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Serious cutaneous adverse drug reactions: Pathomechanisms and their implications to treatment

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ABSTRACT

Severe cutaneous adverse drug reactions pose diagnostic and therapeutic challenges to the medical community. Understanding the pathomechanisms can prevent their onset and improve their management, while timely and judicious intervention can reduce their mortality.

Key Words: Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), Drug hypersensitivity syndrome (DHS)

An adverse drug reaction (ADR) is defined as an undesirable clinical manifestation resulting from the administration of a particular drug.[1] The skin and mucosae are the commonest organs for initial presentation of many serious adverse drug reactions. The incidence of cutaneous ADRs is about 23% and approximately 2% are potentially serious.[2] Fatal reactions are almost always unpredictable, due to the complex underlying immunological mechanisms. Judicious management of these reactions requires a proper understanding of the various immunological phenomena in their pathomechanism.

Characteristics of severe cutaneous ADRs include:[1]

- Prior exposure to the drug is necessary for the sensitization to occur and such exposure is without any effect.
- Once sensitization occurs, the reaction may occur within minutes to seconds.
- The reaction does not simulate pharmacological actions of the drug.
- It may follow exposure to doses that are far below the therapeutic dose.
- It is reproducible on re-administration of the drug.

Factors which may influence the occurrence of these drug reactions are:[1]

- *Age:* Immunological drug reactions are less common at the extremes of age, probably due to altered immunological responsiveness.
- *Environmental factors:* Infectious agents, sun exposure, etc. may precipitate severe cutaneous ADRs.
- *Genetic predisposition:* A genetic susceptibility in the causation of different cutaneous adverse drug reactions has been postulated. The association of SJS-TEN and drug hypersensitivity syndrome to specific HLA subtypes has been reported. Because of genetic basis, many drug reactions, especially to anticonvulsants, may occur within the family.
- *Metabolic abnormality:*[3] Severe cutaneous ADR are commoner in individuals with specific metabolic abnormalities. These involve defects in the different enzyme systems metabolizing the respective drugs, especially the phase II enzymes like glutathione-S transferase and epoxide hydroxylase. Slow acetylators are known to develop adverse drug reactions to sulphonamides. However, as about 50% of the population among any race are slow

acetylators and serious drug reactions are rare events, other cofactors may be responsible for precipitating such occurrence in predisposed individuals.[4] The metabolic defect involved in each drug reaction seems to be highly specific for individual drugs as cross reactivity is not seen between different groups like sulphonamides and anticonvulsants.[4] In genetically predisposed individuals, the toxic metabolites generated from the defective metabolic pathway may bind covalently to keratinocyte proteins and these metabolite-protein adducts may trigger an immune response.

SJS-TEN

SJS-TEN are a spectrum of severe and devastating cutaneous ADRs. The pathomechanisms involved in their development are gradually being understood. This has not only led to newer therapies for these conditions, e.g. intravenous immunoglobulins, but also explained why drugs like corticosteroids are less helpful than expected.

The role of a cell mediated immune reaction for keratinocyte necrosis is well established.[5] Persons with HLA-A29, -B12 and -DR7 haplotypes are more susceptible to develop SJS-TEN.[1] Drugs or their toxic reactive metabolites act as haptens and render the keratinocytes antigenic by binding to their surface. The average time from first drug administration to the onset of reaction is 1-45 days (mean 2 weeks).[5] There is drug specific T cell activation, including both CD4+ and CD8+ T cells, with production of inflammatory cytokines, especially IL-5. The lymphocytic infiltrate is variable; in the epidermis it is predominantly CD8+ cytotoxic T cells and macrophages, whereas the dermal infiltrate consists mainly of memory CD4+ T lymphocytes.[5] Langerhans cells are reduced or absent. Keratinocytes express ICAM-1 and MHC class II antigens.

Both macrophages and keratinocytes produce TNF-α and IFN-γ by mutual stimulation.[4,5] There are significantly raised levels of Fas ligand (FasL/CD95L) and TNF-α, the important cytokines from the tumor necrosis factor family.[4,6] TNF-α, FasL and IFN-γ are synergistic in action and probably play an important role in epidermal destruction by inducing apoptosis directly and also by attracting cytotoxic T cells.[5] The widespread apoptosis is partially mediated by binding of FasL with CD95 (Fas) death receptors and TNF-α with TNF-R1 receptors present on target keratinocytes.[6,7] Intravenous immunoglobulin (IVIG), an effective therapeutic modality in SJS-TEN, possesses anti-Fas activity in a high concentration.[7-9] The naturally occurring Fas blocking antibodies present in human immunoglobulin preparations inhibit keratinocyte apoptosis. This effect involves inhibition of binding of the Fas ligand to Fas receptors on keratinocytes.[7-9]

One interesting fact in the evolution of SJS-TEN is the remarkable duality in the actions of TNF-α and the Fas ligand system.[4] Initially they induce inflammation, cell damage and apoptosis, followed by promotion of cell growth, resistance to apoptosis and suppression of inflammation. These contrasting effects allow the initial, intense inflammatory response to be brief. Thus, thalidomide, a potent TNF-α inhibitor, is not effective in SJS-TEN.[10] It is likely to inhibit the late onset beneficial reparative process induced by TNF-α, and thus delays healing.[4] Physical factors like UV rays and X-rays are known to stimulate TNF-α expression in keratinocytes and thus precipitate or accentuate drug induced SJS-TEN.[5]

