



## Role of Pharmacogenomics in Clinical Implementation of Co-trimoxazole-Induced Severe Cutaneous Adverse Reactions

Puriputt Akachaipaibul<sup>1</sup>, Patompong Satapornpong<sup>2,3</sup>

Faculty of Pharmacy, Srinakharinwirot University Ongkharak Campus, Nakhon Nayok, Thailand

<sup>2</sup> Excellence Pharmacogenomics and Precision Medicine Centre, College of Pharmacy, Rangsit University, Pathum Thani, Thailand

<sup>3</sup> Division of General Pharmacy Practice, Department of Pharmaceutical Care, College of Pharmacy, Rangsit University, Pathum Thani, Thailand

**\*Corresponding Author:**

**Patompong Satapornpong, Ph.D**

Excellence Pharmacogenomics and Precision Medicine Centre, College of Pharmacy, Rangsit University, Pathum Thani, Thailand, 12000

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### Abstract

Co-trimoxazole is an antibiotic composing of trimethoprim and sulfamethoxazole in which is commonly used to treat bacterial infection. However, co-trimoxazole, especially sulfonamides antibiotic can cause severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). The investigation between co-trimoxazole and severe cutaneous adverse reactions has shown that the cause is mainly associated genetic polymorphisms in human leukocyte antigen. Previous studies in Thai population, had shown that HLA-B\*15:02 [(odds ratio = 3.91, P=0.0037) and (OR = 6.00, P= 0.0074)], HLA-C\*06:02 (OR = 11, P=0.0131) and HLA-C\*08:01 [(OR = 3.53, P=0.0108) and (OR = 5.79, P= 0.0049)] alleles were significantly associated with CTX-induced SJS/TEN. Furthermore, HLA-B\*13:01 allele was significantly associated with CTX-induced DRESS (OR = 15.20, P= 7.2×10<sup>-5</sup>) in Thais whereas in Taiwan studies, HLA- B\*13:01 allele was significantly associated with CTX-induced DRESS (OR = 61, P=1.8×10<sup>-19</sup>). Additionally, HLA-B\*15:02(OR = 3.2, P= 0.017) and HLA-B\*38:02 (OR = 5.1, P= 8.9×10<sup>-4</sup>) alleles were significantly associated with CTX-induced SJS/TEN. Nevertheless, there was reported the association between HLA-B\*38:01 (OR = 4.3, P= 0.022) and HLA-B\*38:02 (OR = 76, P= 0.027) alleles and sulfamethoxazole-induced SJS-TEN in European patients. Thus, pharmacogenetics markers have influenced to clinical implementation of co-trimoxazole and avoid SCARs. The patients might be screening and compared the pharmacogenetics markers among their ethnicity before administering with co-trimoxazole.

**Keywords:** Co-trimoxazole, Human Leukocyte Antigen, Pharmacogenomics, Severe cutaneous adverse reactions

### INTRODUCTION

#### Co-trimoxazole

Co-trimoxazole is the combination of trimethoprim (TMP) and sulfamethoxazole (SMX). It has a wide range of uses against both gram-positive and gram-negative aerobic bacteria and prophylaxis of Pneumocystis jirovecii pneumonia (PJP) or Toxoplasma gondii encephalitis in HIV-positive

patients. (1, 2) The standard ratio of trimethoprim and sulfamethoxazole for effective Cotrimoxazole is 1 to 5 or 1 to 40, respectively. (3, 4) It can be administered through oral tablet, intramuscular injection and intravenous fluid. Therapeutic use of this medication is used often to treat or prevent most oral, ear, nose, throat and urinary bacterial infection or even

antimicrobial chemotherapy. Both trimethoprim and sulfamethoxazole can be administered alone to prevent bacterial infection by inhibiting bacterial folate metabolism. (2, 3, 4) Sulfamethoxazole inhibits the synthesis of dihydrofolic acid while trimethoprim is a competitive inhibitor of dihydrofolic in the folic pathway which both are able to inhibit the synthesis of tetrahydrofolic acid as described in Figure 1. Biosynthetic pathways in bacteria such as amino acid synthesis can be interrupted by the insufficient production of tetrahydrofolic acid which is a necessary component. However, it is proved to be more effective combined and reduce the chance of antibiotic resistance due to chromosomally mediated resistance and R-factor plasmids of mutated microbial. (4)

