HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens–Johnson syndrome and toxic epidermal necrolysis

Introduction: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening severe cutaneous adverse reactions. Recently, strong associations of *HLA-B*1502* and *HLA-B*5801* with carbamazepine- and allopurinol-induced severe cutaneous adverse reactions were found in Han Chinese patients, respectively, but ethnic differences in the associations have been reported. The objective of this study is to clarify the involvement of *HLA-B*1502* and *HLA-B*5801* in Japanese SJS/TEN patients. **Methods:** *HLA-B* genotyping was performed on 58 Japanese SJS/TEN patients between July 2006 and April 2008 from multicenters in Japan. **Results:** There were no *HLA-B*1502* carriers among 58 SJS/TEN patients. This patient group included seven carbamazepine-related and 11 aromatic anti-epileptic agent-related SJS/TEN patients. In addition, there were five *HLA-B*5801* carriers, which included four allopurinol-related SJS/TEN patients. **Conclusion:** While *HLA-B*1502* is unlikely to be associated with carbamazepine-related or aromatic anti-epileptic agent-related SJS/TEN, *HLA-B*5801* was significantly associated with allopurinol-related SJS/TEN in Japanese.

KEYWORDS: allopurinol, anti-epileptic drugs, carbamazepine, *HLA-B*1502*, *HLA-B*5801*, Japanese patient, Stevens–Johnson syndrome, toxic epidermal necrolysis

Nahoko Kaniwa†, Yoshiro Saito, Michiko Aihara, Kayoko Matsunaga, Masahiro Tohkin, Kouichi Kurose, Jun-ichi Sawada, Hirokazu Furuya, Yukitoshi Takahashi, Masaaki Muramatsu, Shigeru Kinoshita, Masamichi Abe, Hiroko Ikeda, Mariko Kashiwagi, Yixuan Song, Mayumi Ueta, Chie Sotozono, Zenro Ikezawa & Ryuichi Hasegawa; on behalf of the JSAR research group

†Author for correspondence: Division of Medicinal Safety Science, National Institute of Health Sciences, 1-18-11 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
Tel: +81 337 009 654
Fax: +81 337 009 788
nkaniwa@nihs.go.jp

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening severe adverse drug reactions with mucosal and cutaneous disorders, and very often accompanied by high fever and systemic complications. Some investigators have proposed that SJS and TEN are variations of the same disease expressed with different severity [1,2], although this is controversial. Although SJS and TEN incidence is very low (0.4–6 per million per year) [3,4], more than 100 different causative drugs have been reported [5]. The diseases are probably T-cell-mediated delayed allergic reactions [4], and typically begin within 1–3 weeks after first exposure to a drug.

Recently, an extremely strong association (odds ratio: ~2504) between human leukocyte antigen (*HLA*)*-B*1502* and carbamazepine-induced SJS/TEN in Han Chinese patients in Taiwan was reported [6]. Another Taiwanese study showed that *HLA-B*5801* was detected in all Han Chinese patients with SJS/TEN or drug-induced hypersensitivity (DIHS) induced by allopurinol [7]. The involvement of *HLA-B* 1502* was also confirmed in SJS/TEN caused by other aromatic epileptic agents such as phenytoin in Han Chinese or Thai population [8,9]. However, such a strong association between *HLA-B*1502* and carbamazepine-induced SJS/TEN was not detected in Caucasian patients [5]. These reports suggested that HLA involvement in severe cutaneous adverse reactions may be drug-specific as well as ethnic group-specific. Thus, we started a retrospective case–control study to explore genetic biomarkers related to SJS and TEN in Japanese patients living in Japan.

