Genetic testing for prevention of severe drug-induced skin rash

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Authors

Ana Alfirevic[1], Munir Pirmohamed[1], Branka Marinovic[2], Linda Harcourt-Smith[3], Andrea L Jorgensen[4], Tess E Cooper[5]

[1]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK
[2]Department of Dermatology and Venereology, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia
[3]c/o Cochrane Skin Group, The University of Nottingham, Nottingham, UK
[4]Centre for Medical Statistics and Health Evaluation, University of Liverpool, Liverpool, UK
[5]Cochrane Kidney and Transplant, Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia

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Contact person

Ana Alfirevic

Lecturer in Pharmacogenomics
Department of Molecular and Clinical Pharmacology
Institute of Translational Medicine, University of Liverpool
Centre for Personalised Medicine, Block A: Waterhouse Building
1-5 Brownlow Street
Liverpool
L69 3GE
UK

E-mail: Ana.Alfirevic@liverpool.ac.uk

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What's new

Date	Event	Description

History

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Abstract

Background

Drug-induced skin reactions present with a range of clinical symptoms, from mild maculopapular skin rashes to potentially fatal blistering skin rashes — such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) — which may result in death. Milder reactions may be troublesome and lead to low drug compliance. The pathogenesis of these drug reactions is not yet fully understood; however, there is evidence that pretreatment genetic testing may help to predict and prevent these reactions in some cases.

Objectives

To assess the effects of prospective pharmacogenetic screening to reduce drug-associated skin reactions in a patient population.

Search methods

We searched the following databases up to July 2018: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE,

Embase and LILACS. We also searched five trials registers, and checked the reference lists of included studies and relevant reviews for further references to relevant randomised controlled trials (RCTs).

Selection criteria

We included RCTs of participants who had prospective pharmacogenetic screening to determine genetic variants associated with hypersensitivity reactions, compared with those who did not have prospective pharmacogenetic screening. We included participants in any setting, who were of any age, gender, and ethnicity, who had been prescribed drugs known to cause delayed type hypersensitivity reactions.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. To assess studies for inclusion, two review authors independently screened all of the titles and abstracts of publications identified by the searches. Because there was only one included study, many of the planned data analyses were not applicable to the review. We used GRADE to assess the quality of the included study.

The review's primary outcomes were the incidence of severe skin rashes with systemic symptoms (such as fever and multiple organ involvement), and long-term effects (such as scarring of eyelids or lung tissue). Secondary outcomes were hospitalisation for drug-induced skin reactions, blistering skin reactions (such as SJS, hypersensitivity (HSS) syndrome), and death.

Main results

One study, which was a randomised, double-blind, controlled, multicentre trial, fulfilled our inclusion criteria. The trial included 1956 adult participants (74% men, with a mean age of 42 years) across 265 centres (medical centres, hospitals, outpatient clinics) in 19 countries around the world who were infected with HIV-type 1 and who had not received abacavir previously. The participants, who had a clinical need for treatment with an antiretroviral-drug regimen containing abacavir, were randomly assigned to undergo prospective human leukocyte antigen (HLA) Class I, locus B, allele 57:01 (HLA-B*57:01) screening (prospective-screening group) before this treatment, or to undergo a standard-care approach of abacavir use without prospective HLA-B*57:01 screening (control group). Participants who tested positive for HLA-B*57:01 were not given abacavir; instead, they received antiretroviral therapy that did not include abacavir. The control group did have retrospective HLA-B*57:01 pharmacogenetic testing. The trial duration was six months. Each participant was observed for six weeks. Assessments were performed at the time of study entry, at baseline (day one of abacavir treatment), and at weeks one, two and six. This study was funded by the manufacturer of abacavir, GlaxoSmithKline.

The study did not assess any of our primary outcomes, and it measured none of our secondary outcomes in isolation. However, it did assess an outcome of (characteristically severe) hypersensitivity reaction which included (but was not limited to) our secondary outcomes of HSS and SJS/TEN.

The study demonstrated that prospective HLA-B*57:01 screening probably reduces the incidence of hypersensitivity reaction to abacavir. The incidence of clinically diagnosed HSS reaction to abacavir was lower in the screening arm (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.28 to 0.67; 1650 participants; moderate-quality evidence), as was immunologically confirmed HSS reaction (RR 0.02, 95% 0.00 to 0.37; 1644 participants; moderate-quality evidence). A positive result from an epicutaneous patch test performed six to ten weeks after clinical diagnosis provided immunological confirmation.

Overall, the study demonstrates a low risk of bias across five out of seven domains. There was a high risk of detection bias because hypersensitivity reactions were diagnosed by the principal investigator at the recruitment site without the use of predefined clinical criteria. Although there was also high risk of attrition bias due to excluding participants with incomplete follow-up from analyses, the authors did undertake a series of sensitivity analyses based on the intention-to-treat population, which demonstrated consistent results with the primary analysis. We rated the study quality as moderate-quality using GRADE criteria.

Authors' conclusions

Prospective screening for HLA-B*57:01 probably reduces severe hypersensitivity skin reactions to abacavir in patients positive for HIV-type 1. However, these results are only based on one study, which was at high risk of attrition and detection bias.

Our primary outcomes (incidence of severe skin rashes with systemic symptoms, and long-term effects) were not assessed by the trial, and only one of the review’s secondary outcomes was measured (hypersensitivity reaction); thus, we found no evidence relating to hospitalisation, death, or long-term conditions resulting from drug injury.

We found no eligible evidence on genetic testing for severe drug-induced skin rash in relation to different drugs and classes of drugs. Further clinical trials based on other drugs, and in different patient populations, would be useful for advising policy changes for improving the prevention of adverse skin reactions to drug treatments.

Plain language summary

Genetic testing for predicting and preventing severe skin rashes caused by drugs

Review question

The aim of this Cochrane Review was to find out if genetic testing for certain genotypes (i.e. the presence or absence of a particular gene variation) before prescribing drugs can prevent serious skin reactions in people prescribed drugs that are known to cause delayed type hypersensitivity reactions (i.e. allergic skin rash up to six weeks after taking the prescribed

medicine). People who had this type of test were compared with those who did not. We searched for all relevant studies so we could analyse them to answer this question, but we found only one study.

Background

Different types of medications can cause unwanted effects, which include skin rashes. These reactions are often a mild skin rash; however, rarely (but possibly) the drug may cause skin detachment, fever, and internal organ involvement, which can be life-threatening. Severe cases may require hospitalisation and treatment in specialised burns units. It is not fully understood how these reactions occur and which people are at increased risk of developing these reactions, but it is known that genetic factors may play a role. Research has been conducted into the use of simple genetic tests to predict these reactions and thus prevent them.

Study characteristics

We found only one relevant study. It included 1956 adult participants, of whom 74% were men, who tested positive for HIV-type 1 and were eligible to start highly active antiretroviral therapy including a medication called abacavir. (Antiretrovirals are a drug class used for treating patients with HIV infection.) The age of study participants ranged from 18 to 77 years; the average age was 42 years. The participants were from 19 countries around the world in 265 healthcare centres (e.g. hospitals, clinics). This study investigated whether the following can reduce the rate of serious skin reactions to abacavir: genetic testing for the genetic marker HLA-B*57:01 before prescribing abacavir (i.e. prospective testing) versus no prospective genetic testing for HLA-B*57:01. HLA-B*57:01 is known to be key in developing severe skin reactions to the HIV antiretroviral drug, abacavir. Participants who tested positive for the genotype were not given abacavir; instead, they were given a different antiretroviral therapy. The study lasted six months and each participant was observed for six weeks. GlaxoSmithKline, the company that manufactures abacavir, funded the study. Control participants had HLA-B*5701 pharmacogenetic testing after they had received abacavir as standard of care.

Key results

Our one included study did not report data for all participants, and clinical assessment of hypersensitivity (HSS) was done at the time of study entry, at baseline (day one) and at weeks one, two and six, without using predefined criteria. These can be important sources of bias and the quality of evidence was therefore judged to be moderate. Available data showed that prospective HLA-B*57:01 screening probably reduces the incidence of hypersensitivity reaction to abacavir (including, but not limited to, our secondary outcomes of hypersensitivity (HSS) syndrome and Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (i.e. severe and blistering skin reactions caused by medications)).

Based on these results, we would expect that out of 1000 people who did not have prospective pharmacogenetic screening (i.e. screening to assess how someone might respond to a particular drug), 78 would experience a hypersensitivity reaction including SJS/TEN (clinical assessment), compared with between 22 and 52 people who did have prospective pharmacogenetic screening to test for HLA-B*57:01.

Furthermore, we would expect that out of 1000 people who did not have prospective pharmacogenetic screening (standard care), 27 would experience a hypersensitivity reaction including SJS/TEN (immunologically confirmed), compared with zero participants who had prospective pharmacogenetic screening to test for HLA-B*57:01. A patch test on the skin provided immunological confirmation 6 to 10 weeks after clinical diagnosis.

The study did not measure the other outcomes of this review.

The evidence is current to July 2018.

Quality of the evidence

The included study was rated as being of moderate quality. Some patients were withdrawn from the study and not included in the analyses, and the investigator that diagnosed HSS reactions did not use a predefined clinical criteria of hypersensitivity. These issues caused us to downgrade the certainty of the evidence.

Background

We have explained some terms we have used in a glossary. Please see Table 1.

