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Review

Effects of Biologic Therapies for Cutaneous Inflammatory Diseases in HIV-Infected Individuals: Reliable or Not?

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Abstract

Purpose: Patients with cutaneous inflammatory diseases often present with more aggressive and refractory clinical course in the presence of accompanying human immunodeficiency virus (HIV) infection. Therefore, biologic therapies may be needed to improve outcomes of these patients. The use of biologic agents in HIV positive patients is conflicting because such treatment can lead to increase the risk of infection and malignancy in already immunocompromised patients. On the other hand, some researchers have recommended that HIV management should also include the blockade of tumour necrosis factor-alpha (TNF-α). We discuss the reliability and effectiveness of biologic therapies for patients with cutaneous inflammatory diseases and accompanying HIV infection.

Methods: The Medline literature database search through PubMed using the key words 'human immunodeficiency virus', 'cutaneous inflammatory diseases', 'TNF-α inhibitor', 'biologic therapy', 'biologic treatment', 'adalimumab', 'etanercept', 'infliximab,' 'ustekinumab', and 'rituximab' was performed. Literature data associated with biologic therapies of cutaneous inflammatory diseases in HIV-positive patients were evaluated.

Results: The literature search identified a total of 17 patients with HIV infection receiving biologic therapy for cutaneous inflammatory diseases (psoriasis, psoriatic arthritis, hidradenitis suppurativa and pemphigus vulgaris) from two case series and 12 case reports.

Conclusion: In HIV-infected patients with severe and refractory cutaneous inflammatory diseases, biologic therapies should only be reserved for those whom HIV status is stable at baseline. Screening for tuberculosis prior to treatment and close monitoring for potential side effects are mandatory. Further multicentre randomised controlled trials about the use of biologic agents in these patient groups are necessary.

Keywords: human immunodeficiency virus, cutaneous inflammatory diseases, psoriasis and psoriatic arthritis, hidradenitis suppurativa, pemphigus vulgaris, biologic therapy

INTRODUCTION

Biologic agents targeting specific molecular pathways in the immune system play an important therapeutic role for management of patients with severe or refractory dermatologic diseases (1). The most of biologic therapies used for inflammatory conditions target 'tumour necrosis factor-alpha (TNF-α)' , which is very important in host defense against intracellular pathogens (2, 3). The biologic agents are commonly used for the management of psoriasis and psoriatic arthritis in dermatology patients (4). In the immunocompetent population, patients with moderate to severe plaque psoriasis who have failed to respond to conventional systemic therapies and phototherapy or the person is intolerant to, or has a contraindication to these treatments, biologic immunotherapy is usually recommended (5). These biologic agents in the treatment of psoriasis include monoclonal antibodies specific to TNF-α (infliximab, adalimumab), fusion proteins targeting TNF-α (etanercept), T cells (alefacept) and the p40 subunit of interleukin (IL)-12/IL-23 (ustekinumab) (6). The use of biologic agents has also been considered for treatment of the other cutaneous inflammatory diseases such as inflammatory dermal processes encompassing both granulomatous and neutrophilic processes within the dermis, autoimmune bullous skin diseases, connective tissue diseases and hidradenitis suppurativa (HS) (4).

Human immunodeficiency virus (HIV)-associated psoriasis, psoriatic arthritis and other cutaneous inflammatory diseases such as HS often present more severe clinical manifestations and are refractory to standard treatments (7, 8). For this reason, biologic therapies have begun to be used in these patients despite their

potential infectious complications in already immunosuppressed ones (7). In a retrospective study of patients (n: 100) treated with etanercept or infliximab mainly for rheumatologic conditions including psoriatic arthritis (n: 4) and psoriasis (n: 3), acute bacterial infections were the most common infectious event (etanercept group: 16.8%, infliximab group: 12.1%). Anti-HIV screening test were done for only 5 patients, all of results were negative. Active pulmonary tuberculosis (n: 1), hepatitis-B virus reactivation (n: 1) and herpes zoster skin infection (n: 2) were the other infectious events determined in the study (9). A network meta-analysis and Cochrane overview including randomized controlled trials and extension studies, found that tuberculosis reactivation and serious infections were also significantly higher in the HIV-seronegative population receiving biologic agents compared with placebo groups (10).

