Chapter 6

Treatment of Psoriasis with Topical Agents

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Additional information is available at the end of the chapter

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1. Introduction

The history of immunosuppressive drugs is linked to both the evolution of scientific understanding of inflammatory diseases and the development of organ allografts. These drugs are part of a valuable arsenal for the treatment of diseases mediated by the immune system. As medical and public health practices have evolved, infectious processes are no longer the primary diagnostic and therapeutic challenge posed by dermatological conditions. Emerging in this void are cutaneous manifestations mediated by the immune system that present new management issues and require extensive use of the group of drugs described as immunomodulating agents. Psoriasis, among many other diseases in the purview of the dermatologist, is treated with these medications. Observing the use of these medications also helps to illustrate the evolution of dermatologic therapeutics. Some of these drugs, such as topical corticosteroids, are considered the basis of the dermatological therapeutic arsenal. To use these medications appropriately, it is important to be aware of both facts and myths concerning the action of immunosuppressive agents and the burden of side effects. [1]

The objective of this chapter is to discuss some characteristics of modern immunomodulators that are still useful for psoriasis treatment in the biological era. Moreover, it aims to dispel myths that might have a negative impact on the use of such drugs by clinicians. The primary focus is on immunomodulators that have been successfully used in the treatment of psoriasis. As such, several aspects of psoriasis immunopathophysiology and regulatory pathways of immune cells are explored [2]. Furthermore, it is likely that there is a considerable amount of similarity in concepts within this class of medications, given that these mechanisms describe immunomodulator drugs. Within this framework, the intention is to provide important insight into how the immune system can be modulated by these drugs used to treat psoriasis in a more traditional fashion.

2. Clinical manifestation of psoriasis

Psoriasis is a chronic, inflammatory, multi-system disorder characterized by abnormal epidermal differentiation and hyperproliferation thought to be related to abnormal immune system activity. According to data from various resources, about 2-3% of the general population suffers from psoriasis. Accepting and extrapolating these rates globally, approximately 140 to 210 million people live with psoriasis Although psoriasis is usually benign, it is a lifelong illness with remissions and exacerbations and is sometimes refractory to treatment. Nonetheless, the majority of the cases are mild or moderate psoriasis [3]. A recent study observed 75.8% of patients to have a psoriasis area severity index (PASI) of <20 [4]. Moreover, 17-55% of patients experience remissions of varying lengths. Plaque-type psoriasis is the most common form, affecting 80 – 90% of patients. Inverse, erythrodermic, pustular and guttate forms of psoriasis have also been described. Patients present with sharply demarcated, erythematous plaques covered by silvery white scales, most commonly on the extensor surfaces and the scalp. The natural history is variable but is often chronic and relapsing, and patients may experience extracutaneous manifestations commonly including nail involvement and psoriatic arthritis in up to 20% of patients [5].

3. Psoriasis pathogenesis

In the context of a complex multifactorial genetic background, environmental stimuli, such as bacterial antigens, act agonistically on Toll-like receptors (TLR) on the surface of keratinocytes (KC). In psoriatic patients, this stimulus induces the production of several inflammatory mediators by KC that are released to the adjacent underlying dermis. In this pro-inflammatory environment, endothelial cells from small vessels start to express adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1 or CD54), vascular cell adhesion molecule-1 (VCAM-1, or CD106), and E-selectin (CD62E). These superficial molecular modifications allow leukocytes and lymphocytes to migrate to the dermis, attracted by inflammatory chemokines released by KC. Macrophage inflammatory protein-3 A (MIP3A), produced by the keratinocytes, binds to its receptor CCR6 on leukocyte surface, blocks the leukocyte migration, and induces the formation of structure lymphoid tissues in the dermis. The CD11c+ plasmacytoid dendritic cells (DC) and CD3+ T cells in the organized lymphoid tissue initiate a process of cross communication based on cytokine production.

