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SHORT COMMUNICATION

# A Case of Toxic Epidermal Necrolysis Induced by Allopurinol with Human Herpesvirus-6 Reactivation

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Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms (DRESS) (1, 2) are severe adverse drug reactions (ADRs). Recently, human herpesvirus 6 (HHV-6) reactivation has been observed frequently in patients with DIHS/DRESS, but not in SJS/TEN (3–5). Therefore, it has been suggested that HHV-6 is closely related to the pathogenesis of DIHS, but not to that of SJS/TEN (6, 7). We report here a case of TEN induced by allopurinol, accompanied by HHV-6 reactivation.

## CASE REPORT

A 73-year-old woman was treated for gout with allopurinol (300 mg/day). Twelve days later, she developed a rash with sore throat and fever. Three days after that, on day 4, erosions appeared on her lips and oral mucosa. She had had a past history of rash induced by allopurinol. She was diagnosed as having SJS, and allopurinol was discontinued. Although systematic betamethasone (6 mg/day) was started the next day, the rash increased rapidly and became confluent. She was referred to our hospital on day 9. Physical examination revealed high fever and haemorrhagic erosions on the lips, oral mucosa (Fig. S1; available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1610), and genital region, as well as skin rash. Multiple erythematous lesions, including atypical target lesions, were observed on her entire body, and were confluent with blisters and erosions (Fig. 1a). No lymphoadenopathy was observed. Approximately 80% of the body surface area was detached. Laboratory investigations disclosed a high white blood cell count ($12.49 \times 10^9$/l) with atypical lymphocytes (1.5%), hypoproteinaemia (4.0 g/dl), increased serum creatinine (1.24 mg/dl), hypoimmunoglobulinaemia (IgG, 352 mg/dl), and a high CD4/CD8 ratio (2.9). There was no liver dysfunction (aspartate aminotransferases (AST) 8 U/l and alanine aminotransferase (ALT) 8 U/l), but there was pulmonary oedema. Eosinophil was not detected in the blood, but increased later (Fig. 2). A skin biopsy obtained from the left thigh showed epidermal necrosis and subepidermal blisters. Infiltration with mononuclear cells was observed in the upper dermis (Fig. 1b). Taken together, the diagnosis on admission was TEN due to allopurinol. Later, it was established that she had the HLA-B*58:01 leukocyte antigen type.

The patient was treated with steroid pulse therapy with methylprednisolone at 1,000 mg/day for 3 days, and twice with plasma exchange. In addition, 5 g/day of immunoglobulin was administered for 3 days because of hypoimmunoglobulinaemia.

With these treatments, progression of the rash stopped, and re-epithelialization began. Eye lesions, which are often observed in TEN, such as conjunctival injection and pseudomembranes appeared after day 51. The anticytomegalovirus IgG titre was as high as 128 by enzyme-linked immunosorbent assay (ELISA) on day 66.

Peripheral blood samples were obtained for virological examination. Titres of IgG antibodies to HHV-6 were determined using an immunofluorescent (IF) antibody assay. The HHV-6 IgG antibody titre increased from 1:40 on day 12 to 1:1,240 on day 21. The HHV-6 DNA level in a sample of peripheral blood was $3.0 \times 10^4$ copies in $10^6$ peripheral blood mononuclear cells and $3.5 \times 10^5$ copies/ml serum on day 12 by real-time quantitative PCR. There were no significant changes in specific IgG titres for herpes simplex virus, HHV-7, or Epstein–Barr virus during the course of the study. The DNA of these viruses was not detected in the serum.

The results of lymphocyte transformation tests and patch tests were negative for allopurinol and oxypurinol. On day 66, the patient was transferred to another hospital near her home. After that, the patient's erosive rash recurred, and eventually, she died of sepsis.

## DISCUSSION

The patient was diagnosed with an ADR due to allopurinol. This diagnosis was supported by the development of a rash after administration of allopurinol, by the past history of allopurinol-induced rash, and by HLA-

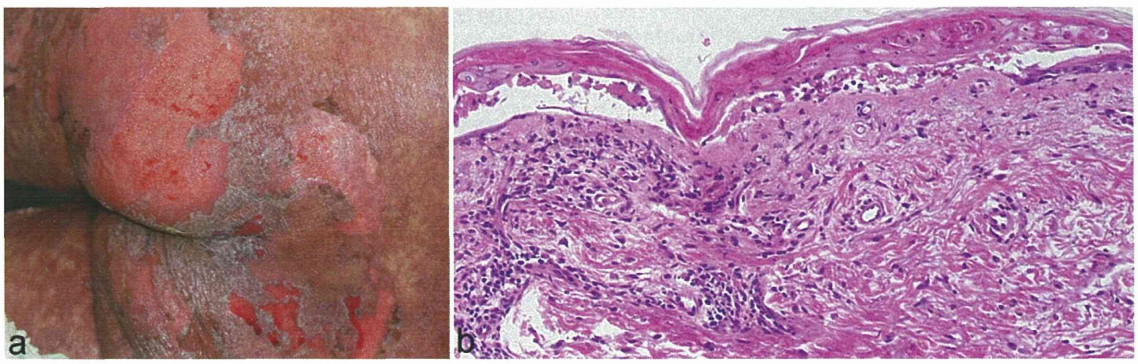


*Fig. 1.* Clinical features: (a) multiple erythematous lesions were confluent and widely detached. Histopathological features: (b) a skin biopsy showed necrosis of the epidermis and subepidermal blisters.

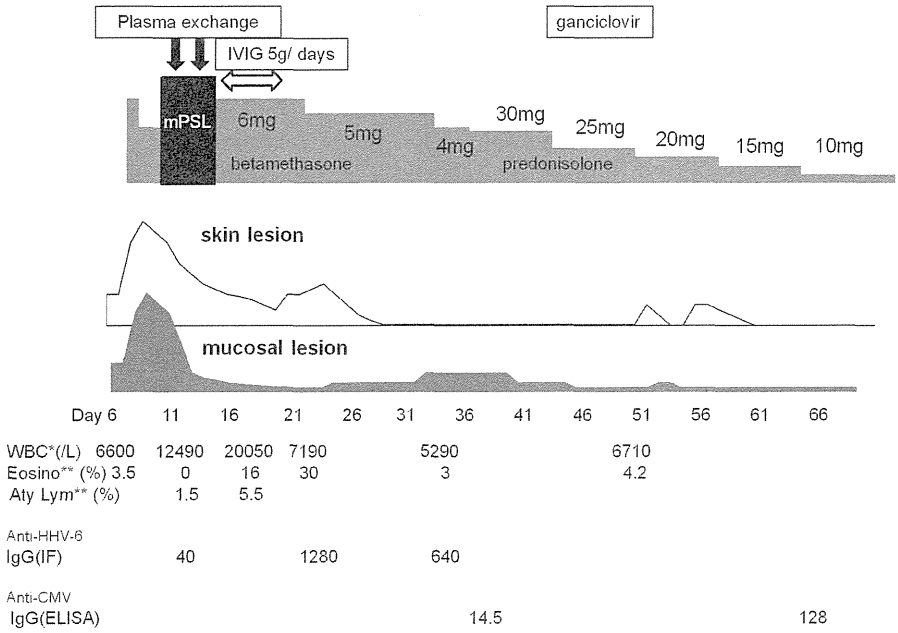


*Fig. 2.* Clinical course. Lesions on the patient's skin and oral mucosa recurred several times, with high fever, increase in atypical lymphocytes, eosinophilia, and human herpesvirus (HHV)-6 and cytomegalovirus (CMV) reactivation. *WBC: white blood cell count; **Eosino: eosinophils; ***Aty Lym: atypical lymphocytes.

B*58:01 positivity. It was concluded that the type of ADR was TEN with HHV-6 reactivation. Symptoms consistent with TEN were as follows: (*i*) severe mucosal lesions, (*ii*) widespread skin detachment, and (*iii*) histopathological findings of epidermal necrosis and subepidermal blisters. Some symptoms consistent with DRESS were also observed as follows: (*i*) high fever, (*ii*) acute skin rash, (*iii*) peripheral blood abnormalities, such as leukocytosis, eosinophilia, and atypical lymphocytosis. In addition, reactivation of HHV-6 and CMV as well as several recurrences of skin rash were consistent with DIHS. Although serious internal organ involvement was not observed, pulmonary oedema and a mild increase in serum creatinine were observed.

HHV reactivation is rarely observed in patients with SJS/TEN. Only a few cases have been reported as SJS/TEN associated with HHV-6 reactivation (8, 9), and TEN with HHV-7 reactivation (10). These patients did not show frequent recurrence and haematological abnormalities as observed in our patient. Since our patient showed clinical features of TEN accompanied with some symptoms of DRESS with HHV-6 and CMV reactivation, we conclude that viral reactivation is involved in the clinical course. Clinicians should consider sequential testing for HHV-6 with prolonged SJS/TEN, especially when induced by drugs known to be causative of DIHS, including allopurinol and anti-epileptics.

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CPD

# 1 Utility of patch testing for patients with drug eruption

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## Summary

**Background.** Patch testing is less dangerous than oral provocation testing for identification of the causative drug for patients with drug eruption; however, its usefulness for such identification is controversial.

**Aim.** To clarify the rates of positive patch testing for patients with drug eruption, classified by causative drugs and clinical features.

**Methods.** We analysed results during the period 1990–2010 for 444 patients (151 men, 293 women; mean ± SD age 49.9 ± 18.6 years) who were tested for drug eruption. In the patient group, there were 309 (69.1%) with maculopapular eruption and 31 (6.9%) with severe drug eruption. The test materials were applied to the back and left for 2 days under occlusion, then results were assessed by the International Contact Dermatitis Research Group (ICDRG) scoring system 3 days after application. Reactions of + to +++ were regarded as positive.

