Method for Evaluating the Risk of Drug Hypersensitivity Reaction Induced by Sulfamethoxazole and/or Trimethoprim

FILED OF THE INVENTION

The present invention provides a method for evaluating the risk of drug hypersensitivity reaction, in particular the method for the risk of drug hypersensitivity reaction induced by antibiotics sulfamethoxazole (Sulfamethoxazole) and/or trimethoprim (Trimethoprim).

BACKGROUND

Drug hypersensitivity reaction has been a major clinical problem, its manifestation is very diverse, ranging from mild rash (maculopapular eruption, MPE), fixed drug eruption (FDE) to severe cutaneous adverse drug reactions (SCAR), which includes: drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and so on. Drug allergies are often correlated with immune response. If a patient is allergic to a specific drug and later takes the same drug, the second exposure to the same drug elicits a faster and more severe drug hypersensitivity reaction.

Sulfamethoxazole and trimethoprim (tradenames include Baktar ™ or Bactrim ™, herein after referred to as Baktar) is a broad-spectrum bactericidal agent, often used to treat infections induced by Staphylococcus, Streptococcus, Streptococcus pneumoniae, Escherichia coli, dysentery bacteria and Pseudomonas, such as: respiratory tract, gastrointestinal tract, urinary tract, reproductive tract, skin, ENT, eye and oral cavity infections. There is no shortage of clinical cases of drug hypersensitivity reaction induced by Sulfamethoxazole and/or Trimethoprim, and both antibiotics are

considered to be one of the common causes of SJS / TEN. Prior literature reported that HLA-B*38 is associated with sulfamethoxazole induced drug hypersensitivity reaction in European [Lonjou et al.,Pharmacogenet Genomics., 2008], but this association is not seen in Asian. Therefore, there remains a need to evaluate the risk of drug hypersensitivity reaction induced by sulfamethoxazole and/or trimethoprim in Asian. The present invention addresses this need.

SUMMARY

Disclosed herein is a method for evaluating the risk of developing a drug hypersensitivity reaction in a patient, comprising the step of detecting the presence of HLA-B*1301 allele, wherein the presence of the HLA-B*1301 allele indicates the patient has a higher risk of developing drug hypersensitivity reaction compared to a subject without the HLA-B*1301 allele, wherein the drug is antibiotic sulfamethoxazole and/or trimethoprim.

Disclosed herein is a reagent for evaluating the risk of drug hypersensitivity reaction, wherein the reagent detects the presence of HLA-B*1301 allele and the presence of the HLA-B*1301 allele indicates the patient has a higher risk of developing drug hypersensitivity reaction compared to a subject without the HLA-B*1301 allele, wherein the drug is sulfamethoxazole and/or trimethoprim.

Disclosed herein is the use of a reagent for detecting the HLA-B*1301 allele in the manufacture of a kit to evaluate the risk of developing a drug hypersensitivity reaction induced by antibiotics sulfamethoxazole and/or trimethoprim.

DESCRIPTION OF THE INVENTION

The present invention provides a method for evaluating the risk of developing drug hypersensitivity induced by antibiotics sulfamethoxazole and/or trimethoprim in a patient, wherein the drug hypersensitivity reaction comprises: maculopapular eruption, fixed drug eruption and severe cutaneous adverse drug reaction. The severe cutaneous adverse drug reaction includes: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug rash with eosinophilia and systemic symptoms (DRESS). The present invention is directed to the discovery of the association of HLA-B*1301 allele and drug hypersensitivity reaction induced by antibiotics sulfamethoxazole and/or trimethoprim.

The present invention provides a method for evaluating the risk of developing a drug hypersensitivity reaction in a patient, comprising the step of detecting the presence of HLA-B*1301 allele, wherein the presence of HLA-B*1301 allele is an indicator of the risk of drug hypersensitivity reaction.

In one or more embodiments, the drug is antibiotic Baktar (sulfamethoxazole and trimethoprim).

In one or more embodiments, the drug is antibiotic sulfamethoxazole.

In one or more embodiments, the drug is antibiotic trimethoprim.

