compared with adults (Rheims et al., 2008). Several factors may explain this discrepancy. Our work analyzed trials with five AEDs assessed in both adults and children with partial epilepsy, whereas Beyenburg et al. compared the pooled effect of 14 AEDs in adults with that of only 5 AEDs studied in children with different epilepsy syndromes. In addition, we assessed responder rates in an intention-to-treat (ITT) analysis over the whole treatment period, whereas Beyenburg et al. in Figure 2 seem to have used in many trials a modified ITT or a per-protocol analysis. Beyenburg et al. used risk differences, whereas we used relative risk, which provides more robust estimates than absolute measures (Deeks, 2002). In fact, the heterogeneity between the same five pediatric trials was greater in the model of Beyenburg et al. (I^2 = 62%) than in our model (I^2 = 31%), which might indicate inadequate model fit (Deeks, 2002).

Overall, we believe that meta-analyses should be performed on datasets comparable in terms of effective (or most effective) doses, seizure type, and efficacy endpoints. Efficacy data should ideally focus on completers to avoid the bias deriving from LOCF analysis, and editorial policies should be standardized to ensure that authors disclose in their publications those datasets that are most meaningful clinically.

Disclosure

We have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

Beyenburg S, Stavem K, Schmidt D. (2009) Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. *Epilepsia* DOI:10.1111/j.1528-1167.2009.02299.x.

Deeks JJ. (2002) Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. *Stat Med* 21:1575–1600.

Gazzola DM, Balcer LJ, French JA. (2007) Seizure-free outcome in randomized add-on trials of the new antiepileptic drugs. *Epilepsia* 48:1303–1307.

Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. (2008) Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. *PLoS Med* 5:e166.

HLA-B 1502* screening: Time to clinical practice

To the Editors:

Association between *HLA-B*1502* and carbamazepine (CBZ)–induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) has recently been reported in certain Asian populations (Han Chinese, Thai, and Malay) (Chung et al., 2004; Hung et al., 2006; Man et al., 2007; Chang et al., 2008; Locharernkul et al., 2008; Tassaneeyakul et al., 2010). Summation of the linkage from all documents showed an odds ratio (OR) of 84.75 [95% confidence interval (CI) 42.53–168.91; p = 8.96*10E-15], the strongest HLA correlation ever been found in human disorders, with 98% negative predictive value, 92% sensitivity, and 4.2–19% false positivity. The association was not found in studies of Caucasian and Japanese patients (Alfirevic et al., 2006, Lonjou et al., 2006; Kaniwa et al., 2008; Ikeda et al., 2009), making *HLA-B*1502* a genetic biomarker for CBZ-induced SJS/TEN with ethnic preponderance. These Asian studies are from the region having high *HLA-B*1502* allele frequency (10–15% in Asians vs. 1–2% in Caucasians) and high incidence of SJS/TEN (17–25: 10,000 in Thailand and Taiwan vs. 1–6: 10,000 in Caucasians) (Tennis & Stern, 1997; Mockenhaupt et al., 2005, Hung et al., 2006; Locharernkul et al., 2008).

To prevent susceptible individuals from life-threatening SJS/TEN, it is time to implement *HLA-B*1502* screening before prescribing CBZ (FDA 2007, FDA 2008). The ethnic preponderance of the association helps to guide determinations of which populations should be screened. The benefit is most obvious in ethnic groups showing strong association (eastern China, Taiwan, Thailand, and Malaysia). The biomarker testing may also be useful in those carrying high *HLA-B*1502* allele (Singapore, Vietnam, Indonesia, the Philippines, southwestern India) as well as in people of Asian ancestry in other continents (FDA 2007). The yield is apparently low in populations showing no genetic susceptibility (Japanese and some Caucasians). However, no estimation of the screening advantages can be made in those for which *HLA-B*1502* prevalence and the genetic susceptibility are unknown.

