Psoriasis Treatment in HIV-Positive Patients: A Systematic Review of Systemic Immunosuppressive Therapies

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PRACTICE **POINTS**

- There are limited data on the use of systemic immunosuppressive therapies for the treatment of psoriatic disease in human immunodeficiency virus–positive patients.
- The limited data suggest that biologic therapies may be effective for cases of psoriasis recalcitrant to other systemic agents and may have a positive effect on CD4 and viral counts when used in combination with highly active antiretroviral therapy.
- Further research is needed.

The management of psoriatic disease in the human immunodeficiency virus (HIV)–positive population is challenging. The clinical course often is progressive and refractory; therefore, first- and second-line therapies including topical agents, phototherapy, and oral retinoids often are inadequate. Most other currently available systemic therapies for psoriatic disease are immunosuppressive, which poses a distinct clinical challenge. A comprehensive systematic review of the literature via a PubMed search of articles indexed for MEDLINE using the terms *psoriasis and HIV* and *psoriatic arthritis and HIV* combined with several systemic immunosuppressive agents yielded a total of 25 reported cases of systemic immunosuppressive therapies used to treat psoriatic disease in HIV-positive patients including methotrexate, cyclosporine, etanercept, adalimumab, infliximab, and ustekinumab. The limited data suggest that biologic therapies may be effective for cases of psoriasis recalcitrant to other systemic agents and may have a positive effect on CD4 and viral counts when used in combination with highly active antiretroviral therapy (HAART); however, further studies are needed.

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The prevalence of psoriasis among human immunodeficiency virus (HIV)–positive patients in the United States is reported to be approximately 1% to 3%, which is similar to the rates reported for the general population.[1] Recalcitrant cases of psoriasis in patients with no history of the condition can be the initial manifestation of HIV infection. In patients with preexisting psoriasis, a flare of their disease can be seen following infection, and progression of HIV correlates with worsening psoriasis.[2] Psoriatic arthropathy also affects 23% to 50% of HIV-positive patients with psoriasis worldwide, which may be higher than the general population,[1] with more severe joint disease.

The management of psoriatic disease in the HIV-positive population is challenging. The current first-line recommendations for treatment include topical therapies, phototherapy, and highly active antiretroviral therapy (HAART), followed by oral retinoids as second-line agents.[3] However, the clinical course of psoriasis in HIV-positive patients often is progressive and refractory[2]; therefore, these therapies often are inadequate to control both skin and joint manifestations. Most other currently available systemic therapies for psoriatic disease are immunosuppressive, which poses a distinct clinical challenge because HIV-positive patients are already immunocompromised.

There currently are many systemic immunosuppressive agents used for the treatment of psoriatic disease, including oral agents (eg, methotrexate, hydroxyurea, cyclosporine), as well as newer biologic medications, including tumor necrosis factor (TNF) α inhibitors

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etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol. Golimumab and certolizumab pegol currently are indicated for psoriatic arthritis only. Other newer biologic therapies include ustekinumab, which inhibits IL-12 and IL-23, and secukinumab, which inhibits IL-17A. The purpose of this systematic review is to evaluate the most current literature to explore the efficacy and safety data as they pertain to systemic immunosuppressive therapies for the treatment of psoriatic disease in HIV-positive individuals.

Methods

To investigate the efficacy and safety of systemic immunosuppressive therapies for psoriatic disease in HIV-positive individuals, a PubMed search of articles indexed for MEDLINE (1985-2015) was conducted using the terms *psoriasis and HIV* and *psoriatic arthritis and HIV* combined with each of the following systemic immunosuppressive agents: *methotrexate*, *hydroxyurea*, *cyclosporine*, *etanercept*, *adalimumab*, *infliximab*, *golimumab*, *certolizumab pegol*, *ustekinumab*, and *secukinumab*. Pediatric cases and articles that were not available in the English language were excluded.

For each case, patient demographic information (ie, age, sex), prior failed psoriasis treatments, and history of HAART were documented. The dosing regimen of the systemic agent was noted when different from the US Food and Drug administration–approved dosage for psoriasis or psoriatic arthritis. The duration of immunosuppressive therapy as well as pretreatment and posttreatment CD4 and viral counts (when available) were collected. The response to treatment and adverse effects were summarized.

