ABOUT THE AUTHOR

Philip Doiron, MD

Dr. Doiron holds a degree in pharmacy from Dalhousie University, completed medical school at McMaster University, dermatology residency at the University of Toronto, and a fellowship in HIV dermatology and male genital skin disease at the Chelsea & Westminster Hospital in London, UK. He holds a Master's in Health Science Education from McMaster University. He currently works as an Assistant Professor and Clinician Teacher at Women's College Hospital and the University Health Network.

USE OF BIOLOGICS TO TREAT PSORIASIS IN HIV

Background

Standard treatments for moderate-to-severe, refractory psoriatic disease generally involve immunosuppressant medications, which can complicate treatment in patients with concomitant immune suppression, including human immunodeficiency virus (HIV) infection. HIV is uniformly an exclusion criterion for clinical trials of biologic therapy, leaving dermatologists with scant evidence to support clinical treatment decisions for this subpopulation of patients. Patients with HIV also experience healthcare related inequality in disproportionately higher levels compared to the general population. It is important for dermatologists to have some degree of knowledge and comfort treating and managing patients with significant, refractory psoriatic disease and comorbid HIV infection.

Two sets of guidelines for the treatment of psoriatic disease in patients with HIV infection were published in 2010, each having similar recommendations.[1,2] For mild-to-moderate disease, topical therapy including corticosteroids, vitamin D analogues, tazarotene and tar derivatives are recommended as first-line treatment options. For moderate-to-severe disease, phototherapy and oral retinoids are subsequently recommended. In refractory moderate-to-severe disease, the use of cyclosporine, methotrexate and tumor necrosis factor (TNF) inhibitors can be considered. The paucity of evidence for methotrexate use in psoriasis and HIV makes informed and evidence-based clinical decisions difficult to incorporate into treatment management. Very few published cases exist in the literature. An article describing 9 published cases of patients with HIV (some with AIDS) receiving methotrexate therapy describes 8 developing infectious complications.[3] Six of the eight were not on concomitant antiretroviral therapy. The three receiving antiretroviral therapy were on zidovudine monotherapy, which is no longer the standard of care. It should also be noted that one of the patients was receiving high dose intravenous methotrexate as part of a treatment protocol for Kaposi sarcoma, the other

eight received standard doses for psoriasiform disease. The paucity of published cases, combined with the few patients who are described not matching the clinical context of the majority of North American patients with HIV today, make results difficult to interpret. It is unknown if patients would have experienced the same rate and extent of complications had their HIV been well controlled on antiretroviral therapy, which is the current recommendation for any patient with HIV being started on immunosuppressant therapy.

It is worth noting that since the above guidelines were published, apremilast has become available as an additional non-immunosuppressive option to treat psoriasis. Several case reports have been published illustrating effective and safe use of apremilast to treat psoriatic disease in patients with HIV.[4,5] Biologic agents with mechanisms of action not involving TNF inhibition have also become available.

TNF inhibitors – etanercept, adalimumab, infliximab

Current evidence for TNF inhibitors in patients with HIV consists mainly of case reports and small case series. As the TNF inhibitor class of biologics has been available to treat inflammatory dermatologic, rheumatologic and gastrointestinal diseases for over two decades, physicians understandably have developed the most experience and, by extension, comfort with their use. However, it is important to not automatically conflate the length of time a medication has been in use with superior efficacy or safety. The literature shows that individual patients have been followed for time ranges varying from months to almost 10 years.

Etanercept

Currently available evidence consists of 19 patients captured in 9 case reports.[6-14] All patients had clinical responses consistent with what would be expected in the general population, with five patients switching to alternate biologic therapy due to lack of efficacy. No significant changes in relevant laboratory parameters such as CD4 count and viral load were observed. One patient experienced multiple polymicrobial infections, which continued for 4 months after etanercept was discontinued, and eventually led to the patient's death. There were no other significant adverse events or opportunistic infections reported.

Adalimumab

Currently available evidence consists of 7 patients in 4 case reports.[7,8,15,16] Six patients had satisfactory clinical responses, and one being treated for psoriasis was switched to an alternate biologic therapy due to unsatisfactory response. No significant changes in relevant laboratory parameters were observed. There were no other significant adverse events or opportunistic infections reported.

