Asia Pacific allergy

pISSN 2233-8276 · eISSN 2233-8268

Current Review

http://dx.doi.org/10.5415/apallergy.2013.3.4.215
Asia Pac Allergy 2013;3:215-223

Stevens-Johnson syndrome / toxic epidermal necrolysis: an Asia-Pacific perspective

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCAR) to drugs which are associated with significant morbidity and mortality. High risk drugs in Asia are similar to those reported worldwide. Human leukocyte antigen (HLA)-related risk alleles for carbamazepine and allopurinol SCAR are unique to Asians. Although prognostic scoring systems like the SCORTEN have been used for more than a decade, pitfalls and caveats need to be recognized, in particular in patients with multiple medical co-morbidities and systemic features in SJS/TEN. In centres without a tertiary Burns Centre, SJS/TEN patients can still be managed successfully in general and dermatology wards with well-executed supportive/nursing care. Controversy remains regarding the effectiveness of immunomodulation in reducing SJS/TEN morbidity, mortality and hastening re-epithelialization. Despite paucity of robust evidence, intravenous immunoglobulins and ciclosporin remain the most commonly used modalities worldwide. Acute and long-term ocular effects are an important source of morbidity for which emerging ophthalmic therapies appear promising. Quality of life issues have now become an important outcome in patients with SJS/TEN as they often impact survivors' future attitudes towards pharmacotherapy. Even though pharmacogenetic testing for high-risk drugs appears to be the panacea for preventing carbamazepine- and allopurinol-induced SJS/TEN in ethnic Asians, many issues remain before health regulators in our region can conclusively determine whether testing should be made mandatory or highly recommended as standard of care.

Key words: HLA antigens; Immunomodulatory therapy; Pharmacogenetics; Quality of life

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCAR) to drugs which are associated with significant morbidity and mortality [1]. Initially thought to be discrete entities with different pathogenesis, we now know that SJS/TEN may be a continuum depending on the extent of body surface area (BSA) affected by epidermal detachment (>30% in established TEN versus 10-30% in SJS/TEN overlap), and the extent of mucosal involvement (at least 2 mucosal surfaces comprising ocular, oral and genital) [2, 3]. SJS/TEN may also have organ-specific or systemic involvement found in drug reaction with eosinophilia and systemic symptoms (DRESS) or drug induced hypersensitivity syndromes (DiHS) [4-6].

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Received: September 16, 2013
Accepted: September 22, 2013

These include fever, leukocytosis, eosinophilia, hepatitis and acute interstitial nephritis where viral reactivation of herpes viruses have been demonstrated to be one of the known triggers [6].

Risk factors: drug- and human leukocyte antigen (HLA)-related

Drugs with increased risk for SJS/TEN have been classified based on data from the RegisSCAR/ EuroSCAR registry into [7, 8]:

- high risk drugs e.g. allopurinol, carbamazepine, cotrimoxazole and other anti-infective sulfonamides, sulfasalazine, lamotrigine, nevirapine, non-steroidal anti-inflammatory drugs (NSAID - oxicam type; e.g. meloxicam), phenobarbital, phenytoin;
- moderate risk drugs e.g. cephalosporins, macrolides, quinolones, tetracyclines, NSAIDs (acetic acid type; e.g. diclofenac);
- low risk e.g. beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, thiazide diuretics (with sulfonamide structure), sulfonylurea anti-diabetics (with sulfonamide structure) , insulin, NSAIDs (propionic acid type; e.g. ibuprofen)

The pattern of causative drugs for SJS/TEN is similar in many countries within the Asia-Pacific region [9-12].

Genetic risk factors for SJS/TEN have been found to be generally ethnicity- and drug-specific [13]. Much of the work on genetic risk factors for SJS/TEN have originated from Asian ancestry. HLA-B*1502 was first found by the Taiwanese to be associated with carbamazepine (CBZ) induced SJS in Han Chinese [14] in 2004, then subsequently among the Thais [15], Indians [16] and Malays [17] as well. However, HLA-B*1511 was found to be associated with CBZ SJS/TEN and A*3101 with CBZ SJS/DiHS in Japanese [18, 19] and Koreans [20] rather than HLA-B*1502.

