Controversies in the Management of Cutaneous Adverse Drug Reactions
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Abstract
Some cutaneous adverse drug reactions (CADRs) are severe life-threatening conditions due to multisystem involvements with a high morbidity and mortality rates ranging from 25 - 70% and require immediate medical care. But there are huge controversies regarding the management because large clinical trials are lacking. Most frequent discussion and division occur regarding the use of systemic corticosteroid as early intervention with corticosteroids controls inflammation. Corticosteroids are potent agents that target several intracellular processes to modify almost all components of inflammatory and immune responses but their impact on the long term disease course is not known. Controlled relapses of rash and hepatitis may occur as corticosteroids are tapered. A chronic HHV6 activation promoted by systemic steroids could explain these relapses. Second important issue is the use of antitubercular drugs (ATD) in case of CADR due to multidrug therapy of ATD. As both the tuberculosis and CADR are life threatening conditions and we can not spare treatment of tuberculosis for CADR, we should come to a conclusion which is not yet decided. In the same way the use of antileprotic MDT in CADR due to MDT raises a similar controversy. So, here we focus on those controversies and discuss the issues.

Key words: Antileprotic drugs, antitubercular drug, cutaneous adverse drug reaction, systemic corticosteroid

Introduction
Controversies galore in every aspect of cutaneous adverse drug reaction (CADR), be it etiopathogenesis, with new hypotheses coming into light or with advent of newer molecules, their implications. More important is whether these molecules cross react. It is also difficult often to stamp a diagnosis of CADR only on the basis of causality association, so other tests have been introduced although their sensitivity at times are low. Also controversial are when to undertake provocation tests, whether ethical or not. In the absence of randomized control trials in Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), it is difficult to find out the most effective treatment and that too in a resource poor setting like India.

We have selected three main issues for discussion; use of corticosteroids, continuation of antileprotic therapy and of antitubercular therapy in the event of CADR to these therapies. Most other debatable issues are discussed in other symposium articles.

Systemic Corticosteroids in the Management of SJS/TEN: Is it Still Controversial?
Apart from the withdrawal of the culprit drug and supportive care, there are no universally accepted guidelines for the specific treatment of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Because of ethical issues randomized controlled trials with systemic corticosteroids are lacking and so also are lacking any definite guideline for the use of systemic corticosteroids in these conditions. The usage of steroids in SJS/TEN continues to be debated.
Actually, if one tracks the literature on this subject, the use of systemic steroids has been swinging like a pendulum with periods of time favoring followed by a couple of years of voices against their use.

From the beginning in mid-50's, when the Lyell syndrome was first described till mid-70's, the systemic corticosteroids were the mainstay of treatment.\textsuperscript{[1-3]}

However, in 1976, when Rasmussen\textsuperscript{[4]} showed for the first time that the use of systemic steroids was in fact associated with higher rate of complications and delayed wound healing.

Moreover, subsequently between late 70's and 80's, this observation was further supported by numerous studies\textsuperscript{[5-8]} from different parts of the world with similar conclusion. Hence, most of the physicians worldwide either stood divided or were confused.

However, again in the 1990's, number of studies appeared in the literature which once again showed that in relevant cases systemic steroids when used in high to very high doses for shorter duration of time and very early on in the course of disease, was associated with higher chances of survival.\textsuperscript{[9-12]}

Kardaun and Jonkman in 2007\textsuperscript{[13]} proposed the use of dexamethasone pulse therapy to avoid the long-term steroid use. They had based their arguments on the newer developments in the pathogenesis of TEN, and showed that the mechanism of action included suppression of various cytokines such as tumor necrosis factor (TNF-\textit{\textalpha}{\textsuperscript{}}), inhibition of Interferon gamma-induced apoptosis, and also inhibition of Fas-mediated keratinocyte apoptosis. Kardaun and Jonkman concurred that the “general negative opinion of corticosteroids is probably because they are often given too late, in too low a dose, and for too long a period” and admitted that during “the healing phase corticosteroids may indeed impair wound healing and promote sepsis.”