In addition, and contrary to previous data, there are a number of reports indicating that biologic therapies can be safely and effectively used in the treatment of HIV-associated reactive arthritis, Crohn's disease and rheumatoid arthritis without any significant changes in HIV status (3, 11, 12). Furthermore, early in vitro studies demonstrated that TNF-α is able to stimulate the replication of HIV-1 in de novo infected CD4+ T cells and promyelocytes dependent upon the TNF-α dose (13, 14). TNF-α is thought to be involved in mechanisms of the disease manifestations such as aphtous ulcers, dementia, fatigue, fever, and cachexia observed in AIDS. Therefore, several researchers have recommended that HIV management should also include blockade of TNF-α (7, 15). Anti-TNF therapy has also been used to treat immune reconstitution inflammatory syndrome in a few patients with HIV infection after the failure of steroid treatment (16).

According to Joint United Nations Programme on HIV/AIDS data from the end of 2015 and in mid-2016, total 36.7 million people are living with HIV, 19.0 million of whom are from Eastern and Southern Africa (17). Although there are some promising results from only a few studies, clinical data reporting the efficacy and safety of biologic agents in HIV infected patients with inflammatory skin diseases are insufficient. Due to the limited evidence and the substantial risks of TNF-α inhibitors, the medical board of the National Psoriasis Foundation recommends their use for only severe and refractory HIV-associated psoriasis disease (18). In this article, we aimed to review the published data on the use of biologic therapies for cutaneous inflammatory diseases in terms of both treatment effectiveness and reliability in patients with HIV infection.

METHODS

The Medline literature database was searched through PubMed using the key words, individually and in combination: 'human immunodeficiency virus', 'cutaneous inflammatory diseases', 'inflammatory skin disorders', 'tumour necrosis factor-alpha inhibitor', 'biologic therapy', 'biologic treatment', 'adalimumab', 'etanercept', 'infliximab,' 'ustekinumab' and 'rituximab'. Case reports, clinical trials, cohort studies, systematic reviews and meta-analyses associated with biologic therapies of cutaneous inflammatory diseases in HIV-positive patients published up until now were evaluated. Only articles available in original or translated English were reviewed.

Cutaneous manifestations in HIV-infected patients

The impairment in the immune system leads to several cutaneous disorders in patients infected with HIV (19). Both rare and common viral, bacterial and fungal infections and also inflammatory cutaneous diseases have been reported to increase as the CD+4 T cell counts decrease (20). The most common cutaneous disorders observed in HIV infected patients have been classified into two broad categories-primary and secondary, as demonstrated in Table 1 (21, 22). HIV associated secondary cutaneous manifestations are directly associated with decline in CD4+ T cell counts. In addition to this, shift into a Th2 cytokine profile, the molecular mimicry, and overexpression of superantigens/xenobiotics are suggested to play a role in the pathogenesis of HIV associated primary cutaneous disorders but they are not completely understood yet (21). After being available the highly active antiretroviral therapy (HAART) in the mid-1990s, the cutaneous manifestations associated with HIV infection have been altered. A previous study was performed by Zancanaro et al. to evaluate the use of HAART on the prevalence and the spectrum of cutaneous manifestations in 897 HIV-infected patients. The most common dermatologic disorder was folliculitis (18%) and the next common conditions were condyloma acuminatum (11.5%), seborrheic dermatitis (10.6%), xerosis cutis (9.7%) and dermatophyte infection (7.1%). The rate of drug eruption was higher and the prevelance of molluscum contagiosum and photosensitivity were statistically significantly higher among patients using HAART. Patients with viral load more than 55000 copies/mL had a higher frequency of idiopathic pruritus and candidiasis whereas patients with CD+4 T cells less than 200 cells/mm^3 had increased prevalence of folliculitis and prurigo nodularis (20).