The activated DC (CD11c+) produces TNF-α, IL-12, IL-20 and IL-23. CD3+ T cells in response to IL-12, initially produce IFN-γ and are considered Th1 (Phase I of the cytokine pathway). Later in the process, the continuous activation of KC induces the presence of transforming growth factor (TGF)-β in the field. In the presence of IL-23 and TGF-β, the IL-12 chronic stimulated CD3+ Th1 cells evolve into Th17 CD3+ T cells (Phase II of the cytokine pathway). Th17 cells produce IL-17 and IL-22. IL-17 and IL-22 act in synergy with IL-19, IL-20 and IL-24, produced by IL-20-activated resident macrophages, to induce keratinocyte activation and proliferation (Phase III of the cytokine pathway). The activated and proliferative keratinocytes

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produce other proinflammatory cytokines, which maintain the vicious inflammatory cycle of plaque psoriasis. Among the proinflammatory cytokines is IL-8 (recently converted to CXCL8), is related to the migration of neutrophils to the plaque in psoriasis. Growth-regulated oncogene (GRO)-α, also known as CXCL1, predisposes tissues to further cellular proliferation. Human beta defensin (HBD)-2, HBD-3, and LL-37 induce microbacterial destruction and the release of further bacterial antigens to the immunological environment.

4. Immunomodulators – Basic concept of drugs used to treat psoriasis

In a homeostatic situation, the immune system interacts with many antigens without notice in a healthy individual [6]. However, the development of a hypersensitivity response induced by the chronic stimulation of the immune system results in the clinical manifestation of a specific group of illnesses [7]. The lack of control of the immune response is the basis of the clinical manifestation of these diseases. In the majority of these cases, there is an increase in the immune response activity. Therefore, the manifestation of a hypersensitivity reaction induces the pathogenesis of autoimmune and other inflammatory diseases [8].

The basic approach for treatment of these illnesses is manipulating the immune system to reduce its activity. In these cases, the therapeutic goal is fine-tuning of the milieu to downgrade the pathological response and return the immune system to a state of controlled homeostasis [9, 10]. However, the modulation of the system has to bring the balance to its normal limits without reducing it beyond these boundaries. It can be compared to adjusting the volume and the tone of music in an orchestra. High volume and distortions reduce the beauty of the music and can cause discomfort. In adjusting the volume and correcting the distortions, the maestro modulates the music, creating a pleasant sensation while still ensuring that each component remains audible.

Medications for treatment of autoimmune diseases modulate the immune system [11]. They do not cause immunosuppression because they treat a hyper-activated system [12]. Rather, they bring the immune system to its normal levels (Figure 1).

Bringing the immune system to its normal levels resolves the symptoms caused by the overactive inflammatory response. Immunosuppression occurs only when the immune system is reduced to a level below its physiological level by these drugs [13]. Therefore, the correct use of the various immunomodulators intends to bring the patient to a controlled homeostasis with an absence of symptoms.

4.1. Development of the actual recommendations for treatment of psoriasis

There has been considerable debate in the literature regarding the most appropriate method to determine the initial treatment in psoriasis. The general observation of the psoriasis guideline therapy reveals that the basic decisions are based on psoriasis intensity and its form of clinical manifestation. Body Surface Area (BSA) and Psoriasis Area and Severity Index (PASI) are the main criteria to decide therapeutic strategy in psoriasis.

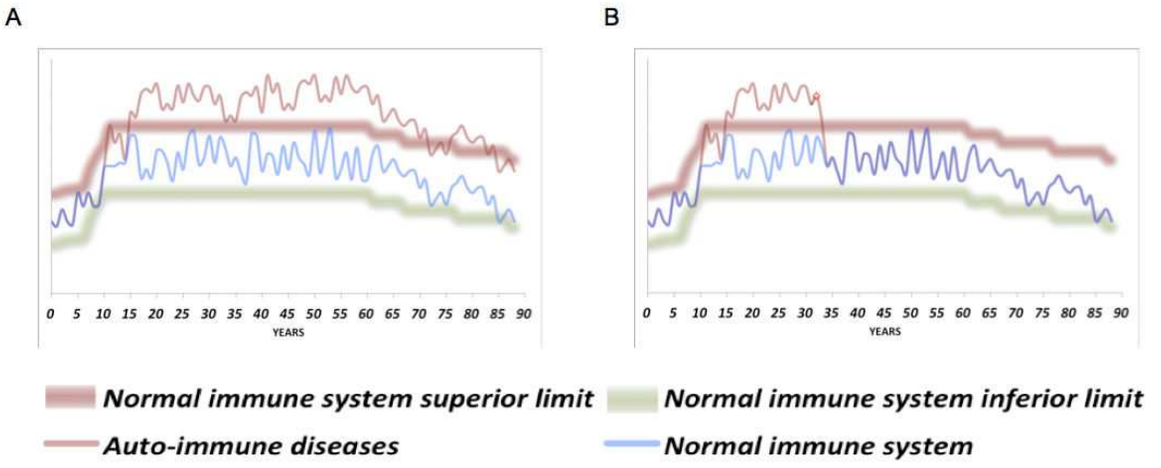

Figure 1. Schematic representation of immune system activity and its limits over the life-course. The blue line shows the immune system action within the normal limits boundaries. The red line displays the hyper-activated portion of the system immune activity that creates the autoimmune disease. A. It expresses a patient with untreated autoimmune disease. B. It illustrates a patient treated with a successful immunomodulator (orange diamond). The immunomodulator brings the immune system within normal immune system limits and not cause immunosuppression.

