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Treatment of plaque-psoriasis in HIV-positive patients

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Abstract

Psoriasis is a chronic inflammatory disease that can often accompany human immunodeficiency virus (HIV) epidemics. Development of psoriasis in HIV patients is correlated with a decrease in CD4+ count. Significant variability in the clinical presentation of psoriasis makes it a challenging disease to diagnose. Furthermore, associated immunodeficiency complicates standard treatment with immunosuppressive and biological therapy.

Articles that match the terms *psoriasis* and *HIV* were searched in MEDLINE and Embase and selected based on their relevance.

Highly active antiretroviral therapy (HAART) is a medication regimen used to manage and treat HIV infection. In treating mild psoriasis in HIV-positive patients, topical agents combined with HAART are considered first-line therapy, followed by phototherapy. Second-line therapy includes oral retinoids, alone or combined. In treating challenging cases, apremilast has been used due to its lack of immunosuppressive effect. In case of progressive and refractory disease, limited data from studies suggest that immunosuppressive or biological therapy may be effective.

Treatment of psoriasis in HIV patients remains a challenge, which is largely attributable to its complicated etiopathology and lack of an approved therapy option. In treating severe psoriasis, close collaboration with an infectious disease specialist is highly recommended. Further research is needed, preferably with an aim toward developing individualized therapy.

Keywords: biologics, biological therapy, HIV, psoriasis, systemic therapy

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Introduction

Acquired immunodeficiency syndrome (AIDS) is a disease caused by the human immunodeficiency virus (HIV), and it has affected about 39 million people (between 33.1 and 45.7 million) worldwide, as estimated in 2022 (UNAIDS/WHO estimates, 2023). The decrease in immune system function associated with HIV leads to an increased risk of development of various pathologies, including psoriasis. This associated immunosuppression in HIV-positive patients limits potential treatment options (1). The use of biological therapy in treatment of severe and refractory psoriasis in individuals with AIDS has been described in the literature thus far only through case reports (2).

Psoriasis is a chronic inflammatory skin disease with a complex background. Its prevalence differs depending on geographical location, with countries closer to the equator reporting fewer cases than northern countries. In Croatia, it is estimated that 1.6% of the population is affected by it. Psoriasis displays a bimodal peak of disease, with the first occurring at age 20 to 35 and the second at 50 to 60 (3). There are various psoriatic phenotypes, with psoriasis vulgaris being the most common. A typical clinical presentation of plaque psoriasis includes symmetrical, red, and erythematosquamous plaques typically appearing on the extensor surfaces of the arms and legs (4). The etiopathology is multifactorial, with a combination of genetic, immunological, and environmental influences playing a part in its development. In terms of genetics, various single nucleotide polymorphisms exist, along with at least 12 significant psoriasis susceptibility (*PSORS*) loci that have so far been identified to cause psoriasis. The complexity of the disease largely stems from the multitude of potential multifactorial environmental triggers. Thus far, only a few of them have been shown to be clearly associated with the development of psoriasis: stress, infections (streptococcal pharyngitis), alcohol, and smoking (3). From an immunological point of view, psoriasis is an organ-specific inflammatory disease that activates the release of cytokines from active T-lymphocytes, resulting in keratinocyte proliferation (4).

HIV infection is a globally recognized problem associated with high morbidity and a greater prevalence of inflammatory dermatoses, including psoriasis. Coexisting comorbidities in HIV such as concomitant hepatitis C virus (HCV) infection result in difficulty in determining whether the prevalence of psoriasis in HIV-positive patients is greater than in the general population (1). Although psoriasis can develop regardless of the stage of HIV infection, its prevalence becomes higher as the CD4+ count drops (5). It is not uncommon for an HIV-positive patient to present with more than one clinical type of psoriasis. The progressive and refractory nature of psoriasis in HIV-positive patients makes it more challenging to treat (6).

Although psoriasis can potentially manifest in HIV-positive patients regardless of stage, it has a tendency to most often appear in the advanced stages of HIV infection, correlating with a low CD4+ count. Notably there is a nine-times higher risk of developing psoriasis once the CD4+ count is lower than 200 cells/mm^3. Psoriasis is generally mediated by type 1 cytokines, whereas in HIV type 2 cytokines tend to predominate. In psoriasis, there is an overexpression of interleukin-12 (IL-12), IL-23, and tumor necrosis factor alpha (TNF-α), whereas in HIV infection there is an overexpression of IL-4, IL-6, and IL-10 (4).