Psoriasis is a common chronic disease with the prevalence of 2–3% in the adult population that is considered to be an autoimmune

Table 1. The classification of cutaneous disorders most frequently observed in HIV-infected patients [21, 22]

Primary cutaneous disorders	Secondary cutaneous disorders
	Herpes simplex virus infections
	Varicella zoster virus infections
	Human papilloma virus infections
	Molluscum contagiosum infections
	Staphylococcus aureus infections
Seborrheic dermatitis	Mycobacterial cutaneous infection
Xerosis cutis	Bacillary angiomatosis
Atopic dermatitis	Pseudomonas aeruginosa cutaneous infection
Eosinophilic folliculitis	Oral candidiasis
Psoriasis	Proximal subungual onychomycosis
Pruritus	Crusted scabies
Cutaneous drug reactions	Cutaneous histoplasmosis
	Cutaneous cryptococcosis
	Kaposi's sarcoma
	T cell lymphoma
	Basal cell carcinoma
	Squamous cell carcinoma

disorder on the basis of T cells in the pathogenesis (23). The frequency of HIV-related psoriasis is similar to HIV-seronegative population (19, 21). Psoriasis might worsen or occur for the first time with HIV. Psoriasis usually presents late with the increasing immunodysfunction and CD4+ T cell counts are less than 100 cells per μL in many patients. Uncommon and severe clinical presentations such as erythrodermic psoriasis, rupioid psoriasis, sebopsoriasis, and reactive arthritis-like psoriasis sydrome are characteristic in HIV-associated psoriasis (19). The prevalence of psoriatic arthritis is increased in HIV-infected patients (23–50%) compared with the seronegative population (21). Additionally, psoriatic arthritis is more severe and refractory to conventional treatments in patients with HIV/AIDS than HIV-seronegative patients (7).

Seborrheic dermatitis, xerosis cutis, atopic dermatitis and eosinophilic folliculitis are the other HIV-associated primary cutaneous disorders that are commonly observed in these patient groups (21).

Efficacy of biologic therapies for cutaneous inflammatory diseases in HIV-infected patients

The literature search identified two case series and 12 case reports of patients with HIV infection receiving biologic therapy for cutaneous inflammatory diseases (8, 24–36). There are no randomised placebo-controlled trials evaluating use of biologic agents in HIV-infected patients with cutaneous inflammatory disorders. Table 2 shows the data including all 17 patients with HIV infection who have been treated with biologic agents for their inflammatory skin diseases and psoriatic arthritis. This table demonstrates the age and gender of the patients, the use of HAART at the time of biologic therapy, CD4+ cell counts, viral load, concomitant treatments, treatment durations and adverse effects.

All reviewed patients with cutaneous inflammatory disorders were refractory to previous conventional treatments. Their viral load and CD4+ cell counts were closely monitored. Biologic agents were started to 2 of 17 patients who were not on HAART (28, 30). Subsequently, HAART was indicated in one of them due to increase in viral load and decline in CD4+ T cell counts after six infusions of infliximab. After initiation of HAART, his CD4+ T cell counts increased and HIV-1 RNA was undetectable (30).

Median CD4+ T cell count prior to biologic therapy was 372 cells/mm^3. Biologic therapy was given to 2 patients who had severe psoriasis and psoriatic arthritis with CD4+ cell counts of 20 cells/mm^3 or less (24, 27). One of the patients showed improvement in within 3 weeks but etanercept was discontinued due to the recurrent infectious complications (24). The other patient had dramatic improvement in the skin and joint complaints after first infusion of infliximab and no recurrent infections occurred during the treatment. Only repeated changes in the antiviral regimen were required because of the adverse effects and viral load increases (27).