The absorption rate of co-trimoxazole (SMX and TMP) was approximately 85-90 % within 8 hours after oral administration. (5, 6, 7) After absorption, co-trimoxazole is distributed to all body organs including plasma, cerebrospinal fluid, aqueous humor, breast milk, prostatic and seminal material, vaginal fluid, placental, bile fluid, erythrocytes, bone, other tissue and organs. (8, 9) SMX is metabolized in the liver via acetylation, glucuronidation, N-hydroxylation and 5-hydroxylation. Approximately 50 % of co-trimoxazole is excreted in urine in the first 24 hours by renal function. (10) Several studies have found SMX-hydroxylamine is major cause of the drug hypersensitivity reactions. (11)

However, co-trimoxazole can lead to adverse drug reactions (ADR) consist of mild gastrointestinal symptoms (nausea, vomiting and diarrhea), hepatotoxicity, hematological reactions (anemia, agranulocytosis and pancytopenia), renal disorders, urticarial, erythema multiforme and severe cutaneous adverse reactions (SCARs: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) or (Lyell's syndrome)). (1, 2, 6, 9, 12, 13, 14) A particular study on CTX-induced SCARs shows that CTX-induced SJS/TEN is usually manifested between the  $20.14 \pm 20.33$  days after initiation of treatment and is clinically characterized by skin lesions and mucosal involvement. (1) Moreover, sign of SJS/TEN of HIV-positive patients may take longer delayed onset with a mean of  $24.93 \pm 21.38$  days which is about 2.5 times longer than HIV-negative patients at  $8.88 \pm 14.64$  days. Furthermore, in HIV-positive patients with *Pneumocystis jirovecii* pneumonia (PJP) who were

treated co-trimoxazole have a higher chance of hypersensitivity reaction between 10 to 25 times than HIV-negative patients. (15)

According to the data from the spontaneous reports during 1984-2016 by the Health Product and Vigilance Center of Thailand, co-trimoxazole is the 1st ranked culprit drug causing SJS and TEN and the 3rd ranked culprit drug who suffered from drug reaction with eosinophilia and systemic symptoms (DRESS) in Thailand ([http://thaihpvc.fda.moph.go.th/thaihvc/Public/News/uploads/hpvc\\_1\\_3\\_4\\_1007\\_18.pdf](http://thaihpvc.fda.moph.go.th/thaihvc/Public/News/uploads/hpvc_1_3_4_1007_18.pdf)) are shown in Figure 2 and 3.

#### Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) are potentially life-threatening conditions that cause by immune system inappropriately response to a drug. For instance, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP). (16, 17, 18) These symptoms involve inflammation on various parts of the body causing skin rash, skin lesion, skin detachment, fever, epidermal necrolysis or in the worst-case death can occur. (19)

#### Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN)

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered as type IVc hypersensitivity reaction in which are rare but life-threatening cutaneous adverse reactions. (20) SJS is characterized by acute onset and rapid progression of painful skin and mucous membranes lesions. The skin lesions are widespread and predominate on the trunk, with a tendency to become confluent, leading to a restricted detachment of epidermis on less than 10% of the body surface area (BSA). (21) Toxic epidermal necrolysis (TEN) is characterized by the same lesions as SJS but with the detachment of large epidermal on more than 30% of BSA and a frequently positive Nikolsky sign. (22) Epidermal detachment between 10% and 30% of BSA is classified as SJS/TEN-overlap (Table 1). The signs of SJS and TEN appear 1-3 weeks after initial exposure to the culprit drug. The mortality rate of SJS is generally below 5% and 30 to 50 % of TEN patients. (23) Particularly, mortality rates were markedly higher in a series of older patients. (24)

