Efficacy of corticosteroids in oral lesion treatment associated with Steven-Johnson syndrome and toxic epidermal necrolysis in HIV patient (A Case Report)

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Abstract
The use of steroids in an immunosuppressive patient is controversial but steroidshave beneficial effects on correlations of HIV disease. The aim is to discuss the efficacy of corticosteroids in the treatment of oral lesion associated with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

A 23 year old male HIV patient was referred from the Dermatology and Venereology Department with the diagnosis of drug-induced SJS/TEN due to nevirapine or paracetamol. The patient's chief complaint was painful ulcers in the mouth and swallowing difficulty. Extraoral examination revealed erosion and serosanguinous crust on the lips. Intraoral examination revealed erosion of upper and lower labial mucosa, the white plaque on the dorsal of the tongue. Based on anamnesis and clinical examination, the HIV patient was diagnosed with SJS/TEN and oral candidiasis. He was prescribed hydrocortisone 1\%, chlorhexidine gluconate 0.1\%, vitamin B\textsubscript{12}, folic acid, and nystatin oral suspension for nine days. Hydrocortisone 1\% alone was substituted with hydrocortisone 1\% in combination with miconazole nitrate 2\% after two weeks of treatment.

All oral lesions healed within three weeks but the sore on the tongue persisted. At the next visit, the patient was given a corticosteroid locally and systemically at different times because to speed of healing and the condition was improving effectively. The effectiveness of corticosteroids depends on severity, vehicle, the frequency of administration, and duration of treatment.

An appropriate administration of steroid is the key to successful treatment of SJS/TEN in HIV patients.

Keywords: HIV, oral lesion, Steven-Johnson syndrome, toxic epidermal necrolysis.


Introduction
Steven-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in HIV (Human Immunodeficiency Virus) patients are uncommon, rapid onset, and a potentially life-threatening mucocutaneous disease clinically characterized by widespread epidermal necrosis with the involvement of at least two mucous membranes.\textsuperscript{1,2} Clinically, SJS/TEN is characterized by polymorphic lesions such as erythematous macules, papules, plaques, vesicles and bullae that affects distal extremities with positive Nikolsky's sign.\textsuperscript{3,4} SJS also has general symptoms including fever, malaise, headache, cough, chest pain, diarrhoea, vomiting, and arthralgia. SJS, TEN, and SJS/TEN overlap are distinguished primarily by severity and percentage of total body surface area (TBSA) involved. SJS is the less-severe condition, in which skin sloughing is limited to less than 10\% of the TBSA. SJS/TEN overlap syndrome describes patients with involvement of 10-30\% of TBSA. Whereas, TEN involves sloughing of more than 30\% of TBSA and is induced by drugs.\textsuperscript{5,6} SJS/TEN infection (especially mycoplasma pneumonia) is said to be caused by graft versus host disease (GVHD) and vaccinations. Risk factors include concomitant radiotherapy, lymphomas, leukaemia's and systemic lupus erythematosus, and HIV infection.\textsuperscript{3,4,7,8,9}

HIV attacks the immune system resulting in decreased endurance the patient's...
body related with the incidence of opportunistic infections. HIV infection is the most frequent co-morbid condition associated with SJS/TEN. The incidence of SJS/TEN in HIV-active patients is estimated to be about 1-2 per 1000 individuals caused by nevirapine. A drug that also causes SJS/TEN is paracetamol. Allergy towards paracetamol occurs in 1 to 6 cases in every 1 million individuals per years. Nevirapine and paracetamol intake is associated with adverse drug reactions (ADR). ADR is the global phenomenon that affects all ages, with implicated risk factors including drug-related factors that influence its immunogenicity include its ability to act as a hapten, a prohapten, or to bind covalently to immune receptors (P-i concept). The host related factors including drugs intake, concomitant disease states such as immunosuppressed patients, may predispose to the development of allergic drug reactions by altering metabolic pathways and inducing variations in the immunologic responses to drugs. The host genetic factor is related to human leukocyte antigen (HLA) genotypes. HLA molecules function as antigen presenters to immune T-cells via the T-cell receptor (TCR) thus, generating an immune reaction. HLA class I (HLA A, HLA B, HLA C) molecules are ubiquitous. They are found on all nucleated cell surfaces. HLA C may increase the risk of SJS/TEN in nevirapine and all phenotype hypersensitivity. The mechanism involved in drug-induced SJS is cytotoxic T-cells that can express and release perforin and granzyme B and Fas-FasL interaction which can cause the apoptosis mechanism.