In addition, the use of intravenous immunoglobulin (IVIG) and/or plasmapheresis was found to be beneficial by some researchers, based on its mechanism of action of blocking Fas-mediated keratinocyte apoptosis.\textsuperscript{[14,15]}

In 2015, a Japanese group published a multi-center study on the efficacy of combination of high-dose IVIg or plasmapheresis and systemic steroids early on in the management of SJS/TEN.\textsuperscript{[16]} Therein, they concluded that it did help to bring down the overall mortality. The same group further analyzed the mortality outcome of patients treated with systemic steroids with those treated with the combination regimen. They found that the rates were much lower than the predicted mortality rates according to the severity of illness scoring system for TEN prognosis (SCORTEN) score.\textsuperscript{[17]}

In 2016, a retrospective analysis of 7018 patients with SJS/TEN who were hospitalized between January 2008 and May 2015 in the Department of Dermatology, Shandong Provincial Hospital, and treated with corticosteroids, was published. The expected and actual mortality rates in patients treated with different doses of corticosteroids, according to SCORTEN, were compared. The study suggested corticosteroids should be used in a timely manner and in accordance with disease severity, age, underlying diseases, serum albumin level, and concurrent treatment with antimicrobial therapy.

In a meta-analysis\textsuperscript{[18]} published in JAMA as recently as June 2017, the authors analyzed 96 published studies. They concluded that glucocorticosteroids and cyclosporin were the most promising systemic immunomodulating therapies for SJS/TEN.

**Conclusion**

Current scenario: Going by the evidence available in the literature, under the available ground settings, it appears that the use of high-dose systemic steroids for shorter period early on in the relevant cases does not result in improved outcome. In resource-poor set up like India, it is still a good choice for treatment.\textsuperscript{[19]} Combining systemic steroids with either high-dose IVIg or plasmapheresis results in reduced mortality. However, they should not be used late when the sloughing has already set in to avoid setting in of infections and other complications. In addition, the use should be for short period for the same reason.

**Cutaneous Adverse Drug Reaction to Anti Tuberculosis Drugs**

Multidrug anti-tuberculosis (TB) regimen is associated with diverse clinical patterns of cutaneous adverse drug reactions (CADR). The incidence of TB-associated CADR is unknown because of the inconsistency in the design of published studies, population differences, variable presentation, inaccurate reporting, and limitations in case definitions and disease severity grading.\textsuperscript{[20]}

An individual drug can cause multiple types of CADR, and a specific type of CADR can be due to any anti-TB drug.\textsuperscript{[21-24]}

The CADR ranges from mild and moderate, such as pruritus, morbilliform eruptions, lichenoid eruptions, fixed-drug eruptions, cutaneous vasculitis and urticaria to severe and even life-threatening ones, such as drug hypersensitivity syndrome (DHS), acute generalized exanthenmatous pustulosis, SJS and TEN.

CADR can either be confined to only the skin or be part of a multisystem disorder and may complicate anti-TB therapy. In many patients, it presents as a self-limiting complications with minor consequences; however, there
may be considerable morbidity, mortality and significant treatment interruption or a change in regimen.[27]

The emergence of the HIV pandemic has had major impact on the incidence of TB. It is well established that drug hypersensitivity reactions are more common in HIV-infected persons. In addition, there is also a higher incidence of adverse drug reactions (ADRs) and CADR to anti-TB drugs in HIV-infected persons.[28,29] Initiation of highly active antiretroviral therapy and Pneumocystis jirovecii pneumonia prophylaxis, often around the same time as anti-TB therapy, can make it more difficult to identify offending drugs. All these make TB-associated CADR a huge problem for clinicians in high HIV-prevalence settings.

The pathogenesis of hypersensitivity reactions to all drugs including anti-TB drugs, is not fully understood. However, these reactions are known to involve many distinct immune mechanisms.

Morbilliform (measles-like) drug eruption or maculopapular exanthems are the most common presentation of a CADR, accounting for 95% of all cases.[30] In a great majority of cases, morbilliform drug eruptions are self-limiting and treatment can continue uninterrupted.[31] However, maculopapular exanthem can be the initial presentation of more serious reactions such as SJS and DHS.[32] Worsening of the rash, accompanied by systemic symptoms or mucositis, are usually early indicators of severe disease and warrant stopping treatment.