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug-induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS) or hypersensitivity syndrome (HSS) is considered as type IVb hypersensitivity reaction in which is defined by the triad of skin eruption, hematological involvement (eosinophilia or atypical lymphocytes), and internal organ involvement according to the RegiSCAR-Group Diagnosis Score. (25) DRESS has been estimated to occur in about 1 in 10,000 exposures to drugs such as AEDs and sulfonamides. (26) It typically begins 2 to 6 weeks after first drug exposure, later than most other skin reactions. (27) Especially eosinophilia is common and a characteristic feature of this reaction is the appearance of atypical lymphocytosis in the blood circulation. Rash and hepatitis may persist for several weeks after drug withdrawal and mortality rate about 10%. (28)

Acute generalized exanthematous pustulosis (AGEP)

Acute generalized exanthematous pustulosis (AGEP) is type IVd hypersensitivity reaction in which symptom is an extensive pustular eruption similar to pustular psoriasis, usually taking place as a drug reaction in patients without a history of psoriasis. (29) The mortality rate has been consistently reported in the medical literature as 5% and onset of reaction 1-2 days after drug exposure. (30) Proposed diagnosis criteria include acute pustular eruption, fever ( $\geq 38$  °C), neutrophilia with or without a mild eosinophilia, subcorneal or intraepidermal pustules on skin biopsy and spontaneous resolution in less than 15 days

Immunological responses of SCARs: HLA, drug and T lymphocyte

Immunopathogenesis of SCARs are associated with expression of specific HLA allele, T-lymphocyte, structure of drug and peptide molecules. (32, 33) Human Leukocyte Antigen (HLA), also known as major histocompatibility complex (MHC), is a complex protein on surface membrane of cells that responding for immune system. The encoder gene of HLA is found on the 6th chromosome. The HLA consist of HLA class I and HLA class II, these proteins bind and present peptide antigens to T cells. (34) HLA class I (MHC class I) molecules are expressed by most nucleated cells and generally serve to display peptides

that are derived from intracellular proteins to cytotoxic T cells (CD8+ T cells). The HLA class I molecule is a heterodimer containing the transmembrane  $\alpha$  domains and  $\beta$ 2-microglobulin. The  $\alpha$ 1 and  $\alpha$ 2 domains form the peptide binding pocket that can accommodate peptides 9–11 amino acids in length. (35, 36) The HLA class II (MHC class II) expression is antigen-presenting cells (APCs) such as dendritic cells, B-cells and monocytes and interact with helper T cells (CD4+ T cells). The HLA class II is a heterodimer composed of two polypeptide chains,  $\alpha$  and  $\beta$ . The peptide binding pocket is formed by  $\alpha$ 1 and  $\beta$ 1. (37, 38) The open-ended pocket can accommodate peptides of 12–25 amino acids in length. The HLA genes encoding the classical MHC proteins are located on chromosome 6, including HLA-A, HLA-B and HLA-C for HLA class I and HLA-DR, HLA-DQ and HLA-DP for HLA class II.

However, polymorphism of genetics can cause difference response to an antigen in each population. For example, studies in Asia suggests that HLA-B\*15:02 is strongly associated with carbamazepine (CBZ)-induced SJS/TEN in Han Chinese, Thais, Vietnamese, Malaysian and Indian. (39, 40, 41) Additionally, other studies support that HLA-A\*31:01 allele is associated CBZ-induced SJS/TEN, DRESS and MPE in European, Japanese, Taiwan Han Chinese and Korean. Consequently, the distribution of HLA-B\*15:02 and HLA-A\*31:01 alleles are a specific of ethnicity which can lead to SCARs depending on presence of the alleles in certain ethnicity. (42, 43)

