines and immune molecules. IL-22, contained in the Th22 cytokine, effectively modulates the keratinocyte metabolism, which results in abnormal epidermal differentiation. Due to the combined effects of these inflammatory cytokines, the sensory neurons in the peripheral nervous system respond to the inflammation by secreting neuropeptides (GCRP and substance P) [8]. Figure 1 shows the immunology pathway of the innate immune system under atopic dermatitis conditions.
2.2. Genetic factors
Several genes are implicated in the development of AD. The majority of AD cases occur as a result of a combination of genetic and environmental factors (such as air pollution). It is currently discovered that atopic dermatitis can be affected by two different genes, the CARD11 gene and the FLG gene [9].

One of the most common genetic variations involved in AD is related to the FLG gene, which is located on chromosome 1q21. There is evidence that the FLG gene was mutated in 20%–30% of Alzheimer's disease patients, compared to 8%–10% of the general population without atopic dermatitis. The FLG gene provides instructions for the production of a type of protein that functions in retaining the normal structure of the epidermis of the skin, which is called the profilaggrin protein. Profilaggrin proteins are cleaved to produce filaggrin proteins, which form a barrier that prevents foreign substances such as toxins, bacteria, and allergens from entering the skin [10]. Additionally, these proteins help maintain hydration in the outermost layer of the skin. An abnormally short profilaggrin protein resulting from a variant in the FLG gene would have a greater possibility of resulting in impaired skin barrier function. This would further trigger the development of AD.

2.3. Environmental factors
It is suggested by a large amount of research that exposure to certain environmental conditions can be a trigger of AD. Studies showed that AD is associated with an environmental regional pattern, indicating that the disease is more prevalent in wealthier, developed areas than in developing regions. Yet, a limited number of resources mentioned whether the harmful or protective roles of specific environmental conditions would affect AD. In addition, a complex relationship between various environments and genetic factors such as maternal exposures during pregnancy has been proposed in recent studies. Other possible environmental triggers for AD include skin irritants, climate, pollutants, diet, and more [11].
3. Therapeutic Aspects of Atopic Dermatitis

3.1. First line therapeutic strategy
The first-line treatments are the baseline for the AD therapeutic strategy. They focus on skin protection via hydrating the skin, avoiding allergens, and eliminating triggers [3]. As shown in Figure 2, AD patients have impaired skin barriers, which makes their skin more sensitive to allergens and they face severe issues with skin dehydration. Therefore, moisturization is crucial in the first-line therapeutic strategy to prevent trans-epidermal water loss and maintain skin moisture. With more moderate symptoms, some topical treatments are used to ease the discomfort.

![Figure 2. Normal skin barrier and impaired skin barrier.](image)

3.1.1. Topical corticosteroids (TCSs). Topical corticosteroids are essential therapeutic treatments for both children and adults as a first line therapy for inflammatory symptoms such as the itchiness of atopic dermatitis. Since AD is commonly a chronic and long-term disease with no specific cure, TCSs are used to avoid the triggers of AD and alleviate the symptoms. By disrupting antigen processing and presentation by suppressing the release of cytokines that trigger itching, TCS reduces inflammation and pruritus [12].

3.1.2. Therapeutical mechanism. Corticosteroids bind with cytoplasmic corticosteroid receptors in the cells to form a steroid complex which would further migrate into the nucleus. When this complex enters the cellular nucleus, it binds to the glucocorticoid-responsive element in the corticosteroid-responsive target gene and acts as either a stimulator or an inhibitor of target protein transcription and synthesis. Apart from direct regulation of gene transcription, TCS can cause blockage of other transcription factors indirectly to inhibit target gene expression [13]. Studies have shown that corticosteroids’ stimulation of the expression of inhibitory nuclear factor-k B a (IkBa) gene can activate the transcription of mRNA which synthesizes into IkBa protein. IkBa degrades after binding with NFkB, which is activated by T-cells, and NFkB translocates into the nucleus. NFkB genes target inflammation by stimulating the transcription of various inflammatory genes. When a glucocorticoid binds with a corticosteroid, forming the glucocorticoid receptor complex, the effect of NFkB on the expression of an inflammatory gene is diminished. Normal gene expression would result in cytokine synthesis that would cause inflammation symptoms on AD patient skin. With the application of corticosteroids, inflammatory reactions are remitted. Figure 3 shows the mechanism of action for corticosteroids in their regulatory effect on cytokine synthesis.
3.1.3. Limitations. Potential risks for all TCSs are that they would affect the Langerhans’ cells and would cause a reduction in the numbers of Th cells in healthy skin, resulting in possible skin barrier impairment. Also, long-term continuous use of TCSs should be avoided due to possible adverse effects. Possible side effects include adrenal suppression, skin atrophy, perioral dermatitis, and resistance to the treatment [14]. Clinical trials further suggest that TCSs have limited effectiveness in managing AD conditions on sensitive skin.