It is well accepted that a BSA higher than 10% and/ or a PASI higher than 10 is the limit that determines the use of systemic medication (Figure 2) [14]. This elementary principle is found on the balance between risk and benefits of any therapy. The use of this guideline generally results in a ration and effective therapy for psoriatic patients; however, it is not an absolute rule. These therapy guideline suggestions are best paired with a recommended route of administration and should always be mediated by the good judgement of an analytical physician.

Therapy decisions and guidelines for psoriasis treatment have historically been based on clinical trials and empirical experience with available medications. Historical review implies a tendency of an inverse order between pathophysiology understanding and psoriasis treatment. The understanding of psoriasis pathophysiology was not the basis of drug treatment development in the majority of the cases. Studies in other fields, or pure empirical

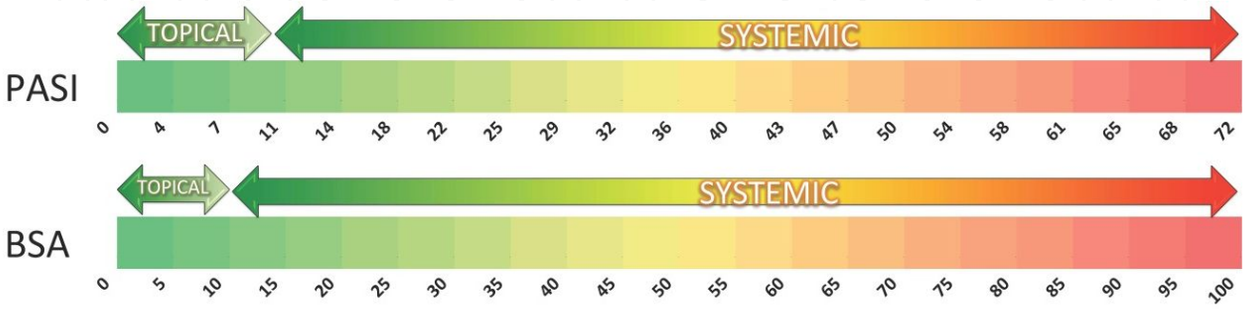

Figure 2. PASI and BSA scales. The putative limit between the use of topical and systemic treatment for psoriasis are demonstrated in both ribbons.

observation, resulted in the use of immunomodulators for psoriasis. The effective use of some of these drugs resulted in the actual immunopathophysiology model of psoriasis, not the other way around. For example, the etiology of psoriasis was once described as primarily and essentially an epidermal problem, independent of immunologic phenomena [15]. The main objective of cytotoxic drugs developed in the 20th century, such as methotrexate, was to reduce keratinocyte proliferation. However, immunological studies on psoriatic patients identified changes in humoral immune response as part of the overall problem but not the cause [16, 17]. The efficacy of cytotoxic drugs in the late 1960s paved the road for ideas about the role of the immune system in psoriasis [18, 19]. Further investigations in the 1970s revealed the role of immunologic factors in psoriasis. Here, these historical developments will be used as a context for the most recent guidelines in treatment of psoriasis.

4.2. Classification of the immunomodulators

To understand the drugs used in the treatment of psoriasis, the novice interested in this subject ought to know how these mediations are classified. Drugs that modulate the immune system can be classified as modifiers of the immune response to a specific antigen or antigens, nonspecific modulators, and agents that affect the inflammatory response. They can also be used in topical and systemic forms.

Antigen specific immune modifiers affect different stages of immune response. An example of this process is the use of anti-Rh antibodies. The desensitization to allergen is another example of antigen-specific immunosuppression.