In SJS, in addition to stopping suspected trigger drugs, is generally treated with an immunosuppressant (steroidic, cyclosporine, Azathioprine). Corticosteroid has advantage that include increasing the speed of healing, minimizing side effects, reducing pain and swelling, and is very efficient. Therole of corticosteroid therapy in SJS/TEN is controversial. Corticosteroids are contra indicated in the treatment of primary bacterial infections and hypersensitivity patients. In this case report, we will discuss the efficacy of corticosteroids therapy in the treatment of oral lesions associated with SJS and TEN in HIV.

Case

A 23 years old male patient was referred from the inpatient polyclinic at the Dermatology and Venereology Department RSIC Bandung with a SJS/TEN diagnosis. The patient has been recognized for HIV infection for three years. Three weeks before being admitted in the hospital, the patient underwent anti-retroviral therapy with a fixed-dose combination (FDC) which contains tenofovir, lamivudine, and efavirenz followed by tenofovir once a day, lamivudine two times a day, and nevirapine once a day. The patient complained of mouth ulcers, difficulty swallowing and opening mouth, a fever with reddish spots on the chest, and felt itchy with blisters that contained clean fluid that had been painful for 5 days previously. Four days previous to his visit, the patient drank paracetamol for his fever resulting in the reddish spots and blisters in the palms of both hands and soles of the feet.

The extraoral examination showed a face full of reddish spots and conjunctiva. The extraoral examination was difficult because the eyes were covered by gauze. Upper and lower lips have erosive lesions, serosanguinous crust with paint. The intraoral examination showed upper and lowered labial mucosa erosive lesions, it was spreading the whole mucosa on the tongue, there was yellowish white plaque along dorsum of the tongue (Figure 1).

Laboratory investigation revealed a decrease of haemoglobin, hematocrit, leucocytes, creatinin, natrium, calcium, and CD4 304 sel/µL. Based on anamnesis, clinical, and laboratory examination, it was determined the oral lesion diagnose was related to SJS/TEN in HIV patient. The patient was hospitalized for two weeks, and within this period, prescribed a regimen from the Dermatology and Venereology department including a topical therapy NaCl 0.9% two times a day and Cendo Lyteers six dropsevery two hours. The patient was also prescribed systemic therapy of NaCl 0.9% 1500cc/24 hour intravenous fluid drip (IVFD), dexamethasone 20mg two times a day (15mg-0-5mg) via intravenous (IV), omeprazole 20mg once a day via IV, and cetirizine 10 mg once a day via per oral if needed. Upon the first visit, one day after admission to hospital, the oral lesions were treated with topical hydrocortisone 1% cream three times a day and antiseptic chlorhexidine gluconate 0.1% three
times a day. The patient also was given nystatin oral suspension 2 mL four times a day, vitamin B₁₂ 50 mcg three times a day, and folic acid 1 mg once a day (Figure 1).

After nine days of therapy, the lesions on the lips were recovering, erosive lesions were reduced, and no crust was found. Intraoral lesions could not be observed because the patient could not open their mouth. Hydrocortisone 1% combined with miconazole nitrate 2% was given to the patient to replace hydrocortisone 1% alone. After two weeks of therapy, the lesions on the lips were healing, but the injuries on the tongue and mucosa on the buccal persisted. Therefore, mouthwash steroids (prednisone 5 mg diluted with distilled water three times a day), theragram M once a day, and vaseline album three times a day were given (Figure 2).