Drug-induced hypersensitivity syndrome is a severe disease that can be associated with mortality of up to 10%. Anti-TB drugs that have been reported to cause DHS include isoniazid, rifampicin, streptomycin, and pyrazinamide.[33,34]

Thiacetazone was identified early on as a common cause of SJS/TEN in TB and HIV coinfected patients. As a result of this, WHO recommended avoiding the drug in HIV-infected patients with a subsequent decline of its use worldwide.[35] SJS/TEN has also been reported with rifampicin, pyrazinamide, isoniazid, ethambutol, streptomycin, cycloserine, and fluoroquinolones.[2,16,37] Lichenoid drug eruption has been reported with isoniazid, pyrazinamide, and ethambutol.[38,39] Antitubercular therapy-associated vasculitis is rare but has been reported with rifampicin and pyrazinamide.[40]

A drug provocation test, defined as a controlled administration of a drug to diagnose drug hypersensitivity reaction, is considered the gold standard in establishing causality.[41] In drug-sensitized patients, the lymphocyte transformation test has been used to measure drug-specific proliferation of T-cells after exploration including α-defensins, alarmins, activation marker CD69, interleukin (IL)–2, IL–5, IL–13, and interferon–γ.[42,43] Other possible markers are perforin and granzyme B released by drug-specific cytotoxic T-cells from the peripheral blood of the affected patients.

There is some evidence that withdrawal of the offending drug improves outcome in severe CADR; so therapy is usually interrupted.[33,44] However, the advantages of reducing morbidity and mortality due to drug withdrawal must be balanced against the risk of mortality due to treatment interruption, enhancing the development of drug resistance due to mono or dual drug therapy, and driving disease transmission by infectious patients to other patients, staff, and the community if treatment is interrupted in the first 2 weeks. Treatment interruption following CADR is usually temporary, but depending on the severity, the duration of interruption may be significant. In the case of severe TB-associated CADR, reintroduction of anti-TB therapy is instituted once the clinical and laboratory parameters (depending on the organ involved) have returned to baseline.[45] It is thus suggested that patients who are clinically ill and who warrant the initiation of treatment, therapy should be started under cover of 2 to 3 anti-TB drugs they have not previously been exposed to, while awaiting rechallenge, to minimize the impact of treatment interruption. These usually comprise drugs such as streptomycin, ethionamide, terizidone, or a fluoroquinolone.

In cases of multidrug-resistant TB, each additional month in which a patient failed to take at least 80% of their prescribed drugs was associated with nearly an additional 20% hazard of developing extremely drug resistant (XDR) TB. Considering the significant mortality associated with suboptimally treated TB, it is justifiable to rechallenge patients who have experienced CADR-associated with first-line drugs. This is to establish causality and eliminate the offending drug from the treatment regimen.[46] However, this approach increases the risk of inducing additional and possibly a fatal CADR. The other option is desensitization that is defined as loss of response after prolonged or repeated application of stimulus.[47] It is also crucial, if possible, to perform drug sensitivity testing before rechallenge is attempted. This will avoid exposing the patient to a potentially life-threatening reaction to a drug that will not benefit them.

How rechallenge should be done is another contentious issue. Whether rechallenge should occur at full dose or with incrementally increasing doses, remain unclear. Furthermore, the sequence in which the drugs are reintroduced is still controversial. Some authors suggest that the drugs least likely to cause a reaction should be reintroduced first, whereas others suggest that the most effective drugs, namely, rifampicin and isoniazid, should be reintroduced first to minimize the risks of suboptimal therapy.[48] In cases reported in the literature, the sequence of re-introduction was arbitrarily selected.[4] The limited efficacy and high toxicity of second-line
anti-TB drugs often make it necessary to re-introduce first-line agents following TB-associated CADR. This carries a risk of recurrence of CADR, which must be balanced against the risk of suboptimal anti TB therapy. Anti-TB drugs are associated with significant ADRs, which can make the treatment of TB a challenge. Thus, it is important to identify the type of CADR as it influences management, including interruption of therapy. Finally, it can be concluded that it is of great importance to identify the best possible treatment and preventive regimens to enable continuity of the anti TB therapy to the full extent.

