ESA Practice Alert: On HLA testing for risk of Stevens-Johnson syndrome prior to commencing AEDs in patients of Asian ethnicity

ESA Recommendations

1. In patients of Han-Chinese ethnicity, testing for HLA-B*1502 should be considered prior to prescribing carbamazepine for the first time. The decision to test or not needs to be balanced by test availability, timeliness of the results and urgency of treatment.

2. If the patient tests positive for HLA-B*1502, do not use carbamazepine or phenytoin unless the potential benefit outweighs the increased risk of Stevens-Johnson syndrome (SJS).

For phenytoin, lamotrigine and oxcarbazepine, there is no unequivocal evidence for an association with HLA-B*1502 and SJS, but the incidence of overlap in allergic skin reactions with carbamazepine warrant some caution. HLA testing for HLA-B*1502 is available in some states (e.g. Victoria) through the Red Cross Blood Bank and is rebatable on Medicare.

Background

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are immune complex–mediated, potentially fatal, hypersensitivity reactions. Both conditions are characterized by blistering of the skin and mucous membranes. In SJS, skin detachment affects <10% of the body surface area, while in TEN >30% is affected; they likely represent different ends of the severity spectrum of the same condition. Mortality is 1-5% for SJS and 25-35% for TEN. SJS/TEN may be caused by drugs, viral infections and malignancies. Common drugs associated with SJS/TEN include anti-epileptic drugs (AEDs), sulphur-based drugs, NSAIDs and penicillins. Of the AEDs, SJS/TEN is most commonly associated with the use of carbamazepine, but it can also occur with phenytoin, oxcarbazepine and lamotrigine. The incidence of SJS in European patients prescribed carbamazepine is approximately 1/10,000 drug exposures [1].

Chung et al. (2004) reported that 100% of 44 Han Chinese patients from Taiwan who had experienced carbamazepine-induced SJS carried the HLA-B*1502 allele, compared with only 3% of 101 carbamazepine treated patients who did not develop a rash and 9% of 93 healthy untreated control patients (OR >1000) [2]. In a follow-up study, the same investigators found that HLA–B*1502 allele was also associated with carbamazepine induced TEN, but not with mild rashes or drug hypersensitivity syndrome [3].

In a case-control study, Man et al. (2007) examined for an association between HLA-B*1502 and the occurrence of cutaneous adverse reactions in 24 Hong Kong Han Chinese patients taking different AEDs (carbamazepine, phenytoin and lamotrigine) compared with 48 AED-tolerant controls [1]. HLA-B*1502 was present in a

significantly higher proportion of patients with AED induced severe cutaneous reactions than in controls (75% vs. 14.5%, OR = 17.6), including all patients with SJS or TEN (100% vs. 14.5%, OR 71.9), but none with drug hypersensitivity syndrome (i.e. skin rash, plus two of the following features: fever, lymphadenopathy, and haematological abnormalities with involvement of at least one internal organ) or those with the more minor maculopapular exanthemas (p=0.32).

The association between HLA alleles and SJS/TEN appears to be ethnic specific. Lonjou et al. (2006) studied 12 carbamazepine induced SJS/TEN patients from France and Germany [4]. The only patients in whom the HLA-B*1502 was present were the four who had a parent of Asian origin. HLA*B-1502 is much less common in Europeans (1–2%) than in Han Chinese (15%) [4]. The HLA-B*1502 allele is also very rare in the Japanese population in whom the presence of HLA-A*0206 is strongly associated with SJS/TEN with ocular complications [5].

Estimating the population attributable risk (PAR) of carrying the HLA-B*1502 allele for SJS/TEN in Asian patients, and therefore the cases prevented per 10,000 tests preformed, is difficult in the absence of firm data regarding the baseline incidence of SJS in Asian patients. The PAR is a function of (a) the baseline risk of SJS/TEN with AEDs, multiplied by (b) the allele frequency and (c) the risk. We only have estimates of (a) in whites, which range from 0.1% to 0.01%. If we assume (a) = 0.1%, (b) = 0.10 and (c) = 70, then it could be estimated using Levin's formula that approximately 88% of carbamazepine induced SJS/TEN in Chinese patients is associated with the HLA-B*1502 allele and therefore could be prevented by HLA testing. Using these figures, testing would reduce the incidence of SJS from 10 in 10,000 to 1 in 10,000 (ie. 0.1% to 0.01% risk). However, there is anecdotal evidence that suggests the baseline risk of SJS could be 10x higher in Asians than it is in whites.

The recommendations from overseas regulatory authorities are that:

> …individuals of Han Chinese, Hong Kong Chinese or Thai origin … should be screened for HLA-B*1502 before prescription of carbamazepine. Those who test positive should not start carbamazepine unless the benefits clearly outweigh the risks of Stevens-Johnson syndrome.
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> (UK Medicines and Healthcare products Regulatory Agency and the Commission on Human Medicines, Volume 1, Issue 9, April 2008)

> … Patients with ancestry from areas in which HLA-B*1502 is present (including Han Chinese, Filipinos, Malaysians, South Asian Indians and Thais) should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine. If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions.
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> (USA FDA Alert 12/12/2007)

> … healthcare providers should consider avoiding phenytoin and fosphenytoin as alternatives for carbamazepine in patients who test positive for HLA-B*1502.
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> (USA FDA Alert 11/24/2008)

Created and approved by the ESA Committee 9/6/2009

References

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