Figure 1. Clinical manifestation of SJS/TEN in HIV patients at the first visit (a) The blackish-brown crust on lips (b) Erosive lesion on labial mucosa and white plaque on the dorsum of the tongue (c) Lesions on neck and (d) Lesions extend throughout the body.

Figure 2. At the second visit (a) Lips have improved, (b) The tongue has lesion persisted (c) and (d) Mucosa on the buccal left and right have erosive lesion.

Figure 3. At the third visit (a) Lips have improved (b) The tongue has begun to appear (c) and (d) Mucosa on the buccal left and right have improvement.
Figure 4. At the last visit (a) Lips were healing (b) Dorsum on the tongue was improved (c) and (d) lesions mucosa on the buccal left and right has improved.

In a two weeks follow-up, the lesion still persisted and the patient was given methylprednisolone 8 mg two times two tablets a day via per oral, nystatin oral suspension 1 mL four times a day, mouthwash prednisone 10 mL three times a day, and theragram M cap once a day (Figure 3). At the last visit, the oral lesion on the tongue and oral mucosa on the buccal improved significantly and the patient was given curvit tablet once a day, vitamin B$_{12}$ 50 mcg two times a day, and folic acid 1 mg once a day as a multivitamin therapy (Figure 4).

Discussion

SJS/TEN are serious immune-mediated delayed hypersensitivity reactions (type IV). This reaction is caused by extrinsic antigens, such as drugs. This involves immunocompetens of T-cells and macrophages. Macrophages (APC) bind to allergens on the cell surface and transfer allergens to T-cells, thereby releasing interleukin T-cells that will cause the symptoms of SJS/TEN. When SJS/TEN occurs in HIV infection patients, the immune status of the individual gets compromised. This could be a cause of the long incubation period and severer cases among HIV-cases as compared to non-HIV cases.

There was the history of nevirapine intake three weeks before patient was admitted to the hospital. SJS/TEN is mostly caused by drugs and occurs in HIV patients. Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used for the treatment of HIV-1 infection. Anti-retroviral therapy (ARV) has side effects of causing SJS and sometimes is associated with life-threatening adverse reactions. Like other anti-retroviral drugs, HIV develops rapid resistance when NVP is used alone. Therefore, the recommended therapy consists of a combination of three or more anti-retrovirals. Other than NVP, lamivudine and tenofovir are very rarely reported. On top of that, the patient drank paracetamol four days before getting admitted to the hospital because patient felt feverish. Paracetamol is one of the most common analgesics and antipyretics because it is easily accessible, safe, cheap, and effective. Although this drug is considered as general medicine, it has a fatal effect and may cause SJS/TEN.

Nevirapine and paracetamol are an example of the p-i concept. The drug acts as an antigen which can bind directly to T-cell receptors (TCRs), then involved in presenting to HLA molecules of antigen presenting cells (APCs) and provoke T-cell activation. The HIV drug TCRs may initiate a series of immune reaction, which result in activation of CD8+ cytotoxic T-cell-mediated and natural killer (NK) cell-mediated cytotoxicity. While CD8+ cytotoxic T-cell and NK cells are activated, they subsequently carry out the cellular mediated immune reactions directed at keratinocytes in an HLA class I restricted manner. Upon activation of these responses, various cytotoxic signalling molecules or cell death mediators, including granulysin, perforin/granzyme B, Fas/Fas ligand, and annexin A1, are relayed to the skin lesions to induce keratinocyte apoptosis. Cytokines (TNFα) mediate the keratinocyte apoptosis leading to epidermal necrosis. TNFα up-regulatedFas (death receptors on effector cells and Fas ligand (FasL) on the keratinocyte leading to their interactions: thus amplifying the apoptotic pathway.