Results

Our review of the literature yielded a total of 25 reported cases of systemic immunosuppressive therapies used to treat psoriatic disease in HIV-positive patients, including methotrexate, cyclosporine, etanercept, adalimumab, infliximab, and ustekinumab (Table). There were no reports of the use of hydroxyurea, golimumab, certolizumab pegol, or secukinumab to treat psoriatic disease in this patient population.

Methotrexate—Eight individual cases of methotrexate used to treat psoriasis and/or psoriatic arthritis in HIV-positive patients were reported.[4-6] Duvic et al[6] described 4 patients with psoriatic disease that was treated with methotrexate with varying efficacy. One patient developed toxic encephalopathy, which improved after discontinuation of methotrexate; however, he died 5 months later from pneumocystis pneumonia. In this early study, none of the 4 patients were on antiretroviral therapy for HIV.[6]

In the cases reported by Masson et al[4] and Maurer et al,[5] 4 patients were treated with a single antiretroviral agent and received appropriate prophylaxis against opportunistic infections. In 1 case, methotrexate was given at a chemotherapeutic dose of 525 mg once weekly for Kaposi sarcoma.[4] In 2 of 4 cases, the patients developed pneumocystis pneumonia.[4,5]

Cyclosporine—There were 2 case reports of successful treatment of psoriatic disease with cyclosporine in HIV-positive patients.[7,8] Skin and joint manifestations improved rapidly without reports of infection for 2[7] and 8 years.[8] Both patients were treated with one antiretroviral agent.[7,8]

Etanercept—There were 5 case reports of successful treatment of psoriatic disease with etanercept. In all 5 cases the patients were on HAART, and the CD4 count increased or remained stable and viral count became undetectable or remained stable following treatment.[9-13] In 2 cases, the patient also had hepatitis C virus, which remained stable throughout the treatment period.[9,12] The maximum duration of treatment was 6 years, with only 1 reported adverse event.[13] In this case reported by Aboulafia et al,[13] the patient experienced recurrent polymicrobial infections, including enterococcal cellulitis, cystitis, and bacteremia, as well as pseudomonas pneumonia and septic arthritis. Therapy was discontinued at 6 months. Four months after discontinuation of etanercept, the patient died from infectious causes.[13]

Adalimumab—There was 1 case of successful treatment of psoriatic disease with adalimumab in an HIV-positive patient. In this case, the patient was on HAART, and CD4 and viral counts improved substantially after 30 months of treatment.[14]

Infliximab—Six individual cases of successful treatment of psoriatic disease with infliximab were reported.[15-17] In a report by Cepeda et al,[15] HIV-positive patients with various rheumatologic diseases were chosen to receive etanercept followed by adalimumab and/or infliximab if clinical improvement was not observed on etanercept. In 3 patients with psoriasis and psoriatic arthritis, inadequate response was observed on etanercept. Two of these 3 patients received adalimumab with only partial response. All 3 were treated with infliximab in the end and showed excellent response. One of the patients experienced facial abscess responsive to antibiotics and was continued on infliximab therapy without further complications. In all 6 cases of infliximab therapy, the patients were on HAART, and CD4 and viral counts improved or remained stable.[15]

Ustekinumab—There were 3 case reports of successful treatment of psoriatic disease with ustekinumab in HIV-positive patients on HAART. CD4 and viral counts improved or remained stable.[18-20]

Comment

Currently, all of the systemic immunosuppressive therapies approved for psoriatic disease have a warning by the US Food and Drug Administration for increased risk of serious infection. Given such labels, these therapies are not routinely prescribed for HIV-positive patients who are already immunocompromised; however, many

Cases of Psoriatic Disease in HIV-Positive Patients Treated With Systemic Immunosuppressive Therapies