In one or more embodiments, drug hypersensitivity reaction includes but are not limited to: maculopapular eruption, fixed drug eruption, SJS,TEN or DRESS.

The present study shows HLA-B*1301 allele does not exist those of European and African ancestry.

In one or more embodiments, the patient has the HLA-B*1301 allele.

In one or more embodiments, the patient is of Asian ancestry.

In one or more embodiments, the patient is not of European or African ancestry.

The present invention provides a reagent for detecting the HLA-B*1301 allele in the manufacture of a kit to evaluate the risk of developing a drug hypersensitivity reaction induced by antibiotics sulfamethoxazole and/or trimethoprim.

In one or more embodiments, the drug hypersensitivity reaction comprises: maculopapular eruption, fixed drug eruption, SJS, TEN or DRESS.

The presence of HLA-B*1301 allele indicates the patient has a higher than two times, higher than three times, higher than four times, higher than five times, higher than six times, higher than seven times, higher than eight times, higher than nine times, higher than ten times, higher than eleven times, higher than twelve times, higher than thirteen times, higher than fourteen times, higher than fifteen times, higher than sixteen times, higher than seventeen times, higher than eighteen times, higher than nineteen times, higher than twenty times, higher than thirty times, higher than forty times, higher than fifty times, higher than sixty times, higher than seventy times, higher than three times to seventeen times, or higher than once time to seventeen times risk of developing drug hypersensitivity reaction compared to a subject without the HLA-B*1301 allele.

Methods known in the art for detecting alleles can be used, such as (but not limited to): an oligonucleotide that specifically hybridizes to the allele, serotyping or microcytotoxicity method to determine cDNA, RNA or protein product of the allele. [Kenneth D. McClatchey. Clinical Laboratory Medicine.2002].

In one or more embodiments, the oligonucleotide specifically hybridizes to the DNA of the peripheral blood of the patient. The oligonucleotide is designed for the most variable sequences of HLA-B*1301 allele, such as: exon 2 and exon 3, which are shown in Table 1 and SEQ ID NO 1.

In one or more embodiments, the sequences of the oligonucleotides used are: 5'-GGAGCCCCGCTTCATCACC-3'(SEQ ID NO: 2) and 5'-TCCTTGCCGTCGTAGGCTAA -3' (SEQ ID NO: 3) (see underlined sequences in Table 1).

In one or more embodiments, the serotyping or microcytotoxicity method is carried out on the RNA, proteins, cells or serum from peripheral blood of the patient.

The present invention provides a reagent for evaluating the risk of drug hypersensitivity reaction induced by antibiotics sulfamethoxazole and/or trimethoprim, by detecting the presence of HLA-B*1301 allele, wherein the presence of HLA-B*1301 allele indicates the risk of drug hypersensitivity reaction, and said drug hypersensitivity reaction comprises: maculopapular eruption, fixed drug eruption, SJS, TEN or DRESS.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

DESCRIPTION OF THE FIGURE

Figure 1 shows the sequences of exon 2 and exon 3 of HLA-B*1301. The lowercase letters indicates the sequence of the intron that connects exon 2 and exon 3. The sequence is exon 2- Intron - exon 3.

WORKING EXAMPLE

The present invention provides a method for evaluating the risk of developing a drug hypersensitivity reaction induced by antibiotics sulfamethoxazole and/or trimethoprim, the drug hypersensitivity reaction comprises: maculopapular eruption, fixed drug eruption and SCAR and said SCAR includes SJS, TEN or DRESS. The present is directed to the discovery that HLA-B allele, HLA-B*1301, is associated with drug hypersensitivity reaction induced by antibiotics sulfamethoxazole and/or trimethoprim.