During the biologic therapy, 7 patients (7/17, 41%) received concomitant immunosuppressive medications including corticosteroids (2 patients), methotrexate (5 patients) and leflunomide (1 patient) (24, 25, 27, 28). Moderate or transient increases in viral load were observed in 3 (3/7, 43%) of these patients who showed improvement after changing the antiviral regimens or temporary discontinuation of the biologic therapy (27, 28). Increases in viral load were seen in 2 of 10 (2/10; % 20) patients who receive biologic agents as monotherapy and recovery was observed after initiation or modification of HAART (30, 33). No significant changes in CD4+ T cell count and viral load were reported in 12 of 17 (70%) reviewed patients (8, 24–26, 28, 29, 31, 32, 34–36).

Treatment duration ranged from the lowest 10 weeks to longest 55 months of maintenance therapy. The treatment responses which were detailed in Table 2, reported in different methods. 12 of reviewed patients (12/17) revealed good clinical response (24–27, 29–33, 35, 36). In one patient (HS), disease was controlled only for a few weeks but recurrence was observed after the fourth infusion (8). Biologic agent was switched in 4 patients (4/17) due to transient or partial response, and the clinical responses were reported as 'excellent' after changing the agent (28, 34).

There are also two case reports who had HIV-associated psoriasis not responding to immunosuppressive therapy including biologic agents (first patient: cyclosporine, methotrexate, etanercept and alefacept; the second patient: cyclosporine, acitretin, systemic steroids, infliximab, adalimumab and etanercept). These reports are not involved in Table 2 because their HIV infections were undiagnosed while taking immunosuppressive therapies. Psoriasis disease of both patients resolved completely after discontinuation of immunosuppressive therapies and the introduction of HAART (37, 38).

The data about the use of biological therapies for other inflammatory cutaneous diseases is limited to single case reports including 2 patients with HS and one patient with pemphigus vulgaris (PV) (8, 30, 35). One of the patients with HS demonstrated an improvement in his cutaneous lesions after the first infusion, while the other one had only transient response as mentioned above (8, 30). The safe use of rituximab in HIV related lymphomas with a positive impact on survival rates has been previously described in literature (39, 40). There is only one HIV-positive patient with PV who achieved complete remission after two courses of rituximab therapy (35).

Safety of biologic therapies for cutaneous inflammatory diseases in HIV-infected patients

Because the biologics target the various immune cells and cytokines, they have been associated with increased risk of serious infections and tuberculosis reactivation. A network meta-analysis and Cochrane overview including 160 randomized controlled trials and 46 extension studies have investigated the potential adverse effects of nine different biologics encompassing adalimumab, etanercept, infliximab and rituximab in patients with any disease condition except HIV/AIDS. Tuberculosis reactivation and serious infections were significantly higher in the groups receiving biologics than the control groups. There was no statistically

Table 2. Responses to biologic therapies of cutaneous inflammatory disorders in HIV-infected patients