Initially it was believed that CD4+ T cells are solely responsible for the immune response leading to psoriasis in HIV-positive patients, but recently this notion has been challenged. Today, it is understood that CD8+ T cells also play an essential role in the pathogenesis of psoriasis. There is a link between the accumulation

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of CD8+ memory cells in the epidermis and the onset or exacerbation of the disease. As HIV infection progresses, the CD4+ levels begin to drop, resulting in a lower CD4/CD8 ratio. This translates to a higher CD8+ T cell count. At the beginning of the disease, the absolute CD8+ T cell count rises and, as the disease progresses, the number continues to steadily rise higher. However, the primary factor influencing psoriasis in HIV-positive patients is the impact of the virus on CD8+ naive and memory cells. This effect involves a reduction in naive cells and an increase in memory cells, which constitute the majority (85%–90%). Consequently, patients become more susceptible to autoimmune diseases such as psoriasis and experience a decreased ability to combat infections (7).

Methods

This article organizes and investigates available therapies for the treatment of psoriasis in HIV-positive patients because of a lack of information in this field. A systematic MEDLINE (PubMed) and Embase search was conducted, searching for articles in English between 2005 and 2022 containing *psoriasis* and *HIV*, *HIV* and *psoriatic*, and *HIV* combined with *biological therapies*. After our initial search, we narrowed our search field, limiting our search to include relevant article headings and text. The final search yielded 25 articles, some of which were case reports of HIV-positive patients with psoriasis.

Results and discussion

The treatment of psoriasis in HIV-positive patients poses a challenge partly due to the complexity of the disease. As previously stated, HIV results in immunosuppression, which can be worsened by the majority of systemic treatment options. Moreover, psoriasis in HIV-positive patients has been shown to be more refractory to treatment along with more frequent relapses compared to the general population (1).

An ideal treatment plan for psoriasis in HIV-positive patients should be individualized based on the disease's severity (Fig. 1, Table 1). This article reviews all potential treatments (2).

Antiretroviral therapy

Antiretroviral therapy is a standard therapy for HIV-positive patients, especially in patients that have a history of AIDS-defining illnesses or a CD4+ count lower than 350 cells/mm^3. HAART alters the progression of HIV and stabilizes the drop in CD4+ T cells. Furthermore, it can also be used to treat psoriasis in HIV-positive patients as a monotherapy or as part of a combined treatment plan. A published open-label trial with HIV-positive patients that have psoriasis showed that therapy with zidovudine led to clinical improvement of psoriasis in 90% of individuals treated. This success could be due to the decrease in viral load and production of TNF-α, one of the primary inflammatory cell mediators in psoriasis (8).

Topical therapy

Treating mild to moderate psoriasis always involves combining HAART with other treatment options due to HIV positivity. It is usually started with topical therapy using emollients, topical corticosteroids, or calcipotriol, and the two-compound formulation of calcipotriol and betamethasone dipropionate (8). Emollients help keep the skin hydrated and healthy. At the same time, they minimize itching, along with the risk of developing other psoriatic lesions that may potentially arise due to the Koebner phenomenon. Along with emollients, mid- to high-potency topical corticosteroids can also be used in the management of psoriasis in HIV-positive patients. Topical corticosteroids should be applied under occlusion, which enhances reduction of inflammation and ultimately hastens resolution of lesions. Often vitamin D analogs can be combined along with topical corticosteroids because they further help modulate T cell and dendritic cell function and reduce the proliferation of keratinocytes (3). Topical therapy can be used alone or with other therapies, such as systemic therapy, phototherapy, or photochemotherapy (PUVA) (8).

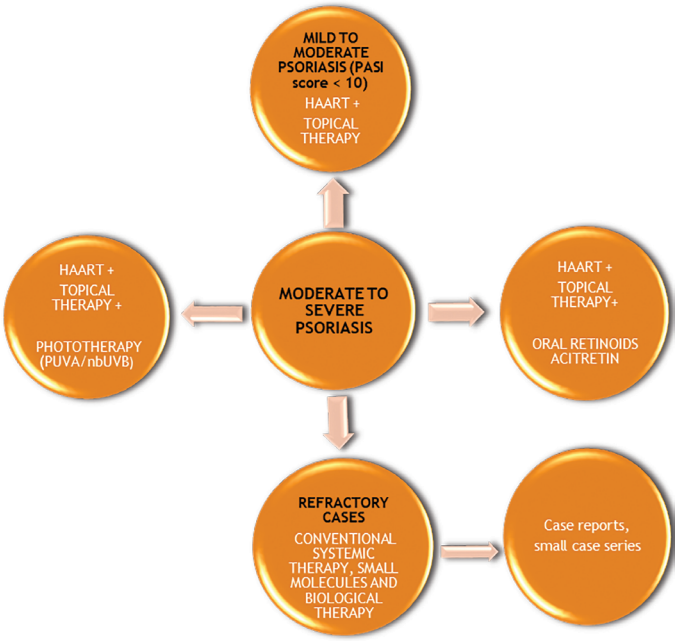

Figure 1 | Treatment algorithm for psoriasis in HIV-positive patients (1). PASI = psoriasis area and severity index, HAART = highly active antiretroviral therapy, PUVA = psoralen plus ultraviolet A, nbUVB = narrowband ultraviolet B.