Description of the condition

Some drugs may cause skin rashes that vary in their severity and incidence. Skin reactions caused by drugs, often termed 'drug-induced skin injury', are common (carbamazepine-induced skin rash has a 10% incidence rate (Marson 2007)); they can present with a range of clinical manifestations, from a mild maculopapular skin rash to life-threatening skin rashes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (Pirmohamed 2004; Roujeau 1987). The most severe forms of hypersensitivity are very rare, but these may result in up to 30% mortality (Roujeau 1994). Less severe forms of hypersensitivity reactions are still troublesome and may prevent people from taking medications that are otherwise effective. Delayed type hypersensitivity reactions are T-cell mediated: they usually occur 24 to 48 hours, and up to six weeks, after exposure to culprit drugs.

The mechanisms involved in the pathogenesis of these drug-induced reactions are still poorly understood; however, immunogenetic and non-immune factors have been implicated (Chung 2004; Pirmohamed 2004; Vitezica 2008; Watanabe 2010). Recent evidence suggests that drug-specific T-cells can be identified in individuals who previously experienced adverse drug reactions to the culprit drug (Illing 2012).

Description of the intervention

There is increasing evidence from clinical trials that pretreatment genetic testing may reduce the possibility of severe drug-induced hypersensitivity (Chen 2011; Mallal 2008).

Figure 1 represents a diagram of decision-making informed by genetic testing.

To date, the strongest association with drug-induced skin injury has been reported with genetic variants in the human leukocyte antigens (HLA) (Amstutz 2013; Chung 2004; Hetherington 2002; Hung 2005; Mallal 2002; McCormack 2011; Ozkaya-Bayazit 2001). HLA are cell surface proteins involved in presenting antigens to the immune system. They are encoded by most polymorphic genes in the human genome. However, different genetic markers are associated with hypersensitivity in different populations, and the effect size varies in different ethnicities. Also, there is evidence that some genetic factors could predispose to drug-induced skin injury irrespective of the underlying drug aetiology. In addition, it is possible that different severity phenotypes can share the same predisposing factor (McCormack 2011). Table 2 shows reported associations between hypersensitivity reactions, which include skin injury and genetic variants in HLA genes.

Standard clinical practice does not include genetic testing for most drugs, despite some strong evidence on the benefits of pretreatment genotyping (Kim 2005; McCormack 2011; Ozeki 2011). There are potential ethical issues with genetic tests, such as the effect on family members, unintended findings, and storage and access of data.

How the intervention might work

Two recent clinical trials suggested that pretreatment genetic testing could reduce the possibility of severe hypersensitivity induced with an anti-AIDS drug, abacavir (Mallal 2008), and an antiepileptic drug, carbamazepine (Chen 2011).

Patients who have a clinical requirement for a particular drug treatment can be stratified on the basis of a genetic test. Those who test positive for the risk marker are not prescribed the culprit drug, while those who test negative are safe to take the medicine of interest. In this way, it may be possible to reduce the incidence of severe drug skin reactions in the genotyped group compared to the randomly assigned group of patients who are not offered genetic testing, but for whom decision on drug choice is based on traditional clinical and biochemical parameters (Chen 2011; Mallal 2008).

Why it is important to do this review

Adverse drug reactions affecting the skin are common; they can have high morbidity and mortality and are a burden for healthcare systems around the world. If we were able to predict these reactions using a simple genetic test, it should be possible to prevent them with one of the following approaches:

- by prescribing alternative therapy, if available;
- by informing patients and healthcare providers so the patients could be monitored more closely if they are at an increased risk;
- by informing drug developers, in order to improve drug design and future drug development.

We aimed to assess current research evidence to determine whether prospective pharmacogenetic screening is effective in reducing drug-associated skin reactions. The planned methods for this review were published as a protocol (Alfirevic 2014).

Objectives

To assess the effects of prospective pharmacogenetic screening to reduce drug-associated skin reactions in a patient population.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) only.

Types of participants

We included participants who were prescribed drugs known to cause delayed type hypersensitivity reactions with skin involvement. We accepted participants in any setting, who were of any age, gender, and ethnicity.

Prescribed drugs included, but were not limited to: antiepileptic drugs, antiretroviral drugs, antigout drugs, and antibiotics such as beta-lactams (penicillin, amoxicillin, piperacillin, cephalosporins) and sulphonamides (sulphamethoxazole and trimethoprim). We would have included studies that described only a subset of relevant participants. Decisions to include studies that only partially addressed the population of interest would have been documented in the review, and we would have conducted a sensitivity analysis to assess the impact of the decisions on the review's findings.

Types of interventions

We considered genetic testing for any genetic variants associated with hypersensitivity reactions using all available techniques to determine individual genotypes, and compared to standard clinical practice, which does not include a genetic test. The intervention was a randomly allocated genetic test; if the test was positive, a drug that can cause hypersensitivity was avoided. We included studies whose purpose was to genotype on the basis of likely adverse skin reaction. We excluded any participants who had previously been administered the study drugs.

Types of outcome measures

We based core outcome measures on several papers describing clinical classification of drug-induced skin reactions, including a paper entitled 'Phenotype standardisation for immune-mediated drug-induced skin injury' (Pirmohamed 2011), as well as papers by the RegiSCAR (European Registry of **S**evere **C**utaneous **A**dverse **R** eactions) consortium (Bouvresse 2012; Kardaun 2013; Sekula 2011).

We assessed clinically defined hypersensitivity reaction, immunologically confirmed hypersensitivity reactions (if skin patch testing or lymphocyte proliferation assay data were available), and long-term sequelae (including ophthalmologic, cutaneous, or liver damage, etc.).

We have provided a full list of clinically relevant outcomes, and distinction between primary and secondary outcomes, in Appendix 1.

Primary outcomes

- The incidence of severe drug-induced skin rash (defined as skin rash with systemic symptoms including fever and multiple organ involvement).
- Long-term sequelae (any of the following: ophthalmologic, cutaneous, or liver damage, etc.) up to 12 months after the severe drug-induced skin rash.

Secondary outcomes

- Hospitalisation for drug-induced skin reaction within three months of exposure to the drug.
- SJS/TEN (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- AGEP (acute generalised exanthematous pustulosis).
- HSS (hypersensitivity syndrome).
- Death.

Additional terminology for HSS includes the following: drug-induced hypersensitivity syndrome (DIHS), drug reaction with eosinophilia and systemic symptoms (DRESS), drug-induced delayed multiorgan hypersensitivity syndrome, and hypersensitivity reaction.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist searched the following databases up to 9 July 2018 using strategies based on the draft strategy for MEDLINE in our published protocol (Alfirevic 2014):

- the Cochrane Skin Specialised Register using the search strategy in Appendix 2;
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2018, Issue 6, in the Cochrane Library using the strategy in Appendix 3;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 4;
- Embase via Ovid (from 1974) using the strategy in Appendix 5; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 6.

Trials registers

We (AA and AJ) searched the following trials registers on 15 July 2018 using the following terms: skin rash, genetic test, drug:

- the ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch); and
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Searching other resources

References from included studies

We checked the bibliographies of the included studies and published reviews for further references to relevant trials.

Correspondence

We requested relevant information from one author of an included study, but they did not reply to us (Appendix 7).

Adverse effects

We did not perform a separate search for adverse effects of the target intervention. We examined data on adverse effects of genotyping from the included study we identified, but we did not find evidence of adverse effects of genotyping.

Data collection and analysis

We included a 'Summary of findings' table in our review which summarised our primary and secondary outcomes for the

comparison of genetic testing versus no genetic testing.

Selection of studies

Two review authors (AA and AJ) independently assessed all the titles and abstracts of publications identified by the searches to assess their eligibility. The full texts of all papers found to be eligible at this initial stage were then assessed for inclusion. Publications found to be irrelevant after reading their full text were excluded, and 'Characteristics of excluded studies' tables were prepared to identify the reasons for exclusion. Consensus on the final list of trials to include was reached by discussion.

Data extraction and management

Two review authors (AA and AJ) independently extracted data from the included studies and resolved disagreements by discussion with a third author (TC). The following information on study characteristics and methods were collected into a standardised data extraction form:

- study design;
- inclusion and exclusion criteria;
- setting;
- country;
- language of publication;
- ethnicity of participants;
- control population (comprising individuals exposed to the culprit drug with no adverse effects or individuals from a healthy population who were not exposed to medications used in the trial);
- description of genotyping techniques used;
- genotyping quality control, which included deviation from Hardy-Weinberg equilibrium (Hardy-Weinberg equilibrium is a crucial concept in population genetics; it predicts how gene frequencies will be inherited from generation to generation and is used as a measure of quality of genetic tests) and genotype call rate;
- age;
- gender;
- concomitant medications;
- time from exposure to the culprit drug to skin reaction;
- type of skin reaction;
- location of skin lesion;
- sequelae of adverse reactions;
- other manifestations indicating systemic involvement; and
- clinical laboratory tests.

No language translations of papers were required.

Assessment of risk of bias in included studies

Two review authors (AA and AJ) independently assessed the risk of bias in each trial. We used Cochrane's tool for assessing risk of bias (Table 8.5.a in the *Cochrane Handbook for Systematic Reviews of Interventions*), which is based on seven domains (Higgins 2011):

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective outcome reporting (reporting bias); and
- other risk of bias.