In 2005, HLA-B*5801 was found by the same Taiwanese group to be associated with allopurinol SJS/TEN in Han Chinese [21], followed subsequently by a similar association in Thais [22], Japanese [23] and Koreans [24].

Human immunodeficiency virus (HIV) infection, which is endemic in certain countries in the Asia-Pacific [25], is associated with a higher incidence of drug hypersensitivity [26], with an increased risk for SJS/TEN associated mainly with nevirapine and cotrimoxazole [27, 28]. Co-infection with HIV and tuberculosis, more than 40% skin involvement, and severe sepsis have been found to be poor prognostic factors [29].

Prognostic scoring systems: pitfalls and caveats

The Score of TEN (SCORTEN) is a severity-of-illness score used to predict the risk of death from TEN upon admission [30]. It comprises the following 7 independent risk factors (variables): age ≥40 years, tachycardia ≥120 beats per minute, presence of cancer/ haematologic malignancy, BSA involved on day 1, elevated serum urea (>10 mmol/L), acidemia (serum bicarbonate <20 mmol/L) and hyperglycemia (serum glucose >14 mmol/L), scored within the first 24 h of admission. Recent criticisms on the use of SCORTEN include the underestimation of the effects of pre-existing common or complex co-morbidities (e.g. diabetes mellitus), severity of these co-morbidities [31], and respiratory involvement [32] on outcomes of TEN. SCORTEN also does not take into account patients with SJS/TEN who may also have other features of DRESS/ DiHS. A recent study showed that 5 independent prognostic risk factors for death in DRESS were: heart rate >90 beats per minute, white blood cells >12,000/mm^3, respiratory rate >20/min (at early disease stage), coagulopathy and gastrointestinal bleeding (at maximal disease stage). DRESS patients with persistent systemic inflammatory response syndrome during hospitalization were also associated with higher mortality risk [33]. Thus SCORTEN may not be the ideal prognostic index for mortality in patients with other non-haematological/non-oncological chronic diseases, and organ/ systems involvement from DiHS/DRESS.

Supportive management: is transfer to a Burns Centre essential?

Immediate cessation of the suspected causative drug is key to the management of SJS/TEN. However, immunological mechanisms in SJS/TEN may continue to progress despite cessation of the correct causative drug. Supportive care includes maintenance of thermoregulation (30-32°C), fluid/ volume replacement with electrolyte and albumin solution, changing of dressing, wound debridement, enteral nutrition if needed, and prevention of infections [34]. Although admission to a specialized Burns Centre is ideal [35, 36], where there are limited resources, when patients present acutely to a rural or district hospital, or may be unfit for transfer, they may need to be managed in the general/ dermatology ward or a high dependency area with strict infection control and where nurses are/can be trained in the dressing of denuded skin. From SJS/TEN cohorts from the Asia-Pacific, there have only been 2 cohorts exclusively managed within a Burns Centre in Singapore [37] and Hong Kong [38]. It is likely that some

http://dx.doi.org/10.5415/apallergy.2013.3.4.215

cohorts of SJS/TEN patients from other centres have also included patients managed in a tertiary burns unit with an attending dermatologist, internist or allergist. From the literature, it is difficult to ascertain whether the outcomes were better because of the higher level of specialist and nursing care available, or worse because these were likely to have been sicker patients. There have been no published cohorts to date of paediatric patients in the Asia-Pacific region with SJS/TEN managed exclusively in a Burns Centre.

Immunomodulation: where are we in 2013?