Drugs such as cyclophosphamide, azathioprine, methotrexate and chlorambucil are the prototype of nonspecific antigen modulators. These drugs derive their immunomodulatory function primarily through cytotoxicity to immune effector cells. They are used in the treatment of both autoimmune and neoplastic diseases as well as in the control of rejection after organ and tissue transplantation. The medical field of transplantation has increased the use and development of these drugs. Another group of non antigen specific modulators inhibit the stimulation of T lymphocytes. They do so by inhibiting the T lymphocyte activation medicated by IL-2 and IL-2 receptors. Consequently, by inhibiting the activation of T lymphocytes these drugs reduce immune system activity. They include cyclosporine, tacrolimus, pimecrolimus and rapamycin.

Immunomudulators are also inhibitors of inflammatory response. Inflammation is the major manifestation of hyper-activation of the immune system. Thus, drugs that suppress the inflammatory response, such as NSAIDs and corticosteroids, can be useful in some circumstances.

5. Topical immunomodulators used in psoriasis

There continues to be significant evolution in psoriasis therapy in recent years. However, it is not surprising that topical forms of therapy are more prescribed than systemic forms in the

treatment of psoriasis. Although psoriasis is usually benign, it is a lifelong illness with remissions and exacerbations and is sometimes refractory to treatment. Nonetheless, the majority of the cases of psoriasis are mild or moderate in severity [3] and can be effectively treated with topical immunomodulators. Some studies suggest that approximately 10% of patients with psoriasis progress to develop psoriatic arthritis. The systemic therapies are used in severe forms of psoriasis.

Topical therapy for psoriasis is used as the first form of treatment. The main objective of the therapy is to achieve short-term suppression of symptoms, and long-term modulation of disease severity. Moreover, topical therapy intends to improve quality of life with minimal adverse effects; however, there is no clear guidelines regarding the topical agent to be used in each type of psoriasis Therefore, the topical medications will be presented here on the basis of their historical evolution (Figure 3). There are some basic rules, which practitioners can apply in assessing when psoriasis can be managed with topical agents alone'. For example, patients with limited disease (usually < 10% of their body surface) can often be managed topically. For plaques, medium- to high-potency corticosteroids used daily is commonly the first choice of therapy. Coal tar preparations can be best used along with topical corticosteroids in rotation. Anthralin is more commonly used in short- term management of chronic plaque psoriasis. Vitamin D3 analogs are an effective treatment for mild to moderately severe plaque psoriasis and are well tolerated on the face and intertriginous areas without the use of corticosteroids.

5.1. Emollients

Emollient creams and lotions were developed because they are helpful in controlling scales and relieving pruritus. Emollients containing ingredients such as mineral oil are particularly helpful at relieving the dryness experienced with psoriasis. Emollients fill cavities and fissures of the skin with fat resulting in moisture retention and soft skin [20].

5.1.1. Emollients: Evidence summary for psoriasis treatment

They are available as over-the-counter preparations and should be applied at least once a day, preferably twice a day, but can be applied more often if required. Although both preparations are effective, most patients prefer creams to ointments, and compliance tends to be better with cream preparations.

5.2. Coal tar

Coal Tar was one of the first topical immunomodulators used for psoriasis treatment. One of the earliest references to its use was by the British Hospital for Diseases of the Skin in 1884. [21] Coal tar preparations can be effective for long-term management of psoriasis, with less side effects and rebound upon cessation than topical steroids. However, the exact mechanism of action of coal tar is not completely understood. The possible mechanism of action is the reduction of mitotic rate in the epidermis. This results in keratoplastic and anti-acanthotic properties. It can have an atrophogenic effect on the human epidermis. Finally, it has a photosensitizing effect with an absorption spectrum of 330–550 nm. This last effect is greatly

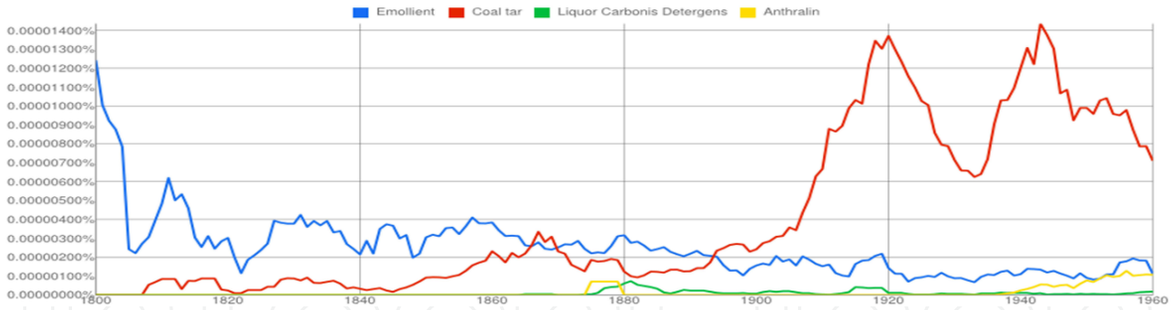

Figure 3. Google Books Ngram Viewer for old topical therapy for psoriasis. It displays a time line of how often the word Emollient, Coal tar, Liquor Carbonis Detergens, and Anthralin have occurred in a corpus of books written in English between 1800 and 1960. It roughly indicates the time of these therapies introduction in medicine.