The tool allows for the risk of bias for each domain to be assessed as 'low', 'high', or 'unclear' (indicating lack of information or uncertainty over the potential for bias). An additional review author (MP) was consulted in the case of disagreements.

Measures of treatment effect

We planned to use statistical methods in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to calculate mean difference (MD) with 95% confidence interval (CI) for continuous data or indeed standardised mean difference (SMD) with 95% CI where all studies reported an outcome using different but similar scales. A risk ratio (RR) with 95% CI was calculated for dichotomous data.

Unit of analysis issues

There were no unit of analysis issues. If such issues arise in an update of this review, we plan to take the appropriate approach to analysis to avoid a unit of analysis error due to repeated observations on participants, multiple treatments, or re-occurring events. In future updates, if we include cluster-randomised trials, we will take into account issues such as recruitment bias, baseline comparability of clusters, and number of clusters, and make sure that appropriate statistical methods are used that take into account weighting, etc. (Higgins 2011).

Dealing with missing data

We considered the possible different types of missing data. We planned to deal with missing studies (and the associated risk

of bias) by assessing for publication bias, and to deal with missing outcomes (and the associated risk of bias) by assessing for selective reporting (see Assessment of reporting biases). However this was not applicable, due to there only being one included study in this review.

The included study did not report on either of our primary outcomes, but instead reported on an outcome of hypersensitivity reaction which included (but was not limited to) our secondary outcomes HSS and SJS/TEN. So in order to deal with missing data we contacted the study author for additional data on the outcomes of our review. We did not receive a response and therefore we are unaware if the outcomes were measured, and were unable to include these data in our review.

Assessment of heterogeneity

Had a meta-analysis been possible, we planned to assess the extent of heterogeneity using the I^2 statistic. We would have used the following thresholds for the interpretation of the I^2 statistic:

- 0% to 40% = might not be important;
- 30% to 60% = moderate heterogeneity;
- 50% to 90% = may represent substantial heterogeneity; and
- 75% to 100% = considerable heterogeneity.

Due to there being only one included study, we did not need to assess heterogeneity. If eligible studies become available in the future during an update of this review, we will perform a meta-analysis, report the I^2 statistic, and interpret the two data together.

Assessment of reporting biases

We planned to assess publication bias by using a funnel plot, Begg test and Egger test (Begg 1989; Egger 1998). Tests for funnel plot asymmetry would only be undertaken when at least 10 studies could be included in the meta-analysis. Due to the fact that there was only one included study, the power of the tests is too low to distinguish chance from real asymmetry; therefore, this was not assessed.

Data synthesis

Had there been sufficient studies and no significant clinical heterogeneity, we planned to synthesise the results in meta-analyses, stratified according to type of intervention (e.g. type of genetic test). A random-effects model would have been assumed.

Where events are rare, a random-effects approach may be inappropriate. Where events were rare, we planned to take extra care to adopt appropriate methods of meta-analysis, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (section 16.9) (Higgins 2011), since many meta-analysis methods are suboptimal where events are rare through results being biased, confidence intervals being too wide, or power being too low. Choice of method would have been guided by control group risk, likely treatment effect size, and consideration of balance in numbers of treated and control participants in the constituent studies. Had the control groups differed — e.g. if they were drawn from a healthy population or from a population of people treated with the culprit drug but without any adverse effects — we planned to conduct separate analyses. We planned to use Review Manager 5 software to undertake the meta-analyses (Review Manager 2014).

As we only included one study, it was not possible to undertake a meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to assess heterogeneity using the I^2 statistic and in the event of substantial heterogeneity, we planned to explore the causes by way of subgroup analyses. We planned to consider the following:

- participant factors (age, ethnicity, classification of adverse drug reactions, and comparability of participant groups); and
- trial design issues (genotyping methodology and quality control, blinding, drugs included, and drug dosage and duration of use).

As we only included one study, it was not possible to assess for heterogeneity and therefore a subgroup analysis was not relevant.

Sensitivity analysis

We planned to evaluate the robustness of the results of the meta-analyses by removing trials of low methodological quality as identified by their risk of bias. As we only included one study, it was not possible to undertake a meta-analysis, or indeed sensitivity analyses.

Results

Description of studies

Results of the search

The searches of the five databases (see Electronic searches) retrieved 1790 records. Our checks of the trials registers and bibliographies of included studies and relevant reviews did not identify any further relevant studies. Once duplicates were removed we had a total of 1786 records. We excluded 1774 records based on titles and abstracts. We obtained the full text of the remaining 12 records. We excluded nine studies (see Characteristics of excluded studies). One study is awaiting classification (see Characteristics of studies awaiting classification). We did not identify any ongoing studies. We included one study (Mallal 2008), which was reported in two papers.

For a further description of our screening process, see the study flow diagram in Figure 2.

Included studies

Only one study fulfilled our inclusion criteria (Mallal 2008). The summary information can be found in Characteristics of included studies.

This study was a randomised, prospective, double-blind, multicentre controlled trial, which included 1956 participants from 265 centres (medical centres, hospitals, outpatient clinics) in 19 countries. The participants were infected with HIV-type 1 (HIV-1) and had not previously been exposed to the antiretroviral drug abacavir. The study population consisted of men and women (74% men) between the ages of 18 and 77 years old (mean age: 42 years) who were predominantly white. The initial target sample size was 1578 participants. The study was supported by GlaxoSmithKline.

Participants were randomly assigned to undergo prospective pharmacogenetic screening for the human leukocyte antigen class I gene HLA-B*57:01 (prospective screening group, i.e. the treatment group) or to undergo a standard care approach without genetic testing (control group). In the prospective screening group, HLA-B*57:01-positive participants were excluded from abacavir treatment to prevent skin rash. These individuals were given a combination of active antiretroviral therapy that did not include abacavir. (Those that tested negative for HLA-B*57:01 were given a combination of active antiretroviral therapy including abacavir.)

All those in the control group were given a combination of active antiretroviral therapy including abacavir without prospective screening for HLA-B*57:01. These participants had retrospective HLA-B*57:01 pharmacogenetic testing.

The study encompassed six-week observation periods conducted over a six-month trial period from April to September 2006.

The primary outcomes reported by the study were to investigate whether there was a reduction in clinically diagnosed hypersensitivity reactions to abacavir in the genotyped group compared to the control group, and to explore the rate of immunologically confirmed hypersensitivity reaction (defined as "clinically diagnosed reaction that was confirmed by a positive result on epicutaneous patch testing 6 to 10 weeks after clinical diagnosis" (Mallal 2008)). Assessment of hypersensitivity was performed at the time of study entry at baseline (day one) and at weeks one, two and six. None of the review's primary outcomes were reported in this trial. In terms of the review's secondary outcomes, HSS and SJS/TEN were reported, but only as a combined outcome under 'hypersensitivity reactions'.

Excluded studies

We excluded nine studies following full-text review. Reasons for exclusion were as follows:

- randomisation was not performed, or not performed according to genotype (Bonnefoi 2011; Cheng 2009; Pusztai 2014; Sequist 2013; Seymour 2013; Young 2008); and
- our primary and secondary outcomes, which we planned to investigate, were not measured (Azuma 2013; Damronglerd 2015; Newman 2011).

Full reasons for exclusion are listed in Characteristics of excluded studies.

Risk of bias in included studies

The overall risk of bias was low, with the exception of a notably high risk of attrition and detection bias (Figure 3; Figure 4).

Allocation (selection bias)

Random sequence generation

All 1956 participants in the study were adequately randomised based on a computer-generated, centralised schedule; thus, allocation to the treatment and control groups (prospective and retrospective testing) indicates a low risk of selection bias.

Allocation concealment

The method of allocation concealment represents low risk of bias because it was performed by the central study-management group without foreknowledge of intervention assignments. The sequence was implemented in the block sizes of four. Stratification was done according to ethnicity to ensure a good balance of ethnic subgroups between the two trial arms, since risk of outcomes can vary across ethnic groups.

Blinding (performance bias and detection bias)

Blinding was undertaken sufficiently, with the investigators, participants and study management team remaining unaware of the participant assignments to the treatment or control group. Therefore we deemed the study to have a low risk of performance bias. In terms of detection bias, the assessors were unaware of the genetic test results and investigators were trained using illustrated guides and an informational video. However, hypersensitivity reactions were diagnosed by the principal investigator at the recruitment site without the use of predefined clinical criteria and this poses a risk of detection bias.

Incomplete outcome data (attrition bias)

Participants treated with abacavir, but for whom there were incomplete follow-up data for various detailed reasons, were excluded from the primary analyses; therefore these analyses are at risk of attrition bias. However, potential bias introduced by the exclusion of the participants who could not be evaluated was addressed by several sensitivity analyses of data from the full intention-to-treat population that had received abacavir, with assumptions about the missing data ranging from 0% to 100% of the exclusions being associated with a hypersensitivity reaction. The results of the sensitivity analyses were in line

with the results of the primary analyses.

Selective reporting (reporting bias)

We judged the study to be at low risk of reporting bias as both prespecified outcomes from the protocol (ClinicalTrials.gov identifier: NCT00340080) were reported. It was not possible to assess for between-study selective reporting as there was only one included study.

Other potential sources of bias

No other potential sources of bias appear within the study.

Effects of interventions

The study did not report on either of our primary outcomes (the incidence of severe drug-induced skin rash; or long-term sequelae). The study did report 'hypersensitivity reactions' which included, but was not limited to, our secondary outcomes HSS (hypersensitivity syndrome) and SJS/TEN (Stevens-Johnson syndrome, toxic epidermal necrolysis).