Despite on-going controversy as to whether high dose intravenous immunoglobulins (IVIg) at a dose of 2 g/kg reduces mortality in TEN [39], up to 50% of practitioners worldwide continue to use this as the most common form of immunomodulatory therapy for TEN [40]. The evidence for IVIg has been confounded by data coming predominantly from retrospective case series, with variable inclusion criteria, high and low-risk patients included, and patients with not just TEN, but also SJS/TEN overlap [41-43]. The most common cause of mortality was renal failure in most of these studies. A recent systematic review and meta-analysis of the literature did not show any clinical benefit of IVIg in both children and adults [44]. Recent case reports/ series on the use of intravenous methylprednisolone with IVIg [45], and corticosteroids with infliximab and IVIg [46] have been reported to be effective in arresting progression of TEN and reducing mortality.

There has been renewed interest in the use of ciclosporin, the second most commonly used treatment for TEN in a worldwide survey [40]. An open, phase II trial to determine the safety and possible benefit of ciclosporin on 29 patients showed that ciclosporin 3 mg/kg/d for 10 days and tapered over a month, when given early was not associated with any mortality in SJS, SJS/TEN and TEN, and stabilized epidermal detachment [47]. In a study from India, where ciclosporin was administered at a dose of 3 mg/kg body for 7 days and then tapered over another 7 days, there was no mortality [48]. The limiting factors precluding the use of ciclosporin and dose optimization would be the development of acute kidney injury as a result of TEN, hypovolemia or sepsis.

The use of systemic corticosteroids was evaluated in a case-control study based on data collected from the EuroSCAR and RegiSCAR studies [49]. The prior use of corticosteroids prolonged the period of disease progression by 2.2 days [95% confidence interval (CI) 1.1-3.2] without influencing the disease severity or mortality, and delayed time to onset of SJS/TEN with exposure to high-risk drugs by 7.1 days (95% CI -0.2 to 14.5). Apart from case series and case reports, of which one showed histological improvement of epidermal necrolysis on serial skin biopsies [50], there remain no controlled studies on the use of systemic corticosteroids in TEN.

The use of cyclophosphamide [51], anti-tumour necrosis factor (TNF) inhibitors [52-54], and plasma exchange remain [55] unsupported by controlled studies. The only randomized controlled trial of immunomodulatory treatment to date has been the use of thalidomide for its anti-TNF effect where there was an increase in mortality demonstrated in the thalidomide group, leading to early cessation of the study [56].

Controlled studies on treatment of SJS/TEN in children are also lacking. In a systematic review, where meta-analysis was found not to be feasible, 4 main treatment modalities were assessed among 128 cases. These were: IVIg, systemic corticosteroids (prednisolone, methylprednisolone, dexamethasone), dressings with or without surgical debridement, and supportive treatment alone. Other miscellaneous treatments analysed included plasma exchange, intravenous pentoxifylline and use of ciclosporin. Steroids and IVIg appeared to improve the outcome of SJS and TEN but the results from different reports were highly variable [57].

Acute and chronic ocular effects

Early involvement of the eye in SJS/TEN may be mild (eyelid edema, mild conjunctival injection, chemosis), moderate (membranous conjunctivitis, corneal epithelial defects, corneal ulceration, corneal infiltrates) or severe (symblepharon, non-healing corneal epithelial defects, visual loss, conjunctival fornix foreshortening). Late effects of SJS/TEN include sicca syndrome due to lacrimal duct damage and trichaitic lashes [58, 59]. The extent and severity of acute ocular involvement need not correlate with the degree of skin severity [60, 61]. Topical steroids, topical antibiotics and lubricants are often used in the acute phase [60-62]. Topical ciclosporin may be useful for inflammation and chronic dry eyes [63]. There is little evidence to date on the effect of IVIg on ocular outcomes [64]. Case series have shown variable benefit of non-steroid immunosuppressive drugs including azathioprine, mycophenolate, ciclosporin, infliximab, and adalimumab for recurrent ocular inflammation/ scleritis [65]. Surgical ophthalmic intervention in the form of amniotic membrane transplantation applied to the eyes and eyelids in the acute phase appear to be useful in preventing scarring and visual problems that characterize the chronic phase of the disease. The severe, chronic ocular

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problems can at least be partially alleviated with autologous serum drops, mucous membrane grafting to replace scarred tarsal conjunctiva, specialized contact lenses, conjunctival replacement surgery, limbal stem cell transplantation and kerotoprostheses [66].