Patients & methods

Patients

The ethics committees of each participating institute of the Japan Severe Adverse Reactions (JSAR) research group approved this study. Written informed consent was obtained from each patient. A total of 58 Japanese patients from unrelated families in Japan were recruited from JSAR research group hospitals or through a nationwide blood-sampling network system in Japan for SJS/TEN onset patients, operated by the National Institute of Health Sciences in cooperation with the Ministry of Health, Labour and Welfare in Japan and the Federation of Pharmaceutical Manufacturers' Association of Japan. All patients, two of whom were referred to in a previous report [10], were diagnosed as SJS or TEN by JSAR research group experts based on diagnostic criteria proposed by Bastuji-Garin *et al.* [1], which are currently used in Japan [11,12] using a standardized case report form including medicinal records,

part of future medicine fsg

disease progress and involvement of systemic complication, as well as SJS/TEN treatment [1]. TEN and SJS are defined as mucocutaneous disorders characterized by extensive erythema, blisters, epidermal detachment, erosions, enanthema and high fever. SJS is defined as skin detachment of 10% or less of the body surface area, and TEN is defined as skin detachment of more than 10%, excluding staphylococcal scaled skin syndrome. The severity of ocular complication was scored as follows: 0: no involvement; 1: only hyperemia of bulbar and palpebral conjuctiva; 2: pseudomembrane formation; 3: defect of conjunctival or corneal epithelia.

HLA-B typing

High-resolution *HLA-B* typing was performed by a sequence-based method using SeCore™ B Locus Sequencing Kit (Invitrogen Corp., WI, USA) and an Applied Biosystems (ABI) 3730 DNA sequencer (ABI, CA, USA). Genomic DNA (250 ng) was used for PCR amplification and sequencing exons 2, 3 and 4. *HLA-B* haplotype was estimated with the Assign SBT software (version 3.2.7b, Conexio Genomics, Western Australia, Australia).

Statistical analysis

*HLA-B*5801* allele frequency reported by Tanaka *et al.,* who performed typing of *HLA-A*, and *-B* for 493 Japanese healthy subjects living in Japan was used as the frequency in control subjects [13]. Fisher's exact test was conducted using Prism 4 (GraphPad Software, Inc., CA, USA) to calculate the odds ratio and the 95% confidence interval.

Results

Demographics of patients recruited in this study are summarized in Table 1. A total of 36 and 22 patients were diagnosed with SJS and TEN, respectively. Approximately 80% of SJS/TEN patients complained of ophthalmic disorders, and two patients were coadministered anti-epileptic agents and allopurinol.

*HLA-B*1502* & *HLA-B*0702* in carbamazepine-related SJS/TEN

In our study, carbamazepine was prescribed for seven patients, and other aromatic anti-epileptic agents, such as phenytoin, phenobarbital or zonisamide, were prescribed for 11 patients. By contrast to data on the Han Chinese [6,8] and Thai populations [9], *HLA-B*1502* was neither detected in patients administered carbamazepine, nor in patients administered other aromatic epileptic drugs (Table 2).

Alfirevic *et al.* reported a potential protecting effect of *HLA-B*0702* against carbamazepine-induced severe cutaneous adverse reactions in Caucasian patients [14]. In line with this, no SJS/TEN patients receiving carbamazepine or other aromatic anti-epileptic drugs carried *HLA-B*0702* in this study. However, we found *HLA-B*0702* in two patients who did not receive anti-epileptic drugs, and there was no significant difference in the carrier frequencies between patients (1.72%) and the Japanese population (5.17%) ($p = 0.1113$).

*HLA-B*5801* in allopurinol-related and -unrelated SJS/TEN patients

As shown in Table 3, we found five carriers of *HLA-B*5801,* and four patients (patients 23,

Table 1. Demographics of Japanese patients recruited in the current study.

Factor	Value
Disease (SJS, TEN)	36, 22
Sex (male, female)	35, 23
Age (mean [range])	55 (5–94)
Severity in ophthalmic disorders	
Score 0 (no ophthalmic involvement)	12
Score 1 (only hyperemia of bulbar and palpebral conjunciva)	21
Score 2 (pseudomembrane without epithelial defect)	1
Score 3 (conjunctival and/or corneal epithelial defect)	14
Severity unknown ocular disorders	9
No description on ophthalmic symptom	1
Administered drugs before development of SJS/TEN	
Carbamazepine	7
Other aromatic anti-epileptic drugs	11
Allopurinol	10*

**One patient was treated with both carbamazepine and allopurinol, and another patient was treated with phenytoin and allopurinol.*
SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis.