Certain specific HLA genotypes have been implicated in TEN caused by nevirapine, namely HLA C. People with altered drug metabolism, especially slow acetylator, leading to deficient detoxification of intermediary drug...
metabolites may be more prone to develop TEN.\textsuperscript{7,8}

The patient began by complaining of mouth ulcers as well as difficulty swallowing and opening the mouth. The patient had drank paracetamol for his fever four days prior to being admitted to the hospital and had a widespread rash on his body. The initial of signs and symptoms of SJS/TEN occur 4 to 28 days after exposure to the drug. Thus can start, although not always, with a typical prodromal phase which may proceed with 1-2 days of rash. Flu-like symptoms, such as malaise, fever, and anorexia, can last up to a week. A sore throat, cough, burning sensation of the eyes, myalgia, and arthralgia could appear in this phase.\textsuperscript{4} After this phase, the initial skin rash, which appears suddenly and symmetrically, may be erythematous maculopapular with irregular shape or similar to a morbilliform rash, urticarial, purpuric, or targetoid, and specifically tender. They usually begin in the presternal region of the trunk and rapidly spread over 3-12 days to involve the face, neck, and extremities, also the palms and soles of the feet. The patient complained of erosive lesions on upper and lower labial mucosa, crust on lips, and oral candidiasis in the dorsum of the tongue. Mucosal involvement may precede or follow the skin manifestations and occurs in two or more distinct mucosal surfaces, such as ocular, ear, nose, throat, oral, and genital lesions with clinical morphologies including erythema, oedema, and vesiculobullous which cause painful hemorrhagic erosions, coated by greyish-white pseudo-membranes formations.\textsuperscript{1,2,6,8} Involvement of oral mucosa is seen in most of the cases with burning sensation, oedema, and erythema following with widespread and painful mucosal erosions or ulcerations, mostly on buccal, palatal mucosa, tongue, gingiva, and lips. The extensive erosions and hemorrhagic crusting can interfere with oral functions causing odynophagia, inability to tolerate solid foods, and increased risk for aspiration.\textsuperscript{2}

There are no universal diagnostic criteria for SJS/TEN. The diagnosis of SJS/TEN is based on anamnesis, clinical manifestation, and histopathological findings.\textsuperscript{1} All medications must be considered especially new drugs taken in the 8 weeks prior to the skin reaction. A comprehensive physical examination consists of prodromal phase, followed by erythema, maculopapular rash, bullae desquamation, mucosal inflammation, or positive Nikolsky’s sign and with other systemic involvement must be assessed to get an accurate diagnosis of SJS/TEN. The laboratory investigation is mostly nonspecific.\textsuperscript{1,8} Laboratory investigation in this patient revealed a decrease of haemoglobin, hematocrit, leucocyte, creatinin, natrium, calcium, and CD4 304 sel/µL. There is inconsistency in the indication for biopsy, there may be satellite cell necrosis which later progresses to full thickness epidermal necrosis, resulting in the subepidermal separation at histopathology. Based on anamnesis, clinical examinations, and without biopsy examination, we diagnosed the case of our patient as oral lesions associated with SJS/TEN.\textsuperscript{7}

The therapy used in this case report is a corticosteroid. Corticosteroids are a class of medications that have been long used for their immunosuppressive and anti-inflammatory effects for treatment of a wide spectrum of disorders.\textsuperscript{6} At the first visit, hydrocortisone1% alone was given because it has strong inflammatory effects, used for mild to moderate inflammatory components, and supresses the clinical manifestations of SJS/TEN. Hydrocortisone 1% is a short-acting drug and is used to lubricate the lips in the form of the cream.\textsuperscript{15} After nine days, we used a antifungal-corticosteroid combination (hydrocortisone 1% and miconazole nitrate 2%) for the treatment of superficial fungal infections and inflammation. A combination of antifungal-corticosteroid was the right consideration. Degradation of keratin (through the release of keratinized and the liberation of other pathogenic factors by the fungi) induces the immune response and the subsequent release of pro-inflammatory cytokines, leading to increased spread and susceptibility to infection due to anti-inflammatory and immunosuppressive action. The lips of the patient improved after administering hydrocortisone 1% and miconazole nitrate 2%.\textsuperscript{15} Steroid mouthwash prednisone was given because it can cover all area of lesions and has excellent control over the contact time between drug and lesion. Prednisone is intermediate-acting, and the method of administration is by gargling.\textsuperscript{16} Furthermore, the patient was given methylprednisolone 8 mg per oral because after several visits the lesions on the tongue were persisting and this medication