References	Diagnosis, age, gender	ART (+)	Baseline CD4+ count (cells/mm³); Viral Load (copies/mL)	Treatment	Last documented CD4+count (cells/mm³); Viral Load (copies/mL)	Treatment duration	Clinical response	Adverse effects	
								Infectious	Noninfectious
Aboulafia et al.. 2000 (24)	Psoriasis+PsA, 45 y, M	Yes	20; 14000	Etanercept + corticosteroid	Stable for 6 months (not available)	6 mo Then discontinued because of adverse effects	Improvement dramatically in 3 wk	Recurrent polymicrobial bacterial infections causing death from sepsis	No
Bartke et al., 2004 (25)	Psoriasis+PsA, 46 y, M	Yes	193; 1040	Infliximab + prednisolone	107; undetectable	3 mo	Improvement in skin lesions and inflammation of the joints in 2 days	No	Moderate lumbosacral bone pain
Linardaki et al., 2007 (26)	Psoriasis+PsA, (HCV), 43 y, M	Yes	380; < 50	Etanercept	>450; undetectable	2 y	Complete remission of arthritis in 1 mo	No (stable HCV infection)	No
Sellam et al., 2007 (27)	Psoriasis+PsA, 27 y, M	Yes	425; <50	Infliximab and Methotrexate	350-480; 2018	2 y	Dramatic improvement in the skin and joints	No	Moderate increase in viral load, poor compliance could not be ruled out, antiviral regimen was changed
	Psoriasis+PsA, not available, M	Yes	16; 300000	Infliximab and Methotrexate	233; 5900	4 y	Dramatic improvement in the skin and joints with first infusion	No	Sustained control of the HIV infection although increase in viral load, antiviral regimen was changed
Cepeda et al., 2007 (28)	Psoriasis+PsA, 39 y, M	No	750; 22148	Etanercept Adalimumab Infliximab + Methotrexate and leflunomide	741; 54227	34 mo	Etanercept: transient Adalimumab: partial Infliximab: excellent	No	Infusion reaction to infliximab (resolved with premedication with corticosteroids), transient rise in viral load improvement after the temporary discontinuation
	Psoriasis+PsA, 52 y, M	Yes	268; <50	Etanercept Infliximab + Methotrexate	417; <50	55 mo	Etanercept: none Infliximab: excellent:	Facial abscess (infliximab), responded to antibiotic therapy	No
	Psoriasis+PsA, 47 y, F	Yes	446; <400	Etanercept Adalimumab Infliximab + Methotrexate and sulfasalazine	456; <400	13 mo	Etanercept: transient Adalimumab: transient Infliximab: excellent	No	Etanercept allergy
Mikhail et al., 2008 (29)	Generalised pustular Psoriasis+PsA, 32 y, M	Yes	435; <75	Etanercept	633; undetectable	20 wk	Complete remission in 4 wk	No	No
Alecsandru et al., 2010 (30)	Hidradenitis suppurativa, 47 y, M	Started mid therapy	546; 24780	Infliximab Clindamycin for 10 wk after initiation of infliximab	644;<50	>1 y	Improvement of cutaneous lesions 2 wk after the first infusion	No	Decrease in CD4 (347) and increase in viral load (78300), improved with ART initiation
Husein-ElAhmed et al., 2011 (8)	Hidradenitis suppurativa, 47, M	Yes	623; 1335	Infliximab	581; 1406	10 wk	Decrease in discharge from the lesions and in tenderness but recurrence was observed 2 wk after the fourth infusion	No	No

Table 2. Continued

References	Diagnosis, age, gender	ART (+)	Baseline CD4+ count (cells/mm³); Viral Load (copies/mL)	Treatment	Last documented CD4+count (cells/mm³); Viral Load (copies/mL)	Treatment duration	Clinical response	Adverse effects	
								Infectious	Noninfectious
Paparizos et al., 2012 (31)	Psoriasis, 65 y, M	Yes	429; <50	Ustekinumab	530, <20	7 mo	75.9 % improvement in the PASI score (11.9 to 2.7)	No	No
Di Lernia et al., 2013 (32)	Psoriasis (HCV), 51 y, M	Yes	200-499; 7039	Etanercept	Stable, undetectable Also a decrease of HCV-RNA	132 wk	Marked improvement at 12 wk	No	No
Lindsey et al., 2014 (33)	Psoriasis+PsA, 49 y, M	Yes	127; 14000	Adalimumab	>500, <50	30 mo	Complete response	No	Transient decrease in CD4 and increase in viral load, improved with ART modification
Saeki et al., 2015 (34)	Psoriasis, 47y , M	Yes	602; 29	Adalimumab Ustekinumab	916 ; <20	20 mo	Adalimumab: transient Ustekinumab: excellent	No	No
Polansky et al., 2015 (35)	Pemphigus vulgaris, 54 y, M	Yes	444; 223	Rituximab	Stable, undetectable	>12 mo	Complete remission after 2 courses of rituximab	No	No
De Simone et al., 2016 (36)	Psoriasis (previous HBV and active HCV), 50 y, M	Yes	445; not available	Etanercept	No significant change in CD4+ T lenfosit counts and viral load (not available)	6 mo	PASI score decreased from 24.2 to 1.8	No (no activation of HBV, stable HCV infection)	No

PsA: psoriatic arthritis; M: male; F: female; ART: Antiretroviral therapy; y: year; mo: month; wk: week; HCV: hepatitis C virus; HBV: hepatitis B virus; PASI: psoriasis area and severity index

significant difference in serious side effects, lymphoma and congestive heart failure between biologics and control. Infliximab treatment was related to statistically significantly higher risk of total adverse effects (10).