Table 2. Characteristics of SJS/TEN patients administered aromatic anti-epileptic drugs.

ID number	Sex	Age (years)	Disease	Aromatic anti-epileptic drugs prescribed	Severity score in ophthalmic disorders	*HLA-B* diplotype
1	M	73	SJS	Carbamazepine	1	*1511/*4801
2	F	42	SJS	Carbamazepine	3	*4001/*5201
3	M	45	SJS	Carbamazepine	3	*4801/*5601
4	M	54	SJS	Carbamazepine	0	*1501/*3501
5*	F	6	SJS	Carbamazepine	Severity unknown	*4006/*5101
6*	F	52	SJS	Carbamazepine/zonisamide	Severity unknown	*4601/*5901
7	M	17	TEN	Carbamazepine/zonisamide	3	*4601/*5601
8	M	67	SJS	Phenytoin	Ocular involvement unknown	*4001/*4601
9	F	5	SJS	Phenytoin	0	*5504/*6701
10	F	64	TEN	Phenytoin	3	*1501/*5101
11	F	56	TEN	Phenytoin	0	*1501/*5401
12	M	6	SJS	Phenobarbital	Severity unknown	*1501/*5101
13	M	69	SJS	Phenobarbital	1	*1501/*5101
14	F	42	TEN	Phenobarbital	0	*5101/*5401
15	M	25	SJS	Zonisamide	2	*1301/*4601
16	F	71	SJS	Zonisamide	1	*4002/*5101
17	M	52	TEN	Zonisamide	Severity unknown	*3501/*4601
18	M	78	TEN	Zonisamide	Severity unknown	*3901/*6701

These patients were reported in the previous report [10]. F: Female; M: Male; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis.

24, 27 and 28) received allopurinol. Since a total of ten patients received allopurinol, *HLA-B*5801* carrier frequency in allopurinol-related patients was 40.0%. Table 4 shows a significant increase in *HLA-B*58*01 allele frequency in allopurinol-administered patients when compared with the Japanese population (odds ratio: 40.83, $p < 0.0001$). *HLA-B*5801* was detected in one patient (patient 41) who did not receive allopurinol. This is the first report that *HLA-B*5801* was detected in a SJS/TEN patient unrelated to allopurinol.

Discussion

Recently, involvement of *HLA* loci have been detected in idiosyncratic adverse drug reactions, including cutanenous [6,7,15] or liver [16] injury. Regarding severe cutaneous reactions, some HLA class I antigen genotypes, such as *HLA-B*1502* [6], *HLA-B*5801* [7] and *HLA-B*5701* [15], have been reported to be very promising biomarkers for discriminating patients at high risk of SJS, TEN or DIHS induced by carbamazepine, allopurinol or abacavir, respectively. The very strong association of *HLA-B*1502* with

Table 3. Characteristics of SJS/TEN patients administered allopurinol and an allopurinol-unrelated patient carrying *HLA-B*5801*.

ID number	Sex	Age (years)	Disease	Allopurinol prescribed	Severity score in ophthalmic disorders	*HLA-B* diplotype§
1	M	73	SJS	Yes	1	*1511/*4801
8	M	67	SJS	Yes	Severity unknown	*4001/*4601
23	F	53	SJS	Yes	1	*4002/**5801**
24	M	77	TEN	Yes	Severity unknown	*5201/**5801**
25	M	75	SJS	Yes	Severity unknown	*4002/*4006
26	M	67	SJS	Yes	1	*3901/*4001
27	F	81	SJS	Yes	1	*4601/**5801**
28	M	83	SJS	Yes	1	*3901/**5801**
29	M	58	TEN	Yes	1	*1501/*5601
30	M	75	TEN	Yes	0	*3501/*5201
41	F	55	TEN	No‡	Severity unknown	*5401/**5801**

‡*Leflunomid was prescribed for this patient.*
§**5801 is indicated in bold.*
F: Female; M: Male; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis.

Table 4. Associations of *HLA-B*5801* with Japanese SJS/TEN patients.