Table 1 | Treatment of psoriasis in HIV-positive patients (1).

Category	Therapies			
Topical	Emollients Corticosteroids Keratolytics	Vitamin D3 analogue	Topical retinoids	Ditranol
Phototherapy	UVB	PUVA (bath)		
Conventional systemic	Oral retinoids: – Acitretin	Immunosuppressives: – Cyclosporine – Methotrexate		
Small molecule	Apremilast			
Biological inhibitors	Anti-TNF-α: – Adalimumab – Etanercept – Infliximab	IL-12/23: – Ustekinumab	IL-17: – Secukinumab – Ixekizumab – Brodalumab	IL-23: – Guselkumab – Risankizumab

UVB = ultraviolet B, PUVA = psoralen plus ultraviolet A, anti-TNF-α = anti-tumor necrosis factor alpha, IL = interleukin.

Phototherapy

First-line treatment for moderate to severe psoriasis in HIV-positive patients is phototherapy: PUVA and ultraviolet B radiation (UVB). Phototherapy inhibits cell proliferation and the release of inflammatory cell mediators. It is considered a clinically effective and generally safe treatment option in HIV-negative patients with psoriasis, although UV radiation along with its immunosuppressive effect have raised a safety concern in treating HIV-positive patients. In vitro studies and studies with transgenic animals have shown that UV radiation activates HIV and UVB activates psoriasis in the epidermis. Nevertheless, this concern has yet to be proven clinically (8). Photosensitivity in HIV-positive patients is the main limiting factor of phototherapy. Patients with HIV can experience photosensitivity because of the virus, HAART, or other photosensitive drugs, such as trimethoprim. Other significant potential adverse events of phototherapy include a higher risk of non-melanoma skin cancer (4).

Conventional systemic therapy

Oral retinoids are the most commonly used oral systemic therapy in treatment of psoriasis in HIV-positive patients. This therapy can be administered alone, as a monotherapy, or in combination with other therapies. Oral retinoids are considered an effective non-immunosuppressant therapy for HIV-positive patients. Oral retinoids such as acitretin have a synergistic effect when administered along with phototherapy, which allows for the radiation dose to be potentially lowered. Dosing in HIV-positive patients is similar to the general population, 0.5 to 1.0 mg/kg/day, but in more refractory cases it can be higher. The safety profile is the same as in psoriasis in HIV-negative patients, although there is a recorded interaction with certain HAART medications (1). Some side effects include teratogenicity, pancreatitis, and hypertriglyceridemia (5).

Systemic oral immunosuppressives are not often used in treatment of HIV-positive patients and are typically reserved for the most refractory cases. Due to the nature of HIV disease, the use of immunosuppressive medications could increase the risk for development of opportunistic infections. Few published articles and papers discuss the use of immunosuppressants in HIV-positive patients, limiting the evidence supporting their use. The most commonly used immunosuppressive medications are cyclosporine and methotrexate (5, 9).

Cyclosporine inhibits the activation of CD4+ T cells by calcineurin inhibition, therefore resulting in an immunomodulatory effect. This therapy is usually reserved for recalcitrant cases for a limited period of 12 weeks to induce a response. The use of cyclosporine in treating psoriasis in HIV-positive patients is limited, even though as of yet no other opportunistic infections have been reported as a result of administration of this therapy. This limitation of cyclosporine as a potential treatment option results from its potential serious side effects, such as hypertension and nephrotoxicity (5).

Methotrexate is the most commonly used oral immunosuppressive for psoriasis. The use of methotrexate in HIV-positive patients can potentially lead to opportunistic infections and toxic encephalopathy (9). When treating psoriasis with methotrexate, the addition of prophylaxis against opportunistic infections has been shown in reports to increase safety and efficacy of the treatment. Recent reports have described low doses of methotrexate along with anti-TNF-α to be an additional safe treatment option (8).

Small molecule

Apremilast is an oral phosphodiesterase-4 inhibitor (PDE4) that modulates inflammatory mediators involved in psoriasis. It elevates intracellular cyclic adenosine monophosphate (cAMP) levels and decreases pro-inflammatory cytokines (IL-23, TNF-α) (10). There are few published case reports or studies on the use of apremilast in HIV-positive patients with psoriasis. Treatment with apremilast has been shown to be effective, without reported complications, thus making it a promising new therapy for HIV-positive patients. Apremilast is an excellent option for psoriasis in HIV-positive patients because of its anti-inflammatory mechanism of action. Further, it is not considered an immunosuppressive drug, which makes it a good candidate for more challenging cases. In the few published case reports, it has been reported that treatment with apremilast was effective with no noted complications (10, 11).