Infliximab

Currently available evidence consists of 7 patients in 3 case reports.[8,17,18] All patients had clinical responses consistent with what would be expected in the general population. No significant changes in relevant laboratory parameters were observed. There were no other significant adverse events or opportunistic infections reported.

Other Anti-TNFs

No published evidence exists regarding the use of certolizumab in the treatment of patients with HIV. It is also worth noting that several patients in the case reports described above had concomitant hepatitis C virus (HCV) infection and none experienced elevations in alanine aminotransferase (ALT), HCV viral load or substantial changes on hepatic ultrasound.[7,10,12]

Another review looked at the rate of serious infection in patients with HIV treated with TNF inhibitors in a series of 24 patients.[19] Two cases of serious infection over 86.7 person years of follow up were identified. This equates to a serious infection rate of 2.3 per 100 patient years, which is comparable to the serious infection rate seen in registries of patients with rheumatoid arthritis treated with TNF inhibitors. The two cases were *Streptococcus pyogenes* pneumonia complicated by empyema and bacteremia, and methicillin-sensitive *Staphylococcus aureus* infection of a chest tube placed for pleural effusion of unknown etiology. The incidence of serious infection was not significantly different based on viral load and there were no cases of opportunistic infection.

IL-12/23 (ustekinumab)

Currently available evidence consists of 8 patients captured in 5 case reports.[7,14,16,20,21] All patients had clinical responses consistent with what would be expected in the general population. No significant changes in relevant laboratory parameters such as CD4 count and viral load were observed. There were no other significant adverse events or opportunistic infections reported. Of note, one patient with minimal and stable concomitant Kaposi sarcoma maintained stability while on ustekinumab therapy.[20]

IL-17 (secukinumab)

A single case report currently exists detailing secukinumab use in an

HIV positive patient.[22] A 48-year-old woman with a long history of psoriasis and psoriatic arthritis who was found to be HIV positive during screening for biologic therapy eventually went on to start both antiretroviral therapy and secukinumab, achieving control of her HIV, psoriasis and psoriatic arthritis. Her laboratory parameters remained stable and seven months into treatment she was found to have esophageal candidiasis which was successfully treated with fluconazole. Secukinumab therapy was not discontinued and her disease remained under good control at the 12-month follow up mark.

No published evidence exists regarding the use of ixekizumab or brodalumab in the treatment of patients with HIV.

IL-23 (guselkumab)

A single case report currently exists of guselkumab use in an HIV positive patient.[23] A 51-year- old-male with longstanding refractory psoriasis underwent successful treatment with guselkumab. No alteration in laboratory parameters, adverse events or opportunistic infections were reported.

No published evidence exists regarding the use of risankizumab in the treatment of patients with HIV. Several excellent review articles have been published which summarize sections of the evidence above.[24-28]

It is essential that we develop strategies to adequately treat HIV positive patients who suffer from psoriasis, psoriatic arthritis and other inflammatory skin conditions. As with any given segment of the population, some patients who happen to acquire HIV will have psoriatic disease that is refractory to non-immunosuppressant therapy. HIV infection itself can precipitate or exacerbate psoriasis which is perhaps due to the production of inflammatory cytokines including IL-17, IL-23, interferon and TNF by CD8+ and CD45RO+ T cells.[23] The cytokines which play roles in the pathogenesis of both psoriasis and HIV may serve as common targets for biologic agents.

The existing body of evidence outlined above demonstrates that biologic agents can be used safely and efficaciously in patients with HIV. It is important to realize however, that the current best level of evidence available to clinicians consists of case reports and small case series and that we lack randomized controlled trials. These descriptive data, such as case reports and case series, are prone to publication bias in that cases of biologic use in the context of HIV leading to a negative outcome are less likely to be published than those leading to a positive outcome. The prospective, deliberate study of HIV positive patients on biologic therapy, be that in the form of a registry or inclusion in clinical trials, would significantly add to our existing knowledge regarding this particular clinical scenario.