3.2. Second line therapeutic strategies
In the second-line therapy of AD, drugs with short-term effects are commonly used. Because Alzheimer’s disease frequently manifests as chronic symptoms, patients are at risk of bacterial, fungal, and viral superinfections, and the lesioned skin is particularly vulnerable to substances that cause pruritus. Studies show that antibiotics such as cephalosporin can be effective in protecting the skin from infections. In response to itchiness and pruritus as AD symptoms, increasing amounts of histamines are released, thus affecting the quality of life of AD patients. Therefore, antihistamines are also used as second-line medications. Other types of medications such as oral sedation, topical calcineurin inhibitors, and phosphodiesterase inhibitors are also applied as second-line treatments for moderate to severe AD patients.

3.2.1. Non-steroid topical calcineurin inhibitors (TCIs). Non-steroid topical calcineurin inhibitors suppress immune activity by inhibiting the activation of mast cells and T cells. They reduce the number of pro-inflammatory cytokines produced and thus the inflammatory reaction in AD [15]. They do not have harmful effects such as that of TCSs and TCIs, which would not cause significant weakening in the skin barrier by prolonged use. TCIs are more safe for the skin compared to other topical treatments.

Tacrolimus Therapeutic Mechanism. Tacrolimus ointment is a macrolide lactone with unique immunomodulatory properties, belonging to the class of topical immunomodulators. Having a mechanism that inhibits the function of a protein phosphatase, calcineurin, effectively results in decreasing T-cell activation and inflammatory cytokine release. For its small molecular size and higher potency compared with TCIs, tacrolimus has become one of the most effective topical agents in treating AD [16]. When it is used as a topical treatment, tacrolimus is absorbed passively into the skin, and it effectively reduces skin inflammation and pruritus.
Tacrolimus (FK506) binds to a class of ubiquitous peptidyl-prolyl cis-trans isomerases (PPIase) that is called designated FK506-binding proteins. The binding complex therefore inhibits the T-cell activation and forms another complex in which further suppress the functioning of enzyme calcineurin.

Under normal conditions, the calcineurin dephosphorylates a cytosolic transcription factor called the nuclear factor of activated T-cell protein (NF-ATp). This process allows the NF-ATp to migrate to the nucleus and therefore stimulates the activation of genes that are involved in T-cell activation which promotes the production and cytokines such as IL-2. However, when tacrolimus diffuses into the skin, the complex formed via the binding with PPlase inhibits the ability of calcineurin to dephosphorylate the transcription factor (NFAT). Since NFAT initiates the IL-2 gene transcription, as a result, when it is inhibited, the synthesis and release of the IL-2 gene are restrained [17]. The inhibition of calcineurin decreases the production of pro-inflammatory cytokines, tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor [18]. The inhibited factors are those that would contribute to allergic inflammation in the human body. Figure 3 shows the mechanism of action for tacrolimus to regulate the synthesis of cytokines.

Tacrolimus, as a medication in AD, in terms of the pathological pathway, can relieve the symptoms of inflammation. Furthermore, various clinical trials have also shown that topical tacrolimus is highly effective in reducing symptoms of AD. Figure 4 shows the mechanism of tacrolimus regulation on IL-2 gene synthesis.