enhanced by irradiation of the treated skin with UVA but not with UVB or UVC [22]. It seems that coal tar does not have a specific effect on the immune system of the skin [23].

When crude coal tar is refined or separate in different extracts, the result compound is called brown tar or liquor carbonis detergens (LCD). It is available in many different formulas such as soaks and shampoos. LCD is less effective than coal tar when combined with UVB for psoriasis therapy [24].

5.2.1. Coal tar: Evidence summary for psoriasis treatment

Tar preparations were once a popular treatment for psoriasis but have largely been replaced by topical corticosteroids due to the fact that these preparations are messy to use, can stain clothes, and have an unpleasant odor. They are effective in treating mild to moderate psoriasis [25].

5.3. Anthralin

Anthralin was developed from an herbal medication called Goa powder made from the bark of the South American araroba tree. Anthralin can be compounded in various vehicles and strengths, from 0.1% up to 10% or higher when specially compounded. It is usually necessary to add 3 to 10% salicylic acid in the formulation, not only as a keratolytic but also as a preservative to retard the oxidation of anthralin. Anthralin also causes a brown–red discoloration of the skin [26].

It is moderately effective and quite safe in plaque psoriasis. As for the main mechanism of action in psoriasis, anthralin is known to have antimitotic activity. The major side effect is occasional irritation. Use on acute, exudative, inflamed psoriatic plaques should be prevented. Irritation is more likely to occur in the perilesional skin than on the psoriasis plaque. Short contact treatment is used to reduce irritation but application for 8–12 hours is more effective [27]. The combination of the anthralin compound and UVB phototherapy is known as the Ingram regimen [28].

5.3.1. Anthralin: Evidence summary for psoriasis treatment

Anthralin used to be a mainstay for the topical treatment of psoriasis in the inpatient setting. However, its use has declined because of the availability of alternatives. It has been reported to be successful in treating mild to moderate psoriasis. When using Anthralin, it is best to start at the lowest strength and increase gradually as required according to response. Adverse effects include severe skin irritation, staining of clothing, and unpleasant smell.

5.4. Topical steroids

Topical steroids are the most used medication in the treatment of psoriasis. Corticosteroids were discovered in 1935 as compound E or cortisone [29]. The first therapeutic uses were in the treatment of rheumatoid arthritis and rheumatic fever followed by the treatment of inflammatory skin disease [30]. The topical use of steroids originated in 1952 as compound F or hydrocortisone [31]. Finally, psoriasis was included in the list of skin diseases treatable with hydrocortisone in 1955 [32].

The next step in the development of topical steroids included numerous modifications of the molecule and improvements in delivery systems of the drugs to increase their anti-inflammatory activity. Application of a thin film to psoriatic plaques two to three times daily is the basic instruction of topical steroids usage. Topical steroids have different potencies based on their formulations [33]. The efficacy is directly related to the skin penetration of steroid molecules and the rate of absorption is influenced by the steroid chemical structure. Other factors such as formulation vehicle and status of the skin also play a role in the absorption of the medication [34, 35].

It is not an easy decision to prescribe topical steroid for psoriasis. Among many other factors, anatomical site, amount, frequency of application should be considered too' [36]. For example, no topical corticosteroids should be used on the face, axilla, or groin, other than low-potency ones, unless otherwise recommended by the doctor. These concerns are related to the action of corticosteroids on the epidermis, which is to reduce the epidermis' ability to proliferate by interfering with RNA synthesis. Steroid antimitotic effect in cutaneous psoriasis demonstrates that the therapeutic effects are under the stratum corneum [33, 37].