In terms of real-world clinical practice, dermatologists often consider efficacy, safety and the availability of existing published evidence when making treatment decisions. Etanercept, while perhaps relatively limited in terms of efficacy, has the largest body of evidence for use in HIV and the shortest half-life, making it the most easily discontinued therapy should complications occur. In contrast, biologics that have a longer half-life, such as ustekinumab and secukinumab, prohibit the drug being withdrawn quickly if complications occur--- a consideration which should be balanced against their greater efficacy, more targeted mechanism of action and subsequent theoretically reduced rate of infectious complications.

Important clinical considerations when treating patients with psoriasis and HIV include ensuring that patients are adherent to antiretroviral therapy, have stable CD4 counts and undetectable viral loads, and are followed regularly by their physician. Non-immunosuppressive therapies should be exhausted before immunosuppressive therapies are considered. Follow up and monitoring of HIV patients on biologic therapy do not differ greatly from that required for non-HIV patients on biologic therapy in general. Although no formal consensus exists, monitoring could include more frequent follow up visits, diligent education on how and when to report any possible symptoms of infection, ensuring relevant vaccinations are up to date, and the consideration of annual screening for tuberculosis infection. HIV parameters including CD4 count and viral load should be regularly monitored by the patient's physician.

Biologic therapies continue to play an important role in the management of moderate-to-severe psoriatic disease and HIV infection is not an absolute contraindication to the use of biologic therapy. These agents can be used safely when prescribed and monitored as part of a team-based approach to care which involves the patient, the HIV physician and the dermatologist.

References

1. Menon K, Van Voorhees AS, Bebo BF Jr, et al. Psoriasis in patients with HIV infection: from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol. 2010;62(2):291-299. doi:10.1016/j.jaad.2009.03.047

2. Morar N, Willis-Owen SA, Maurer T, Bunker CB. HIV-associated psoriasis: pathogenesis, clinical features, and management. Lancet Infect Dis. 2010;10(7):470-478. doi:10.1016/S1473-3099(10)70101-8

3. Maurer TA, Zackheim HS, Tuffanelli L, Berger TG. The use of methotrexate for treatment of psoriasis in patients with HIV infection. J Am Acad Dermatol 1994;31:372-5.

4. Zarbafian M, Cote B, Richer V. Treatment of moderate to severe psoriasis with apremilast over 2 years in the context of long-term treated HIV infection: A case report. SAGE Open Med Case Rep. 2019;7:2050313X19845193. Published 2019 May 6. doi:10.1177/2050313X19845193

5. Shah BJ, Mistry D, Chaudhary N. Apremilast in People Living with HIV with Psoriasis Vulgaris: A Case Report. Indian J Dermatol. 2019;64(3):242-244. doi:10.4103/ijd.IJD_633_18

6. Aboulafia DM, Bundow D, Wilske K, Ochs UI. Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. Mayo Clin Proc. 2000;75(10):1093-1098. doi:10.4065/75.10.1093

7. Bardazzi F, Magnano M, Campanati A, et al. Biologic Therapies in HIV-infected Patients with Psoriasis: An Italian Experience. Acta Derm Venereol. 2017;97(8):989-990. doi:10.2340/00015555-2698

8. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis. 2008;67(5):710-712. doi:10.1136/ard.2007.081513

9. De Simone C, Perino F, Caldarola G, D'Agostino M, Peris K. Treatment of psoriasis with etanercept in immunocompromised patients: Two case reports. J Int Med Res. 2016;44(1 suppl):67-71. doi:10.1177/0300060515593250

10. Di Lernia V, Zoboli G, Ficarelli E. Long-term management of HIV/hepatitis C virus associated psoriasis with etanercept. Indian J Dermatol Venereol Leprol. 2013;79(3):444. doi:10.4103/0378-6323.110807

11. Lee ES, Heller MM, Kamangar F, Park KK, Koo JY. Long-term etanercept use for severe generalized psoriasis in an HIV-infected individual: a case study. J Drugs Dermatol. 2012;11(3):413-414.

12. Linardaki, G., Katsarou, O., Ioannidou, P., Karafoulidou, A., & Boki, K. (2007). Effective etanercept treatment for psoriatic arthritis complicating concomitant human immunodeficiency virus and hepatitis C virus infection. The Journal of rheumatology, 34(6), 1353-1355.