**Results.** Of the 444 patients, 100 (22.4%) had a positive patch test result to a suspected drug. Positive rates were 23.6% and 20.0% for maculopapular eruption and fixed drug eruption, respectively. The class of materials to which most patients reacted positively was contrast medium ($n$ = 53; 41.1%), followed by drugs acting on the central nervous system ($n$ = 18; 28.6%). In the latter group, 16 of the 18 patients were positive to antiepileptics.

**Conclusions.** Positive rates depend on the causative drug rather than the clinical features of the drug eruption. Patch testing is useful when contrast medium or antiepileptics are suspected to be the causative drugs. However, standardization of patch test materials and method of reading is needed, as well as guidelines regarding when testing should be performed. Although patch testing for drug eruption has significant potential, it requires further validation.

## Introduction

The oral provocation test is a reliable method to identify causative drugs for patients with drug eruption.[1] However, it may be dangerous in some serious drug eruptions, such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug-induced hypersensitivity syndrome (DIHS), as these conditions have a guarded prognosis.[2,3] Patch testing is less dangerous than the oral challenge test, but its usefulness for drug eruption is controversial.[4] To determine the utility of patch testing for patients with drug eruption, we analysed the results of patch testing for patients with drug eruption over a 20-year period.

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## Methods

### Patients

We analysed the results for patients patch-tested at the Department of Dermatology, Showa University Hospital, during the period April 1990 to March

2010. In total, 444 patients (151 male, 293 female; mean ± SD age 49.9 ± 18.6 years, range 2–93) suspected of having drug eruption were tested (Table 1). Table 2 shows the frequency of the clinical types of drug eruptions. Of the 444 patients, 309 (69.6%) had maculopapular eruption. Because this type of eruption is often difficult to distinguish from viral infection, patients were identified on the basis of their medical history and the clinical course pf the disease, as follows: (i) rash occurring up to 4 weeks after drug administration, and (ii) improvement of lesions after the suspect medication was stopped. There were 55 (12.4%) and 37 (8.3%) patients, respectively with fixed drug eruption (FDE) and erythema multiforme (EM). A further 31 patients (7.0%) were diagnosed as having severe drug eruptions (SJS, TEN or DIHS). Table 3 shows the number of tested patients for each class of drug: 129 were tested with contrast media, 126 with antibacterial agents and 101 with nonsteroidal anti-inflammatory drugs (NSAIDs).

### Patch testing

Patch-testing materials (Manufacturing Laboratory, Showa University Hospital Pharmacy) were applied to the back of each participant, and left for 2 days under occlusion. Two types of patch-test unit were used: vinyl plaster (Mini-plaster or Patch Tester Torii; Torii Pharmaceutical Co, Ltd, Tokyo, Japan) for water-based materials and Finn Chamber® (Smart-Practice Co. Ltd, Yokohama, Japan) for petrolatum-based materials. In 33 of the 55 patients with FDE, patch tests were performed both on normal skin and on the affected site, while the other 22 were tested on the back because of difficulty applying the drug to the affected sites (e.g. lip, genital region). In four cases of suspected photosensitivity, photopatch testing was preformed: two materials were applied to the back, then one was removed after 24 h and the area irradiated with half the minimal erythema dose of ultraviolet (UV)A/UVB (Dermaray UV; Eisai Co. Ltd, Tokyo, Japan).

**Table 1** Patient characteristics.

| Group | *n* | Age, years |
|---|---|---|
| All | 444 | 49.9 ± 18.6* |
| Men | 151 | 50.9 ± 18.4 |
| Women | 293 | 49.5 ± 18.8 |

*Data are mean ± SD.

All the tests were performed between 2 weeks and 4 months after onset of eruption. Results were assessed using the International Contact Dermatitis Research Group (ICDRG) scoring system 3 days after application.[5] Reactions of + to +++ (Ph+ to Ph+++ for photopatch testing) were regarded as positive. Any results that were difficult to assess because of technical limitations were excluded.

**Table 2** Incidence and positive rate related to clinical features/condition.

| Clinical features/condition | Patients, *n* | Positive reaction, *n* | Positive rate, % |
|---|---|---|---|
| Maculopapular eruption | 305 | 73 | 23.9 |
| FDE | 55 | 11 | 20 |
| EM | 37 | 3 | 8.1 |
| Photosensitivity | 4 | 2 | 50 |
| AGEP | 3 | 0 | 0 |
| Severe reactions | | | |
| SJS | 7 | 1 | 14.3 |
| TEN | 8 | 0 | 0 |
| DIHS | 16 | 9 | 56.3 |
| Others | 9 | 1 | 11.1 |
| Total | 444 | 100 | 22.5 |

AGEP, acute generalized exanthematous pustulosis; DIHS, drug-induced hypersensitivity syndrome; EM, erythema multiforme; FDE, fixed drug eruption; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

**Table 3** Incidence and positive rate related to drugs.

| Drug | Patients, *n* | Positive reaction, *n* | Positive rate,% |
|---|---|---|---|
| Contrast agent | 129 | 53 | 41.1 |
| Drugs acting on the CNS | 63 | 18 | 28.6 |
| Antiepileptics | 39 | 16 | 41.0 |
| Nonsteroidal anti-inflammatory drugs | 101 | 11 | 10.9 |
| Antibacterial and antifungal agents | 126 | 9 | 7.1 |
| Drugs acting on the respiratory system | 51 | 3 | 5.9 |
| Cold remedies | 65 | 2 | 3.1 |
| Traditional Chinese medicine | 14 | 2 | 14.3 |
| Muscle relaxants | 4 | 2 | 50.0 |
| Drugs affecting metabolism and GI function | 74 | 1 | 1.4 |
| Metal antagonists | 4 | 1 | 25.0 |
| Drugs acting on the cardiovascular system | 48 | 0 | 0 |
| Drugs acting on the immune response | 34 | 0 | 0 |
| Vitamins | 10 | 0 | 0 |
| Others | 20 | 0 | 0 |

CNS, central nervous system; GI, gastrointestinal.

## Results

Of the 444 patients suspected of having drug eruption, 100 (22.4%; 39 men, 61 women; age 51.2 ± 17.1 years, range 17 to 86) had positive patch-test results. Positive rates in cases of maculopapular eruption, FDE and EM were 23.9%, 20.0% and 8.1%, respectively (Table 2). Regarding the severe drug eruptions, positive rates in cases of SJS, TEN and DIHS were 14.3%, 0% and 56.3%, respectively (Table 2). Contrast medium was the most common source of positive patch test ($n$ = 53; 41.1%), and the second most common ($n$ = 18; 28.6%) was the class of drugs acting on the central nervous system (CNS) (Table 3). In the latter group, 16 of 18 (41.0%) reacted to antiepileptics and 12 of the 16 had positive reactions to carbamazepine (Table 3). Of 101 patients tested with NSAIDs, 11 (10.9%) had a positive reaction (Table 3), while of 126 patients tested with antibacterial or antifungal agents, 9 (7.1%) tested postive (Table 3). Rates of positive reactions to drugs acting on the respiratory system, cold remedies, and traditional Chinese medicines were 5.9%, 3.1% and 14.3%, respectively (Table 3). No patients reacted to drugs acting on the cardiovascular system or the immune response, or to any vitamins (Table 3).

## Discussion

In this study, the positive response rate to suspected drugs in our cohort of 444 patients was 22.4% but positive rates in patients with photosensitivity or DIHS were > 50% (Table 2). The drug to which most patients reacted was contrast medium (Table 3). Numerous drug eruptions were reported in Japan shortly after the introduction of nonionic iodinated contrast media,[6] with the main clinical feature being papulomacular eruption, partticularly oedematous erythema and papules, mainly on the trunk.[6] We suggest two reasons for the numerous cases of drug eruption caused by contrast media in Japan.[6] First, deficiency of aldehyde dehydrogenase (ALDH), a migrating isoenzyme of liver acetaldehyde dehydrogenase, which occurs in around 50% of Japanese (i.e. they have a low Michaelis constant and $K_m$ for acetaldehyde) may play a role.[7,8] Second, until 2000, the rate of annual exposure to contrast medium was higher, as it included pretesting performed with a small amount of contrast medium, as it was thought that this pretesting might predict those patients likely to have adverse reactions.[6,9] The ddiscontinuation of this pretesting procedure might be the reasons for the decrease in the positive rates and numbers of patients affected: 43.4% (46/106) during the period April 1990 to March 2000, and 30.4% (7/23) in the period April 2000 to March 2010.

Drugs acting on the CNS made up the second largest group of positive tests, with 18 patients reacting to them (Table 3): 16 reacted to antiepileptics and 12 to carbamazepine.Regarding DIHS, 9 of 16 tested patients with DHHS (56.3%) had positive results (Table 2); this high positive rate was not due to DIHS itself, but rather to the causative drugs, as 8 of the 9 patients reacted to carbamazepine. It is well known that carbamazepine results in high positive rates in patch testing.[10] Indeed, a limitation of patch testing for drug eruption lies in differentiating between systemic and cutaneous metabolism of drugs.[11] We speculate that this difference might be less for carbamazepine than for other drugs because this drug has a uniform distribution through the body,[12] and cases of flare-up phenomena during patch testing with carbamazepine have been reported[13]. Our data therefore suggest that the positive rates may depend on the causative drug rather than on the clinical features of the drug eruptions. However, the positive rate for FDE might have been affected by the negative reactions occurring in 22 patients who had the materials to their back, as positive results are more likely when materials are applied to the involved skin.

Patch testing is much safer than oral challenge or intracutaneous test for the identification of a causative drug in patients with drug eruption.[14] Our results suggest that patch-testing can be useful when contrast medium or antiepileptic is suspected as the causative drug, and can be relevant to patient management.[11,15] However, the general opinion of patch testing for patients with drug eruption is not high,[16] and negative reactions are not useful.[17] To perform patch testing for drug eruptions, patient consent must be gained after they are informed as to the limitations of the testing, as described above and the influence of the testing on their social life, e.g. avoidance of showers, sunbathing and exercise. Although some guidelines have been defined,[11,18] we consider that three standardized metrics are needed to overcome the issues described above if patch testing is t be used for drug eruptions.