Steroid antimitotic effects on the skin can cause a thinning of the epidermis. This can occur within 7 days of use of high dose topical steroids. All layers of the epidermis are reduced in thickness by 3 weeks of strong topical steroid use. The thinning of the epidermis impairs physiological functions of the epidermis and may be associated with the rebound of inflammation, which is a paradoxical effect. Thus, potent topical glucocorticosteroids will cause anti-inflammatory effects when first applied but with subsequent applications their therapeutic action rapidly diminishes, which is known as tachyphylaxis [38]. However, after a rest period of a few days, the same initial beneficial response may be produced again, but this will also disappear if the steroid is again continued topically. Therefore, steroids should be used for 2 to 3 weeks and then tapered with the intention of discontinuing the use of the steroid cream [39].

Effect of topical steroid action is not limited to the epidermis as they are able to penetrate the stratum corneum and are absorbed into both the epidermis and the dermis. Reduction of dermis volume occurs within 1-3 weeks of using high dose topical steroids. This acute effect also results from interference of RNA synthesis in fibroblasts' [40]. These cells do not produce primarily hyaluronic acid, which decreases dermal water content. However, the chronic use causes abnormal synthesis of collagen and elastin that is the cause of dermal atrophy and impaired wound healing [41, 42].

The steroid molecules are also absorbed to some degree into circulation when they reach the dermis. The absorption in large areas of skin after chronic use may be sufficient to cause systemic effects such as adrenocortical suppression. Therefore, systemic side effects have become a very real concern with the use potent topical steroids [43]. This is one of the most important criteria for use of BSA or PASI 10 to initiate systemic medication. Although it is rare to see clinical systemic effects in an adult patient, there have been reported cases of hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, cataracts, and glaucoma. Moreover, children are more at risk for systemic side effects because they have greater body mass to body surface ratio than adults. In general, high dose super potent topical steroids are not recommended for children under age 12 because they can cause growth retardation and failure to thrive [44, 45].

As immunomodulators, steroids initiate their mechanisms of action by binding to intracellular receptors, and inhibits protein synthesis resulting in immunosuppression. The majority of these events occur at the dermis. Steroids effect cell trafficking since they reduce the expression of adhesion molecules on the vascular endothelium. Corticosteroids also have functional effects. They alter the release of neutrophil lysosomal enzymes, decrease production of IL-1 by monocytes, induce reduction of IL-2 by T lymphocytes, and interfere with macrophage antigen presentation. Corticosteroids reduce the binding of immunoglobulin Fc and C3b receptors. They block lymphocyte proliferation and reduce delayed hypersensitivity responses. Many other effects are observed with corticosteroids, but these are considered to be the most important [44, 46].

5.4.1. Topical steroids: Evidence summary for psoriasis treatment

One systematic review of topical corticosteroid preparations versus placebo for psoriasis clearly indicated that all corticosteroids performed better than placebo. The same study showed that potent corticosteroids had smaller benefits than very potent corticosteroids [47]. Therefore, with this in mind, pharmacological treatment of psoriasis should begin with the use of topical corticosteroids. They are easy to apply and suitable for combination with other therapies where monotherapy is insufficient. Generally, the lowest potency of topical corticosteroid should be used. Low-potency treatments are appropriate for lesions on the face or intertriginous areas or for infants. Adults mainly respond to a mid-potency agent. High-potency topical corticosteroids are usually reserved for adults requiring short-term treatment of thick plaques that are resistant to lower-potency agents [48].

5.5. Analogues of vitamin D3 for psoriasis

Calcipotriol, calcitriol and tacalcitol are analogues of vitamin D3. Calcitriol is the naturally occurring active form of vitamin D3. Keratinocytes possess receptors for 1,25-dihydroxyvitamin D. All vitamin D3 derivatives inhibit cell proliferation and stimulate differentiation of keratinocytes. These observations inspired the use of analogues of vitamin D3 for the treatment of psoriasis [49]. Vitamin D derivatives are more effective at improving psoriasis severity scores at 3 to 8 weeks when compared with placebo. However, the overall data has moderate-quality evidence [50].

Indicated for mild to moderately severe plaque psoriasis, there are more effects on the skin than simply the enhancement of epithelial cell differentiation. Calcitriol can modulate the skin's immune system through interfering with antigen presenting cells, regulatory T cell activation, cutaneous cytokine patterns, and adaptive immunity [52]. The final result is that vitamin D3 analogues effect inflammatory cell infiltration. Interestingly, like topical corticosteroids, tachyphylaxis can occur after a few weeks of use Vitamin D3 analogues. Therefore, rotational is a useful strategy to ensure maximum therapeutic benefit. This involves rotating vitamin D with other treatments every few weeks. Moreover, there is considerable evidence to suggest that the hyperproliferation and inflammatory components of the disease can be more rapidly controlled using mixtures of drugs such as the vitamin D3 analog calcipotriol and the steroid betamethasone dipropionate [53].