Pharmacogenomics of co-trimoxazole-induced SCARs

Co-trimoxazole (sulfonamide and trimethoprim) is sulfonamides antibiotic and the most common culprit drug for SJS-TEN in many countries and Thailand. (1,44) The strongly associated between HLA and CTX-induced SCARs in many studies. According to study in Thailand, patients who were administered with co-trimoxazole with HLA-B\*15:02 (odds ratio [OR] = 3.91 [95% confidence interval [CI]: 1.42-10.92], P=0.0037), HLA-C\*06:02 (OR = 11.84 [95% CI: 1.24- 566.04], P=0.0131) and HLA-C\*08:01 (OR = 3.53 [95% CI: 1.21-10.40], P=0.0108) alleles were significantly associated with SJS/TEN. (1) Patients with these alleles have about 3 to 11 times higher risks to get CTX-induced SCARs compared with those who did not carry these alleles. (1) Moreover, the HLA-

B\*15:02 and HLA-C\*08:01 alleles were significantly associated with CTX-induced SJS/TEN in Thai population (OR = 6.00 [95% CI: 1.72 - 20.88], P= 0.0074) and (OR = 5.79 [95% CI: 1.79 - 18.70], P= 0.0049), respectively. (45) Interestingly, pharmacogenetics marker shows that HLA-B\*13:01 allele was statistical association with CTX-induced DRESS (OR = 15.20 [95% CI: 3.68 - 62.83], P=  $7.2 \times 10^{-5}$ ) as shown in Table 2. (45) In further studies should be considered the association of this HLA alleles and CTX-induced DRESS in other population.

From whole genome sequencing study, there was found the association between CTX-induced DRESS and HLA-B\*13:01 allele with P= $1.8 \times 10^{-19}$  and OR = 61 (95% CI = 21.5 - 175) in Taiwanese. (46) Additionally, HLA-B\*38:02 allele was significantly associated with CTX-induced SJS/TEN in Taiwanese (OR = 5.1 [95% CI: 2.0-13.5], P=  $8.9 \times 10^{-4}$ ) compared with another study, there was reported the association between HLA-B\*38:01 (OR = 4.3 [95% CI: 1.4 - 12.7], P= 0.022) and HLA-B\*38:02 (OR = 76 [95% CI: 4.6 -1250], P= 0.027) and sulfamethoxazole-induced SJS-TEN in European population. (47)

Additionally, there were studies the drug metabolism enzymes of CTX-induced SCARs in Caucasians. The CTX-induced SCARs with HIV infection group carried CYP2C9\*2 variant and CYP2C9\*3 variants along with controls group. There was found in 12 % (CYP2C9\*2) and 8% (CYP2C9\*3) of the HIV positive patients with CTX-induced SCARs and 13 % (CYP2C9\*2) and 5% (CYP2C9\*3) of the healthy controls. CTX-induced SCARs with HIV positive group were not significantly associated with CYP2C9\*2 and \*3 variants (p-value = 1.0 and 0.4, respectively) (48)

#### Conclusions and Future Directions

Pharmacogenetics markers have influenced to clinical implementation of co-trimoxazole. Patients with specific pharmacogenetics markers can have different response to culprit drugs. In the review study we found the CTX-induced SCARs strongly associated with pharmacogenetics markers and there were present in Thai population should be checked for the presence of HLA-B\*15:02, HLA-C\*06:02, HLA-C\*08:01 and HLA-B\*13:01 alleles before prescribing co-trimoxazole. Similarly, in Taiwan region, people should be screened for HLA-B\*13:01. Contrariwise, reported incident markers were HLA-B\*38:01 and

HLA-B\*38:02 for sulfamethoxazole-induced SJS-TEN in European. Therefore, patients must be checked for specific markers among their ethnicity before administering with co-trimoxazole to prevent SCARs. There is insufficient research in pharmacogenomics and co-trimoxazole-induced SCARs in some continent such as Africans and Americans in screening potential markers which could be ethnic specific gene that should be looked before administrating CTX. Future Directions, this study need more further research and screening tests.

#### Conflicts of Interest

The authors have no 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.