**Figure 4.** Mechanism of action of tacrolimus (FK506).

Limitation of TCIs. TCIs may result in momentary itching or burning sensations at the site of application, which would potentially affect a patient’s mental health and quality of life [19]. TCIs such as tacrolimus have been shown in clinical trials to cause kidney dysfunction, is a possibility of developing lymphoma after exposure to high doses of TCIs (in mouse models). According to the FDA Black Box Warning, TCIs have possible theoretical risks of malignancy associated with systemic calcineurin inhibitors in animal studies and transplant patients [3]. However, clinical trials and various pharmacokinetic and toxicology studies indicate that the overall rates of such risks are extremely low in the general population of patients with TCIs as medical treatments. The suggested time length for use is 6 months since long-term application of TCIs may result in resistance and high reliance on the medication.
3.2.2. Phosphodiesterase inhibitor – crisaborole. A more recent study into the therapeutic aspects of AD suggests that phosphodiesterase inhibitors can effectively remit the AD symptoms. It is observed among AD patients with an increasing production of chemokines and cytokines that significantly promote the level of phosphodiesterase 4 (PDE4). By degrading cAMP, PDE4 regulates pro-inflammatory and anti-inflammatory cytokine production in the body [20]. With a high PDE4 level, abnormalities might appear in human immunological functions. Hence, phosphodiesterase inhibitors are applied in AD therapeutic strategies. As a novel topical non-steroid medication treatment for atopic dermatitis, approved on December 14, 2016, crisaborole ointment acts as a phosphodiesterase-4 (PDE4) inhibitor in modulating the response of inflammatory cytokines and cell proliferation [21]. Using crisaborole as an AD therapeutic medication in phase III clinical trials, it has been demonstrated that a 2% ointment containing the crisaborole compound has both good efficacy and safety in adult and pediatric patients suffering from mild to moderate AD [22]. Crisaborole has a chemical structure as shown in Figure 5.

Figure 5. Crisaborole Chemical Structure.

Crisaborole Therapeutic Mechanism. In terms of the therapeutic mechanism of crisaborole, since it has a less immunosuppressive pathway, the skin barrier is less affected by the treatment. Crisaborole in AD patients’ bodies interrupts the itch-scratch cycle, a constant source of aggravation in AD patients, which usually occurs within the first few days of treatment. Because of the positive safety profile demonstrated by crisaborole, it can significantly help control the disease in the early treatment of mild to moderate AD patients and thus enhance their quality of life.

When crisaborole is used in the form of ointment as a topical treatment, its low molecular weight allows it to diffuse through the epidermis and the dermis of the human skin layer to reach the inner site of inflammation for inhibition [23]. Crisaborole has boron in its benzoxaborole structure. This allows its ability to mimic the phosphate of cAMP and therefore inhibit PDE4. The geometry of the chemical structure enables the inhibition of PDE4, which results in the degradation of cAMP in binding to the transcriptional starting site. Since fewer cAMPs can bind to the binding site, there is an increase in the intracellular cAMP level, which promotes the suppression of the activity of NF-kB and other possible pathways that are responsible for the production of various inflammatory cytokines such as CREB, NFAT, Rapl. Crisaborole therefore further suppresses the synthesis of cytokines.

Several viral experimental studies suggest that crisaborole has the potential to inhibit the production of Th1 and Th2 pro-inflammatory cytokines, which are responsible for an immune response towards external antigens. Hence, crisaborole can effectively control inflammation in AD to reduce the overexpression of certain proteins. Figure 6 shows the therapeutic mechanism of crisaborole in AD treatment.
Limitations of PDE4 Inhibitors. Randomized controlled trials have shown that this drug is safe and effective when used for up to a year [15]. The most common adverse events reported were skin blistering and itching. However, since topical PDE4 inhibitors are novel medications for AD, more data and experimental clinical trials are needed for further investigations into their limitations as long-term treatments.

4. Conclusion
The paper looks at both internal and external factors leading to atopic dermatitis diagnosis as well as currently worldwide applied medications targeting AD. The review makes an analysis of different types of drug treatments by interpreting the mechanism of action of specific treatments in AD patients’ bodies. The review suggests that for all three types of treatments, TCSs, TCIs, and phosphodiesterase inhibitors, significant adverse effects appear. Based on the seriousness of AD conditions and different personal physical conditions, the application of each type of medication should be carefully considered to be effective and minimize the side effects.

Based on the similarities among each type, based on their therapeutic mechanisms, the medications mentioned in this review can directly or indirectly affect the synthesis of inflammatory genes. This allows them to have remission effects on the itch and pruritus symptoms of AD. However, these treatments can not cure the disease and are unable to stop the recurrence of AD. Besides, long-term use of drugs is not suggested due to the adverse effects of resistance and patients’ reliance on the drug. Besides the mechanisms of drugs, the concentration and the age of patients used would also affect the effectiveness of drug treatments.

Although AD is a common skin disease, the pathophysiology and specific causes of the disease are still poorly understood. More research into personalized treatments is needed to reduce side effects and be more effective in treating disease from triggers rather than immune pathways.

References