5.5.1. Analogues of vitamin D3: Evidence summary for psoriasis treatment

Vitamin D3 analogues have the advantage of being cosmetically more acceptable to patients than coal tar or anthralin preparations, but they may cause irritant dermatitis and photosensitivity in some patients. Calcitriol can be used on the scalp and flexural areas. Cream formulation may be well tolerated on the face and intertriginous areas. They should be avoided in generalised pustular erythrodermic exfoliative psoriasis and individuals with calcium metabolism disorders. Patients are limited to a maximum of 100 g/week because there is a potential risk of hypercalcemia and hypercalciuria, although this occurrence is rare.

5.6. Tazarotene

The use of oral retinoids for psoriasis treatment precedes that of their use topically. However, the success of these oral therapies, and the development of topical retinoids for other dermatoses, triggered the development of tazarotene. Tazarotene is a selective topical retinoid for psoriasis treatment. Efficacy and safety of this agent has been established as a monotherapy or in combination with other therapies, particularly topical corticosteroids and phototherapy [54, 55].

Like other retinoid derivatives, tazarotene binds the retinoic acid receptor (RAR) but in a class-specific manner. It preferentially binds to RAR-γ and RAR-β over RAR-α and it does not bind retinoid X receptor (RXR) [56]. As a result of the binding at the RAR receptor, tazarotene seems to cause a reduction in proliferation and normalizes the differentiation of keratinocytes [57]. It

also possesses indirect anti-inflammatory properties by affecting keratinocyte chemokine production which reduces the dermal infiltration [58].

Tazarotene may be effective in the short term at improving symptoms of mild to moderate chronic plaque psoriasis [59]. It may cause skin irritation, including burning, stinging and itch in up to 30% of users [60]. It is potentially teratogenic and is contraindicated in women who may be/become pregnant [61, 62].

5.6.1. Tazarotene: Evidence summary for psoriasis treatment

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5.7. Topical calcineurin inhibitors

Calcineurin inhibitors (CIs), such as tacrolimus and pimecrolimus, are large lipophilic molecules that may be used topically in the treatment of psoriasis [63]. Their lipophilicity and size keep them in the skin with minimal systemic absorption [64, 65]. The main advantage of these drugs is the possibility of maintenance therapy for long periods eliminating the need for prolonged corticosteroids and their side effects [66].

Tacrolimus and pimecrolimus interact intracellularly by inhibiting the protein NFAT activation (Nuclear Factor Activating T cell) by calcineurin [67]. This works by blocking T lymphocyte mediated signaling and cytokine production. Topical CIs prevent transcription of inflammatory cytokines, including interleukin (IL)-2, IL-3, IL-4, IL-5, interferon (IFN)-γ and tumor necrosis factor (TNF)-α, which normally contribute to psoriatic lesions [68]. Downregulation of the high-affinity IgE receptor on Langerhans cells and inhibition of the release of inflammatory mediators from mast cells and basophils may also partly explain the effect of CIs when used topically [69]. Finally, recent evidence suggests that topical CIs may not act primarily by inhibiting the calcineurin/NFAT axis in lymphocytes in the skin but rather that they may instead act by decreasing NFAT2 activity in follicular keratinocytes [70]. These characteristics further support the topical use of CIs in the treatment of psoriasis.

Currently, calcineurin inhibitors are approved for atopic dermatitis (AD) treatment only. Despite their efficacy in AD management, CIs are ineffective in non-intertriginous psoriatic plaques management. This lack of efficacy is credited to the inability of CIs to penetrate the thick psoriatic plaques, however, they may be effective when used under occlusion on descaled small plaques. Tacrolimus therapy is more effective in the treatment of the face and intertriginous areas and is particularly useful because it does not cause skin atrophy or changes in collagen synthesis [71].

Most studies about the safety of CIs are centered on patients with atopic dermatitis. However, these products continue to be used off-label for psoriasis. Topical adverse effects of CIs may actually occur less frequently on the thick plaques of psoriasis. Both topical tacrolimus and

pimecrolimus may cause a stinging or burning sensation. Occasionally, patients using CIs experience flu-like symptoms, headaches, folliculitis and increased flushing after alcohol use. The FDA has raised concerns about the safety of CIs and has issued a black-box warning regarding the use of both tacrolimus and pimecrolimus. This concern is based on evidence of malignancy after long-term use of oral CIs and is not related to topical use. However, the FDA did not confirm a casual relationship between the use of CIs and the cases of malignancy. Further investigations regarding the safety of topical immunomodulators did not confirm the FDAs concerns. Furthermore, clinical evidence up to this point has not shown an enhanced risk of cancer after the use of either topical tacrolimus or pimecrolimus.