Patient group	Allele frequency (%)		p-value (Fisher's exact test)	Odds ratio	95% confidence interval for odds ratio
	SJS/TEN patients	*Japanese population**			
Allopurinol-related patients	20.0 (4/20)	0.61 (6/986)	<0.0001	40.83	10.50–158.9

**Data of 493 healthy Japanese reported in* [13].
SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis.

carbamazepine-induced SJS/TEN found in Han Chinese patients in Taiwan [6] was further confirmed by an extended study in Taiwan [17], and studies on Asian patients living in Europe [5], Han Chinese patients in Hong Kong [8] and the Thai population [9]. Man *et al.* and Locharernkul *et al.* reported that *HLA-B*1502* was also detected in patients who suffered from SJS/TEN caused by aromatic anti-epileptic agents such as phenytoin and lamotrigine [8,9]. By contrast, no SJS/TEN patients receiving aromatic anti-epileptic drugs including carbamzepine carried *HLA-B*1502* in our study using Japanese patients. Thus, we could not confirm the association of *HLA-B*1502* with SJS/TEN in Japanese patients. This is reminiscent of the lack of the association in Caucasian carbamazepine-induced SJS/TEN patients [5]. *HLA-B*1502* was not detected in 486 healthy Japanese [13], while its allele frequency in Han Chinese was reported to be 8.6% [6]. The very low allele frequency of *HLA-B*1502* in the Japanese may account for why no association between *HLA-B*1502* and SJS/TEN was detected in our study. To date, useful genetic biomarkers have not been found for carbamazepine-induced SJS/TEN in ethnic groups other than some Asian ethnic groups, including Han Chinese.

Alfirevic *et al.* reported a significant low carrier frequency of *HLA-B*0702* in Caucasian patients with carbamazepine-induced severe cutaneous adverse reactions, and its potential protecting effect against severe cutaneous adverse reactions [14]. Since we detected *HLA-B*0702* in two SJS/TEN patients unrelated to carbamazepine administration, further studies are necessary to clarify the relationship between *HLA-B*0702* and SJS/TEN.

The association of *HLA-B*5801* with allopurinol-induced severe cutaneous adverse reactions detected in Han Chinese in Taiwan [7] has been confirmed in Caucasians [5]. Although the association observed in Han Chinese in Taiwan was extremely strong (odds ratio: ~580), only a moderate association of *HLA-B*5801* with allopurinol-induced SJS/TEN was observed in a European study by Lonjou *et al.* ($p < 10^{-18}$, odds ratio: 80) [5]. In their study, the carrier frequency in European patients was 55.6%, while that in a European population was 1.5%. A moderate but statistically significant association ($p < 0.0001$, odds ratio: ~40) between *HLA-B*5801* with allopurinol-administered SJS/TEN was also detected in the current study using Japanese patients. Although the carrier frequency of *HLA-B*5801* in the Japanese population (1.2%) [13] is comparable to that in the European population (1.5%), the carrier frequency of *HLA-B*5801* in allopurinol-administered Japanese patients (40.0%) was lower than that observed in European patients. The sample size of our study was not sufficient to estimate the accurate carrier frequency in patients. Recently, Ueta *et al.* reported a case–control study on relationships between HLA class I and II genetic polymorphisms with severe ocular

Executive summary

Backgrounds of genetic biomarkers for severe cutaneous adverse reactions

- Recently, strong drug-specific associations of human leukocyte antigen (*HLA*)-*B*1502* and *HLA-B*5801* with carbamazepine- and allopurinol-induced severe cutaneous adverse drug reactions were found in Han Chinese patients, respectively.
- However, a European study suggested that HLA involvement in severe cutaneous adverse reactions may be ethnic-group-specific, as well as drug-specific.

Objective of this study

- We began a retrospective case–control study to explore genetic biomarkers related to Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Japanese patients living in Japan.