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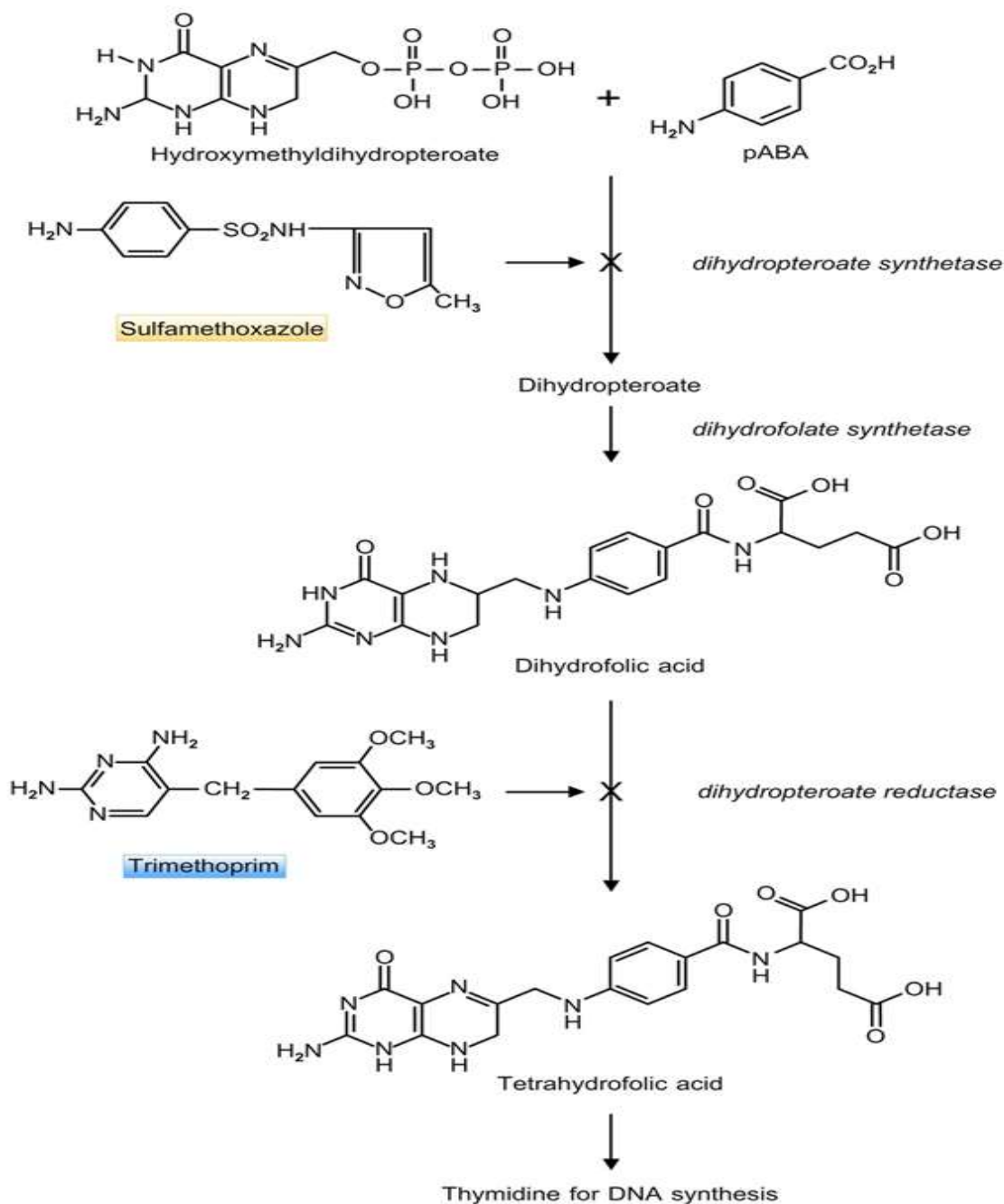
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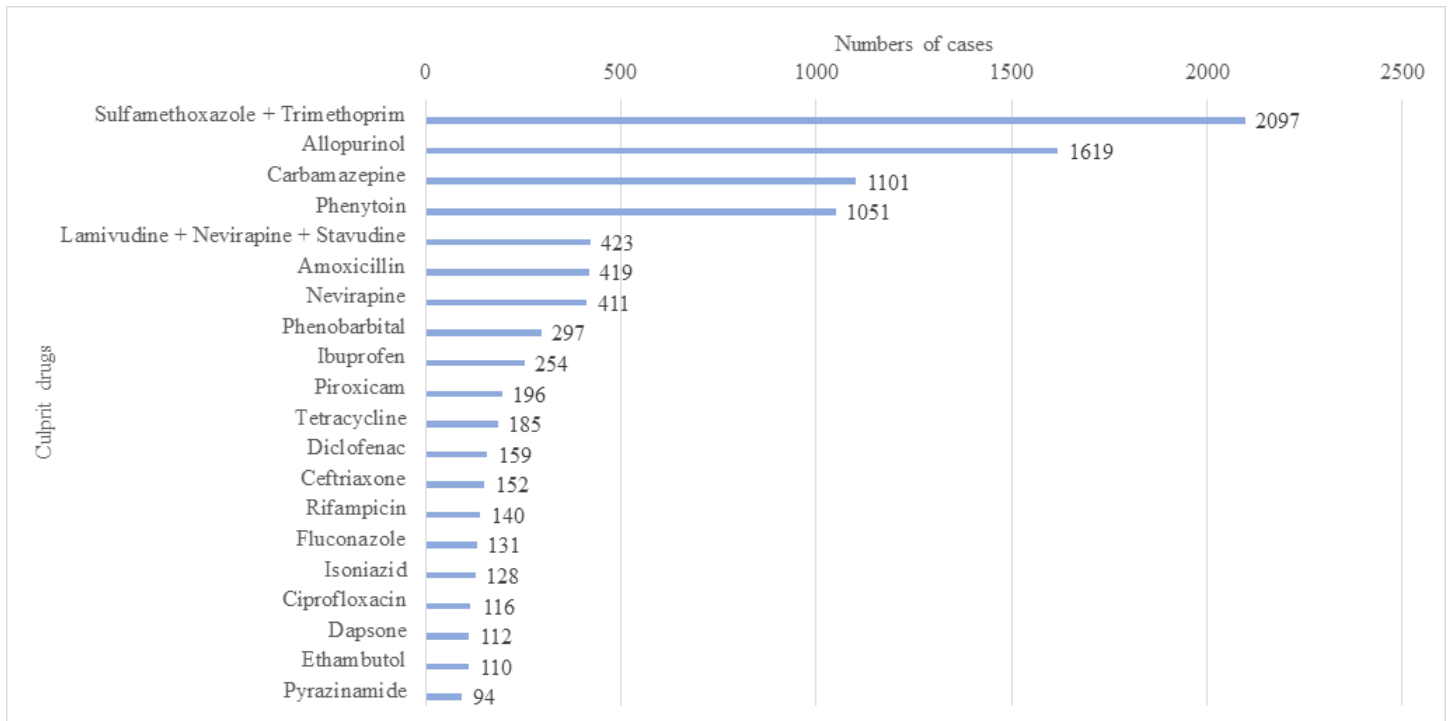
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**Figure 2. Number of Steven-Johnson syndrome and Toxic epidermal necrolysis (SJS-TEN) cases in Thailand between 1984-2016.**



