Antiepileptics Induced Severe Cutaneous Adverse Drugs Reactions (SCARs): a Study of Clinical Characteristics, Complications and Cross Sensitivity Follow-up of 154 Cases in Taiwan

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Background
Antiepileptic drugs (AEDs) have been reported to be associated with severe cutaneous adverse drug reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). To investigate the characteristics of SCARs caused by AEDs (AEDs-SCARs) in Taiwan, we conducted a perspective study of patients with SJS, TEN, SJS-TEN overlap and DRESS induced by AEDs. We also followed the subsequent antiepileptic treatments in patients diagnosed with AEDs-SCARs to clarify the cross-sensitivity of aromatic AEDs such as phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ), oxcarbazepine (OXC), and lamotrigine (LTG).

Methods
All the hospitalized patients (total number: 154) diagnosed as SJS, SJS-TEN overlap, TEN and DRESS caused by AEDs from January 2003 to December 2009 at Chang Gung Memorial Hospital in Taiwan were enrolled into this study. Clinical courses, culprit drugs (CBZ, PHT, LTG, OXC and PB), latent period, organ involvement and complications, and the mortality were analyzed. The organs involvement and laboratory data were compared between AEDs-SJS/TEN and AEDs-DRESS. (The term “SJS/TEN” is used to refer collectively to SJS, TEN, and SJS/TEN overlap.) We follow up the tolerance to the alternative AEDs of patients with AEDs-SCARs. In addition to aromatic AEDs, the non-aromatic or new generation AEDs is considered alternatively in cross-sensitivity study, including clonazepam (CLO), topiramate (TPM), sodium valproate (VPA), gabapentin, vigabatrin, and levetiracetam.

Results
Based on our analysis, we found that carbamazepine (67.8%) is the most common causative drug for SJS/TEN and phenytoin (43.6%) is the most common causative drug for DRESS in Taiwan. The average age of patients is located in late middle-age (48.2 years old), ranging from 47.1 to 53.9 years old. About the ratio of gender, there are more females than males in AEDs-SJS/TEN but the result is opposite in AEDs-DRESS. Moreover, peripheral neuropathy is the most common underlying disease (23.4%) in our study, excluding other medical situation such as hypertension, stroke, hepatitis, etc. The onset of DRESS takes longer time than SJS/TEN and the average intake duration of AEDs-SJS/TEN and AEDs-DRESS is 20.63 days and 22.35 days, respectively. Therefore, for patients prescribed AEDs, it is necessary to monitor patients for at least a month in order to achieve safe drug use. The average dosages of AEDs-SCARs were about the same in either SJS/TEN or DRESS. Moreover, the exposure duration and average dosages of control cases were much greater than AEDs-SCARs cases. It implies that AEDs-SCARs might be related to neither the dosage nor the intake duration. Although the delayed onset, prolonged clinical course, hepatic dysfunction and hematological abnormalities are considered characteristics of DRESS, they may also be seen in other adverse drug reactions caused by antiepileptics. The clinical and laboratory characteristics of AEDs-SJS/TEN are similar to AEDs-DRESS, including fever, hematological abnormalities and liver dysfunction. However, organs involvements, especially liver function impairment, were more common seen in AEDs-DRESS, whereas blood dyscrasia, particularly eosinophilia, and ocular complications such as corneal ulcer are more common in AEDs-SJS/TEN. Systemic corticosteroid is the primary focus of management of SCARs in Taiwan. Although intravenous immunoglobulin (IVIG) may be effective in blocking the progression of SCARs, there is only one case receiving purely IVIG therapy and IVIG is usually combined with
corticosteroid. The mortality rate of AEDs-SJS/TEN was 6% (7 of 115 SJS/TEN cases) and mostly caused by phenytoin (6 phenytoin and 1 carbamazepine). When we look at the mortality rate of SJS, SJS-TEN overlap and TEN separately, TEN has the highest mortality rate (50%). This result conforms to the previous studies that TEN is of greater life-threatening. Three cases died from AEDs-DRESS with the mortality rate of 7.7% (3 of 39 SJS/TEN cases) and were also mostly caused by phenytoin (2 phenytoin and 1 lamotrigine). Mortality of AEDs-SCARs seems to be highly associated with phenytoin. Cross-sensitivity of cutaneous rash has been reported between various AEDs and is most commonly encountered in patients treated with aromatic AEDs. By following up AEDs usage after patients with AEDs-SCARs, most of patients were well tolerant to non-aromatic AEDs, e.g. sodium valproate and topiramate, and only one case of oxcarbazepine-DRESS was cross reacted to lamotrigine. Based on the discussion of cross-sensitivity, the nature of SCARs will be identified and specific cross-sensitivity provided here may be useful for AED selection and counseling in individual patients.