When we review the possible adverse effects of biologic therapies in those patients summarized in Table 2, infectious complications were determined in 2 of 17 patients (% 12) treated with biologic agents. The first patient had low CD4+ T cell count (20 cells/mm³) and his viral load was 14000 copies/ml at baseline of therapy. Etanercept was started because of progressive disabling psoriasis and psoriatic arthritis. He was under HAART and taking corticosteroid concurrently. In spite of the dramatic improvement within three weeks of treatment, etanercept was discontinued due to frequent polymicrobial infections and the patient died of sepsis (24). The second patient with psoriasis and psoriatic arthritis had facial abscess during infliximab therapy which responded to antibiotic therapy without any further complications (28).

There was no tuberculosis reactivation in all reviewed patients. Only 7 of 17 case reports indicated the details about screening patients for tuberculosis prior to treatment (tuberculin test, chest radiograph and Quantiferon TB Gold test) (8, 24, 28–32) One of the screened patients with psoriatic arthritis had a history of pulmonary tuberculosis and latent tuberculosis. He was treated previously with isoniazid prophylaxis and active tuberculosis was not observed during the biologic therapy (28).

In 3 patients co-infected with HIV and hepatitis C virus, hepatitis C viral loads were stable during the biologic therapy. Besides, one of them had both hepatitis B and hepatitis C virus and no activation of hepatitis B virus was observed (26, 32, 36).

An infusion reaction to infliximab therapy resolved after premedication with corticosteroids, etanercept allergy and moderate lumbosacral bone pain were the non-infectious side effects reported in three patients (25, 28). There was no other adverse effects such as lymphoma or congestive heart failure in none of the reviewed patients.

CONCLUSION

Several cutaneous disorders including viral, bacterial and fungal infections, cutaneous malignancies as well as cutaneous inflammatory diseases may occur in HIV infected patients as the CD4+ T cell counts decrease. Psoriasis and psoriatic arthritis in seropositive patients often present more aggressive disease course and are refractory to traditional treatments when compared to seronegative patients. Therefore, biological therapies have begun to be used in such patients in spite of their risk of infections with mycobacterium tuberculosis and the other organisms.

Unfortunately, the data about safety and efficacy of biologic agents for HIV-infected patients with cutaneous inflammatory diseases are limited to the case reports and case series. The majority of reported patients have psoriasis and psoriatic arthritis; there are only two patients with HS and one patient with PV. All reviewed patients

revealed improvement in their disease although some of them need to use more than one biologic agent due to partial or transient clinical response. Only one serious infectious side effect (1/17, 6%) (recurrent polymicrobial bacterial infections) was reported in one patient which lead to death. There was no tuberculosis reactivation. Although the rate of infectious side effects (12%) is low in the reviewed patients, it is not possible to compare the safety of biologic therapies between HIV-infected and uninfected populations. Further multicentre randomised controlled trials are needed to evaluate the efficacy and the safety of biologic therapies in HIV-infected patients with cutaneous inflammatory diseases.

Consequently, biologic therapies should be reserved for patients with severe and refractory HIV-associated cutaneous inflammatory diseases whose CD4+ T cells and viral load are stable at baseline, as the medical board of the National Psoriasis Foundation recommended. In HIV-infected patients with moderate to severe psoriasis, ultraviolet therapy and antiretrovirals are recommended as first line treatment and oral retinoids are suggested secondarily. Some patients with psoriasis and psoriatic arthritis may benefit from antiretroviral therapy alone (18). All patients should be screened for tuberculosis prior to treatment and prophylaxis should be given if it is needed. It is also necessary to monitor these patients closely for CD4+ T cell counts and viral load. If viral load increases during the biologic therapy, HAART modification can be made. Potential infectious side effects should also be evaluated with infectious disease specialist.

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