**Figure 3. Number of Drug reaction with eosinophilia and systemic symptoms (DRESS) cases in Thailand between 1984-2016.**

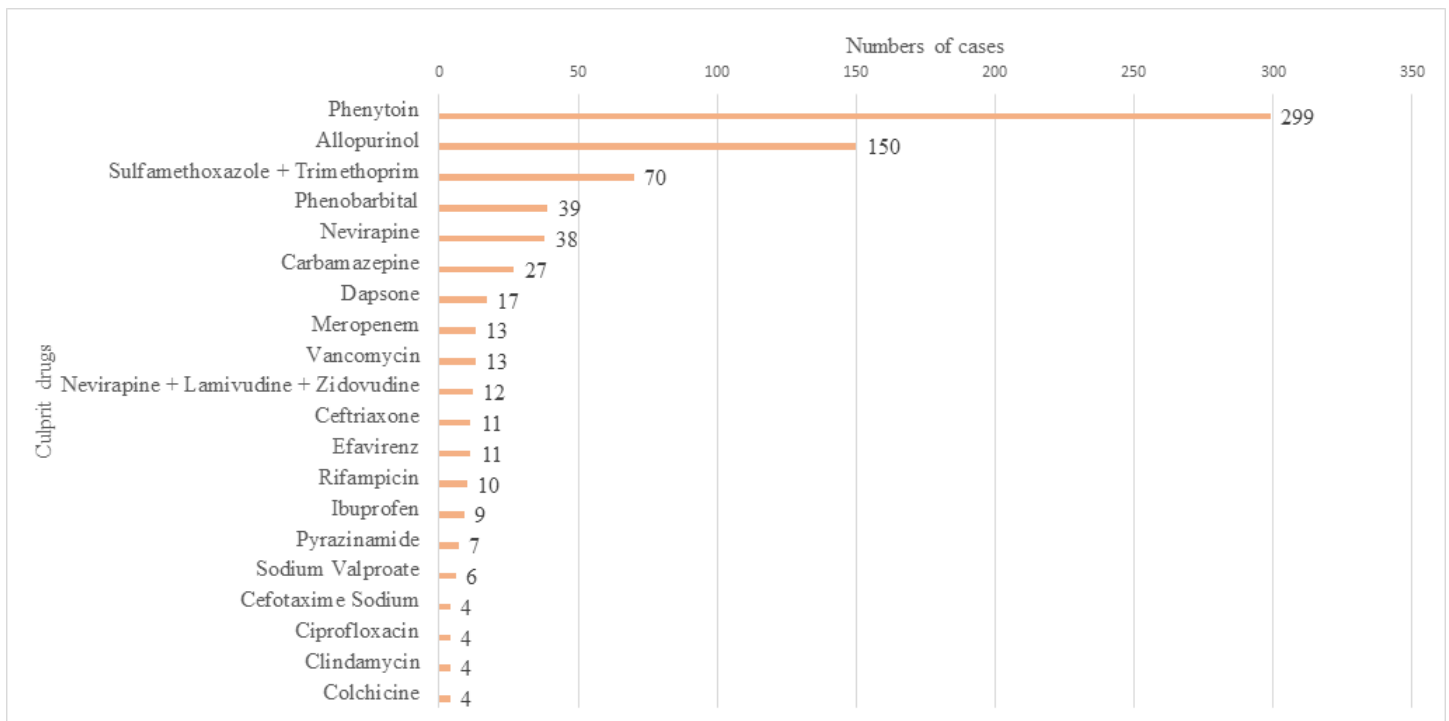




Table 1. Classification of Severe cutaneous adverse reactions (SCARs)