Conclusion

- We could not find any association between *HLA-B*1502* and carbamazepine-aromatic anti-epileptic agent-associated SJS/TEN in Japanese patients.
- We detected a moderate association of *HLA-B*5801* with Japanese allopurinol-related SJS/TEN patients.

complications using 71 Japanese drug-unspecified SJS/TEN patients and 111 Japanese controls, and they did not detect any *HLA-B*5801* carriers both in cases and controls [18]. However, no allopurinol-induced patients were included in their sample [Ueta M, Tokunaga K, Sotozono C *et al.*: Prefectural University of Medicine, Kyoto, Japan. Pers. Commun.]. On the other hand, Dainichi *et al.* detected three *HLA-B*5801* carriers in all three allopurinol-associated patients diagnosed with SJS, DIHS and TEN, respectively [19]. Their data and the current study lead to a conclusion that *HLA-B*5801* is one of the (surrogate) genetic biomarkers for allopurinol-associated SJS/TEN also in Japanese patients.

Conclusion

While *HLA-B*1502* is unlikely to be associated with carbamazepine-related or aromatic anti-epileptic agent-related SJS/TEN, *HLA-B*5801* was significantly associated with allopurinol-related SJS/TEN in Japanese.

Future perspective

Recently, the US FDA approved the revision of the label of products containing carbamazepine. In the updated label, it is clearly stated that patients with Chinese ancestry should be screened for the *HLA-B*1502* allele before starting treatment with carbamazepine, and that *HLA-B*1502*-positive patients should basically not be given the drug. On July the 24th, 2008, FDA published an 'alert' [101] based on several studies [15,20–22] informing healthcare professionals that the screening for *HLA-B*5701* is necessary before initiating treatment with abacavir ,and that abacavir should not be administered to *HLA-B*5701* carriers. The Committee for Medicinal Products for Human Use (CHMP) is also considering the revision of the Summary of Product Characteristics (SPC) of abacavir-containing products. Thus, personalized medicine based on pharmacogenomics using biomarkers with excellent performance characteristics has started to identify patients at high risk of idiosyncratic adverse reactions. However, biomarkers only for restricted drugs such as carbamazepine (*HLA-B*1502* for some Asian ethnic groups excluding Japanese), abacavir (*HLA-B*5701* for people living in the USA and Europe) or allopurinol (*HLA-B*5801*) among more than 100 causative ones have been detected to date. Therefore, more intensive, nationwide or even international case–control studies are necessary to find corresponding biomarkers identifying patients at high risk for individual ethnic populations or individual causative drugs. The accumulation of such data may uncover pathogenic mechanisms of SJS/TEN, which will be useful for the identification of new molecules that cause severe cutaneous adverse reactions at an early stage of the drug-development process.

Acknowledgement

We deeply appreciate the Federation of Pharmaceutical Manufacturers' Association of Japan for their assistance in recruiting patients. We also thank all patients and medical doctors for their cooperation with our study.

Financial & competing interests disclosure

This study was supported in part by the Health and Labor Sciences Research Grant (Research on Advanced Medical Technology) from the Ministry of Health, Labor and Welfare. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

▶1 Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC: Clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. *Arch. Dermatol.* 129(1), 92–96 (1993).

2 Roujeau JC: Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J. Dermatol.* 24(11), 726–729 (1997).

3 Roujeau JC, Stern RS: Severe adverse cutaneous reactions to drugs. *New Eng. J. Med.* 331(19), 1272–1285 (1994).

4 Chave TA, Mortimer NJ, Sladden AP, Hall AP, Hutchinson PE: Toxic epidermal necrolysis: current evidence, practical management and future directions. *Br. J. Dermatol.* 153(2), 241–253 (2005).

▶5 Lonjou C, Borot N, Sekula P *et al.*: A European study of *HLA-B* in Stevens–Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet. Genomics* 18(2), 99–107 (2008).

▪ **The associations between *HLA-B* genotypes and Steven–Johnson syndrome (SJS) were confirmed to be less significant in Europeans than in Han Chinese in Taiwan.**

▶6 Chung WH, Hung SI, Hong HS *et al.*: Medical genetics: A marker for Stevens–Johnson syndrome. *Nature* 428(6982), 486 (2004).