First, the actual treatment drugs should be used as patch test allergens. There is a limited number of drugs that are commercially available for patch testing,[19–21] thus most are formulated by each local facility, leading to difficulties in comparing data between different facilities. Each drug also has an optimal patch test concentration that is not irritant, and optimal

**Table 4** Patch test concentration and vehicles of main causative drugs.

| Classification | Drug | Concentration, % | Vehicle |
|---|---|---|---|
| Contrast medium | Iohexol | As supplied (water) | |
| | Iopamidol | As supplied (water) | |
| | Iomeprol | As supplied (water) | |
| Drugs acting on the CNS | Carbamazepine | 1 | Pet. |
| | Phenytoin | 1 | Pet. |
| | Phenobarbital | 1 | Pet. |
| NSAIDs | Diclofenac sodium | 10 | Pet. |
| | Mefenamic acid | 10 | Pet. |
| | Acetoaminophen | 10 | Pet. |
| | Piroxicam | 1 | Pet |
| Antibacterial agents | Amoxicillin trihydrate | 10 | Pet. |
| | Ampicillin hydrate | 10 | Pet. |
| | Minocycline hydrochloride | 10 | Pet. |
| | Clarithromycin | 10 | Pet. |
| | Cefaclor | 10 | Pet. |
| | Cefalexin | 10 | Pet. |
| Others | Dihydrocodeine phosphate | 10 | Pet. |

CNS, central nervous system, NSAID, nonsteroidal anti-inflammatory drug, pet., petrolatum.

vehicle(s). Table 4 shows the patch-test concentrations and vehicles of the main causative drugs used in this study. There is a limited number of commercially available drugs for patch testing,[19–21] thus most are formulated by each local facility, leading to difficulties in comparing data between different facilities. In addition, where possible, patch testing should also be carried out using the individual ingredients of the medicines,[22] as these ingredients may also be used in other products.

Second, assessment of patch-test reactions for drug eruption needs to be standardized. The ICDRG scoring system is an established method of identifying allergens in cases of allergic contact dermatitis (ACD), but it can be difficult to interpret a reaction of '?+'in drug eruptions. In our study, 13 of 14 patients (92.9% with '?+' reactions to contrast media had a positive reaction to intracutaneous testing). In addition, although it is recommended that for ACD, readings should be performed on day 2, day 3 or 4, and day 7 in ACD, there are no similar data for drug allergy.

Third, it is unclear when patch testing should be performed immediately after improvement of the rash or several weeks later. Bruyzeel and Maibach[4] suggested the latter is better than the former, but Grandhe *et al.*[23] reported a longer interval occurred between the rash and evaluation in patients with negative patch-test reactions than in patients with positive patch-test reactions.

However, each clinical condition might have an optimal time for patch testing. Kano *et al.*[24] suggested that the lymphocyte transformation test should be performed within 1 week after the onset of rash in patients with maculopapular drug eruption and SJS/TEN, but should be delayed until 5–8 weeks after rash onset in DIHS. Similar data for patch testing will be necessary to increase its usefulness.

The fact that the oral challenge test is rarely used for drug verification demonstrates that this test is also not well standardized. It is also necessary to clarify when intradermal testing should be carried out if patch testing is negative.[2] Thus, further studies are necessary, both for patch testing and for other tests to detect the causative drug in patients with drug eruptions.

## Conclusion

in terms of increased refinement of the evidence-based diagnosis of clinical relevance, patch testing for drug eruption has significant potential.[25] However, further validation is necessary to overcome the limitations of the test and to clarify the optimal conditions for its performance.

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## CPD questions

### Learning objective

To detail how to use patch testing to identify the causative drug for in patients with drug eruption.

### Question 1

Which type of drug-induced eruption is the most common?
a) Maculopapular eruption.
b) Fixed drug eruption.
c) Erythema multiforme-type.
d) Photosensitivity.
e) Stevens–Johnson syndrome.

### Question 2

Which of the following factors has the greatest effect on positive rates of drug eruption?
a) Patient age.
b) Clinical features of the drug eruption.
c) Clinical course of the drug eruption.
d) Severity of the drug eruption.
e) Causative drug.

### Question 3

Which of the following is the most useful for identification of the cause of drug eruption by patch testing?
a) Antibacterial and antifungal agents.
b) Cold remedies.
c) Contrast medium.
d) Drugs acting on the cardiovascular system.
e) Drugs affecting metabolism and gastrointestinal function.

### Question 4

Which of the following is the best vehicle for carbamazepine for patch testing?
a) 0.1% pet.
b) 0.1% water.
c) 1% pet.
d) 1% water.
e) 10% pet.

**Question 5**

As a method to identify the causative drug for patients with drug eruption, how should patch testing be regarded?

a) Not useful.
b) Useful only when antiepileptics are suspected.
c) Useful when clinical feature is not severe.
d) It has significant potential, but further validation is necessary.
e) Perfect.

## Instructions for answering questions

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ORIGINAL ARTICLE

# Dermatological side-effects of telaprevir-based triple therapy for chronic hepatitis C in phase III trials in Japan

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## ABSTRACT

**Telaprevir-based triple therapy is highly effective for chronic hepatitis C. However, concern has been expressed over the high frequency and severity of its dermatological side-effects compared with those associated with peginterferon (PEG-IFN) and ribavirin (RBV) therapy. Thus, here, we evaluated the dermatological adverse reactions of telaprevir-based triple therapy in Japanese multicenter phase III clinical trials in an attempt to characterize the dermatological side-effects and establish appropriate management plans. In these trials, 126 treatment-naïve patients and 141 treatment-failure patients were administrated telaprevir, PEG-IFN-α-2b and RBV for 12 weeks followed by PEG-IFN-α-2b and RBV for another 12 weeks (T12/PR24 group), and 63 treatment-naïve patients were administrated PEG-IFN-α-2b and RBV for 48 weeks (PR48 group). Dermatological adverse reactions developed in over 80% patients in both groups, and most of them were grade 1 or 2. In the T12/PR24 group, there were more grade 2 or grade 3 events, and the time to onset was earlier than that in the PR48 group. Most reactions could be managed with topical corticosteroids and oral antihistamines, and the rates of discontinuation due to dermatological reactions were not high even in the T12/PR24 group. In the T12/PR24 group, however, two cases of Stevens–Johnson syndrome and one case of drug rash with eosinophilia and systemic symptoms, which corresponds to drug-induced hypersensitivity syndrome in Japan, were reported. For appropriate treatments of individual dermatological adverse reactions, the judgment of discontinuation of antiviral drugs and treatment based on the severity are extremely important in this triple therapy.**

**Key words:** chronic hepatitis C, dermatological adverse reaction, drug rash with eosinophilia and systemic symptoms, Stevens–Johnson syndrome, telaprevir.

## INTRODUCTION

Telaprevir, a novel direct-acting antiviral, inhibits the NS3-4A serine protease of hepatitis C virus (HCV) and suppresses HCV replication.[1] Triple therapy of telaprevir, peginterferon (PEG-IFN) and ribavirin (RBV) has proved to be more effective for treating chronic hepatitis C (CHC) compared to PEG-IFN and RBV combination therapy.[2–7]

In Japan, three phase III trials for telaprevir-based triple therapy were performed on treatment-naïve (TN) patients (patients who had never been treated with IFN agents), relapsers (patients who had undetectable HCV RNA during previous therapy for CHC), and non-responders (patients who never achieved undetectable HCV RNA during previous therapy for CHC). In these trials, the sustained virological response (SVR) rates of patients were as follows: TN patients, 73.0% in T12/PR24 group, 49.2% in PR48 group; relapsers, 88.1%; and non-responders, 34.4%.[6,7] The established duration of telaprevir-based triple therapy is 24 weeks, which is half of that for PEG-IFN and RBV therapy. Therefore, the higher efficacy of triple therapy achieved over a shorter period make it markedly superior to PEG-IFN and RBV therapy.

Dermatological side-effects were also observed in Japanese trials of telaprevir monotherapy that lasted for 12 or 24 weeks. The severity of the side-effects was mild to moderate, and two patients discontinued telaprevir due to development of skin disorders (pruritic rash or herpes zoster).[8,9]

Peginterferon and ribavirin combination therapy has also been known to cause cutaneous adverse reactions.[10,11] Even with IFN monotherapy, dermatological reactions were observed

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locally at injection sites or systemically on occasion, and combination therapy with RBV has been reported to cause an increased incidence of cutaneous reactions. These reactions include generalized pruritus, xerosis, erythematous papules and microvesicles mainly localized to the limbs and areas of friction.[10–14] Usually, topical corticosteroids or emollients are effective in managing the cutaneous reactions, and discontinuation of the antiviral drugs is not required.[10]

Because dermatological adverse reactions have been observed in telaprevir monotherapy and PEG-IFN and RBV combination therapy, there is a possibility that dermatological reactions develop even more frequently in the triple therapy. Phase II trials in the USA and in European countries (EU) show a higher incidence of dermatological adverse reactions in the telaprevir, PEG-IFN and RBV group than in the PEG-IFN and RBV group.[2,3] On the basis of this finding, for the Japanese phase III trials, we classified the severity in the same manner as that of the US/EU trials (Table 1) and collected detailed information. We hereby show the characteristics of the dermatological adverse reactions of telaprevir-based therapy, and consider the criteria for drug discontinuation and management plan for these reactions.