Reference	Patient Age, y/Sex	Type of Psoriatic Disease	HAART (Yes/No)	Prior Failed Treatment(s)[a]	Duration of Immunosuppressive Therapy, mo	CD4 Count, cells/μL		Viral Count, copies/mL	
						Pretreatment	Posttreatment	Pretreatment	Posttreatment
Methotrexate									
Masson et al[4]	31/M	PsO, PsA	No	Acitretin	7	<200	291	NR	NR
Maurer et al[5]	39/M	PsO, PsA	No	Phototherapy, etretinate	29	144	30	NR	NR
	42/M	PsO, PsA	No	Phototherapy, etretinate	240	582	10	NR	NR
	32/M	ED PsO, PsA	No	None	5	40	40	NR	NR
Duvic et al[6]	32/M	Gutt PsO	No	None	1	NR	NR	NR	NR
	42/M	Gutt PsO	No	Phototherapy	NR	NR	NR	NR	NR
	25/M	Gutt PsO, ED PsO	No	Phototherapy	NR	NR	NR	NR	NR
	56/M	ED PsO	No	None	1.5	100	NR	NR	NR
Cyclosporine									
Tourne et al[7]	32/M	Pustular PsO, PP PsO, PsA	No	Prednisone, SS, acitretin, methotrexate	24	150	NR	NR	NR
Allen[8]	48/M	PsO	No	Etretinate, methotrexate	96	400	NR	NR	NR
Etanercept									
Di Lernia et al[9]	51/M	ED PsO	Yes	Phototherapy, prednisone, acitretin, cyclosporine	36	200	S	7930	UD
Lee et al[10]	46/M	PsO	Yes	Phototherapy, acitretin	78	1370	S	UD	UD
Mikhail et al[11]	32/M	Pustular, PsA	Yes	None	5	435	633	<75	UD
Linardaki et al[12]	43/M	PsO, PsA	Yes	Methotrexate, cyclosporine	24	280	>450	<50	UD
Aboulafia et al[13]	45/M	PsO, PsA	Yes	Phototherapy, prednisone, HCQ	6	200	S	14,000	S

(continued)

Reference	Patient Age, y/Sex	Type of Psoriatic Disease	HAART (Yes/No)	Prior Failed Treatment(s)[a]	Duration of Immunosuppressive Therapy, mo	CD4 Count, cells/μL		Viral Count, copies/mL	
						Pretreatment	Posttreatment	Pretreatment	Posttreatment
Adalimumab									
Lindsey et al[14]	49/M	PsO, PsA	Yes	Phototherapy, acitretin	30	127	550	14,649	UD
Infliximab									
Cepeda et al[15]	39/M	PsO, PsA	No	SS, methotrexate, etanercept, adalimumab	34[b]	750	741	22,148	54,227
	52/M	PsO, PsA	Yes	Prednisone, etanercept	55[b]	268	417	<50	<50
	47/F	PsO, PsA	Yes	SS, methotrexate, etanercept, adalimumab	13[b]	446	456	<400	<400
Sellam et al[16]	28/M	PsO, PsA	Yes	Prednisone, methotrexate	26	425	435	<50	2818
	Unknown/M	PsO, PsA	Yes	Acitretin, methotrexate	50	16	233	300,000	5900
Bartke et al[17]	46/M	PsO, PsA	Yes	Phototherapy, prednisone, acitretin, methotrexate	1.5	193	107	1040	UD
Ustekinumab									
Saeki et al[18]	47/M	PsO	Yes	Phototherapy, etretinate, cyclosporine, adalimumab	NR	755	910	<20	<20
Wieder et al[19]	39/M	PsO, PsA	Yes	Phototherapy, acitretin, methotrexate, HU, etanercept, adalimumab, GOL	17	847	856	UD	UD
Paparizos et al[20]	61/M	PsO	Yes	Phototherapy, acitretin, methotrexate, cyclosporine, etanercept	7	429	530	<50	<20

Abbreviations: HIV, human immunodeficiency virus; HAART, highly active anti-retroviral therapy; M, male; PsO, psoriasis; PsA, psoriatic arthritis; NR, not recorded; ED, erythrodermic; Gutt, guttate; PP, palmoplantar; SS, sulfasalazine; S, stable; UD, undetectable; HCQ, hydroxychloroquine; F, female; HU, hydroxyurea; GOL, golimumab.