Corticosteroids, the most extensively used therapeutic modality for SJS-TEN, have not been proved to be very much effective. TEN has been reported to occur in patients on long-term, high dose corticosteroid therapy.[11] The initial events in the genesis of SJS-TEN, the classical cell mediated immune response, may be delayed and modified by steroids, while the further steps of epidermal necrosis are insensitive to this drug. In patients already on treatment with corticosteroids, it may delay the onset of TEN, but the final evolution and ultimate outcome of the disease remain unaltered.[11]

DRUG HYPERSENSITIVITY SYNDROME (DHS)

Another form of severe cutaneous adverse drug reaction

is the drug hypersensitivity syndrome. It is characterised by a clinical triad of fever, skin rash and internal organ involvement.[4] It is a rare entity associated with considerable morbidity and mortality. Because of systemic involvement, it may mimic several other disorders. Since its first description in relation to dapsone administration, it has been given several descriptive names[4] such as dapsone syndrome, febrile mucocutaneous syndrome, graft-vs-host disease-like illness, Kawasaki-like illness, drug induced delayed multiorgan hypersensitivity syndrome (DIDMOHS),[12] and drug reaction with eosinophilia and systemic symptoms (DRESS).[13]

Common drugs causing this syndrome are dapsone and other sulphonamides, carbamazepine, barbiturates, phenytoin, minocycline, azathioprine and the antiretroviral drug abacavir.[4] This reaction characteristically occurs with the first exposure to the drug, but not with the first dose; there is an interval of 1-8 weeks when the patient is on optimal dosage of the drug and during this time a hypersensitivity develops.[4]

In a genetically susceptible individual, inability to handle reactive drug metabolites appropriately is the initiating event in the pathogenesis of DHS. There are two hypotheses regarding the onset of immunological cascade.[4] According to the hapten hypothesis, reactive drug products bind to tissue macromolecules to form complete antigens, which then initiate the immunological process. The danger hypothesis postulates that the reactive drug metabolites cause oxidative cell damage with release of cytokines, which carry the warning signals to the body immune system about cellular damage and stress. This promotes an immune response in body to eliminate these modified and potentially damaged cells. Intercurrent diseases involving specific organs like pneumonitis, pulmonary tuberculosis, and poorly controlled asthma may enhance the local toxic effects of reactive drug metabolites and facilitate production of local danger signals.[4] Such factors can also influence the distribution and severity of organ involvement in DHS. Exogenous precipitating factors for development of DHS include viruses such as HIV and HHV-6.[14]

In the absence of an appropriate animal model, there are few studies of the pathogenesis of DHS. However, there is circumstantial evidence of a multifactorial causation, which is either protective or predisposing. There is initiation of a specific T cell response, but drug or drug metabolite specific antibodies have also been demonstrated by some investigators.[15] Depending on the initiating factors, there is onset of either a Th-1 or a Th-2 type of response.[4] The early event is usually a Th-2 type of response, with the release of the eosinophil chemotactic cytokine IL-5,[16] which may explain the intense eosinophilia and exanthem associated with this syndrome. However, the cytokine profile in DHS is dynamic and may change to or start as a Th-1 type of response. Such changes in the Th cell activation profile may be responsible for the evolution of the disease. The Th-1 cytokines can give rise to granulomatous infiltrates, vesiculobullous lesions, Coomb's positive hemolytic anemia and organ specific disorders like thyroiditis.[5] Drug-induced lymphoma histologically resembles DHS, but is a distinct syndrome.[17]

Thus, DHS is an immunologically mediated symptom complex occurring in some genetically susceptible individuals exposed to an optimum dosage of a specific drug for a sufficient duration; the onset, sequence of events and clinical features are dependent upon endogenous and exogenous factors.

Corticosteroids inhibit the cellular production of many cytokines including IL-5, and are thus effective in treating DHS. However, since the disease may run a prolonged relapsing course, IFN-γ, which reduces the level of IL-5 mRNA, has been proposed to treat long standing DHS.[15] As suggested by Wong et al,[18] the initial administration of a subtherapeutic dose of a drug, followed by a gradual escalation to the optimum dose, can reduce the risk of severe cutaneous ADRs like SJS-TEN and DHS. This has been demonstrated with the anticonvulsant drug lamotrigine. Such a gradual increase in the dosage may induce adaptive immunologic changes or alternative detoxifying metabolic pathways for the drug or its reactive metabolites in a susceptible individual. This type of dosage schedule acts as a form of prophylactic drug desensitization.[4]

Serious adverse cutaneous drug reactions pose a challenge to the medical community since our knowledge regarding their pathogenesis is limited. In most cases, there is profound alteration of the normal immunological milieu of the body. Due to the relative rarity of such reactions and the absence of ideal animal models, the scope of research regarding the pathomechanisms is restricted. However, new in vitro evaluation systems and molecular techniques are likely to change the scenario.

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