▪ **A promising genetic biomarker for carbamazepine-induced SJS in Han Chinese patients in Taiwan was detected.**

▶7 Hung SI, Chung WH, Liou LB *et al.*: *HLA-B*5801* allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc. Natl Acad. Sci. USA* 102(11), 4134–4139 (2005).

▪ **A promising genetic biomarker for allopurinol-induced SJS in Han Chinese patients in Taiwan was detected.**

▶8 Man CB, Kwan P, Baum L *et al.*: Association between *HLA-B*1502* allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 48(5), 1015–1018 (2007).

9 Locharernkul C, Loplumlert J, Limotai C *et al.*: Carbamazepine and phenytoin induced Stevens–Johnson syndrome is associated with *HLA-B*1502* allele in Thai population. *Epilepsia* (2008) (Epub ahead of print).

10 Kashiwagi M, Aihara M, Takahashi Y, Muramatsu M, Ikezawa Z: *HLA* genotypes in carbamazepine induced severe cutaneous adverse drug response in Japanese patients. *J. Dermatol.* (2008) (In Press).

11 Hashimoto K, Iijima M, Shiobara T *et al.*: Stevens–Johnson syndrome. In: *Treatment Manuals for Individual Severe Adverse Reactions (Volume 1)*. Shudo K (Ed.). Japan Pharmaceutical Information Center, Tokyo, Japan, 5–19 (2007).

12 Hashimoto K, Iijima M, Shiobara T *et al.*: Toxic epidermal necrolysis (TEN). In: *Treatment Manuals for Individual Severe Adverse Drug Reactions (Volume 1)*. Shudo K (Ed.). Japan Pharmaceutical Information Center, Tokyo, Japan, 21–35 (2007).

13 Tanaka H, Akaza T, Juji T: Report of the Japanese Central Bone Marrow Data Center. *Clin. Transpl.* 139–144 (1996).

▶14 Alfirevic A, Jorgensen AL, Williamson PR, Chadwick DW, Park BK, Pirmohamed M: *HLA-B* locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics* 7(6), 813–818 (2006).

▶15 Martin AM, Nolan D, Gaudieri S *et al.*: Predisposition to abacavir hypersensitivity conferred by *HLA-B*5701* and a haplotypic *Hsp70-Hom* variant. *Proc. Natl Acad. Sci. USA* 101(12), 4180–4185 (2004).

▶16 O'Donohue J, Oien KA, Donaldson P *et al.*: Co-amoxiclav jaundice: clinical and histological features and HLA class II association. *Gut* 47(5), 717–720 (2000).

▶17 Hung SI, Chung WH, Jee SH *et al.*: Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet. Genomics* 16(4), 297–306 (2006).

18 Ueta M, Tokunaga K, Sotozono C *et al.*: HLA class I and II gene polymorphisms in Stevens–Johnson syndrome with ocular complications in Japanese. *Mol. Vis.* 14, 550–555 (2008).

▶19 Dainichi T, Uchi H, Moroi Y, Furue M: Stevens–Johnson syndrome, drug-induced hypersensitivity syndrome and toxic epidermal necrolysis caused by allopurinol in patients with a common *HLA* allele: what causes the diversity? *Dermatology* 215(1), 86–88 (2007).

▶20 Mallal S, Phillips E, Carosi G *et al.*: *HLA-B*5701* screening for hypersensitivity to abacavir. *N. Engl. J. Med.* 358(6) 568–579 (2008).

▶21 Hughes CA, Foisy MM, Dewhurst N *et al.*: Abacavir hypersensitivity reaction: an update. *Ann. Pharmacother.* 42(3), 387–396 (2008).

▶22 Saag M, Balu R, Phillips E *et al.*: High sensitivity of human leukocyte antigen-*B*5701* as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin. Infect. Dis.* 46(7), 1111–1118 (2008).

Website

101 FDA ALERT (7/24/2008): Information for healthcare professionals regarding abacavir (marketed as Ziagen®) and abacavir-containing medications www.fda.gov/cder/drug/InfoSheets/HCP/abacavirHCP.htm