## METHODS

### Patients

Multicenter, randomized, phase III trials were performed at 42 Japanese medical institutions from 2008 to 2010. In these trials, 126 TN patients and 141 treatment-failure (TF) patients were administrated telaprevir, PEG-IFN and RBV for 12 weeks followed by PEG-IFN and RBV for another 12 weeks (T12/PR24 group, $n$ = 267), and 63 TN patients were administrated PEG-IFN and RBV for 48 weeks (PR48 group).[6,7] The TF patients comprised 109 relapsers and 32 non-responders.[7] The principal eligibility criteria were as follows: (i) a diagnosis of CHC; (ii) infection with HCV-1; (iii) HCV RNA levels of 5.0 $\log_{10}$ IU/mL or more; (iv) age at entry, 20–65 years; and (v) bodyweight of more than 40 kg and 120 kg or less. The main exclusion criteria were as follows: (i) hemoglobin level of less than 12 g/dL, neutrophil count of less than 1500/mm$^3$ and platelet count of less than 100 000/mm$^3$; (ii) positive for antibodies against hepatitis B surface antigen or HIV; and (iii) chronic renal failure or a creatinine clearance of 50 mL/min or less.

Each patient gave a written informed consent before participating in these studies.

### Study design

The clinical trial involving TN patients was a multicenter, randomized, controlled study, where 189 patients were assigned to either the T12/PR24 group or the PR48 group.[6] The trials that included TF patients (relapsers and non-responders) were open-label studies that included the T12/PR24 group alone.[7]

For patients in the T12/PR24 group, telaprevir was administrated p.o. t.i.d. every 8 h at a dose of 750 mg after meals for 12 weeks. PEG-IFN-α-2b (PegIntron®; MSD, Tokyo, Japan) was administrated s.c. once a week (1.5 μg/kg; range, 1.250–1.739 μg/kg) and RBV (Rebetol®; MSD) was administrated p.o.

**Table 1.** Severity classification of dermatological adverse reactions in phase III trials in Japan

| Severity | Criteria | Management |
|---|---|---|
| Grade 1 | Involvement of ≤50% of the body surface, localized<br>No evidence of systemic symptoms | Consultation with a dermatologist, if needed |
| Grade 2 | Involvement of ≤50% of the body surface, multiple or diffuse lesions<br>Or rash with any of the following characteristics:<br>Mild systemic symptoms<br>Mucous membranes involved but with no ulceration/erosion | Discontinuation of the study drugs is generally not necessary, the investigators can consider the following, if needed:<br>Discontinuation of telaprevir<br>Discontinuation, interruption, or reduction of PEG-IFN and RBV |
| Grade 3 | Generalized rash involving >50% of the body surface<br>Or rash with any of the following characteristics:<br>Appearance of significant systemic symptoms that are new and are considered to be related to the onset and/or progression of the rash<br>Ulceration/erosion of mucous membranes<br>Epidermal detachment (epidermal necrosis or separation of epidermis from underlying dermis)<br>Target lesions<br>Vesicles or bullae<br>Palpable purpura | Consultation with a dermatologist<br>Discontinuation of telaprevir (in principle)<br>Consider discontinuation or reduction of PEG-IFN and RBV |
| Life-threatening | SJS, TEN, DRESS,† EM‡<br>Or other life-threatening symptoms,<br>Or cases where features of serious disease are observed | Consultation with a dermatologist<br>Immediate discontinuation of all drugs |

†DRESS corresponds to the Japanese term for DIHS.
‡EM is not life-threatening, but in severe cases, mucous membrane lesions and systemic symptoms are encountered. In phase III trials, EM was reported in five patients and was serious in one patient. DIHS, drug-induced hypersensitivity syndrome; DRESS, drug rash with eosinophilia and systemic symptoms; EM, erythema multiforme; PEG-IFN, pegylated interferon; RBV, ribavirin; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

b.i.d. after meals (200–600 mg/dose; daily dose, 600–1000 mg) for 24 weeks. The patients in the PR48 group received PEG-IFN-α-2b and RBV at the aforementioned doses for 48 weeks. The doses of PEG-IFN-α-2b and RBV were reduced when the patients' hemoglobin level, white blood cell count, neutrophil count or platelet count decreased, or when adverse events developed.[6,7] Patients in the T12/PR24 group and PR48 group were followed up for 24 weeks.

### Assessment

Dermatological adverse reactions were investigated during the administration period of 24 weeks in the T12/PR24 group and 48 weeks in the PR48 group, and during the 24-week follow-up period in both groups. We integrated the data of the 126 TN patients and 141 TF patients (109 relapsers and 32 non-responders) who were administrated telaprevir, PEG-IFN-α-2b and RBV in three phase III trials (Table 2).

Table 1 shows the severity classification system used to evaluate dermatological adverse reactions. When the skin reactions were detected, the investigators referred the patients to a dermatologist as needed, and reported the events in reference to the diagnosis of the dermatologist. In cases where the severity was considered as grade 3, telaprevir was discontinued in principle. In addition, in cases where severe cutaneous reactions including Stevens–Johnson syndrome (SJS) and drug rash with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) were suspected, all study drugs were immediately discontinued.

Of the dermatological adverse reactions reported by investigators, we examined 355 events in the T12/PR24 group (190 events in 111 TN patients and 165 events in 115 TF patients), and 102 events in the PR48 group (among 53 TN patients). The events such as contact dermatitis and impetigo that were unlikely to be attributable to the study drugs were excluded (Table 2).

## RESULTS

### Study patients

In the T12/PR24 (TN) group, the T12/PR24 (TF) group, and the PR48 group, the number of men was 66 (52.4%), 83 (58.9%), and 33 (52.4%), respectively; the median age was 53 (range: 20–65), 57 (range: 20–65), and 55 (range: 20–65) years, respectively; and the median body mass index was 22.55 (range: 16.2–31.1), 23.00 (range: 17.1–32.4), and 23.30 (range: 17.9–30.8) kg/m$^2$, respectively.

### Incidences of dermatological adverse reactions

Table 3 summarizes the incidences of dermatological adverse reactions. The incidence of localized or systemic rash-related events, excluding reactions on the injection site only, was higher in the T12/PR24 groups than in the PR48 group, whereas events limited to the injection site were more common in the latter. The incidences of grade 2 and grade 3 rash-related events were also higher in the T12/PR24 groups than in the PR48 group. No statistical difference was observed in the incidence of rash-related events between the T12/PR24(TN) and T12/PR24(TF) groups.

Table 4 shows the rates of serious adverse events, discontinuation, interruption, and reduction of study drugs due to the dermatological events. No dermatological problem led to death. Serious adverse events requiring hospitalization or prolongation of inpatient care were observed in only the T12/PR24 (TN) and T12/PR24 (TF) groups, respectively. Two patients developed SJS and one developed DRESS/DIHS.

Because no clear differences were found in incidences, grades and features of dermatological adverse reactions between TN and TF patients in the T12/PR24 group, we integrated the data of these two patient groups to evaluate the reactions associated with triple therapy as described below.

### Time to onset

Figure 1 shows the cumulative incidence of dermatological adverse reactions obtained using the Kaplan–Meier method. The incidence up to week 4 was 77.1% in the T12/PR24 groups and 55.6% in the PR48 group. Time to onset of the first reaction was earlier in the T12/PR24 group than in the PR48 group (Fig. 1a).

Most grade 1 events occurred within 2 weeks in the T12/PR24 group, and were approximately the same timing as those in the PR48 group. Grade 2 events occurred early in the T12/PR24 group, with increased incidence during weeks 4–8 after the initial administration (Fig. 1b). Regarding grade 3 events, papuloerythematous rashes affecting more than 50% of the body surface area occurred within 1 week, and rashes with

**Table 2.** Number of patients and dermatological adverse events in each study

| | | T12/PR24 group | | | PR48 group | | |
|---|---|---|---|---|---|---|---|
| | | Dermatological reactions | | | Dermatological reactions | | |
| | | *n* | No. of patients | No. of events | *n* | No. of patients | No. of events |
| Study on treatment-naïve patients | – | 126 | 111 | 190 | 63 | 53 | 102 |
| Studies on treatment-failure patients | Relapser | 109 | 85 | 124 | – | – | – |
| | Non-responder | 32 | 30 | 41 | – | – | – |
| | Total | 141 | 115 | 165 | – | – | – |

T12/PR24: telaprevir, pegylated interferon (PEG-IFN)-α-2b and ribavirin (RBV) for 12 weeks followed by administration of PEG-IFN-α-2b and RBV for 12 weeks. PR48: PEG-IFN-α-2b and RBV for 48 weeks.

**Table 3.** Incidence of dermatological adverse reactions

| | T12/PR24 | | | | | | PR48 | |
|---|---|---|---|---|---|---|---|---|
| | Treatment-naïve $n = 126$ | | Treatment-failure $n = 141$ | | Total $n = 267$ | | Treatment-naïve $n = 63$ | |
| Total | 111 | 88.1% | 115 | 81.6% | 226 | 84.6% | 53 | 84.1% |
| Rash-related events[†] | 94 | 74.6% | 106 | 75.2% | 200 | 74.9% | 37 | 58.7% |
| Grade 1 | 53 | 42.1% | 63 | 44.7% | 116 | 43.4% | 31 | 49.2% |
| Grade 2 | 43 | 34.1% | 47 | 33.3% | 90 | 33.7% | 12 | 19.0% |
| Grade 3[§] | 15 | 11.9% | 9 | 6.4% | 24 | 9.0% | 3 | 4.8% |
| Injection site-related events[‡] | 60 | 47.6% | 36 | 25.5% | 96 | 36.0% | 37 | 58.7% |
| Grade 1 | 59 | 46.8% | 36 | 25.5% | 95 | 35.6% | 37 | 58.7% |
| Grade 2 | 1 | 0.8% | 0 | – | 1 | 0.4% | 0 | – |
| Grade 3 | 0 | – | 0 | – | 0 | – | 0 | – |

[†]Localized or systemic rash-related events, excluding reactions on the injection site only. The terms reported more than 10% were rashes (T12/PR24 vs PR48: 38.6% vs 28.6%), drug eruptions (26.6% vs 3.2%) and erythema (6.0% vs 20.6%).
[‡]The terms reported more than 10% were injection site erythema (T12/PR24 vs PR48: 19.1% vs 33.3%) and injection site reaction (16.1% vs 25.4%).
[§]Including life-threatening events, two Stevens–Johnson syndrome (SJS) cases, and one drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome case. T12/PR24: telaprevir, pegylated interferon (PEG-IFN)-α-2b and ribavirin (RBV) for 12 weeks followed by administration of PEG-IFN-α-2b and RBV for 12 weeks. PR48: PEG-IFN-α-2b and RBV for 48 weeks.