Biological therapy

Biological drugs approved for treatment of psoriasis in HIV-positive patients include monoclonal antibodies and enzyme inhibitors. Both treatment modalities target pro-inflammatory cytokines, thereby reducing inflammation, and thus impairing the appropriate immune response to infections (5). Biological therapy is considered a potential therapy option for treating psoriasis in patients with stable HIV infection (12). The American Academy of Dermatology and National Psoriasis Foundation and the British Association of Dermatologists guidelines recommend treatment with biologics as long as HIV is treated and closely monitored (12, 13).

TNF-α inhibitors were the first biological therapies used in the treatment of psoriasis (5). TNF-α inhibitors used in the treatment of psoriasis in HIV-positive patients are etanercept, infliximab, and adalimumab (14). When managing psoriasis in HIV-positive patients, the risk of complications presents a discernable concern, in part due to the increased risk of developing infections connected with a worsening of immunosuppression. Before considering the introduction of a TNF-α antagonist, coexisting infectious such as HCV, hepatitis B virus (HBV), and tuberculosis should be ruled out. (4). In published case reports, as of yet no side effects associated with treatment with TNF-α inhibitors have been reported; furthermore, throughout therapy a stable CD4 count was observed (14). Regardless, use of TNF-α inhibitors in treating HIV-positive patients with psoriasis is still infrequent.

IL-12/23 inhibitors: ustekinumab is a biological drug that targets IL-12 and IL-23. It has been proven safe and effective in treating psoriasis in HIV-positive patients. A stable CD4 count during treatment with ustekinumab has been reported in a number of studies, and a few have also observed an improvement in CD4 count with a preserved undetectable HIV viral load (15–17). Ultimately, the choice between anti-TNF-α and ustekinumab should ideally be individualized for the patient.

IL-17 inhibitors: due to IL-17 being a "peripheral cytokine" in the pathophysiology of psoriasis, it is thought that anti-IL-17 agents are relatively safer than others (14).

Secukinumab is an anti-IL-17A monoclonal antibody that can be used in treatment of psoriasis in HIV-positive patients. Complete clinical remission during treatment with secukinumab has been described in a case report. In that report, the CD4 count remained stable throughout treatment and the virus was undetectable. Reported side effects during the treatment were *Candida*

esophagitis and erosive gastritis. The side effects were managed without stopping treatment with secukinumab (18).

Ixekizumab is a newer biological agent that targets IL-17A. A network meta-analysis shows that it is one of the most rapid and effective agents for treating psoriasis (19). A satisfactory result was documented in a case report describing the treatment of an HIV-positive patient with psoriasis with ixekizumab. After 5 months of treatment, the patient reached Psoriasis Area and Severity Index (PASI) 90, with a stable CD4 count (20).

Brodalumab is a biological drug that inhibits the IL-17RA receptor. During treatment with brodalumab, there was a significant regression of psoriasis, with a documented absolute PASI score of 0 after 6 weeks (21). After 6 months of therapy, the patient remained free of psoriasis, with no other negative side effects, as well as a stable CD4 count and an undetectable viral load.

IL-23 inhibitors: guselkumab is an anti-IL-23 monoclonal antibody showing promising results for treating psoriasis. In an illustrative case report, guselkumab showed an excellent clinical response along with few side effects (6).

Risankizumab is a newer biological agent targeting the IL-23 cytokine. There is one case report in which risankizumab was successfully used for psoriasis in HIV-positive patients. In that case report, the patient attained a PASI score of 75 with no reported adverse side effects (22). Unfortunately, even though its effectiveness is promising, there is still not enough information on this agent.

Conclusions

The treatment of psoriasis in HIV-positive patients presents a challenge mainly due to an impaired immune system. Therefore, ideal management for these patients should consider an appropriate risk–benefit ratio. Potential treatments are selected according to the severity of the disease. HAART, first-line topical therapy, and phototherapy treatments are used for mild to moderate psoriasis. Moderate to severe psoriasis requires phototherapy (PUVA and UVB) or systematic therapy such as oral retinoids, aparemilast, immunosuppressives, and biological drugs. This type of therapy consists of immunosuppressive drugs or biologics, which are still not approved for HIV-positive patients (12). Close collaboration with an infectious disease specialist should be encouraged, and severe psoriasis cases should be discussed with them.

Information regarding the use of the medications mentioned above for psoriasis in HIV-positive patients derives from various case reports or small studies that have documented an excellent therapy response (23). Biological therapy has great potential as a therapeutic option in treatment of psoriasis in HIV-positive patients, and therefore further research on its safety profile and long-term efficacy is warranted.

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