The study demonstrated that prospective HLA-B*57:01 screening can reduce the incidence of hypersensitivity reaction to abacavir. The incidence of immunologically confirmed hypersensitivity reaction to abacavir was lower in the screening arm (risk ratio 0.02; 95% CI 0.00 to 0.37; P < 0.001; 1644 participants; Analysis 1.1), as was the incidence of clinically diagnosed hypersensitivity reaction to abacavir (risk ratio 0.43; 95% CI 0.28 to 0.67; P < 0.001; 1650 participants; Analysis 2.1). These results are presented in Summary of findings table 1, Figure 5 and Figure 6.

However, we are aware of some potential long-term effects of abacavir. In order to determine any further effects of the intervention, we made an attempt to contact the study authors for information on our remaining primary and secondary outcomes (as mentioned above in Dealing with missing data). We did not receive a response, and therefore are unable to estimate any further effects of the intervention.

Discussion

Summary of main results

Our one included study (with a total of 1956 participants) did not report on either of our primary outcomes of interest, which were:

1. the incidence of severe drug-induced skin rash (defined as skin rash with systemic symptoms including fever and multiple organ involvement); and
2. long-term sequelae (any of the following: ophthalmologic, cutaneous, or liver damage, etc.) up to 12 months after the severe drug-induced skin rash.

The study addressed a combination of our second and fourth secondary outcomes, which were: SJS/TEN (Stevens-Johnson syndrome, toxic epidermal necrolysis) and HSS (hypersensitivity syndrome). Based on moderate-quality evidence, prospective HLA-B*57:01 screening probably reduces the incidence of hypersensitivity reaction to abacavir compared to when prospective pharmacogenetic screening is not performed. However, hypersensitivity reactions were diagnosed by the principal investigator at the recruitment site without the use of predefined clinical criteria and therefore there is a high risk of detection bias.

Carriers of HLA-B*57:01 were excluded from receiving abacavir; the rate of clinical diagnosis of hypersensitivity reaction was 7.8% in the control group (who received no screening, but underwent HLA typing retrospectively after abacavir exposure) compared to 3.4% (95% CI 2.2% to 5.2%) in the prospective-screening group (risk ratio (RR) 0.43, 95% CI 0.28 to 0.67) (Summary of findings table 1; Figure 5).

In addition, undertaking skin patch testing to confirm the diagnosis of hypersensitivity and excluding carriers of HLA-B*57:01 from receiving abacavir, reduced the rate of immunologically confirmed diagnosis of hypersensitivity from 2.7% in the control group (no screening) to zero in the prospective-screening group (RR 0.02, 95% CI 0.00 to 0.37) (Summary of findings table 1; Figure 6).

Based on this trial, pretreatment genetic testing for the HLA-B*57:01 allele has been recommended by the Clinical Pharmacogenetics Implementation Consortium (Martin 2014) and several regulating agencies, including the Food and Drug Administration (FDA), European Medicines Agency (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA).

Overall completeness and applicability of evidence

The included study is not sufficient to address all the objectives of this review (Mallal 2008). Whilst it did provide some data related to two secondary outcomes, and was generally at low risk of bias, more studies are required if our objectives are to be explored fully. The study is the only randomised controlled trial that assessed efficacy and safety of genetic testing in prediction of adverse drug reactions. Included individuals were representative of the study population of interest. However, it will be important in future studies to explore ethnic variability as this study has been conducted in a predominantly white population. The follow-up period was short and there was no information on long-term sequelae in drug-hypersensitivity survivors. The study did not report on either of our primary outcomes of interest. In addition, information on hospitalisation, AGEP (acute generalised exanthematous pustulosis), or death were not reported either. We found no eligible evidence with regard to genetic testing for severe drug-induced skin rash in relation to different drugs and classes of drugs.

Quality of the evidence

The study included in this review has adequate randomisation methods, as well as methods of allocation

concealment. However, the included trial did not report on the characteristics of the 55 participants (5.6%) who were positive for HLA-B*57:01 and therefore did not receive abacavir treatment and were excluded from data analysis. Information on outcomes within this patient group would have been informative. There is also potential for detection bias as the principal investigator diagnosed hypersensitivity reactions without the use of predefined clinical criteria. Therefore, we downgraded the quality of evidence by one level due to study limitations (risk of bias). We did not find any reason to downgrade the evidence for the other GRADE domains (inconsistency, imprecision, indirectness, or publication bias). Therefore, quality of evidence was rated as moderate using the GRADE criteria (Schünemann 2013).

Potential biases in the review process

We did not identify any sources of potential bias in the review process. We carefully assessed diverse terminology used to describe drug-induced hypersensitivity and included alternative search terms in our literature searches. We clearly defined the outcomes and patient subgroups. As we included only RCTs in our protocol, no other study designs were considered. We did not impose any date restrictions on the search. We contacted the study authors to provide additional data, but that did not generate any additional information.

Agreements and disagreements with other studies or reviews

To our knowledge there have been no previous systematic reviews addressing this research question, and the only previous study addressing the research question is included as the only study in this review (Mallal 2008). Due to there only being one identified RCT, there are remaining uncertainties about the effects of prospective pharmacogenetic screening to reduce drug-associated skin reactions in a patient population. Several studies have recently reported clinical utility of pretreatment genetic testing that can predict and prevent serious cutaneous adverse drug reactions (Chen 2011; Fang 2019; Liu 2019; Mushiroda 2018; Park 2019; Stainsby 2019). However, these studies are not RCTs and therefore were not included in our review; they use historical frequency data on adverse drug reactions over a period of several years to control for HLA allele screening that helps to predict and prevent adverse drug reactions in carriers of risk alleles. The findings in these studies agree with the conclusions of our review.

Authors' conclusions

Implications for practice

We identified only one randomised controlled trial (RCT), which assessed the effects of prospective pharmacogenetic screening to reduce drug-associated skin reactions. The trial did not report on our primary outcomes, which included long-term assessment, and outcomes were only measured up to six weeks.

Based on the trial results, there is moderate-quality evidence that prospective HLA-B*57:01 screening before abacavir treatment probably reduces the incidence of both clinically diagnosed or immunologically confirmed hypersensitivity reaction (including Stevens-Johnson syndrome and toxic epidermal necrolysis) to abacavir, when compared with use of the drug without prospective HLA-B*57:01 screening.

However, as our evidence is limited to a test for one gene, relating to one drug, we cannot make broad conclusions. We cannot predict whether this principle of pretreatment testing can be applied to different drugs and classes of drugs.

Implications for research

There is a shortage of RCTs that assess the effects of prospective pharmacogenetic screening to reduce adverse drug reactions. Serious adverse drug reactions are rare, and although RCTs are the gold standard for investigating the effects of interventions, they are not an optimal design for investigations of rare adverse outcomes, particularly if the outcomes take a long time to develop, such as long-term sequelae following severe cutaneous adverse drug reactions (Higgins 2011). Therefore, new methodology to address the effects of preventative genetic interventions is needed.

Further research should explore ethnic variability in genetic testing and different drugs and classes of drugs; studies should report on incidence and long-term sequelae in drug-hypersensitivity survivors. Core outcome measures would be useful, and these should include approved predefined clinical criteria for diagnosing hypersensitivity. Participants who undergo genetic risk assessment may have high levels of anxiety and therefore this should be assessed where possible in similar trials.

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Contributions of authors

AA was the contact person with the editorial base.
AA co-ordinated contributions from the co-authors and wrote the final draft of the review.
AJ and AA screened papers against eligibility criteria.
AJ and AA obtained data on ongoing and unpublished studies.
AJ and AA appraised the quality of papers.
AJ and AA extracted data for the review.
AA sought additional information about papers.
AA entered data into Review Manager 5.

AA, AJ, MP and BM analysed and interpreted data.
AA, AJ, MP and BM worked on the methods sections.
AA and MP drafted the clinical sections of the background and responded to the clinical comments of the referees.
AJ responded to the methodological and statistical comments of the referees.
LHS was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.
AA is the guarantor of the update.

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Declarations of interest

AA: none known.
MP: none known.
BM: none known.
LHS: none known.
ALJ: none known.
TC: none known.

Differences between protocol and review

Our objectives and eligibility criteria remained the same between the protocol and the review. After the protocol stage, two new outcomes were added to our secondary outcomes: safety of abacavir and cost-effectiveness. However, these were not in any way conditional to our eligibility criteria, nor were they influenced by the availability of the data from included studies.

We were unable to implement several methodologies from the protocol, due to there only being one included study. The following methods are not applicable with one study: addressing unit of analysis issues; dealing with missing data (contact was made but we did not receive a response); assessment of heterogeneity; assessment of reporting bias; data synthesis; subgroup analysis and investigation of heterogeneity (not applicable with one study, and outcomes not addressed); and sensitivity analysis.

Types of participants: we clarified how we would handle a study with only a subset of relevant participants; however, we did not encounter such studies.

Types of interventions: in the review, we additionally stated that we excluded any participants who had previously been administered the study drugs because of accurate causality assessment. Furthermore, we clarified the comparator in the review and included the following statement "and compared to standard clinical practice which does not include a genetic test".