**Table 4.** Incidence of serious events and rates of discontinuation, interruption and reduction of study drug(s) due to dermatological events

| | T12/PR24 | | | | | | PR48 | |
|---|---|---|---|---|---|---|---|---|
| | Treatment-naïve $n = 126$ | | Treatment-failure $n = 141$ | | Total $n = 267$ | | Treatment-naïve $n = 63$ | |
| Serious adverse events | 3 | 2.4% | 5 | 3.5% | 8 | 3.0% | 0 | – |
| Discontinuation of any study drug | 12 | 9.5% | 11 | 7.8% | 23 | 8.6% | 2 | 3.2% |
| Telaprevir only | 4 | 3.2% | 7 | 5.0% | 11 | 4.1% | – | – |
| All study drug(s) | 8 | 6.3% | 4 | 2.8% | 12 | 4.5% | 2 | 3.2% |
| Interruption of PEG-IFN or RBV | 0 | – | 2 | 1.4% | 2 | 0.7% | 0 | – |
| Reduction of PEG-IFN or RBV | 2 | 1.6% | 2 | 1.4% | 4 | 1.5% | 0 | – |

T12/PR24: telaprevir, pegylated interferon (PEG-IFN)-α-2b and ribavirin (RBV) for 12 weeks followed by administration of PEG-IFN-α-2b and RBV for 12 weeks. PR48: PEG-IFN-α-2b and RBV for 48 weeks.

pyrexia and lymphadenopathy, such as SJS and DRESS/DIHS, occurred during weeks 4–8 in the T12/PR24 group.

## Characteristics of dermatological adverse reactions

Table 5 shows the characteristics of the 355 events in the T12/PR24 group and 102 events in the PR48 group.

*Area of dermatological adverse reactions on the body surface.* In the T12/PR24 group, 27.9% of dermatological adverse reactions (multiple or diffuse reactions) affected 50% or less of the body surface, while 5.4% affected more than 50% of the body surface. Compared with the PR48 group, the involved areas tended to be large in the T12/PR24 group.

*Distribution.* The dermatological reactions appeared mainly in the extremities and the trunk, and sometimes on the face. In case of SJS, DRESS/DIHS and serious erythema multiforme (EM), the intraoral areas, lips and pharynx were affected.

*Features of lesions.* Most of the dermatological adverse reactions in the T12/PR24 groups were papuloerythematous or maculopapular rashes (Figs 2a,b), which were similarly observed in the PR48 group; a few cases were judged as EM. In some cases, florid rashes developed at the injection site (Fig. 2c). In the SJS and DRESS/DIHS cases, superficial ulceration and erosion of mucous membranes or epidermal detachment were also observed.

*Pruritus.* Most dermatological adverse reactions were accompanied by pruritus in both the T12/PR24 group (82.5%) and the PR48 group (82.4%) (Table 5).

*Systemic symptoms.* In the T12/PR24 group, 7.0% of dermatological adverse reactions were accompanied by systemic symptoms, and pyrexia occurred most frequently. In the SJS, DRESS/DIHS and serious EM cases, pyrexia of 38–39°C and lymphadenopathy were observed (Table 5).

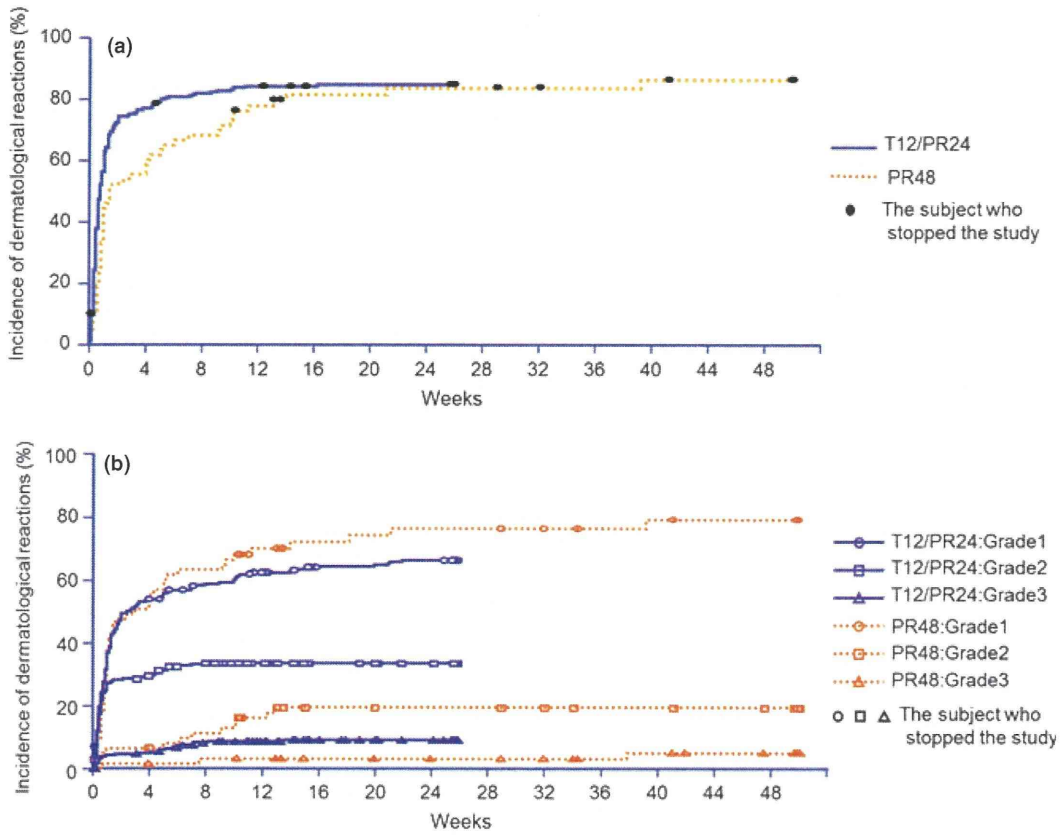


**Figure 1.** Time to onset of first dermatological adverse reaction. Cumulative incidence of dermatological adverse reactions (a) in total and (b) by grade in the T12/PR24 and PR48 groups obtained using the Kaplan–Meier method. T12/PR24: telaprevir, pegylated interferon (PEG-IFN)-α-2b and ribavirin (RBV) for 12 weeks followed by administration of PEG-IFN-α-2b and RBV for 12 weeks. PR48: PEG-IFN-α-2b and RBV for 48 weeks.

## Serious cases

*SJS.* Stevens–Johnson syndrome was reported in two patients (0.7%) in the T12/PR24 group.

In one patient (female, 50 years old), a grade 1 rash was observed 8 days after the initiation of drug administration and it resolved 4 days later. On day 35, another rash appeared, and on day 44, when the patient was hospitalized, erythema affecting approximately 30% of the body surface with erosion of the intraoral mucous membrane was observed. The maximum body temperature was 39.3°C. All antiviral drugs were discontinued, and the patient was treated with systemic corticosteroids. Erythema progressed till 4 days after drug discontinuation (Fig. 2d) and resolved after 7 weeks.

In the other patient (female, 47 years old), "EM major" was diagnosed by a dermatologist but was integrated as SJS according to the clinical trial's coding rule. A localized rash was observed on day 3. Pyrexia up to 38.5°C and worsening of the rash were observed on day 25, and the patient was hospitalized due to erosion appearing on the lips and the mucous membrane of the pharynx. All study drugs were discontinued, and the patient recovered with the use of systemic corticosteroids 8 weeks after discontinuation.

*DRESS/DIHS.* In one patient (0.4%), a 60-year-old female, in the T12/PR24 group, DRESS/DIHS developed. Grade 1 rash was observed on day 7. On day 44, new redness appeared on the waist and legs, and on day 64 erythema worsened with persistent high fever; all study drugs were subsequently discontinued. The patient developed erythema with target lesions (Fig. 2e) and erosion of the oral mucous membranes on day 66. After discontinuation of the drugs, pyrexia over 38°C (maximum, 39.7°C) was observed. On the basis of symptom progression and laboratory test findings (increased white blood cell count [46300/μL], appearance of atypical lymphocytes [23.3%], raised eosinophil count [45.7%], high ferritin level, high lactate dehydrogenase level, lymphadenopathy and reactivation of human herpesvirus six based on a rise in titer from 1:160 [29 days after onset] to 1:2560 [57 days after onset]), a diagnosis of DRESS/DIHS was made. On administration of systemic corticosteroids, the patient recovered 11 weeks after discontinuation.

