Dean&Francis

ISSN 2959-409X

MS003752

Treating Psoriasis: Simple Introduction about Acitretin and Tacrolimus

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Abstract:

Psoriasis is a skin infection disease that is related to dysfunction of the immune system. Plaque psoriasis is a common and typical psoriasis; it can be triggered by multiple factors, for example, environmental triggers and genetic factors. Skin with plaque psoriasis can be itchy and red, appear inflamed, and have scaly patches; the infected region can last for months and may leave permanent pigmentation. Keratinocytes (skin cells) are related to psoriasis; as homeostasis is disturbed, excess keratinocytes are produced, and surplus skin cells lead to psoriasis. Acitretin and tacrolimus are both drugs that can help with psoriasis but with different mechanisms.

Keywords:- psoriasis, keratinocytes, acitretin, tacrolimus, cytokines

1. Introduction

Psoriasis is a skin infection disease that The National Institutes of Health estimate that the disorder affects ~ 2.2% of the US population or 7.5 million Americans, and has a worldwide prevalence of ~ 2–3%, affecting > 125 million individuals [1]. Plaque psoriasis can be triggered by environmental triggers and genetic factors [2]. Skin with plaque psoriasis appears to be itchy and red, inflamed and scaly patches, with silver-white scales at the infected region. Psoriasis can affect daily routine and cause problems in social life. Infected skin can feel pain when wearing clothes and become vulnerable, so patients have to be more cautious in daily life. Psoriasis can last for months and may leave permanent pigmentation. Keratinocytes are related to psoriasis, as homeostasis is disturbed, excess keratinocytes are produced, and surplus skin cells lead to psoriasis. Although the exact reason for psoriasis is still unknown, it means that there is no cure for psoriasis, but systematic, oral, and topical treatments can relieve the discomfort. By inhibiting the proliferation of keratinocytes and stopping excess skin cells from being produced.

2. Psoriasis under the skin

Psoriasis happens in the epidermis layer, means that keratinocytes are produced at an unusual speed. The structure of the skin is explained in the next part in order to explain psoriasis.

2.1 Structure of skin

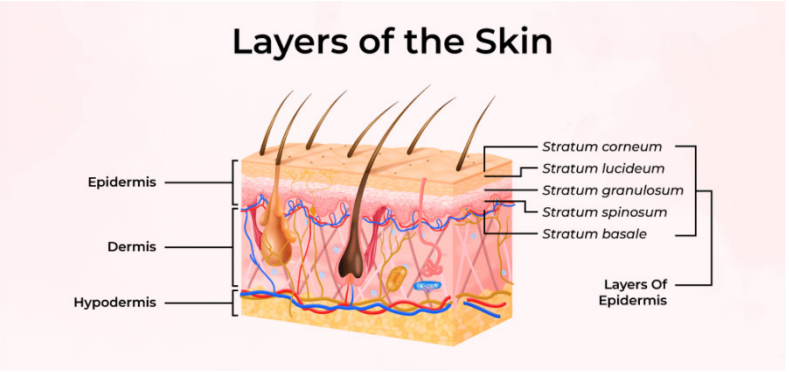

Fig.1 Structure of skin [3]

Skin is a crucial barrier for humans; it separates the interior environment from the outside. It prevents the human body from various dangers such as viruses, bacteria, and other physical bumps; the special arrangements of cells also allow the skin to control body temperature and water loss. The skin can be separated into 3 layers, as labeled in Fig 1: the epidermis, the dermis, and the subcutaneous layer (hypodermis). The epidermis is the outer layer that consists of keratinocytes (skin cells), coenocytes, and melanocytes (pigment cells). Keratinocytes are formed at the base layer; new cells will be continuously produced and move to the surface to replace the dead cells; as keratinocytes die, they become coenocytes, forming the stratum conium; this protective layer will gradually wear away. The dermis layer (inner layer) includes sweat glands, hair follicles, and sebaceous glands. This layer of the skin helps to regulate body temperature. Under the dermis layer is the subcutaneous layer, made up of fat and other connective tissues.