| SCARs           | Type of hypersensitivity | Delayed onset after drug exposure | Clinical characteristics   | Mortality rate (%) | Reference      |
|-----------------|--------------------------|-----------------------------------|--|--------------------|----------------|
| SJS             | IVc                      | 4 to 28 days                      | <ul style="list-style-type: none"> <li>- dusky red lesions</li> <li>- flat atypical targets</li> <li>- skin detachment: less than 10 % of BSA</li> <li>- distribution: isolated lesions confluence (+) on face and trunk</li> </ul>  | 1-5                | 19,22,23       |
| SJS-TEN Overlap | IVc                      | 4 to 28 days                      | <ul style="list-style-type: none"> <li>- dusky red lesions</li> <li>- flat atypical targets</li> <li>- skin detachment: between 10 to 30% of BSA</li> <li>- distribution: isolated lesions confluence (++) on face and trunk</li> </ul>  | 5-25               | 19,22,23       |
| TEN             | IVc                      | 4 to 28 days                      | <ul style="list-style-type: none"> <li>- poorly delineated erythematous plaques</li> <li>- epidermal detachment</li> <li>- dusky red lesions flat atypical targets, skin detachment: more than 30 % of BSA</li> <li>- Distribution: isolated lesions (rare) confluence (+++) on face, trunk and elsewhere</li> </ul> | 25-35              | 19,22,23       |
| DRESS           | IVb                      | 2 to 6 weeks                      | <ul style="list-style-type: none"> <li>- triad of skin eruption</li> <li>- atypical lymphocytosis</li> <li>- eosinophilia</li> <li>- internal organ involvement</li> </ul>   | 10                 | 19, 25, 26, 27 |
| AGEP            | IVd                      | 1 to 2 days                       | <ul style="list-style-type: none"> <li>- Extensive pustular eruption similar to pustular psoriasis</li> <li>- Acute rash with pinhead-sized pustules on an erythematous edematous base</li> <li>- fever (<math>\geq 38</math> °C)</li> <li>- Neutrophilia</li> <li>- Leukocytosis</li> </ul>                         | 5                  | 19, 29,30,31   |

Steven-Johnson syndromes; SJS, Toxic epidermal necrolysis; TEN, Drug reaction with eosinophilia and systemic symptoms; DRESS, Acute generalized exanthematous pustulosis; AGEP, Body surface area; BSA, hypersensitivity type 4b; IVb, hypersensitivity type 4c; IVc, hypersensitivity type 4d; IVd

**Table 2. Association between HLA allele and co-trimoxazole-induced SCARs (SJS-TEN and DRESS)**

| HLA markers | Culprit drug | Ethnicity | SCARs type | Case n/total (%) | Tolerant Control n/total (%) | P-value               | OR (95% CI)           | Reference |
|-------------|--------------|-----------|------------|------------------|------------------------------|-----------------------|-----------------------|-----------|
| HLA-B*13:01 | CTX          | Taiwanese | DRESS      | 35/41 (85.4)     | 12/138 (8.7)                 | 1.8×10 <sup>-19</sup> | 61 (21.5 - 175)       | 45        |
|             |              | Thai      |            | 9/12 (75.00)     | 15/91 (16.48)                | 7.2×10 <sup>-5</sup>  | 15.20 (3.68 - 62.83)  | 44        |
| HLA-B*15:02 | CTX          | Thai      | SJS/TEN    | 14/43 (32.56)    | 10/91 (10.99)                | 0.0037                | 3.91 (1.42 - 10.92)   | 1         |
|             |              |           |            | 6/18 (33.33)     | 7/91 (7.69)                  | 0.0074                | 6.00 (1.72 - 20.88)   | 44        |
| HLA-B*38:01 | SMX          | European  | SJS/TEN    | 4/25 (16)        | 78/1822 (4.3)                | 0.022                 | 4.3 (1.4 - 12.7)      | 47        |
| HLA-B*38:02 | SMX          | European  | SJS/TEN    | 1/25 (4)         | 1/1822 (0.05)                | 0.027                 | 76 (4.6 - 1250)       | 47        |
| HLA-C*06:02 | CTX          | Thai      | SJS/TEN    | 5/43 (11.63)     | 1/91 (1.10)                  | 0.0131                | 11.84 (1.24 - 566.04) | 1         |

|                    |     |      |         |                  |             |        |                        |    |
|--------------------|-----|------|---------|------------------|-------------|--------|------------------------|----|
| <i>HLA-C*08:01</i> | CTX | Thai | SJS/TEN | 12/43<br>(27.91) | 9/91 (9.89) | 0.0108 | 3.53 (1.21<br>- 10.40) | 1  |
|                    |     |      |         | 7/18<br>(38.89)  | 9/91 (9.89) | 0.0049 | 5.79 (1.79<br>- 18.70) | 44 |

Human Leukocyte Antigen; HLA, Co-trimoxazole; CTX, Sulfamethoxazole; SMX