*EM with mucous membrane lesions.* Serious EM with mucous membrane lesions was observed in one patient (0.4%), a 58-year-old female, in the T12/PR24 group. On day 14, the patient developed a grade 1 rash, which resolved

**Table 5.** Characteristics of dermatological adverse reactions

| | T12/PR24 | PR48 |
|---|---|---|
| No. of dermatological adverse reactions | 355 | 102 |
| Distribution area | | |
| ≤50% of body surface, localized | 237 (66.8%) | 87 (85.3%) |
| ≤50% of body surface, multiple or diffuse | 99 (27.9%) | 15 (14.7%) |
| >50% of the body surface | 19 (5.4%) | 0 (0.0%) |
| Features of lesions[†] | | |
| Erythema without target lesions | 296 (83.4%) | 89 (87.3%) |
| Erythema with target lesions | 8 (2.3%) | 0 (0.0%) |
| Purpura | 22 (6.2%) | 0 (0.0%) |
| Vesicles or bullae | 7 (2.0%) | 2 (2.0%) |
| Pustule | 7 (2.0%) | 0 (0.0%) |
| Ulceration or erosion of mucous membranes | 4 (1.1%) | 1 (1.0%) |
| Epidermal detachment | 2 (0.6%) | 1 (1.0%) |
| Other[‡] | 85 (23.9%) | 22 (21.6%) |
| Pruritus | | |
| Yes | 293 (82.5%) | 84 (82.4%) |
| No | 62 (17.5%) | 18 (17.6%) |
| Systemic symptoms | | |
| No | 330 (93.0%) | 102 (100.0%) |
| Yes[†] | 25 (7.0%) | 0 (0.0%) |
| Pyrexia | 23 (6.5%) | 0 (0.0%) |
| Angioedema | 2 (0.6%) | 0 (0.0%) |
| Lymphadenopathy | 6 (1.7%) | 0 (0.0%) |
| Other[§] | 2 (0.6%) | 0 (0.0%) |

[†]Multiple features may co-exist.
[‡]For example, redness and papules.
[§]Inflammation of lips and dry skin. T12/PR24: telaprevir, pegylated interferon (PEG-IFN)-α-2b and ribavirin (RBV) for 12 weeks followed by administration of PEG-IFN-α-2b and RBV for 12 weeks. PR48: PEG-IFN-α-2b and RBV for 48 weeks.

4 days later. The drug rash developed again on day 34, followed by pyrexia and enlargement of the rash on day 39, resulting in hospitalization of the patient. Pyrexia of up to 39.0°C was observed. Despite treatment with oral corticosteroids at 20 mg/day, the rash worsened and intraoral redness was observed 9 days after hospitalization; thus, all study drugs were discontinued. The patient's condition was diagnosed as EM, the dose of oral corticosteroids was increased to 60 mg/day and the patient recovered 11 weeks after drug discontinuation.

### Treatment of dermatological adverse reactions

Figure 3 shows the medical treatments used for the dermatological events that developed during the antiviral administration period in the T12/PR24 group (347 events) and in the PR48 group (100 events). The main medical agents were topical corticosteroids and oral antihistamines in both groups. The strength of topical corticosteroids most often used were either class III (potent) or class IV (very potent).

Among the 347 dermatological events in the T12/PR24 group, 324 events did not require discontinuation of any of the study drugs. Approximately 21% events resolved without treatment. Events mainly treated with topical corticosteroids comprised 44.4%, and those treated with topical corticosteroids and oral antihistamines made up 17.9%. The frequency of treatment with systemic corticosteroids was only 4.6%. On the basis of these results, we considered almost all dermatological adverse reactions to be manageable with topical corticosteroids and oral antihistamines.

In the T12/PR24 group, 23 dermatological events required drug discontinuation. For these events, systemic corticosteroids were used more frequently (30.4%) in addition to topical corticosteroids and oral antihistamines.

### Period of resolution

In the T12/PR24 group, 61.4% of the dermatological events resolved during the treatment period: 38.6% during the telaprevir treatment period and 22.8% during the PEG-IFN-α-2b and RBV treatment period. The proportion of dermatological events that resolved after completion or discontinuation of all the study drugs was 37.2% (Fig. 4).

In the PR48 group, 59.0% (59/100 events) of the dermatological events resolved by the end of the treatment period.

## DISCUSSION

Compared to the dermatological adverse reactions associated with PEG-IFN and RBV therapy in phase III clinical trials, those caused by the telaprevir-based triple therapy: (i) developed early; (ii) affected large areas of the body; and (iii) were accompanied in several cases by severe rashes, mucous membrane lesions, epidermal detachment or systemic symptoms associated with high pyrexia or lymphadenopathy, including SJS and DRESS/DIHS. In addition, target lesions, purpura, and pustule were reported only in the triple therapy.

The dermatological adverse reactions associated with triple therapy were mostly of grade 1 or grade 2, and they were pruritic papuloerythematous lesions similar to the ones associated with PEG-IFN and RBV therapy. These adverse reactions could be managed with topical corticosteroids and oral antihistamines, and the associated discontinuation rate was low. Over 60% of the events resolved during the treatment phase. In view of these results and the therapeutic effect on CHC, early discontinuation of antiviral therapy due to mild or moderate dermatological adverse reactions should be avoided.

On the other hand, we cannot ignore the occurrences of SJS and DRESS/DIHS in the clinical trials. Aggravation of these serious events may lead to death and sequelae such as blindness. Therefore, on observation of clinical signs and symptoms that may lead to these serious conditions, all drugs must be discontinued immediately and appropriate treatment for these reactions should be administrated as soon as possible.

The criteria for drug discontinuation and treatment for dermatological reactions based on severity are illustrated in the algorithm in Figure 5. In addition to discontinuation of all drugs in cases of serious adverse reactions, a basic principle is to discontinue telaprevir in cases where the affected area exceeds 50% of the body surface (corresponding to grade 3) or where symptoms continued to worsen, notwithstanding a

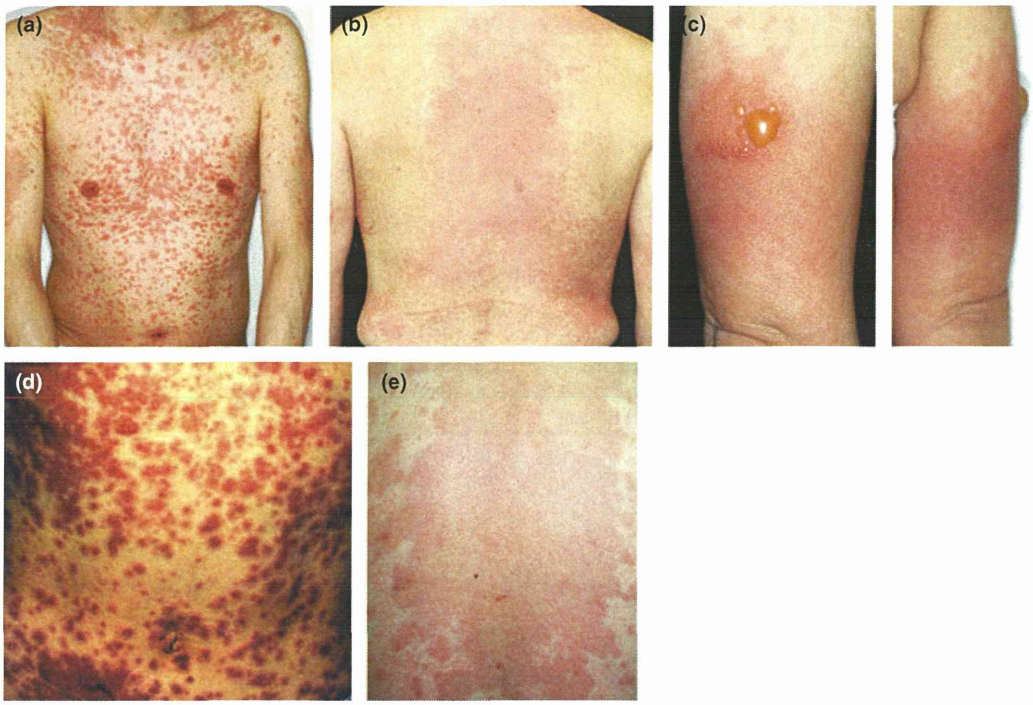


**Figure 2.** Examples of dermatological adverse reactions in the T12/PR24 group. (a,b) Grade 2 rashes, (c) injection site reaction, (d) Stevens–Johnson syndrome case, and (e) drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome case in the T12/PR24 group. T12/PR24: telaprevir, pegylated interferon (PEG-IFN)-α-2b and ribavirin (RBV) for 12 weeks followed by administration of PEG-IFN-α-2b and RBV for 12 weeks.

grade 2 reaction. If symptoms worsen during the remaining period when only PEG-IFN and RBV are administrated, discontinuation of these two drugs is likewise recommended. Regarding the antiviral effects observed in the patients who discontinued any of the study drugs due to dermatological reactions, seven of the 11 patients who discontinued only telaprevir achieved SVR, and eight of the 12 patients who discontinued all study drugs achieved SVR.

Grade 1 and grade 2 reactions could be managed with topical corticosteroids and oral antihistamines. These medications were used for grade 3 reactions in a similar manner without any problems, although in some cases, such as SJS, DRESS/DIHS and other severe reactions, the systemic use of corticosteroids was required. In some patients, who continued to receive the study drugs concomitant with systemic corticosteroids, further aggravation of dermatological reactions was noted when the dose of corticosteroids was reduced or when their administration was discontinued. There is a possibility that use of systemic corticosteroids masked serious problems and the tapering of steroids aggravated reactions; hence, telaprevir discontinuation should be taken into consideration when systemic use of corticosteroids is required.

The cases of SJS, DRESS/DIHS and serious EM were accompanied by pyrexia of 38–39°C, erosions affecting the mucous membranes or conjunctival lesions. It is, therefore, important to detect early signs of serious diseases, and empowering patients to identify such symptoms by informing them about the features associated with these diseases, like pyrexia and mucous membrane erosion, will enable early detection.