2.2 Skin infected by psoriasis

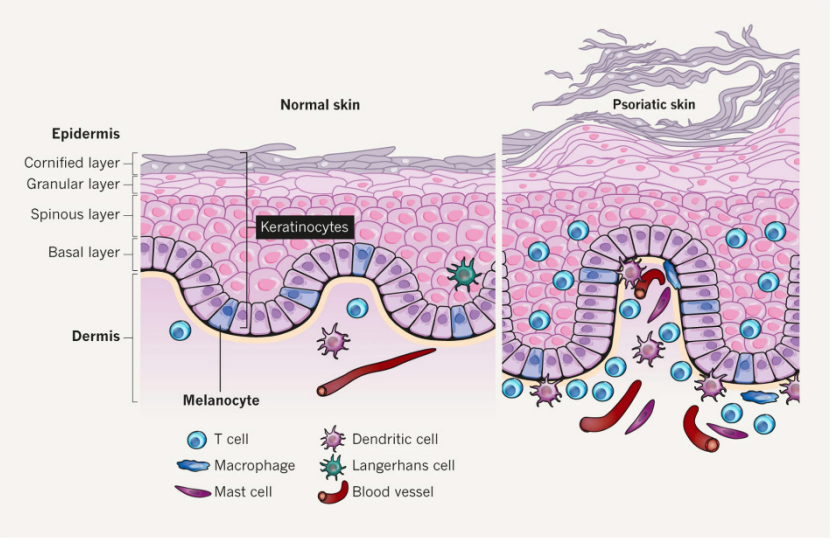

Fig.2 Skin with psoriasis [4]

Psoriasis happens in the epidermis layer, a disorder of the immune system, T cells get activated, lead to increased production of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ). These cytokines stimulate keratinocyte proliferation, making the base layer produce keratinocytes abnormally; the life cycle of skin cells is fastened; in normal skin, a complete cycle takes about 311 h, whereas infected skin only takes about 36h [5]. The skin appears to be bumps and scaly skin like it as shown in Fig.2. The accumulated skin cells on the surface of the skin could feel burning caused by pruritus. The dysfunctional epidermis layer will lead to further inflammation [6].

The Th1 cytokines, including IL-12, IFN-γ, and TNF-α,

ISSN 2959-409X

are predominantly expressed in psoriatic cases. IFN-γ is synthesized by both CD4+ and CD8+ T cells and is important in psoriasis, as evidenced by the ability of intradermal IFN-γ injections to induce lesion formation [7]. Dendritic cells (DCs) and keratinocytes also produce a great amount of various cytokines and chemokines. Then, IFN-γ and TNF-α can stimulate keratinocytes to produce a range of cytokines and growth chemicals, including IL-6, IL-7, IL-8, IL-12, IL-15, IL-18, and TNF-α. IL-18 acts synergistically with IL-12, which is also produced by DCs, greatly enhancing IFN-γ production. What is more, IL-17, produced by activated CD4+ T cells, works in concert with IFN-γ to fasten the production of pro-inflammatory cytokines by human keratinocytes, for example, IL-6 and IL-8, thereby shortening the life cycle of T cells in the skin [8]. This interaction between cytokines in psoriasis can lead to a self-perpetuating cycle.

TGF-α, IL-20, and IFN-γ are examples of autocrine factors that promote keratinocyte hyperproliferation; on the other hand, IFN-γ and IL-15 strengthen the apoptotic resistance of these cells. The cytokine network in psoriasis appears to be getting more complex, as evidenced by the discovery of new Th1 cytokines such as IL-23 and IL-27. TNF-α and IFN-γ are key players in the etiology of psoriasis, as evidenced by the effectiveness of anti-TNF-α therapy, even if the exact role of TNF-α in the disease's pathogenesis is still unclear. The immune-mediated cascade in psoriasis depends heavily on chemokines generated by keratinocytes and inflammatory cells, especially when it comes to leukocyte recruitment, adhesion, compartmentalization, and trafficking during the disease phase.

The relationships between these and other growth factors and cytokines found in psoriatic lesions can explain a variety of psoriasis clinical symptoms, such as inflammation, enhanced neovascularization, and hyperproliferation of keratinocytes. Though it is still an obstacle, identifying the primary cytokines and chemokines involved in the illness process may eventually lead to viable treatment targets.