13. Mikhail, M., Weinberg, J. M., & Smith, B. L. (2008). Successful treatment with etanercept of von Zumbusch pustular psoriasis in a patient with human immunodeficiency virus. Archives of dermatology, 144(4), 453-456.

14. Paparizos V, Rallis E, Kirsten L, Kyriakis K. Ustekinumab for the treatment of HIV psoriasis. J Dermatolog Treat. 2012;23(6):398-399. doi:10.3109/09546634.2011.579085

15. Lindsey SF, Weiss J, Lee ES, Romanelli P. Treatment of severe psoriasis and psoriatic arthritis with adalimumab in an HIV-positive patient. J Drugs Dermatol. 2014;13(7):869-871.

16. Saeki H, Ito T, Hayashi M, et al. Successful treatment of ustekinumab in a severe psoriasis patient with human immunodeficiency virus infection. J Eur Acad Dermatol Venereol. 2015;29(8):1653-1655. doi:10.1111/jdv.12531

17. Bartke U, Venten I, Kreuter A, Gubbay S, Altmeyer P, Brockmeyer NH. Human immunodeficiency virus-associated psoriasis and psoriatic arthritis treated with infliximab [published correction appears in Br J Dermatol. 2004 Jun;150(6):1235. Gabbay, S [corrected to Gubbay, S]]. Br J Dermatol. 2004;150(4):784-786. doi:10.1111/j.0007-0963.2004.05885.x

18. Sellam J, Bouvard B, Masson C, et al. Use of infliximab to treat psoriatic arthritis in HIV-positive patients. Joint Bone Spine. 2007;74(2):197-200. doi:10.1016/j.jbspin.2006.05.012

19. Wangsiricharoen S, Ligon C, Gedmintas L, et al. Rates of Serious Infections in HIV-Infected Patients Receiving Tumor Necrosis Factor Inhibitor Therapy for Concomitant Autoimmune Diseases. Arthritis Care Res (Hoboken). 2017;69(3):449-452. doi:10.1002/acr.22955

20. Wang DM, Fernandez AP, Calabrese CM, Calabrese LH. Treatment of psoriasis with ustekinumab in a patient with HIV-related Kaposi sarcoma. Clin Exp Dermatol. 2019;44(1):113-115. doi:10.1111/ced.13630

21. Wieder, S., Routt, E., Levitt, J., & Lebwohl, M. (2014, September). treatment of refractory psoriasis with ustekinumab in an hiv-positive patient: A case presentation and review of the biologic Literature. In Psoriasis Forum (Vol. 20, No. 3, pp. 96-102). Sage CA: Los Angeles, CA: SAGE Publications.

22. Di Lernia V, Casanova DM, Garlassi E. Secukinumab in an HIV-positive patient with psoriasis. J Dtsch Dermatol Ges. 2019;17(6):646-648. doi:10.1111/ddg.13851

23. Bartos G, Cline A, Beroukhim K, Burrall BA, Feldman SR. Current biological therapies for use in HIV-positive patients with psoriasis: case report of guselkumab used and review. Dermatol Online J. 2018;24(11):13030/qt3db748cg. Published 2018 Nov 15.

24. Fink DL et al. Systematic review of the efficacy and safety of biological therapy for inflammatory conditions in HIV-infected individuals. Int J STD AIDS 2017;28:110–9. PMID: 27733707

25. Gallitano SM, McDermott L, Brar K, Lowenstein E. Use of tumor necrosis factor (TNF) inhibitors in patients with HIV/AIDS. J Am Acad Dermatol. 2016;74(5):974-980. doi:10.1016/j.jaad.2015.11.043

26. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: Psoriasis comorbidities and preferred systemic agents J Am Acad Dermatol 2019;80:27–40. PMID: 30017705

27. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: Focus on special populations and chronic infections. J Am Acad Dermatol 2019;80:43–53. PMID: 30017706

28. Nakamura M et al. Psoriasis treatment in HIV-positive patients: a systematic review of systemic immunosuppressive therapies. Cutis 2018;101:38-42,56. PMID: 29529104