



Pharmacovigilance in Severe Cutaneous Adverse Reactions

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Introduction

Albert Stevens, a surgeon and Frank Johnson, a pediatrician, published a paper entitled "A New Eruptive Fever Associated with Stomatitis and Ophthalmia" in the American Journal of Diseases of Children in 1922 [1]. The paper described two young boys who were presented with skin eruptions of oval, dark red to purplish spots separated by normal tissue associated with fever, conjunctivitis, inflamed mucous membrane. One boy had a total loss of vision. This was the first ever description of a condition which was later known as Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN). SJS/TEN are a spectrum of rare severe cutaneous adverse reactions (SCARs), most often induced by drugs and less often by infections due to microorganisms such as mycoplasma pneumoniae and herpes simplex, viral infections and vaccines, manifested by clinical features including fever, prodromal symptoms, mucositis, extensive necrosis and detachment of epidermis. SJS and TEN are regarded as a disease continuum and are together known as epidermal necrolysis and are generally classified based on the extent of total body surface area (BSA) detachment with SJS defined as cutaneous detachment of <10% of the BSA; TEN defined as cutaneous detachment of >30% BSA; and SJS/TEN overlap defined as cutaneous detachment of 10% to 30% BSA. Given the rarity of SJS/TEN, the estimated incidence is about 5 to 6 cases per million per year [2-4]. More than two hundred different drugs are known culprit drugs in causing immune-mediated SCARs frequently involving the eyes and may lead to corneal blindness requiring corneal transplantation and conjunctival

lesions requiring amniotic membrane transplantations and may have long-term ocular sequelae. The Human Leukocyte Antigen (HLA) genes are associated with this condition together with the inducing culprit drugs, their precise interactions in the human host system and the pathophysiology of SJS/TEN are not completely understood. Prompt early diagnosis is crucial in the prevention and multidisciplinary management of this condition which may otherwise cause significant morbidity and mortality due to infections, multiorgan failure, and sepsis. The most common drugs implicated are anticonvulsants such as lamotrigine, carbamazepine, phenytoin and phenobarbitone; allopurinol and sulfonamides such as cotrimoxazole and sulfasalazine. It is a systemic disease involving different organs and require multidisciplinary approach in its management. Although the estimated annual incidence is between 2 and 7 per one million per year, in patients with HIV, the incidence may increase to one per one thousand with significant morbidity and mortality. In European Cohort studies, the prevalence of HIV infection in patients with SJS/TEN was 7 to 9 per cent and patients with SJS had a 12-fold increased risk of SJS/TEN [5, 6]. The prevalence of HIV infection was 55% based on a retrospective study of 177 patients of SJS/TEN treated in the Dermatology Department/ Intensive care units in Sub-Saharan Africa [7]. This increased risk could be due to multiple factors. This could be due to the use of highly active antiretroviral therapy like nevirapine and prophylaxis with trimethoprim and sulfamethoxazole, anti-tuberculosis drugs in addition to the immune dysregulation associated with HIV [8-10].

These nucleoside reverse transcriptase inhibitors can also induce mitochondrial dysfunction. NRTI can cause depletion of mtDNA by inhibiting mtDNA polymerase-gamma, resulting in organelle dysfunction and impairment of oxidative phosphorylation [11]. Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medication or vaccine-related problem [12]. There is a growing need for stricter pharmacovigilance strategies and incorporation of improvised cheminformatic-aided pharmacovigilance technologies or Artificial Intelligence (AI) assisted pharmacovigilance strategy in the prevention of SJS/TEN.

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