In one example, 76 patients with Baktar-induced drug hypersensitivity reaction (DHR) were enrolled and their HLA typing was evaluated and compared with 482 healthy individuals. The results show 24 of the 76 patients with drug hypersensitivity reaction (SCAR, MPE or FDE) carried the HLA-B*1301 allele (31.58%). In contrast, 58 of the 482 healthy individuals carried the HLA-B*1301 allele (12.03%). Statistical analysis further indicates the presence of HLA-B*1301 allele is significantly associated with Baktar-induced drug hypersensitivity reaction (DHR vs. control: $P = 4.04 \times 10^{-5}$, OR = 3.37 (1.93-5.88), sensitivity: 31.58%, specificity: 87.97%) (See Table 1). In particular, the association with HLA-B*1301 allele is more significantly correlated with SCAR patients (SCAR vs. control: $P = 4.52 \times 10^{-5}$, OR = 17.06 (4.29-67.81), sensitivity: 70.00%, specificity: 87.97%). Based on the above results, HLA-B*1301 allele can be

used to evaluate the risk of developing drug hypersensitivity reaction induced by Baktar, sulfamethoxazole or trimethoprim.

Table 1: HLA-B*1301 genotype analysis of 76 patients with Baktar-induced DHR and 482 healthy individuals.

Subjects	*HLA-B*13:01* N （%）	Total N	OR （95% CI）	P Value
DHR	24 （31.58%）	76	3.37 （1.93~5.88）	$4.04X10^{-5}$
SCAR	7 （70.00%）	10	17.06 （4.29~67.81）	$4.52X10^{-5}$
Healthy Control	58 （12.03%）	482		

Accordingly, the present invention provides a method for evaluating drug hypersensitivity reaction in a patient after ingesting the drug, comprising the step of detecting the presence of HLA-B*1301 allele, wherein the presence of the HLA-B*1301 allele is an indicator of the risk of drug hypersensitivity reaction. The drug is antibiotic sulfamethoxazole and/or trimethoprim. Drug hypersensitivity reaction includes maculopapular eruption(MPE), fixed drug eruption (FDE), Stevens- Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS).

The preferred embodiments in the foregoing are specifically described technical features of the present invention. However, those skilled in the art can change and

modify the present invention without departing from the spirit and principles of the present invention, and such changes and modifications are intended to be included within the scope of the claims listed below.

WHAT IS CLAIMED IS:

1. A method for evaluating the risk of developing a drug hypersensitivity reaction in a patient of Asian ancestry, comprising the step of detecting the presence of HLA-B*1301 allele, wherein the presence of the HLA-B*1301 allele indicates the patient has a higher risk of developing drug hypersensitivity reaction compared to a subject without the HLA-B*1301 allele, wherein the drug is sulfamethoxazole and the drug hypersensitivity reaction is Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug rash with eosinophilia and systemic symptoms (DRESS).

2. The method according to claim 1, wherein the presence of HLA-B*1301 is detected in the DNA, RNA, proteins, cells or serum from the peripheral blood of the patient.

3. The method according to claim 1, wherein the drug further comprises trimethoprim.

4. The use of a reagent for detecting the presence of HLA-B*1301 allele in the manufacture of a kit to evaluate the risk of developing a drug hypersensitivity reaction induced by antibiotics sulfamethoxazole or sulfamethoxazole and trimethoprim, wherein the presence of the HLA-B*1301 allele indicates a patient has a higher risk of developing drug hypersensitivity reaction compared to a subject without the HLA-B*1301 allele, wherein the drug is antibiotic sulfamethoxazole or sulfamethoxazole and trimethoprim and the drug hypersensitivity reaction is Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug rash with eosinophilia and systemic symptoms (DRESS).

5. The use of claim 4, wherein the reagent comprises an oligonucleotide specifically hybridizes to the HLA-B*1301 allele.

6. A method for evaluating the risk of developing a drug hypersensitivity reaction in a patient not of European or African ancestry, comprising the step of detecting the presence of HLA-B*1301 allele, wherein the presence of the HLA-B*1301 allele indicates the patient has a higher risk of developing drug hypersensitivity reaction compared to a subject without the HLA-B*1301 allele, wherein the drug is sulfamethoxazole and the drug hypersensitivity reaction is Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug rash with eosinophilia and systemic symptoms (DRESS).

7. The method according to claim 6, wherein the presence of HLA-B*1301 is detected in the DNA, RNA, proteins, cells or serum from the peripheral blood of the patient.

8. The method according to claim 6, wherein the drug further comprises trimethoprim.