5.7.1. Calcineurin inhibitors: Evidence summary for psoriasis treatment

Calcineurin inhibitors have moderate efficacy for facial and inverse or intertriginous psoriasis. Their main indications are facial or inverse psoriasis that have not been responsive to weak or moderate strength topical steroids.

6. Summary of topical medications used in psoriasis treatment

Treatment of psoriasis depends on the type and severity of the disease. Typically, topical therapies are used to treat mild and localized psoriasis. Topical treatments are the foundation for mild to moderate psoriasis. However, this approach can decrease the number and thickness of the plaque lesions, and reduce the percentage of body surface involved. In general, pharmacological treatment should start with the use of topical corticosteroids [72].

The complete clearance of lesions is often not a realistic goal with topical therapy but eventually remission can be reached. Frustration related to medication efficacy expectations, poor cosmetic characteristics of topical preparations, time consumption, fear of side effects, and inconvenience were found to be the most important reasons patients chose to deviate from provider recommendations of topical therapy [73]. Studies suggest that adherence with topical treatment in psoriasis is poor. Research has shown that only 50% of topical agent applications prescribed by physicians are actually used [74].

Patients with chronic psoriasis may be candidates for topical therapy depending on their baseline severity. Topical treatments include creams, ointments, and lotions. The choice of formulation depends on the area affected. Physicians should also select formulations that will be acceptable to the patient [75]. There is a consensus that topical emollients and salicylic acid are effective as initial and adjunctive therapy for people with chronic plaque psoriasis, but it is unclear whether tars are effective [76].

6.1. Routine suggestions for classical mild and moderate plaque psoriasis

Topical high-potency corticosteroids may be used as first-line therapies for patients with mild plaque psoriasis. Low-potency treatments are appropriate for infants. Other appropriate first-line options include topical calcipotriol and calcipotriol/betamethasone dipropionate in

combination. Non-medicinal emollients, including creams, ointments, and lotions should be used in combination with the above agents to potentiate their effects and to help restore the natural barrier of the skin. For appropriate patients, tazarotene may be used, either alone or in combination with topical corticosteroids. Patients requiring ongoing treatment with topical agents containing high-potency corticosteroids should be monitored regularly for adverse effects and steroid-sparing concomitant treatments should be introduced. The rotation of a nonsteroidal topical agent following initial treatment is indicated.

6.2. Routine suggestions for facial, flexural, or genital areas

Topical treatment with calcineurin inhibitors (0.1% tacrolimus ointment or 1% pimecrolimus cream) should be used. Topical corticosteroids such as 0.1% betamethasone may be used on an occasional or intermittent basis. Mild- or moderate-potency corticosteroids may also be used on an occasional or intermittent basis to treat facial and genital psoriasis. In moderate to severe facial, flexural, and genital disease, stronger corticosteroids may be applied to address nonresponsive psoriasis or acute flares in these areas.

6.3. Routine suggestions for scalp psoriasis

Topical corticosteroids and calcipotriol are all appropriate topical treatments. Betamethasone dipropionate lotion, clobetasol propionate solution, betamethasone valerate solution, or calcipotriol solution are also possibilities. Calcipotriol/betamethasone dipropionate combination gel is a recently emerging therapy.

6.4. Routine suggestions for palmar-–plantar disease

For mild and moderate manifestations, potent corticosteroid or vitamin D analogues with salicylic acid preparations should be used. For intense forms, high-potency corticosteroids with salicylic acid and urea preparations are the main choice of therapy.

7. Conclusion

The treatment of diseases involving the immune system has progressed in recent years with the introduction of new immunomodulators in clinical practice. These drugs act at different points in the immune response and may significantly alter the immune response of the patient, especially if combined. However, topical therapies continue to serve as the fundamental basis for any physician when dealing with psoriasis. Understanding the mechanism of action of these drugs is necessary for better management and proper application in situations where clinical challenges appear. Further research and development in the field of topical immunomodulators will hopefully result in the design of even more effective drugs, with increased specificity of action and fewer side effects.

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