Types of outcome measures: we added a definition of ‘severe drug-induced skin rash’ to our primary outcome because phenotype definitions vary widely in the literature and some study authors report hypersensitivity reactions and SJS/TEN as severe or serious drug-induced skin rash. We also added 'death' as a secondary outcome.

Searching other resources: although not planned in the protocol, we additionally checked the bibliographies of published reviews for relevant references and we requested relevant information from the authors of the included study.

Data extraction and management: we had planned to consult MP if consensus was not reached, but instead discussed disagreements with TC because authorship changed due to availability.

Assessment of risk of bias in included studies: we had planned in the protocol for all authors to assess the risk of bias of three studies as a pilot but did not do this because only one study fulfilled our inclusion criteria.

Unit of analysis issues: we did not encounter cluster-randomised trials, so did not have to deal with the issues we had planned for in the protocol.

Dealing with missing data: we planned to report the limited results from studies with missing summary data in narrative form in the results section and consider whether they are consistent with the results of the meta-analysis for that outcome. Also, where appropriate, we had planned to make assumptions about the missing data (e.g. assuming all missing values to have a particular value, e.g. an adverse event) and conduct sensitivity analyses to test how sensitive the analyses are to our assumptions. We had planned to address the potential implications of the missing data in the Discussion section. These plans were not implemented because only one study was included in this review which only reported data on two of our secondary outcomes.

Assessment of heterogeneity, Assessment of reporting biases, Subgroup analysis and investigation of heterogeneity, and Sensitivity analysis: we could not implement our planned methods because only one studies was included in this review.

Published notes

Characteristics of studies

Characteristics of included studies

Mallal 2008

Methods	• Parallel randomised controlled trial that is prospective and double-blinded • Multicentre trial • 6-week observation per participant over 6-month trial period (April to September 2006)
Participants	• N = 1956 • Gender: both males and females included • Age: 18 to 77 years • Inclusion characteristics: participants infected with HIV type 1, not previously received abacavir • Participants were predominantly white • Setting: 265 healthcare centres, 19 countries
Interventions	Prospective screening for the human leukocyte antigen class I gene named HLA-B*57:01 or standard of care approach without genotyping 6-week observation period over 6-month trial period (April to September 2006) Treatment group (prospective screening group) (N = 980) • Prospective pharmacogenetic screening for the human leukocyte antigen class I gene HLA-B*57:01, followed by combination of active antiretroviral therapy (including abacavir) Control group (N = 976) • Combination of active antiretroviral therapy (including abacavir), followed by retrospective pharmacogenetic testing for the human leukocyte antigen class I gene HLA-B*57:01
Outcomes	• Reduction in clinically diagnosed hypersensitivity reactions to abacavir in genotyped group compared to the control group • Rate of immunologically confirmed hypersensitivity reaction (defined: clinically diagnosed reaction confirmed "by a positive result in epicutaneous patch testing 6 to 10 weeks after clinical diagnosis")H • Severe skin rashes • Incidence of SJS/TEN, AGEP and HS
Notes	The study was supported by GlaxoSmithKline.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was based on a computer-generated, centralised schedule" Comment: randomisation method unlikely to introduce selection bias
Allocation concealment (selection bias)	Low risk	Quote: "patients received eligibility to receive abacavir from the central study-management group." Quote: "block size of four and stratification according to self-reported race and intention to commence a new NNRTI" Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Investigators, patients and the study management team were unaware of the group assignments" Comment: participants and study personnel were blinded to group assignment
Blinding of outcome assessment (detection bias)	High risk	Quote: "Hypersensitivity reactions were diagnosed by the principal investigator at the recruitment site without the use of predefined clinical criteria and this poses a risk of detection bias." Comment: even though assessors were unaware of genetic test results and training of investigators was performed using illustrated guides and an informational video, the above quote from the publication suggests there was high risk of detection bias.
Incomplete outcome data (attrition bias)	High risk	131 patients were withdrawn from the study with detailed reasons. No outcome data are provided for the screen-positive cohort, i.e. not an intention-to-treat analysis. A series of sensitivity analyses, based on the assumptions made for the intention-to-treat population, showed similar results to the complete case analysis; however, we still considered the study to be at high risk of attrition bias.
Selective reporting (reporting bias)	Low risk	A total of 803 participants were evaluated for clinically identified hypersensitivity reactions in the prospective screening group and 847 in the control group. Both prespecified outcomes from the protocol (ClinicalTrials.gov identifier: NCT00340080) are reported.
Other bias	Low risk	No other sources of bias identified

Footnotes

AGEP: acute generalised exanthematous pustulosis
HS: hypersensitivity syndrome
N: number
SJS/TEN: Stevens-Johnson syndrome, toxic epidermal necrolysis

Characteristics of excluded studies

Azuma 2013

Reason for exclusion	Excluded since our primary and secondary outcomes, which we planned to investigate, were not measured. In this study, drug-induced liver injury was investigated and not skin reaction.

Bonnefoi 2011

Reason for exclusion	Randomisation was between two different chemotherapy regimens, with outcomes compared between two genotype groups in each treatment group separately, and therefore treatment does not differ based on genotype.

Cheng 2009

Reason for exclusion	No randomisation between genotype-guided and non-guided treatment, but rather this was a study to develop and validate new genotyping method.

Damronglerd 2015

Reason for exclusion	Genotyping in this study was not done prospectively as it was not intended to prevent skin rash.

Newman 2011

Reason for exclusion	Data on rash are reported as secondary outcome; genotyping was not undertaken prospectively and it was not intended to prevent skin rash. No evidence of severe hypersensitivity phenotypes in the study.

Pusztai 2014

Reason for exclusion	Only those with one of three gene signatures were given treatment. There was no randomisation.

Sequist 2013

Reason for exclusion	Randomisation was performed only in patients who were positive for mutations, and so treatment does not differ based on genotype.

Seymour 2013

Reason for exclusion	Randomisation was performed only in patients who are KRAS wild-type; therefore, treatment does not differ based on genotype.

Young 2008

Reason for exclusion	No randomisation was performed.

Footnotes

KRAS: a class of genes known as oncogenes that encode K-Ras protein that is part of a cell signalling pathway

Characteristics of studies awaiting classification

Coenen 2015

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	Conference abstract — unclear whether any skin reactions are included as outcome

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 Summary of findings

Prospective genetic HLA-B*57:01 screening compared with standard care for drug-induced skin rash

Patient or population: patients with HIV-1 infection and a pre-established clinical need for treatment with an antiretroviral drug regimen containing abacavir but with an unknown HLA-B*57:01 status.

Settings: secondary care clinics

Intervention: prospective genetic screening for the HLA-B*57:01 allele

Comparison: no prospective genotyping, standard-of-care treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard Care[a]	Prospective genetic HLA-B*57:01 screening				
Severe skin drug-induced rash	No data		-	-	-	Not assessed
Long-term sequelae	No data		-	-	-	Not assessed
Hospitalisation for drug-induced skin reaction	No data		-	-	-	Not assessed
SJS/TEN (Stevens-Johnson syndrome/toxic epidermal necrolysis)	See hypersensitivity		-	-	-	Not assessable
AGEP (acute generalised exanthematous pustulosis)	No data		-	-	-	Not assessed
HSS (hypersensitivity) reaction including SJS/TEN (clinically diagnosed) (6 weeks clinical assessment)	78 per 1000	34 per 1000 (22 to 52)	RR 0.43 (0.28 to 0.67)	1650 participants (1 study)	???? moderate[b]	-
HSS reaction including SJS/TEN (immunologically confirmed) (6 weeks clinical assessment)	27 per 1000	0 per 1000	RR 0.02 (0.00 to 0.37)	1644 participants (1 study)	???? moderate[b]	-
Death	No data		-	-	-	Not assessed

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[a] The assumed risk is estimated from the event rate (confirmed clinically diagnosed occurrences of HSS including SJS/TEN or immunologically confirmed) in the control arm of the included study.

[b] We downgraded the evidence to moderate quality, due to study limitations (high risk of detection and attrition bias).

Additional tables

1 Glossary of terms

Term	Explanation
Allele	One of two or more alternative forms of a gene at corresponding sites (loci) on homologous chromosomes
Antiretroviral	A class of drugs that inhibit the activity of retroviruses that cause HIV infection
Hardy-Weinberg equilibrium	This states that allele and genotype frequencies in a population will remain constant from generation to generation in the absence of other evolutionary influences
HLA	Human leukocyte antigen: a group of protein molecules located on bone marrow and other cells that can provoke an immune response
Hypersensitivity	A state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign substance, such as a drug
Immunologically confirmed	Patch testing is done to see whether a particular drug is causing allergic skin reaction. Patch test can detect delayed allergic or immunological reaction and confirm the diagnosis of hypersensitivity.
Phenotypes	The set of observable characteristics of an individual resulting from the interaction of its genotype with the environment
Polymorphic	A variation in the DNA that is too common to be due merely to new mutation. A polymorphism must have a frequency of at least 1% in a population
Maculopapular rash	A rash with both macules (flat and coloured like a freckle) and papules (a small raised spot)
Sequelae	A condition that is a consequence of a previous disease or injury
T-cells	Another term for T-lymphocyte, a type of cell that participates in immune response