**Cutaneous Adverse Reaction to Anti-leprosy Drugs**

The drugs used in WHO MDT (WHO Multidrug therapy) are a combination of rifampicin, clofazimine, and dapsone for multibacillary leprosy patients and rifampicin and dapsone for paucibacillary leprosy patients.

Pruritus, with or without erythema, occurs in 6% of patients receiving rifampicin. This reaction is generally mild and in most cases does not warrant treatment discontinuation. Morbilliform drug eruption, drug-induced hypersensitivity syndrome, SJS/TEN, and cutaneous vasculitis has been reported with rifampicin.\(^{[49]}\)

The common side effect of clofazimine consists of red and dark skin pigmentation of varying intensity which occurs within 10 weeks of the start of therapy. Ichthyosis is also seen with clofazimine therapy.

Dapsone is known to cause DHS, which is also known as “sulfone syndrome”\(^{[50]}\). It is also called the “5 weeks dermatitis,” because it suddenly occurs 5–6 weeks after starting dapsone and usually subsides on stopping dapsone. This drug-induced hypersensitivity syndrome consists of exfoliative dermatitis and/or other skin rashes, generalized lymphadenopathy, hepatosplenomegaly, fever, and hepatitis.\(^{[51]}\)

This syndrome is characterized by sudden onset of papular or exfoliative rash, accompanied by fever and malaise followed by jaundice, lymphadenopathy, and mononucleosis. All symptoms need not necessarily be present.\(^{[52]}\)

The dermatitis component of dapsone syndrome is always present though others may be absent.\(^{[53]}\) The cutaneous manifestations of this syndrome show wide variations including erythroderma, papular erythematous eruptions, erythema multiforme, SJS, and TEN.

The diagnosis of dapsone syndrome is based on history, clinical, and laboratory findings. Patch testing with dapsone, tablet or injectable form, and intradermal skin test with 0.05% dapsone in saline to demonstrate delayed type of hypersensitivity, may be undertaken. These tests are, however, unreliable.\(^{[44]}\) If facilities are available, lymphocyte stimulation test with dapsone may be done.\(^{[50]}\) Oral challenge test with dapsone may be dangerous in previously sensitized person, hence, must be carried out under supervision.\(^{[54]}\)

The course of dapsone syndrome can vary, but it usually lasts for around 5 weeks.\(^{[55,56]}\) It may be fatal, very rarely. The conditions of most patients improve after stopping of dapsone therapy.\(^{[52]}\) Oral steroids have been found to be useful. Dapsone should be avoided when the antileprosy regimen is reintroduced.\(^{[54]}\) With the availability of other alternative and effective antileprosy drugs, it is not necessary to desensitize these patients as it may lead to dapsone resistance.\(^{[57]}\)

Thalidomide which is given for erythema nodosum leprosum has been reported to cause morbilliform eruptions and severe skin reactions such as erythroderma, erythema multiforme. TEN has also been reported with it.

Regarding the use of rifampicin, ofloxacin and minocycline regimen, pigmented skin changes are the main side effects of minocycline and also include bluish appearance of pigmented lesions in the skin and oral mucosa, soft-tissue pigmentation. Morbilliform eruption, SJS/TEN have been reported with ofloxacin.

**Conclusion**

Going by the evidence available in the literature it appears that use of high dose systemic steroids for shorter period early on in the relevant cases does result in improved outcome. In resource poor set up like India, it is still a good choice for treatment. Combining systemic steroids with either high dose IVIg or plasmapheresis results in reduced mortality. However, the steroid should not be used late when the sloughing has already set in to avoid secondary infection and other complications. Also, the use should be for short period for the same reason. Anti-tubercular drugs are associated with significant adverse drug reactions (ADRs), which can make the treatment of tuberculosis (TB) a challenge. Thus, it is important to identify the type of CADR as it influences management, including interruption of therapy. Finally, it can be concluded that it is of great importance to identify the best possible treatment and preventive regimens in order to enable continuity of the antituberculosis therapy to the full extent; same can also be said about the antileprotic drugs.

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**Conflicts of interest**

There are no conflicts of interest.

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**What is new?**

This article was aimed to help dermatologists to tackle three important controversies in the management of the CADR.
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