The mechanism of telaprevir-related dermatological adverse reactions remains unknown. Because dermatological adverse reactions were observed even in the study on telaprevir monotherapy, it can be said that telaprevir per se is a factor for dermatological reactions. The dermatological adverse reactions in telaprevir monotherapy were, however, relatively milder than those in the telaprevir-based triple therapy. Therefore, it can be suggested that the concomitant administration of telaprevir with PEG-IFN and RBV led to an additive or synergistic effect on the adverse reactions and sometimes resulted in serious cases. In addition, in the triple therapy, the dermatological adverse reactions occurred within 1 week of administration in approximately half of the cases. As the onset time of these reactions was earlier than that of the usual drug rash (i.e. drug allergy), the mechanism underlying these early occurring reactions may be different from that of allergy in general.

In the US/EU clinical trials, pharmacokinetics, human leukocyte antigen genes and multidrug resistance 1 gene were examined to elucidate risk factor(s) for telaprevir-related dermatitis. However, no specific relation was noted between these factors and the development or severity of dermatological reactions.[15]

The incidence of skin adverse reactions (rash-related events) in phase II or phase III studies performed in the US/EU was 55–56% in the triple therapy group and 33–34% in the PEG-

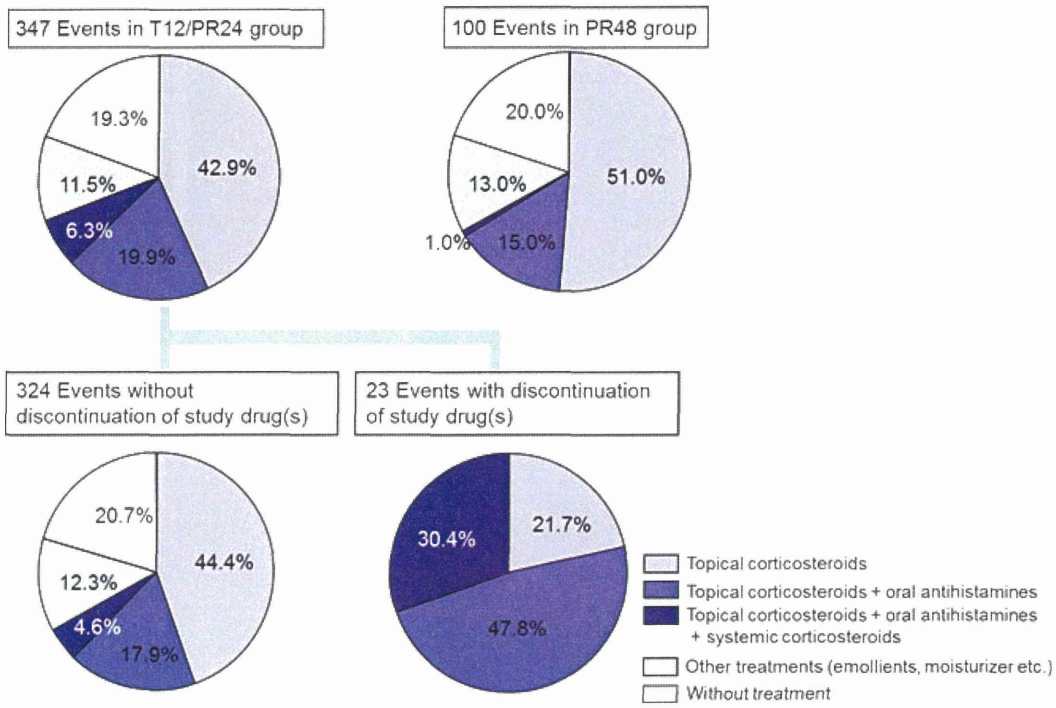


**Figure 3.** Treatment of dermatological adverse reactions. The medical agents shown were used for 347 events that developed during the antiviral administration period in the T12/PR24 group (324 events without drug discontinuation and 23 events with drug discontinuation) and for 100 events in the PR48 group. Treatment is classified according to the use of topical corticosteroids, oral antihistamines, systemic corticosteroids and others agents. T12/PR24: telaprevir, pegylated interferon (PEG-IFN)-α-2b and ribavirin (RBV) for 12 weeks followed by administration of PEG-IFN-α-2b and RBV for 12 weeks. PR48: PEG-IFN-α-2b and RBV for 48 weeks.

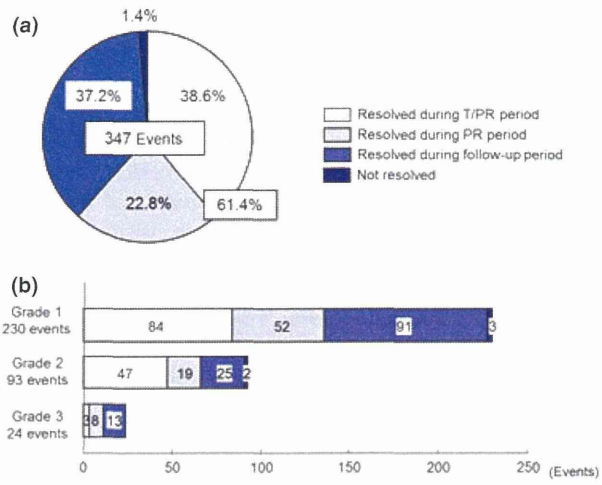


**Figure 4.** Period of resolution in the T12/PR24 group. (a) Of the 347 dermatological reactions that occurred during the treatment phase in the T12/PR24 group, approximately 61% resolved by the end of dosing. (b) The period of resolution of each dermatological adverse reaction is shown by grade. T12/PR24: telaprevir, pegylated interferon (PEG-IFN)-α-2b and ribavirin (RBV) for 12 weeks followed by administration of PEG-IFN-α-2b and RBV for 12 weeks.

IFN and RBV therapy group; these rates are lower than those observed in Japanese patients (74.9% and 58.7%, respectively). In addition, 12–14% and 4–5% of the subjects developed grade 2 and grade 3 reactions, respectively, in the US/EU studies, while in Japan, the respective percentages were 33.7% and 9.0%.[15,16] Although the early onset and symptom features were common between the US/EU and Japan studies, there may be differences in the rate of symptom development and in severity worsening tendency. However, a stringent comparison is difficult between the US/EU and Japan studies, because there may be differences in the interpretation of severity classification systems including definition of the involved area or in the data collection and aggregation methods between these studies.

In conclusion, the telaprevir-based triple therapy often caused dermatological adverse reactions. Most reactions were of grade 1 or grade 2 and could be managed without discontinuation of the study drugs. Some patients, however, developed serious reactions such as SJS and DRESS/DIHS. What is most important is to consider the balance between the risk and benefit for an individual patient, and address individual reactions appropriately. For appropriate treatments of individual dermatological adverse reactions, the judgment of discontinuation of antiviral drugs and treatment based on the severity are extremely important in this triple therapy.

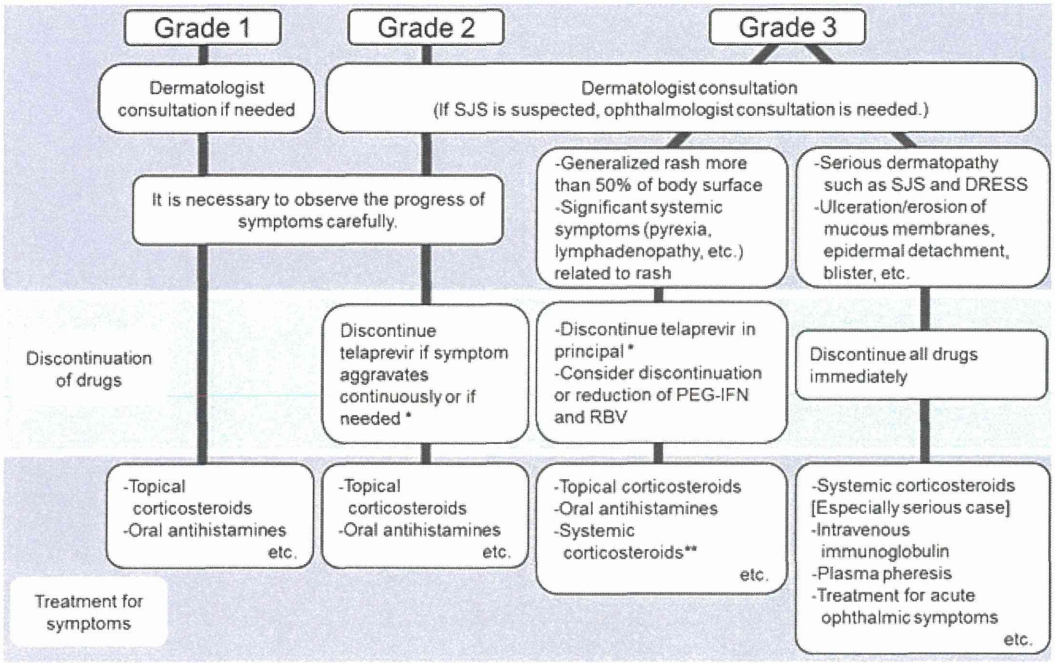


**Figure 5.** Algorithm for the discontinuation of drugs and treatment for dermatological adverse reactions.

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# Letter to the Editor

## HLA-B*58:01 strongly associates with allopurinol-induced adverse drug reactions in a Japanese sample population

*To the Editor,*

Allopurinol, an inhibitor of xanthine oxidase, is widely used for the treatment of hyperuricemia associated with chronic gout, acute uric acid nephropathy, recurrent uric acid stone formation, certain enzyme/blood disorders, and cancer chemotherapy. It has been shown that severe cutaneous adverse drug reactions (ADRs) caused by allopurinol were strongly associated with HLA-B*58:01 in a Han Chinese sample population [1]. Odds ratio (OR) for the association of HLA-B*58:01 with allopurinol-induced severe cutaneous ADR in this population was 580.3 and 95% CI was 34.4–9780.9. Although the relationship between HLA-B*58:01 and allopurinol-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) has subsequently been studied in European and Japanese patients, the association was much weaker than that reported in Han Chinese patients [2,3]. The association study in Japanese patients was examined in only a limited number of allopurinol-induced ADR cases. We therefore conducted a case-controlled study to determine HLA types associated with allopurinol-induced ADR in a Japanese sample population.

