Characteristics of liver injury in drug-induced systemic hypersensitivity reactions

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Background: The liver is the most commonly involved internal organ in drug-induced systemic hypersensitivity. However, data obtained from these patients have yet to be analyzed in depth with respect to liver injury.

Methods: The medical records of 136 patients who developed delayed-type drug hypersensitivity were reviewed at a tertiary referral hospital. Culprit drugs, the pattern and degree of liver injury, and the effect of systemic corticosteroids were evaluated in the group of patients with drug-induced systemic hypersensitivity and liver dysfunction (aspartate aminotransferase or alanine aminotransferase $\geq$80 IU/L). Clinical characteristics of patients with drug-induced systemic hypersensitivity and liver injury were analyzed.

Results: Among the 61 patients with drug-induced systemic hypersensitivity and liver dysfunction, the clinical phenotypes were drug reaction with eosinophilia and systemic symptoms (n = 29, 48%), Stevens-Johnson syndrome/toxic epidermal necrolysis (n = 11, 18%), and maculopapular rash (n = 17, 28%). Antibiotics (n = 27, 44%) were the most common cause of drug-induced systemic hypersensitivity with liver dysfunction. Whereas patients with Stevens-Johnson syndrome/toxic epidermal necrolysis had mild hepatocellular-type liver injury of relatively brief duration, those with drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome had more severe and prolonged hepatocellular injury in addition to moderate to severe cholestatic-type liver injury. The use of systemic corticosteroids did not significantly affect either recovery from liver injury or mortality.

Limitations: This study was retrospective and the number of subjects was small.

Conclusion: The results suggest that the severity, pattern, and duration of liver injury differ according to the drug-hypersensitivity phenotype. Further studies are needed to evaluate the role of systemic corticosteroids in drug-induced systemic hypersensitivity and liver injury. (J Am Acad Dermatol 2013;69:407-15.)

Key words: corticosteroid; drug hypersensitivity; drug-induced liver injury.

Delayed drug hypersensitivity reactions can involve multiple organs, including the liver, kidneys, lungs, heart, hematopoietic system, and, especially, the skin. A rash in response to a drug that is accompanied by the dysfunction of any internal organ is referred to as a drug-induced systemic hypersensitivity reaction.[1] Internal organ dysfunction can develop in the context of various phenotypes of drug hypersensitivity, including drug reaction with eosinophilia and systemic symptoms (DRESS), drug-induced hypersensitivity syndrome (DiHS), Stevens-Johnson syndrome (SJS), toxic

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epidermal necrolysis (TEN), acute generalized exanthematous pustulosis, and even maculopapular rash.

Drug-induced liver injury can be classified into 2 different types: predictable direct toxicity and unpredictable idiosyncratic toxicity.[2] The former is typically dose-dependent, is reproducible in animal models, and presents after a short latency (hours to a few days). Idiosyncratic reactions, which dominate most cases of drug-induced liver injury, are unpredictable adverse reactions that usually occur between 5 and 90 days from the initiation of drug usage.[3] This idiosyncratic type can be further classified as an allergic (or hypersensitivity) reaction, presenting with extrahepatic manifestations, such as fever, rash, eosinophilia, and other organ damage, or as a nonallergic (or metabolic) reaction, in which there are no extrahepatic manifestations.[2,4,5]

The liver is the most commonly involved internal organ in drug-induced systemic hypersensitivity, and liver dysfunction is the major cause of death in some phenotypes of drug hypersensitivity, particularly DRESS/DiHS.[6-10] However, data obtained from these patients have yet to be analyzed in depth, particularly with respect to liver injury. To address this deficit, we analyzed the clinical and laboratory characteristics of patients with drug-induced systemic hypersensitivity reactions and liver injury. In addition, we compared the distinct patterns of liver injury that occur in SJS/TEN and DRESS, and the efficacy of treating these patients with systemic corticosteroids.

CAPSULE SUMMARY

- Stevens-Johnson syndrome/toxic epidermal necrolysis had mild hepatocellular-type liver injury, whereas drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome had more severe hepatocellular-type and moderate to severe cholestatic-type liver injury.
- The liver dysfunction recovery time of patients with drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome was significantly longer than that of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis.
- The use of systemic corticosteroids did not affect the duration of rash, mortality, and liver dysfunction recovery time in drug-induced systemic hypersensitivity with significant liver dysfunction.

METHODS

Subjects and disease definition

Patients with delayed-type drug hypersensitivity (n = 136) were initially selected from the adverse drug reaction (ADR) database of Asan Medical Center, a tertiary hospital in Seoul, Korea. All patients were admitted between January 2008 and February 2011. The phenotypes of delayed-type drug hypersensitivity were defined using the criteria described below.

DRESS/DiHS was diagnosed according to the RegiScar criteria,[11] in which 3 or more of the following criteria must be satisfied in patients hospitalized with an ADR: (1) acute skin eruption, (2) fever with body temperature higher than 38°C, (3) enlarged lymph nodes at 2 or more sites, (4) involvement of at least 1 internal organ, (5) lymphocyte count above or below the laboratory limits, (6) eosinophil count above the laboratory limits, and (7) platelet count below the laboratory limits. SJS/TEN was diagnosed in accordance with the consensus report of Bastuji-Garin et al[12]: detachment involving the skin over 1% or more of the body surface area plus widespread macules or flat atypical lesions. Further classification into SJS, TEN, and overlap syndrome was not carried out in this study because of the similarity of these skin lesions. Instead, when a patient presented with both skin detachment and internal organ dysfunction, the diagnosis was SJS/TEN, not DRESS/DiHS, because of the higher mortality associated with the former. Erythema multiforme was diagnosed when patients had typical target lesions with/without minimal bullous change.[12] Maculopapular rash was defined as a macular or maculopapular eruption that did not fulfill the criteria of DRESS/DiHS. Other diagnosed skin conditions, including fixed drug eruption, purpura, acute generalized exanthematous pustulosis, erythroderma, and bullous drug eruption, were defined according to standard textbook descriptions.[13]

Study design

Medical records were meticulously examined with respect to patient demographics (age, sex, causative agent, and period of drug exposure) and clinical features (type of rash, laboratory/imaging study, duration of disease, liver dysfunction recovery period, pharmacotherapy, and mortality).

Culprit drugs were identified by using the World Health Organization-Uppsala Monitoring Center causality assessment.[14] When the criterion was "probable/likely" or "certain," the drug was