Footnotes

2 Associations between drug-induced skin injury and genetic variants in the HLA genes

Drugs associated with skin injury	Class of drug	HLA allele	Population	Reference
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)				
Allopurinol	Antiuric acid	B*5801	Han Chinese	Hung 2005
-	-	-	Thai	Tassaneeyakul 2009
-	-	-	Japanese	Kaniwa 2008
-	-	-	Malay	Ding 2010
Carbamazepine	Antiepileptic	B*1502	Han Chinese	Cheung 2013; Chung 2004; Chong 2013; Hung 2006; Man 2007
-	-	-	Thai	Kulkantrakorn 2012; Locharernkul 2008; Tassaneeyakul 2010; Tangamornsuksan 2013
-	-	-	Malay	Ding 2010
-	-	-	Indian	Mehta 2009
-	-	A*3101	White	Amstutz 2013; McCormack 2011;
-	-	A*3101	Japanese	Ozeki 2011
Phenytoin	Antiepileptic	B*1502	Han Chinese	Hung 2010; Man 2007
-	-	-	Thai	Locharernkul 2008;
Oxicam	Non-steroidal anti-inflammatory drug (NSAID)	A2, B12	White	Roujeau 1987
Sulphamethoxazole	Antibiotic	A29, B12, DR7	White	Roujeau 1986
Hypersensitivity syndrome (drug-induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS))				
Abacavir	Antiretroviral	B*57:01	White	Hetherington 2002; Hughes 2004a; Mallal 2002; Mallal 2008; Martin 2004

Drugs associated with skin injury	Class of drug	HLA allele	Population	Reference
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)				
-	-	-	African American	Hughes 2004b; Saag 2008
Aminopenicillins	Antibiotic	A2, Drw52	White	Romano 1998
Nevirapine	Antiretroviral	DRB1*01	White - Australian	Martin 2005
-	-	DRB1*01	White - French	Vitezica 2008
-	-	Cw8, B14	White - Italian	Littera 2006
-	-	Cw8	Japanese	Gatanaga 2007
-	-	B*3505	Thai	Chantarangsu 2009
-	-	Cw4	Thai	Likanonsakul 2009
-	-	C*0404	Black African	Carr 2013
-	-	Cw*04	Chinese	Gao 2012
Aspirin	NSAIDs	DRB1*1302, DQB1*0609	-	Kim 2005; Palikhe 2008
-	NSAIDs	DR11	-	Quiralte 1999
Iodine contrast media	-	DR	White - Spanish	Torres 2008
Paraphenylenediamine	Hair dye	DP	White - German	Sieben 2002
Gold sodium thiomalate	Treatment of rheumatoid arthritis	DR5	White - Spanish	Rodriguez-Pérez 1994
Lamotrigine	Antiepileptic	B*5801, A*6801	White	Kazeem 2009
Trichloroethylene	Industrial solvent, dry cleaning	B*1301	Japanese	Li 2007; Watanabe 2010
Fixed drug eruptions				
Co-trimoxazole	Antibiotic	A30, B13, Cw6	White - Turkish	Ozkaya-Bayazit 2001
Feprazone	Analgesic	B22	-	Pellicano 1997

Footnotes

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Mallal 2008

[CRSSTD: 11696990]

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Alfirevic 2014

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Classification pending references

Data and analyses

1 Genetic testing with skin patch testing versus no genetic testing with skin patch testing

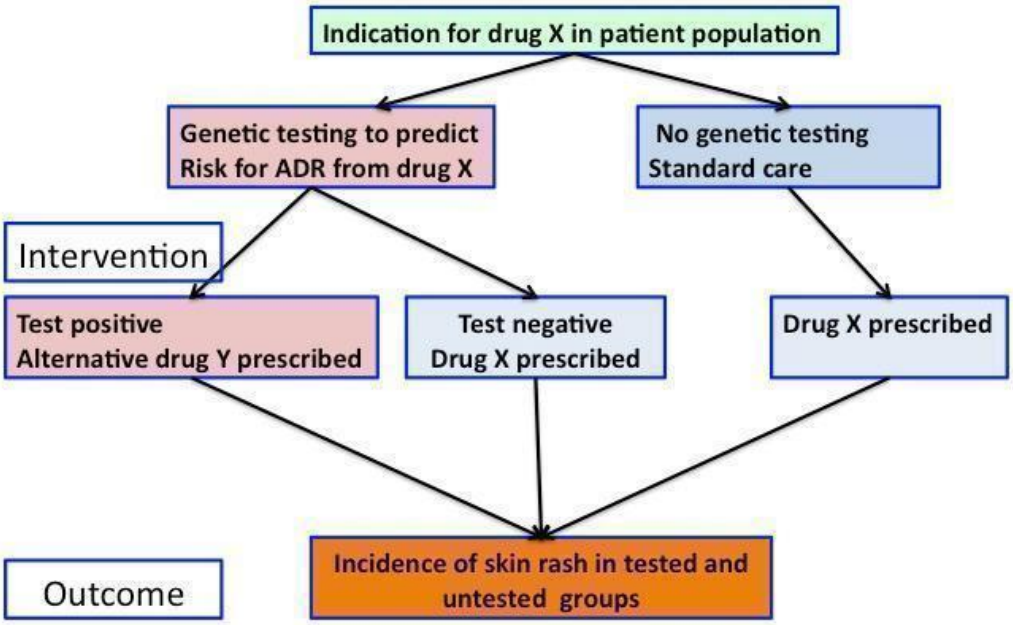
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Hypersensitivity (HSS), immunologically confirmed	1	1644	Risk Ratio(M-H, Fixed, 95% CI)	0.02 [0.00, 0.37]

2 Genetic testing versus no testing

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Hypersensitivity (HSS)	1	1650	Risk Ratio(M-H, Fixed, 95% CI)	0.43 [0.28, 0.67]

Figures

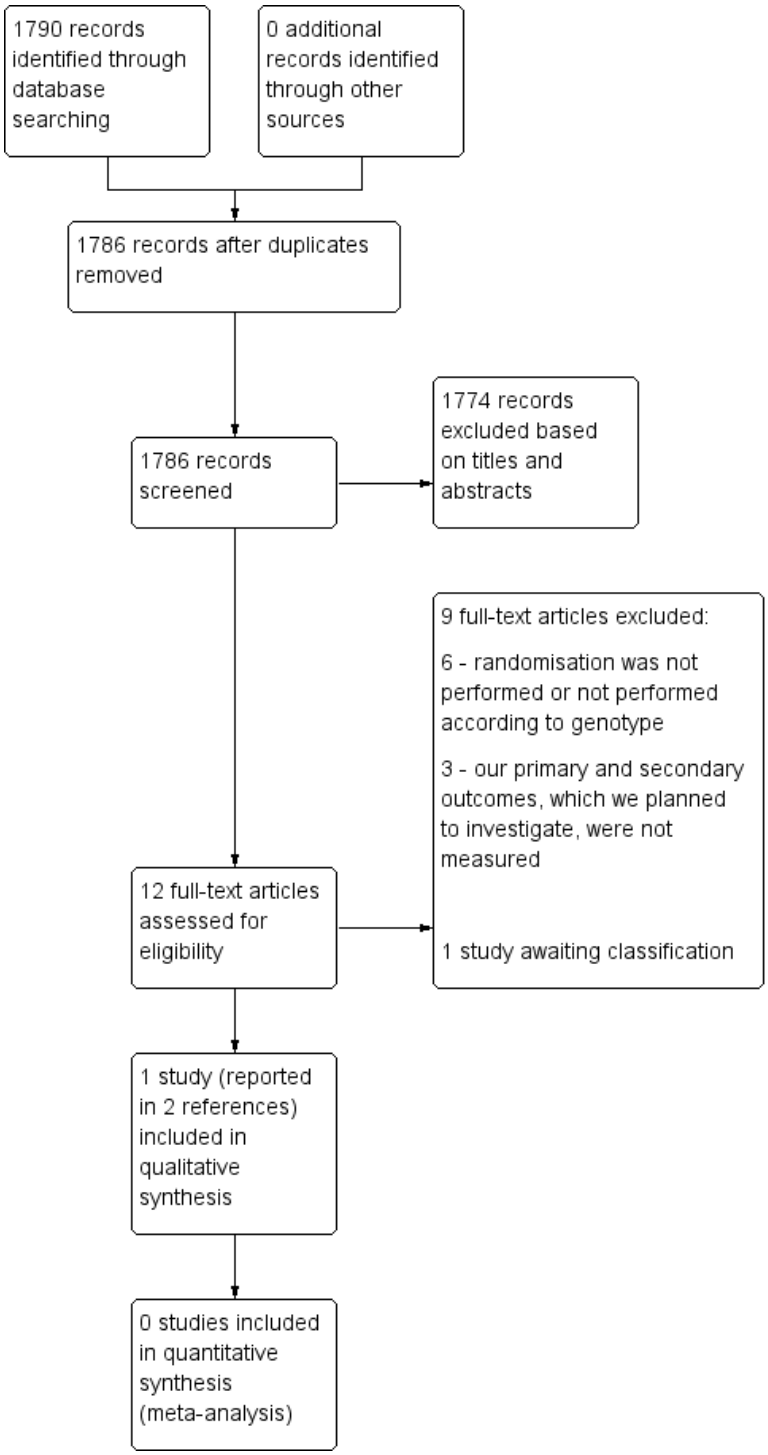
Figure 1



Caption

Flowchart of interventions (genetic testing) and outcomes (skin rash) in a patient population prescribed drug X

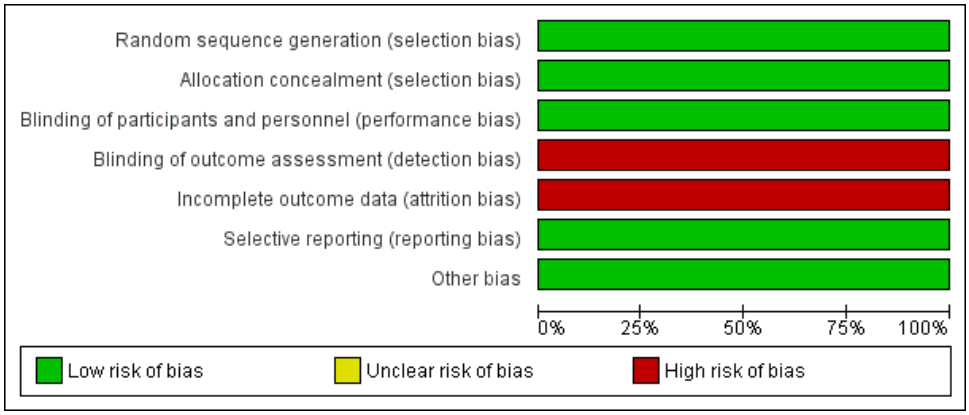
Figure 2



Caption

Study flow diagram.