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accelerated the healing process. Methylprednisolone is a synthetic corticosteroid derived from prednisolone with anti-inflammatory effect. The mechanism of action of methylprednisolone is binding and activating receptors, resulting in altered gene expression and inhibition of pro-inflammatory cytokine production.\(^7\)

We used corticosteroids as a therapy for oral lesions in HIV patients, although controversy still exists over the role of these drugs. However, corticosteroids are still the main treatment methods in many countries, including Indonesia. On one side, corticosteroids can increase risk of secondary infection and delay in epithelialization but on the other hand, corticosteroids are beneficial when started early and in an appropriate dose range. The use of corticosteroids may inhibit immunological responses by suppressing interferon gamma-mediated apoptosis and the function of cytotoxic T lymphocytes.\(^8\) In this case report, we used mouthwash prednisone and methylprednisolone for intraoral and hydrocortisone cream for extraoral. Corticosteroids are highly effective in HIV-infected patients because they have anti-inflammatory properties.

Most of the anti-inflammatory actions of corticosteroids are attributable to their interaction with the cytosolic glucocorticoid receptor. Thus, alters gene transcription to either induce (trans-activate) or repress (trans-repression) gene transcription in both inflammatory leukocytes and in structural cells, such as epithelium.\(^9\) HIV infection is characterized by immune activation. It is manifested by an increase of T- and B-lymphocytes, natural killer (NK) cells, and pro-inflammatory cytokines, such as IL-6 and TNF-\(\alpha\). Immunosuppression that is characterized by blunting of antigen-specific lymphoproliferative responses may be another direct consequence of immune system activation. This state of generalized immune system activation promotes the spread of HIV infection and has been the rationale behind the experimental use of the following immunosuppressive agents as immune-based therapies for HIV-infected patients.\(^9\) HIV patients given corticosteroids have observed a beneficial effect on the immunologic correlation of HIV disease progression. HIV disease had CD4 cell count below 500 cells/\(\mu\)L p24 antigenemia at the beginning of treatment. During treatment, p24 serum antigenemia was significantly lower.\(^1\)

We treated this patient effectively with a corticosteroid and the condition of the patient gradually improved. The effectiveness of steroids depends on severity, vehicle, the frequency of administration, and duration of treatment.\(^9\) High-potency corticosteroids are used in severe erosive lesions of the oral mucosa. Milder lesions can be treated with a lower potential and the safer agent for long-term usage. Based on the vehicle used, topical corticosteroids are available in many formulations including ointments, creams, lotions, gels, and solutions. Selection of corticosteroid vehicle depends on the type of lesion and anatomical region of the lesion site.\(^9\) The frequency of administration and duration of treatment plays an important role related to the effectiveness of corticosteroid therapy. Ultra high potency steroids should not be used for more than three weeks continuously. If a longer duration is required, steroids should be gradually tapered to avoid rebound symptoms, and treatment should proceed after a steroid-free period of at least one week. This intermittent schedule can be repeated chronically until the condition improves. Side effects are rare when low-potency steroids are used for three months or less, except in the intertriginous areas, on the face and neck, and under occlusion. The amounts issued and applied should be considered carefully because too little steroids can cause a poor response, and too much can increase side effects.\(^9\) The basic rule for managing topical corticosteroids in oral medication should be to use the strengths corresponding to the seriousness of clinical symptoms, determined at the lowest concentration, (taking into account the effectiveness of treatment) and in a form that minimizes as much of the mucosal area as possible.\(^9\)

Conclusions

Corticosteroids show the benefits when it is given appropriately and effectively. The effectiveness of corticosteroids depends on severity, vehicle, the frequency of administration, and duration of treatment. A good understanding of these agents enables more rational and effective clinicians to be used clinically. The clinicians must be considered to choose the steroids type and appropriate consideration to care.
Declaration of Interest

None declared

References