[a]Does not include topical therapies.

[b]Treatment duration for all anti–tumor necrosis factor α therapies including etanercept, adalimumab, and infliximab.

HIV-positive patients have severe psoriatic disease that cannot be adequately treated with first- and second-line therapies including topical agents, phototherapy, or oral retinoids.

Our comprehensive review yielded a total of 25 reported cases of systemic immunosuppressive therapies used to treat psoriatic disease in HIV-positive patients including methotrexate, cyclosporine, etanercept, adalimumab, infliximab, and ustekinumab. Although data are limited to case reports and case series, some trends were observed.

Efficacy—In most of the cases reviewed, the patients had inadequate improvement of psoriatic disease with first- and second-line therapies, which included antiretrovirals alone, topical agents, phototherapy, and oral retinoids. Some cases reported poor response to methotrexate and cyclosporine.[4-8] Biologic agents were effective in many such cases.

Safety—Overall, there were 11 cases in which the patient was not on adequate HAART while being treated with systemic immunosuppressive therapy for psoriatic disease.[4-8,15] Of them, 3 were associated with serious infection while on methotrexate.[5,6] There was only 1 report of serious infection[13] of 14 cases in which the patient was on concomitant HAART. In this case, which reported polymicrobial infections and subsequent death of the patient, the infections continued after discontinuing etanercept; thus, the association is unclear. Interestingly, despite multiple infections, the CD4 and viral counts were stable throughout treatment with etanercept.[13]

From reviewing the 4 total cases[5,6,13] of serious infection, HAART appears to be a valuable concomitant treatment during systemic immunosuppressive therapy for HIV-positive patients; however, it does not necessarily prevent serious infections from occurring, and thus the clinician's diligence in monitoring for signs and symptoms of infection remains important.

CD4 and Viral Counts—Although reports of CD4 and viral counts were not available in earlier studies,[4-8] there were 15 cases that reported consistent pretreatment and posttreatment CD4 and viral counts during treatment with etanercept, adalimumab, infliximab, and ustekinumab.[9-20] In all cases, the CD4 count was stable or increased. Similarly, the viral count was stable or decreased. All patients, except 1 by Cepeda et al,[15] were on concomitant HAART.[9-14,16-20]

Although data are limited, treatment of psoriatic disease with biologic agents when used in combination with HAART may have beneficial effects on CD4 and viral counts. Tumor necrosis factor has a role in HIV expression through the action of nuclear factor κβ.[21] An increase in TNF levels is shown to be associated with increased viral count, decreased CD4 count, and increased symptoms of HIV progression, such as fever, fatigue, cachexia, and dementia.[22] Although more studies are necessary, TNF-α inhibitors may have a positive effect on HIV while simultaneously treating psoriatic disease. Other cytokines (eg, IL-12, IL-23, IL-17) involved in the mechanism of action of other biologic agents (ustekinumab and secukinumab) have not been shown to be directly associated with HIV activity; however, studies have shown that IL-10 has a role in inhibiting HIV-1 replication and inhibits its secretion of proinflammatory cytokines such as IL-12 and TNF-α.[21] It may be speculated that the inhibition of IL-12 and TNF-α may create a positive feedback effect to increase IL-10, which in turn inhibits HIV replication.

Conclusion

Although there are limited data on the efficacy and safety of systemic immunosuppressive therapies for the treatment of psoriatic disease in HIV-positive patients, a review of 25 individual cases suggest that these treatments are not only required but also are sufficient to treat some of the most resistant cases. It is possible that with adequate concomitant HAART and monitoring for signs and symptoms of infection, the likelihood of serious infection may be low. Furthermore, biologic agents may have a positive effect over other systemic immunosuppressive agents, such as methotrexate and cyclosporine, in improving CD4 and viral counts when used in combination with HAART. Although randomized controlled trials are necessary, current biologic therapies such as etanercept, adalimumab, infliximab, and ustekinumab may be safe viable options as third-line treatment of severe psoriasis in the HIV-positive population.

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