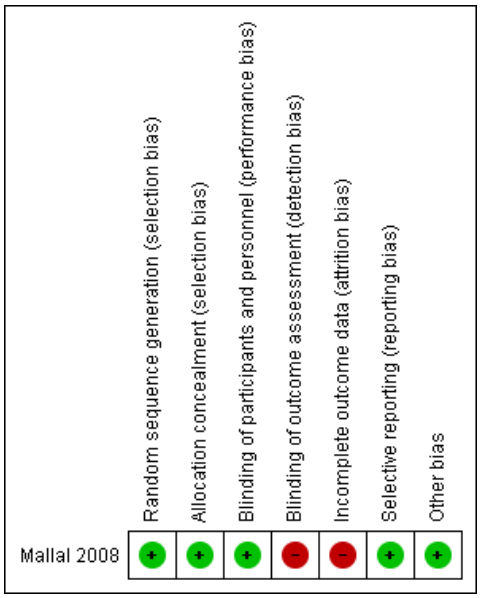
Figure 3



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

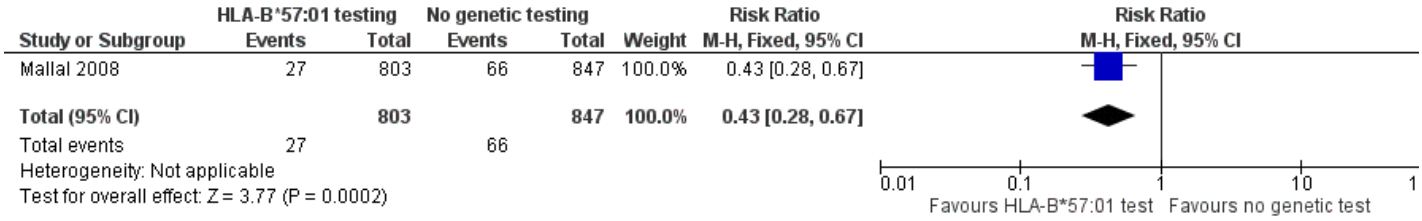
Figure 4



Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

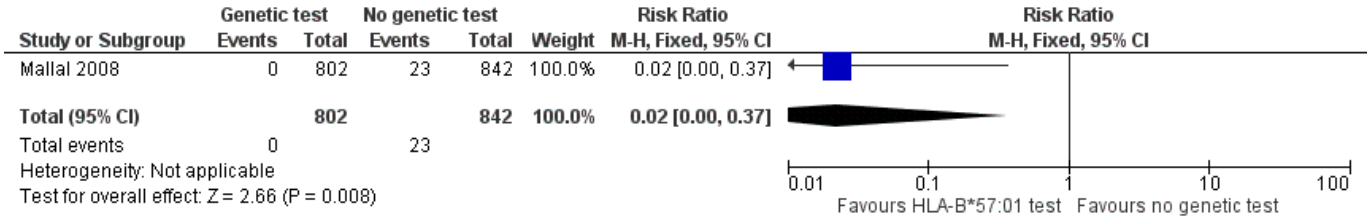
Figure 5 (Analysis 2.1)



Caption

Forest plot of comparison: 1 Genetic testing vs no testing, outcome: 1.1 Hypersensitivity (HSS).

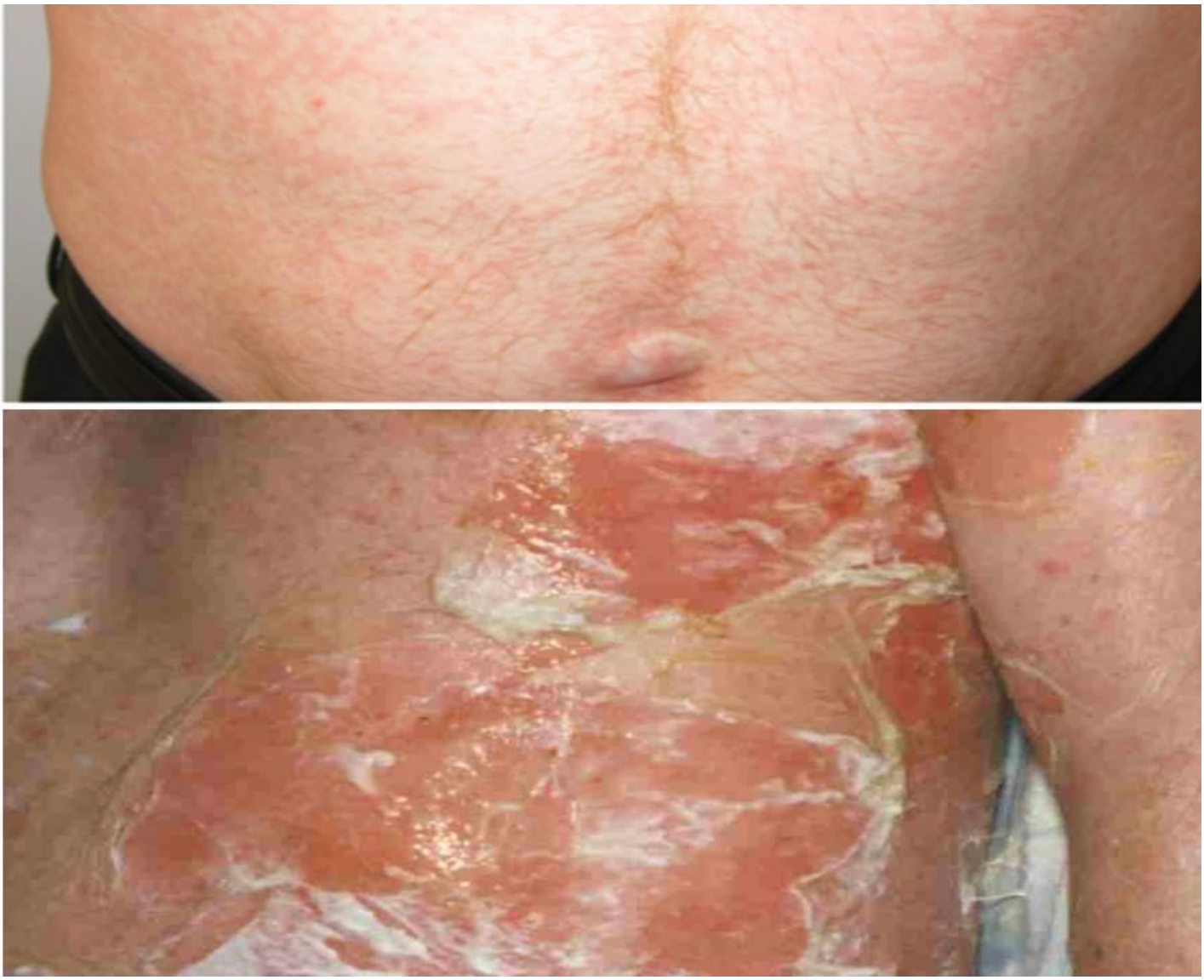
Figure 6 (Analysis 1.1)



Caption

Forest plot of comparison: 1 Genetic testing with skin patch testing versus no genetic testing with skin patch testing, outcome: 1.1 Hypersensitivity (HSS) immunologically confirmed.