All patients were recruited from Shimane University Hospital between 2010 and 2012. These included 7 patients with allopurinol-induced ADR (3 patients with SJS and 4 patients with erythema exudativum multiforme (EEM)) and 25 patients who had been receiving allopurinol for more than 3 months without drug eruption. Diagnoses of SJS were made according to the diagnostic criteria established by Roujeau [4]. Allopurinol-induced ADR was diagnosed using medical histories, indicating that symptoms occurred within 3 months of starting allopurinol administration, and the symptoms resolved upon the withdrawal of allopurinol. If the patients were given other drugs, in addition to allopurinol, 3 months prior to the appearance of symptoms, a drug-induced lymphocyte stimulation test and a patch test were performed with allopurinol/oxypurinol. Allopurinol-induced ADRs were diagnosed by the single medication of allopurinol in 4 of the 7 patients (No. 1, 3, 4, 7), by the positive allopurinol-induced lymphocyte stimulation test in 2 of the 7 patients (No. 2, 6), and by the positive patch test with allopurinol in the patient No. 5. The indication for which drug had been prescribed was the level of hyperuricemia detected in all the patients. All patients were interviewed by investigators regarding the histories of their biological parents and grandparents, and were confirmed as being ethnically Japanese. This study was approved by the ethics committee of Shimane University Faculty of Medicine (approval no. 221).

Low-resolution HLA typing with DNA extracted from peripheral blood was performed using the reverse sequence-specific oligonucleotide with polymerase chain reaction (PCR-rSSO) method [5]. High-resolution HLA-B genotyping was determined using the polymerase chain reaction-sequence based typing (PCR-SBT) method [5]. Statistical analysis of the differences in each allele frequency among patients with ADR and control subjects was performed by Fisher's exact test. The strength of association was estimated by calculating the OR. The OR was determined using Haldane's modification, which adds 0.5 to all cells to accommodate

**Table 1**
HLA DNA typing of allopurinol-induced ADR patients.

| No. | Age/sex | Type of ADR | Low-resolution HLA DNA typing | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1 | 88/F | SJS | A2 | A33 | B61 | B58 | DR9 | DR9 |
| 2 | 72/M | SJS | A2 | A24 | B59 | B58 | DR4 | DR13 |
| 3 | 70/M | SJS ocular type[a] | A24 | A26 | B37 | B55 | DR8 | DR14 |
| 4 | 78/M | EEM minor | A2 | A24 | B52 | B58 | DR4 | DR13 |
| 5 | 75/F | EEM minor | A2 | A26 | B13 | B62 | DR4 | DR12 |
| 6 | 65/M | EEM minor | A2 | A26 | B35 | B35 | DR8 | DR15 |
| 7 | 67/M | EEM minor | A24 | A33 | B58 | B58 | DR13 | DR15 |

[a] SJS ocular type: SJS without eruption but corneal erosion with pseudomembrane formation.

possible zero counts. We used Statistical SPSS statistical package, version 20.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. All reported *P*-values were two-sided. Values of $P < 0.05$ were considered to be statistically significant.

Low resolution HLA DNA typing of allopurinol-induced ADR patients were shown in Table 1. Of the seven patients with allopurinol-induced ADR, two SJS, and two EEM patients had HLA-B58, whereas no allopurinol-tolerated patients had HLA-B58. The high resolution HLA DNA typing revealed that all patients with HLA-B58 were HLA-B*58:01. Comparing the frequency of each type between the allopurinol-induced ADR patients and the allopurinol-tolerant patients, the OR of HLA-B*58:01 was significantly high in the allopurinol-induced ADR patients, as shown in Table 2. The OR of HLA-B*58:01 was the highest and reached to 65.6. The 95% CI was 2.9 to 1497.0. When compared, the OR was 26.0 and the 95% CI was 2.0 to 336.1 (table not shown) between the 4 EEM minor patients and the allopurinol-tolerant patients.

In this study we confirmed the association between HLA-B*58:01 and allopurinol-induced ADR in a Japanese sample population and established the OR of 65.6. This is compatible with the results reported by Tohkin et al. [3], and meta-analysis reported by Somkrua et al. that the risk of developing SJS/TEN among those allopurinol users with HLA-B*5801 was significantly increased by 34–348 times compared to those without the gene [6]. In addition, we confirmed an association between HLA-B*58:01 and allopurinol-induced EEM minor, which is mild type of ADR. Thus indicating that HLA-B*58:01 is associated with the pathogenesis of allopurinol-induced ADR, regardless of the type of severity of ADR. The present study support the assertion that HLA-B*58:01 is a susceptibility gene for allopurinol-induced ADR regardless of populations, although some difference in the

**Table 2**
Statistical analysis in HLA typing of allopurinol-induced ADR patients and allopurinol-tolerant patients.

| HLA low-resolution | Allopurinol-tolerant patients ($n=25$) | Allopurinol-induced ADR patients ($n=7$) | OR[b] | 95% CI | *P*-value[a] | HLA gene frequencies in Japanese ($n=371$) |
|---|---|---|---|---|---|---|
| A2 | 11 | 5 | 2.8 | 0.5–14.9 | 0.394 | 0.222 |
| A11 | 5 | 0 | 0.2 | 0.0–5.1 | 0.560 | 0.083 |
| A24 | 12 | 4 | 1.4 | 0.3–6.8 | 1.000 | 0.380 |
| A26 | 9 | 3 | 1.4 | 0.3–6.8 | 1.000 | 0.130 |
| A31 | 2 | 0 | 0.6 | 0.0–14.6 | 1.000 | 0.071 |
| A33 | 5 | 2 | 1.7 | 0.3–9.9 | 0.632 | 0.097 |
| B7 | 1 | 0 | 1.1 | 0.0–29.6 | 1.000 | 0.065 |
| B13 | 0 | 1 | 11.8 | 0.4–323.7 | 0.219 | 0.018 |
| B35 | 8 | 1 | 0.5 | 0.0–3.4 | 0.640 | 0.076 |
| B37 | 0 | 1 | 11.8 | 0.4–323.7 | 0.219 | 0.013 |
| B39 | 1 | 0 | 1.1 | 0.0–29.6 | 1.000 | 0.050 |
| B44 | 5 | 0 | 0.2 | 0.0–5.1 | 0.560 | 0.075 |
| B46 | 1 | 0 | 1.1 | 0.0–29.6 | 1.000 | 0.039 |
| B48 | 1 | 0 | 1.1 | 0.0–29.6 | 1.000 | 0.037 |
| B51 | 2 | 0 | 0.6 | 0.0–14.5 | 1.000 | 0.101 |
| B52 | 3 | 1 | 1.5 | 0.2–12.1 | 1.000 | ND[c] |
| B54 | 6 | 0 | 0.2 | 0.0–4.0 | 0.296 | 0.036 |
| B55 | 1 | 1 | 3.8 | 0.3–42.5 | 0.395 | 0.022 |
| B56 | 1 | 0 | 1.1 | 0.0–29.6 | 1.000 | 0.006 |
| B58 | 0 | 4 | 65.6 | 2.9–1497.0 | $9.733 \times 10^{-4}$ | 0.004 |
| B59 | 1 | 1 | 3.8 | 0.3–42.5 | 0.395 | 0.018 |
| B60 | 2 | 0 | 0.6 | 0.0–14.6 | 1.000 | ND[c] |
| B61 | 5 | 1 | 0.9 | 0.1–6.4 | 1.000 | ND[c] |
| B62 | 3 | 1 | 1.5 | 0.2–12.1 | 1.000 | ND[c] |
| B67 | 3 | 0 | 0.4 | 0.0–9.3 | 1.000 | 0.003 |
| B71 | 2 | 0 | 0.6 | 0.0–14.6 | 1.000 | ND[c] |
| B75 | 1 | 0 | 1.1 | 0.0–29.6 | 1.000 | ND[c] |
| DR1 | 2 | 0 | 0.6 | 0.0–14.6 | 1.000 | 0.065 |
| DR4 | 17 | 3 | 0.4 | 0.0–1.9 | 0.379 | 0.225 |
| DR8 | 3 | 2 | 2.9 | 0.5–19.0 | 0.296 | 0.121 |
| DR9 | 7 | 1 | 0.6 | 0.0–4.1 | 0.646 | 0.012 |
| DR12 | 1 | 1 | 3.8 | 0.3–42.5 | 0.395 | 0.051 |
| DR13 | 5 | 3 | 2.9 | 0.5–15.6 | 0.327 | 0.084 |
| DR14 | 4 | 1 | 1.1 | 0.1–8.5 | 1.000 | 0.090 |
| DR15 | 5 | 2 | 1.7 | 0.3–9.9 | 0.632 | 0.185 |
| DR16 | 3 | 0 | 0.4 | 0.0–9.3 | 1.000 | 0.009 |

[a] *P*-value: Fisher's exact test.
[b] OR: determined using Haldone's modification, which adds 0.5 to all cells to accommodate possible zero counts.
[c] ND: no data.

ORs are seen among ethnic populations. This is in contrast to carbamazepine-induced ADR with which HLA types associated vary among ethnic populations [5]. A strong association between HLA-B*1502 and carbamazepine-induced ADRs was found in Han Chinese, Thai, Malaysian and Indian sample populations [5,7]. However, recent studies have revealed an association between carbamazepine-induced ADRs and HLA-A*31:01 in Caucasian and Japanese sample populations [5]. These findings indicate that severe cutaneous ADRs induced by allopurinol as well as carbamazepine could be prevented if such genetic information would be known a *priori*. In fact, cost-effectiveness of HLA-B*1502 allele screening before prescription of carbamazepine has recently been reported [8]. Thus the development of a simple and rapid genotyping methods for these susceptibility genes are desirable.

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