3. Introduction of Acitretin

Acitretin is a retinoid discovered in 1972. Acitretin is the retinoic acid metabolite of etretinate. The abolition of etretinate in psoriasis is because it is highly lipophilic. It takes about more than 2 years to fully eliminate etretinate from the human body.

3.1 Chemical Structure of Acitretin

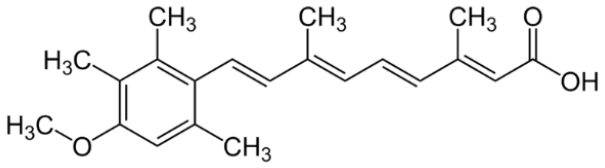

Fig.3 Structure of acitretin

As shown in Fig 3, Acitretin is a systemic retinoid derived from vitamin A that has been used effectively in psoriasis, and it is the first approved oral retinoid for treating psoriasis. Compared to other drugs, it is safer as it is non-immunosuppressive. The exact molecular mechanism of acitretin on psoriasis is still unknown, but acitretin activates nuclear retinoic acid receptors RAR- α, -βand -γ and regulates gene transcription, controlling nuclear differentiation, antiproliferation, anti-inflammation, anti-keratinization [9].

3.2 Mechanism of Acitretin

Acitretin interacts with retinoic acid receptors (RARs), which are nuclear receptors, on a cellular level. These receptors are transcription factors that control the expression of genes related to inflammation, cell division, and growth. Acitretin lessens the symptoms of psoriatic skin by binding to these RARs and assisting in correcting the abnormal gene expression patterns found in the condition. By controlling gene transcription and activating nuclear receptors, retinoids induce its biological effects. The retinoic acid receptor (RAR) and the retinoid X receptor are the two kinds of nuclear retinoid receptors. Three subtypes, a, b, and g, can be further distinguished between the two types of nuclear receptors [10]. Acitretin binds weakly to RAR-subtypes, although stimulating all three of them [11]. These retinoid receptors are part of a wide family of receptors that also include vitamin D3 receptors, thyroid hormone, and glucocorticosteroid receptors. All of these receptors are DNA-binding proteins that operate as trans-acting transcription factors to modify the expression of genes. Acitretin changes the cellular differentiation of the epidermis, which helps to decrease the scaling, erythema, and thickness of the infected areas. There is also evidence that acitretin can reduce the thickness of the outer skin and the inflammation in the epidermis and dermis triggered by psoriasis [12].

4. Introduction of Tacrolimus

A calcineurin inhibitor named tacrolimus inhibits T-cell activation and lowers the production of cytokines that promote inflammation.

4.1 Chemical Structure of Tacrolimus

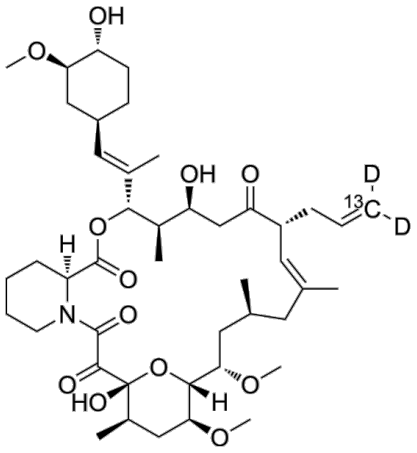

Fig.4 Structure of tacrolimus

Chemically, tacrolimus is a macrolide (Fig 4); it inhibits peptidyl-prolyl isomerase activity by binding to immunophilin FKBP-12 (FK506 binding protein) and forming a new complex that inhibits calcineurin, which in turn inhibits T-lymphocyte signal transmission and transcripts IL-2.

4.2 Mechanism of Tacrolimus

Tacrolimus specifically targets Th1 and Th17 helper T cells, which are important in the pathophysiology of psoriasis. Tacrolimus inhibits calcineurin phosphatase activity by attaching to FK506-binding protein, which stops the nuclear factor of activated T cells (NFAT) from being dephosphorylated and translocated to the nucleus. Reduced transcription of cytokine genes, such as IL-2, IFN-γ, and TNF-α, is the outcome of this disruption in NFAT signaling, which lowers inflammation and promotes skin healing. Tacrolimus has thus been extensively studied for the management of immunological disorders [13,14] and psoriasis. It is legally sold as a topical ointment. However, reports of the ointment's low and extremely uneven absorption caused it to struggle to guarantee sufficient topical drug delivery into deeper layers of the skin [14,15].