Most of the allergic reactions develop within the first 2 months after starting CBZ (Tennis & Stern, 1997). Those who use CBZ for more than 3 months without allergy are

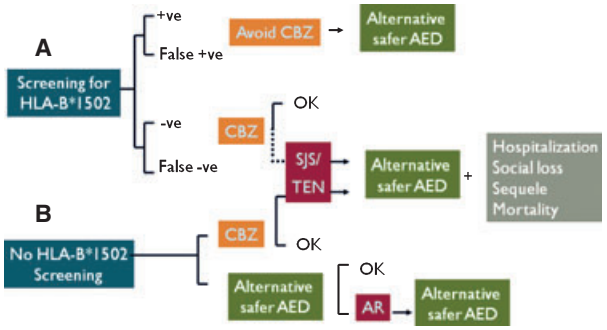

Figure 1.
Strategies in evaluating cost effectiveness of blood screening for *HLA-B*1502* prior to prescribing carbamazepine in an outpatient epilepsy setting. (**A**) Screening for *HLA-B*1502* can prevent the possible Steven-Johnson syndrome/Toxic epidermal necrolysis by avoiding CBZ in test positive individuals, but may be misleading in 4.2–19% of cases with false positivity. In contrast, in most cases with *HLA-B*1502* negativity, CBZ can be used safely since the false negativity is very low (98% negative predictive value). (**B**) Without *HLA-B*1502* screening, there is a small risk of developing SJS/TEN that may increase medical costs, social loss as well as morbidity and mortality. However, alternative safer AED can be used without *HLA-B*1502* screening which, depending on which alternative AED is used, may cost more or carry risk for other hypersensitivity or adverse reactions.
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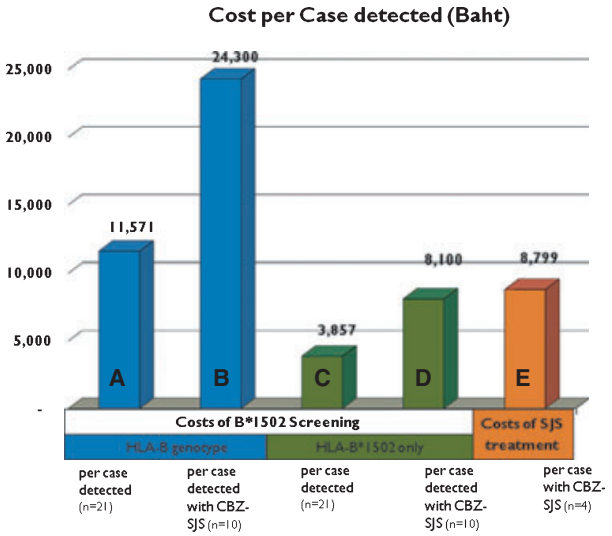

Figure 2.
Cost-effectiveness study of *HLA-B*1502* screening test to prevent SJS/TEN from carbamazepine. The costs of *HLA-B*1502* screening per case detected will exceed those of SJS treatment when a PCR based *HLA-B* genotyping kit was used (**A**, **B** vs. **E**). However, screening costs will be less than SJS treatment if test specific to *HLA-B*1502* is used (**C**, **D** vs. **E**).
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considered having low risk of SJS/TEN and are not required to be tested.

Figure 1 outlines the strategies between *HLA-B*1502* screening and not screening, which will affect cost-effectiveness in practice. The worthiness of screening prior to prescribing CBZ depends upon the extra cost of the test in a given population and whether it outweighs the costs of SJS/TEN treatment, alternative drugs, as well as psychosocial and medical sequelae of the ailment.

A recent retrospective study in Thailand has demonstrated that the screening costs would be less than SJS treatment costs if tests specific to the *HLA-B*1502* allele are used (27 $US or 1,000 Baht per test) instead of testing the whole *HLA* or *HLA-B* genomes (80 $US or 3,000 Baht per test) (Fig. 2). Today, the test for the *HLA-B*1502* biomarker is complicated, expensive, unavailable, financially burdensome, and can postpone starting CBZ. Currently needed is a simple, rapid, and low-cost screening test; more studies on CBZ-SJS/TEN pharmacogenetic in different ethnicities; as well as systemic evaluation of the cost-effectiveness of *HLA-B*1502* screening.