Health related quality of life in survivors

Health related quality of life (HRQL) in allergic and immunologic diseases [67] has been increasingly studied in asthma, rhinoconjunctivitis [68], food allergy [69], and recently drug hypersensitivity [70]. Validated instruments have been generated both for the patient and care givers in certain conditions like food allergy. However, most of these instruments are used as research tools, and are in English. They will thus require translation, back translation and local validation should they be used for clinical care in the Asia-Pacific region. Items in some of the disease specific instruments may not be directly relevant to certain Asian societies/ ethnicities e.g. types of food in a food allergy related HRQL instrument. Despite SJS/TEN being rare, survivors nonetheless experience significant psychological stress and fear following this potentially life-threatening reaction, particularly in their attitudes towards future use of drugs [71]. For instance, a patient with recurrent infections who had experienced SJS/TEN to a betalactam antibiotic may become overly cautious with the next antibiotic course. The choice of an alternative anti-epileptic drug in a patient who has experienced carbamazepine induced SJS/TEN may also create some anxiety. It is thus crucial that health care professionals involved in the care of patients with a history of SJS/TEN be aware of potential long-term psychological sequelae and effects on the doctor-patient relationships [72]. Patients with chronic end-organ impairment or damage e.g. chronic dry eyes and visual impairment would have other physical concerns that need to be addressed. With multiple internet websites and social networking platforms, health professionals need to be even more aware of the extent of accurate information or misinformation, and perceptions that patients and their care-givers may have as a result of their experiences during an episode of SJS/TEN.

Prevention: controversies with HLA pharmacogenetic testing in Asia

In December 2007, the United States Food and Drug Administration recommended HLA-B*1502 testing prior to the use of CBZ in Asians. HLA testing has since been made mandatory in Hong Kong and Taiwan; and highly recommended as standard of care in Singapore since April 2013. In a Taiwanese study using HLA-B*1502 screening to prospectively identify subjects at genetic risk for CBZ SJS/TEN, among 4,877 candidate subjects who had not taken CBZ previously, those who tested HLA-B*1502 positive (7.7%) were advised not to take CBZ; and those who tested HLA-B*1502 negative (92.3%) were advised to take CBZ. Using an estimated historical incidence of SJS-TEN as a control (0.23%), it was found that SJS-TEN did not develop in any of the HLA-B*1502-negative subjects receiving CBZ ($p < 0.001$) [73]. The use of a historical cohort as the control group was a weakness in this study. This is in contrast to the PREDICT-I study on the use of HLA-B*5701 to predict abacavir hypersensitivity, where the control group was an active treatment group with standard-of-care approach to abacavir use without prospective HLA-B*5701 screening [74].

Unanswered questions remain on HLA-B*1502 screening for CBZ SJS/TEN in Asia. Firstly whether other aromatic anticonvulsants should also be avoided (phenytoin (PHT), oxcarbazepine (OXC), lamotrigine (LTG)) in those who test HLA-B*1502 positive remains uncertain. A case-control association study [75] of 26 PHT, 6 LTG and 3 OXC-induced SJS/TEN patients, were compared with 113 PHT-tolerant, 67 LTG-tolerant subjects, and 93 normal subjects from the general population all of Asian ancestry. HLA-B*1502 was present in 8/26 (30.8%) PHT-SJS/TEN (odds ratio (OR) 5.1; 95% CI 1.8-15.1; $p = 0.0041$), 2/6 (33%) LTG-SJS (OR 5.1; 95% CI 0.8-33.8; $p = 0.1266$) and 3/3 (100%) OXC-SJS (OR 80.7; 95% CI 3.8-1714.4; $p = 8.4 \times 10^{-4}$) patients. In addition, HLA-B*1301, Cw*0801 and DRB1*1602 also showed an association with PHT-SJS/TEN ($p = 0.0128$-0.0281; OR 3.0-4.3).