4.3 Side Effects of Tacrolimus

The safety and tolerability of tacrolimus have also been evaluated in clinical trials. In general, tacrolimus is well-tolerated with few systemic side effects due to its minimal absorption into the bloodstream when applied; side effects such as skin irritation, burning sensation, dry mouth, headache, and pruritus occur. Additionally, there is a potential risk of skin atrophy and dyspigmentation with long-term use.

5. Comparison of Acitretin and Tacrolimus

5.1 Difference in Mechanism

Acitretin works by influencing the activity of vitamin receptors within cells. As such, it is in the same pharmacological class as vitamin A. Acitretin mainly functions to restore normal keratinocyte (skin cell) growth and differentiation in the setting of psoriasis. This is done by lessening the uncontrollably high proliferation of these cells, which induces psoriatic plaques to form. Furthermore, acitretin has anti-inflammatory properties that may assist in lessening psoriasis-related inflammation. The binding of the acitretin molecule to particular intracellular retinoid receptors, such as retinoic acid receptors (RARs) or retinoid X receptors (RXRs), is the mechanism of action. When these receptors are activated, they alter the transcription of genes, which results in alterations in cell behavior and a drop in psoriasis symptoms. Acitretin will work better in combination therapy with ultraviolet B (UVB) or psoralen ultraviolet A (PUVA).

Conversely, tacrolimus is a topical inhibitor of calcineurin. When applied topically, it reduces the inflammatory response that results to psoriasis by suppressing the immune system locally. Tacrolimus attains this by preventing T-cell activity, which in turn slows the production of inflammatory mediators, which are immunological molecules that boost inflammation. In particular, tacrolimus binds to an immunophilin known as FK506-binding protein. This complex afterward prevents the phosphatase enzyme calcineurin from activating T cells. In autoimmune diseases like psoriasis, this stops T-cell activation initiating proliferation as well as the release of pro-inflammatory cytokines like interleukin-2 (IL-2). These cytokines are essential for the inflammatory response.

5.2 Difference in Side Effects

Adverse reactions and specific side effects have been linked to both tacrolimus and acitretin. When using tacrolimus, common side effects include dry skin, itching, and redness at the application site. However, acitretin has also been related to joint and muscle pain, dry eyes, and dry mouth. Tacrolimus emphasizes its localized application, which lowers systemic side effects and toxicity, while acitretin contends that its systemic effects on the immune system can offer a more profound and long-lasting resolution of psoriasis.

Comprehending the adverse reactions and side effects of these medications can aid in reducing any possible risks that may arise. Even though each medication has advan-

ISSN 2959-409X

tages and disadvantages, the best course of treatment should be chosen after taking into account the unique requirements and preferences of each patient. Because acitretin has systemic effects and can penetrate deeper layers of the skin, it may be appropriate to consider it for patients with severe psoriasis, including those who have not responded well to topical therapies alone.

Therefore, the effectiveness of acitretin and tacrolimus cannot be compared. They have different mechanism and target when treating psoriasis. For psoriasis, combined therapy can work better to relief this disease, different medicine should be applied decided by individual's situation.

6. Conclusion

Even though the actual pathology of psoriasis is still unclear, there are already a lot of medicines that can relieve the pain. Because of its chemical nature, acitretin targets the epidermis and regulates the immune strategy to better treat psoriasis. For patients with severe forms of the disease, it is a useful therapeutic option potential to restore normal keratinocyte proliferation and differentiation. Tacrolimus, as an effective immunosuppressive inhibit, can swiftly control abnormal production of keratinocytes and T cells. Combined therapy tends to be more effective.

Even though these medications relieve symptoms, medical professionals must comprehend how they work in order to maximize therapeutic approaches and reduce adverse effects. To completely understand the complex interactions between genetic, environmental, and immunological factors that lead to the development of psoriasis and to find new targets for treatment, more research is required.

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