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Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

Alfirevic A, Jorgensen AL, Williamson PR, Chadwick DW, Park BK. (2006) Pirmohamed M. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics* 7:813–818.
Chang CC, Too CL, Murad S, Hussein S. (2008) Association of HLA-B*1502 with carbamazepine-induced toxic epidermal necrolysis and

Stevens-Johnson syndrome in Malaysian population. *Proceeding in 7th Asian-Oceanian Epilepsy Congress*, Xiamen: 32 (abstract).
Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, Wu JY, Chen YT. (2004) Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 428:486. 102:28S–30S.
FDA Alert 12/12/2007. Dangerous or even fatal skin reactions – Carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics) – Healthcare Professional Sheet text version. Available in URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm Accessed January 26, 2009.
FDA Alert on 11/24/2008. Phenytoin (marketed as Dilantin, Phenytek and generics) and Fosphenytoin Sodium (marketed as Cerebyx and generics) – Healthcare Professional Sheet text version. Available in URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124788.htm Accessed January 26, 2009.
Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, Hu SL, Wu MT, Chen GS, Wong TW, Hsiao PF, Chen WH, Shih HY, Fang WH, Wei CY, Lou YH, Huang YL, Lin JJ, Chen YT. (2006) Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 16:297–306.
Ikeda H, Takahashi Y, Yamazaki E, Fujiwara T, Kaniwa N, Saito Y, Aihara M, Kashiwagi M, Muramatsu M. (2009) HLA Class I markers in Japanese patients with carbamazepine-induced cutaneous adverse reactions. *Epilepsia* 19 August [Epub ahead of print].
Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, Sawada J, Furuya H, Takahashi Y, Muramatsu M, Kinoshita S, Abe M, Ikeda H, Kashiwagi M, Song Y, Ueta M, Sotozono C, Ikezawa Z, Hasegawa R; JSAR research group. (2008) HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 9:1617–1622.
Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, Kangwanshiratada O, Hirankarn N, Suphapeetiporn K, Shotelersuk V. (2008) Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 49:2087–2091.
Lonjou C, Thomas L, Borot N, Ledger N, de Toma C, LeLouet H, Graf E, Schumacher M, Hovnanian A, Mockenhaupt M, Roujeau JC; Regi-SCAR Group. (2006) A marker for Stevens-Johnson syndrome: ethnicity matters. *Pharmacogenomics* 6:265–268.
Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, Ng MH. (2007) Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han *Chinese*. *Epilepsia* 48:1015–1018.
Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. (2005) Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 64:1134–1138.
Tassaneeyakul W, Jantararoungtong T, Chen P, Lin SY, Chen WH, Konyoung P, Khunarkornsiri U, Auevitchayapat N, Pavakul K, Kulkantrakorn K, Choonhakarn C, Phonhiamhan S, Piyatrakul N, Aungaree T, Pongpakdee S, Yodnopaglaw P, Tiamkao S. (2010) Relationship between HLA-B*1502 and carbamazepine– induced severe cutaneous adverse reactions in a Thai population. *Epilepsia*, In press.
Tennis P, Stern RS. (1997) Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology* 49:542–546.

ANNOUNCEMENTS

4th Baltic Sea Summer School on Epilepsy

June 6–11, 2010 in Granavollen, Norway. The BSSSE, organized in cooperation between the ILAE Commission on European Affairs and the European Epilepsy Academy, is designed primarily for medical postgraduates and junior researchers with a special clinical/scientific interest in epilepsy. Online application deadline: April 10, 2010. For information contact Petra Novotny/EUREPA at petra@epilepsy-academy.org or go to http://www.epilepsy-academy.org

20th Meeting of the European Neurological Society

June 19–23, 2010 in Berlin, Germany. http://www.ensinfo.org

9th European Congress on Epileptology

June 27–July 1, 2010 in Rhodes, Greece. http://www.eplepsyrhodes2010.org

7th Forum of European Neuroscience

July 3–7, 2010 in Amsterdam, The Netherlands. http://forum.fens.org/2010

San Servolo Summer School

July 18–19, 2010 in San Servolo, Italy. From Basic Knowledge and Clinical Trials to Rational Prescribing in Epilepsy. http://www.epilepsy-academy.org

6th Latin American Congress on Epilepsy

August 1–4, 2010 in Cartagena, Colombia. http://www.epilepsiacartagena2010.org

4th Migrating Course on Epilepsy

August 15–22, 2010 in Serock, Poland. This course, organized in cooperation between the ILAE Commission on European Affairs and the European Epilepsy Academy, is targeted to specialists at the second and third level of epilepsy care. Online application deadline: February 1, 2010. For information contact Petra Novotny/EUREPA at petra@epilepsy-academy.org or go to http://www.epilepsy-academy.org

12th European Conference on Epilepsy and Society

August 25–27, 2010 in Porto, Portugal. http://www.epilepsyandsociety.org