Figure 7



Caption

Drug-induced skin rash: top panel = maculopapular exanthema, bottom panel = Steven Johnson Syndrome (blistering skin rash with skin detachment)

Sources of support

Internal sources

- No financial support, Other

External sources

- The National Institute for Health Research (NIHR), UK
  The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

Feedback

Appendices

1 Outcomes adapted from Pirmohamed 2011

Primary outcome:

- Drug-induced skin reaction (yes, no) Figure 7

Secondary outcomes:

- **SJS/TEN** (Stevens-Johnson syndrome, toxic epidermal necrolysis)
  - Skin detachment 1% to 10% (SJS), 10% to 30% (overlap syndrome), and > 30% (TEN)
  - Severe, often hemorrhagic, erosions of mucous membranes
  - Other manifestations indicating systemic involvement (e.g. fever, liver chemistry elevations, intestinal and pulmonary manifestations, or the presence of lymphopenia)

  - Severe pain and tenderness in the skin
  - Target lesions, representing the degree of epidermal necrosis
- **AGEP** (acute generalised exanthematous pustulosis)
  - Acute widespread edematous erythema followed by a sterile pustular eruption. Often the pustules are first localised in the neck, groin, and axillae, and later become widely disseminated
  - Fever (temperature > 38 °C)
  - Neutrophilia with or without a mild eosinophilia
- **HSS** (Hypersensitivity syndrome)
  - Additional terminology includes Drug-induced hypersensitivity syndrome (DIHS), Drug reaction with eosinophilia and systemic symptoms (DRESS), Drug-induced delayed multiorgan hypersensitivity syndrome
  - Variable skin manifestations; exanthema are most common
  - Increased liver function tests, hepatitis, cholestasis
  - Colitis
  - Nephritis
  - Pneumonitis
  - Aseptic meningitis, encephalitis, inappropriate antidiuretic hormone syndrome
  - Myocarditis
  - Myositis
  - Lymphocytic thyroiditis
  - Eosinophilia, atypical lymphocytes, agranulocytosis, thrombocytopenia, haemolytic anaemia, aplastic anaemia
  - Lymphadenopathy, pseudolymphoma

2 CRSW/Skin Specialised Register search strategy

(Exanthema or rash or rashes or “drug induced skin injur*” or “drug hypersensitiv*” or “hypersensitiv* reaction*” or “hypersensitiv* syndrome*” or “drug eruption*” or “drug toxicity” or “adverse drug reaction*” or “toxic epidermal necrolysis” or ten or “stevens johnson syndrome” or “Acute Generalized Exanthematous Pustulosis” or “erythema multiforme” or “dress syndrome” or “Drug Reaction with Eosinophilia and Systemic Symptoms” or “Drug Rash with Eosinophilia and Systemic Symptoms”) and (“genetic test*” or pharmacogenomic* or pharmacogenetic* or screening or “patch test*” or “HLA Antigen*” or “hla allele*” or “genetic polymorphism*” or “genetic variation*” or “genetic variant*" or "genetic variabilit*”)

3 CENTRAL (Cochrane Library) search strategy

#1 exanthema:ti,ab
#2 MeSH descriptor: [Exanthema] explode all trees
#3 (rash or rashes):ti,ab
#4 drug induced skin injur*:ti,ab
#5 MeSH descriptor: [Drug Hypersensitivity] explode all trees and with qualifier(s): [Genetics - GE, Prevention & control - PC]
#6 drug near/2 hypersensitiv*:ti,ab
#7 hypersensitiv* reaction*:ti,ab
#8 hypersensitivity syndrome*:ti,ab
#9 drug eruption*:ti,ab
#10 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees and with qualifier(s): [Genetics - GE, Prevention & control - PC]
#11 drug toxic*:ti,ab
#12 adverse drug reaction*:ti,ab
#13 toxic epidermal necrolysis:ti,ab
#14 MeSH descriptor: [Stevens-Johnson Syndrome] explode all trees
#15 stevens johnson syndrome:ti,ab
#16 Acute Generalized Exanthematous Pustulosis:ti,ab
#17 MeSH descriptor: [Acute Generalized Exanthematous Pustulosis] explode all trees
#18 erythema multiforme:ti,ab
#19 MeSH descriptor: [Erythema Multiforme] explode all trees
#20 dress syndrome:ti,ab
#21 Drug Reaction with Eosinophilia and Systemic Symptoms:ti,ab
#22 Drug Rash with Eosinophilia and Systemic Symptoms:ti,ab
#23 {or #1-#22}
#24 MeSH descriptor: [Genetic Testing] explode all trees
#25 genetic test*:ti,ab
#26 MeSH descriptor: [Pharmacogenetics] explode all trees
#27 (pharmacogenomic* or pharmacogenetic*):ti,ab
#28 screening:ti,ab
#29 patch test*:ti,ab
#30 MeSH descriptor: [Patch Tests] explode all trees
#31 MeSH descriptor: [HLA Antigens] explode all trees
#32 hla allele*:ti,ab

#33 MeSH descriptor: [Polymorphism, Genetic] explode all trees
#34 genetic polymorphism*:ti,ab
#35 (genetic variant* or genetic variation* or genetic variabilit*):ti,ab
#36 MeSH descriptor: [Genetic Variation] explode all trees
#37 {or #24-#36}
#38 #23 and #37

4 MEDLINE (Ovid) search strategy

1. exp Exanthema/
2. exanthema.ti,ab.
3. (rash or rashes).ti,ab.
4. drug induced skin injur$.ti,ab.
5. exp Drug Hypersensitivity/ge, pc [Genetics, Prevention & Control]
6. (drug adj2 hypersensitiv$).ti,ab.
7. hypersensitiv$ reaction$.ti,ab.
8. hypersensitivity syndrome$.ti,ab.
9. drug eruption$.ti,ab.
10. exp Drug Toxicity/ge, pc [Genetics, Prevention & Control]
11. drug toxic$.ti,ab.
12. adverse drug reaction$.ti,ab.
13. toxic epidermal necrolysis.ti,ab. or exp Epidermal Necrolysis, Toxic/
14. stevens johnson syndrome.ti,ab. or exp Stevens-Johnson Syndrome/
15. exp Acute Generalized Exanthematous Pustulosis/
16. Acute Generalized Exanthematous Pustulosis.ti,ab.
17. erythema multiforme.ti,ab. or exp Erythema Multiforme/
18. dress syndrome.ti,ab.
19. "Drug Reaction with Eosinophilia and Systemic Symptoms".ti,ab.
20. "Drug Rash with Eosinophilia and Systemic Symptoms".ti,ab.
21. or/1-20
22. exp Genetic Testing/
23. genetic test$.ti,ab.
24. exp Pharmacogenetics/
25. (pharmacogenomic$ or pharmacogenetic$).ti,ab.
26. screening.ti,ab.
27. patch test$.ti,ab.
28. exp Patch Tests/
29. exp HLA Antigens/
30. hla allele$.ti,ab.
31. exp Polymorphism, Genetic/
32. genetic polymorphism$.ti,ab.
33. exp Genetic Variation/
34. (genetic variant$ or genetic variation$ or genetic variabilit$).ti,ab.
35. or/22-34
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomized.ab.
39. placebo.ab.
40. clinical trials as topic.sh.
41. randomly.ab.
42. trial.ti.
43. 36 or 37 or 38 or 39 or 40 or 41 or 42
44. exp animals/ not humans.sh.
45. 43 not 44
46. 21 and 35 and 45

[Lines 36-45: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

5 Embase (Ovid) search strategy

1. exp rash/
2. exanthema.ti,ab.
3. (rash or rashes).ti,ab.
4. drug induced skin injur$.ti,ab.
5. exp drug hypersensitivity/pc [Prevention]
6. (drug adj2 hypersensitiv$).ti,ab.
7. hypersensitiv$ reaction$.ti,ab.
8. hypersensitivity syndrome$.ti,ab.

9. drug eruption$.ti,ab.
10. exp drug toxicity/pc [Prevention]
11. drug toxic$.ti,ab.
12. adverse drug reaction$.ti,ab.
13. toxic epidermal necrolysis.ti,ab.
14. toxic epidermal necrolysis/
15. Stevens Johnson syndrome/
16. stevens johnson syndrome.ti,ab.
17. acute generalized exanthematous pustulosis/
18. Acute Generalized Exanthematous Pustulosis.ti,ab.
19. erythema multiforme/
20. erythema multiforme.ti,ab.
21. DRESS syndrome/
22. dress syndrome.ti,ab.
23. "Drug Reaction with Eosinophilia and Systemic Symptoms".ti,ab.
24. "Drug Rash with Eosinophilia and Systemic Symptoms".ti,ab.
25. or/1-24
26. genetic screening/
27. genetic test$.ti,ab.
28. exp pharmacogenetics/
29. (pharmacogenomic$ or pharmacogenetic$).ti,ab.
30. screening.ti,ab.
31. patch test$.ti,ab.
32. patch test/
33. exp HLA antigen/
34. hla allele$.ti,ab.
35. exp genetic polymorphism/
36. genetic polymorphism$.ti,ab.
37. genetic variability/
38. (genetic variant$ or genetic variation$ or genetic variabilit$).ti,ab.
39. or/26-38
40. crossover procedure.sh.
41. double-blind procedure.sh.
42. single-blind procedure.sh.
43. (crossover$ or cross over$).tw.
44. placebo$.tw.
45. (doubl$ adj blind$).tw.
46. allocat$.tw.
47. trial.ti.
48. randomized controlled trial.sh.
49. random$.tw.
50. or/40-49
51. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
52. human/ or normal human/
53. 51 and 52
54. 51 not 53
55. 50 not 54
56. 25 and 39 and 55

6 LILACS search strategy

tw:((exanthema OR exantema OR rash OR rashes OR "toxic epidermal necrolysis" OR "stevens johnson syndrome" OR "erythema multiforme" OR "dress syndrome") AND ("genetic test" OR "genetic testing" OR screening OR "patch test" OR "patch testing"))

In LILACS we searched using the above terms and the Controlled clinical trials topic-specific query filter.

7 Contacted authors

Contacted authors	Study	Reason for the contact	Response
Simon Mallal	Mallal 2008	To ask for details on long term outcomes and patient exclusion	No response