Secondly, the definition of Asian and south-east Asian ancestry can be difficult to define especially with increasing inter-ethnic marriages within the region. Of note, HLA-B*1502 associations with CBZ SJS/TEN do not seem to hold true in certain parts of East Asia (Korea and Japan).

Thirdly, the question of cost-effectiveness may not be a straightforward one to answer as it depends on funding mechanisms for pharmacogenetic testing, and costs of alternative anti-epileptic drugs. In Hong Kong and Taiwan, the HLA-B*1502 tests are free to patients. In Singapore, the tests are subsidized only up to 25% for government-subsidized (public) patients; private full-paying patients pay for the test in full. A cost-effectiveness study using a decision tree model [76] suggested that genotyping for HLA-B*1502 and providing alternate anti-epileptic drugs to those who test positive is cost-effective for Singaporean Chinese and Malays, but not for Singaporean Indians. However, the limitations of the study [77] included both PHT and CBZ being

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used interchangeably in the model rather than CBZ alone, and the costs of long-term sequelae, especially ocular sequelae not being considered in the model. Depending on the health care structure in countries where private general practitioners are not funded, this may drive private primary care providers to refer all their patients to public hospitals to gain easy access to subsidized HLA testing. The costs of alternative, newer anti-epileptic drugs which are generally more expensive (e.g. topiramate, levetiracetam) in the setting of CBZ SJS/TEN, needs to be considered [78].

Lastly, cases with CBZ-induced SJS/TEN negative for HLA-B*1502 have been reported from East and Southeast Asia [79]. Negative correlations between CBZ-induced SJS/TEN and B*0702 or B*4001 have also been reported, suggesting a possible protective role. Thus, physicians should also be vigilant about SJS/TEN in those negative for HLA-B*1502. Other factors for the development of CBZ-induced SJS/TEN in HLA-B*1502-negative patients and protective factors in CBZ-tolerant patients are likely to exist.

It is likely that the Asia-Pacific will next be faced with the problem of testing for HLA-B*5801 prior to prescription of allopurinol, and whether this should be recommended or made mandatory [80]. Apart from similar issues with CBZ SJS/TEN, potential issues in the Asia-Pacific with HLA-B*5801 testing for allopurinol include limited treatment options in patients with tophaceous gout and chronic kidney disease (where uricosuric agents are ineffective), and limited access to and costs of feboxostat and recombinant urate oxidase [81] in the region. On the other hand, patients with chronic kidney disease and positive for HLA-B*5801 have been shown to be at higher risk of allopurinol-induced SCAR. Hence making testing even more beneficial in this group of patients [82].

CONCLUSION

Although the Asia-Pacific region faces many similar issues as western populations in the management of SJS/TEN, differences in ethnic composition and health care financing structures will impact the extent to which pharmacogenetic testing can or should be implemented in different geographic regions. Limited access and poverty in rural regions means that patients with acute SJS/TEN will need to be stabilized quickly and referred to urban tertiary centres with access to expensive immunomodulatory drugs and specialist/ intensive care as soon as possible. Awareness of prescribers of high-risk drugs, close monitoring for drug eruptions/ systemic symptoms, and the use of simple tests like the full (complete) blood count, tests of renal and liver function, with immediate cessation of the culprit drug may be the most "cost-effective" method where specialized tests and specialist care are not readily available. Nonetheless, all health professionals and patients should be educated on potential danger symptoms and signs of SJS/TEN to look out for when taking high-risk drugs. This will go a long way in preventing long-term psychological sequelae in survivors, and disruption of the doctor-patient relationship in clinical decision making.

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 http://dx.doi.org/10.5415/apallergy.2013.3.4.215