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Risks and management of antiepileptic drug induced skin reactions in the adult out-patient setting

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ABSTRACT

Adverse cutaneous reactions caused by mostly aromatic antiepileptic drugs (AED) affect 50.000 people a year in the United Kingdom (UK; incidence 75.7/100.000). Optimal management of these cases is often difficult, as the patient may report symptoms to a general practitioner, attend Accident & Emergency or inform a specialist over the telephone or via email. When clinical assessment is limited it is thought safest to withdraw offending medication and inform the patient of a new drug allergy. This may unjustifiably restrict future treatment choices, and increase cost. Most frequent offenders are aromatic AEDs: carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, lamotrigine, phenobarbitone, primidone (recently licensed lacosamide associated with lower risk) and the sulpha-derivative zonisamide.

Our study provides a summary of severe delayed allergic reactions and offers a pragmatic management pathway for patients suffering a suspected drug-induced rash. We include UK pretreatment screening guidelines, step by step clinical assessment of rash and associated symptoms aiding early identification of patients at risk of developing severe allergic reactions. At the same time our manuscript reviews published data informing best choice and titration of alternative medication when allergy confirmed.

Finally we summarize current knowledge on genetic predisposition and other personalized risks of AED allergies identifying gaps in our current understanding.

1. Introduction

A history of allergic drug reactions often limits the choice of medical treatment. These are reported in 10% of community case notes and for up to 35% of patients attending a US teaching hospital [1]. Current assessment of drug hypersensitivity in the UK relies on self-reporting. This is often misleading. In over 40% of cases, penicillin intolerance is incorrectly labeled as 'allergy' [2].

Immune-mediated adverse reactions are most commonly caused by antibiotics. Though hypersensitivity to antiepileptic drugs (AEDs) is less common [3], the risk of severe allergy (e.g. Stevens-Johnson syndrome) is higher in this group. Over a five year period Arif et al. [4] documented a rash at any time during data collection in 15.9% of 1649 patients taking AEDs. As a group, aromatic AEDs, including phenobarbital (PB), primidone (PRM), carbamazepine (CBZ), oxcarbazepine (OXC), eslicarbazepine (ESL), lamotrigine (LTG), and phenytoin (PHT) are the worst offenders. Large studies on Lacosamide (LCM), a new aromatic AED launched in the UK in 2017 report risk of rash comparable to that on placebo [5]. Hypersensitivity is also commonly associated with Zonisamide (ZNS), a sulphonamide derivative. Though published data on incidence varies [6], annually an estimated 50.000 patients in the UK will suffer a skin rash after AED initiation. This equals annual incidence of 75.7/100.000. Fortunately only a minority of isolated skin reactions are at risk of becoming severe, potentially life threatening allergies [7].

When treating adult patients suffering from epilepsy, we often face the dilemma of adjusting AED dose or withdrawing an offending drug in response to a new skin rash. At other times the challenge is in planning treatment for a patient with a history of previous allergic reaction, with additional factors limiting choice of medication (planned conception, renal failure etc). Some patient groups, such as women of a childbearing age in remission on LTG or CBZ, or those with trigeminal neuralgia, kinesogenic dyskinesia etc. may especially benefit from desensitization. In these patient groups the choice of effective and safe AEDs is often limited. This paper offers not only a pragmatic review, but also recommendations for risk testing and management, based on our own clinical experience in this area; epilepsy service and the immunology/drug allergy clinic. Our aim is to inform clinical decision-

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Abbreviations

AE	Dantiepileptic drug
AGEP	acute generalised pustulosis
APT	atopy patch testing
CBZ	carbamazepine
CRP	c-reactive protein
DRESS	drug reaction with eosinophilia and systemic symptoms
DT	desensitization
ESL	eslicarbazepine
FBC	full blood count
HLA	human leukocyte antigen
IDT	intradermal testing
LCS	lacosamide
LFT	liver function test
LTG	lamotrigine
LTR	lymphocyte transformation responses
mg	milligrams
OXC	oxcarbazepine
PHB	phenobarbitone
PHY	phenytoin
SJS	Stevens Johnson Syndrome
TEN	toxic epidermal necrolysis
U&E	urea and electrolytes
ZNS	zonisamide

making, facilitate early and accurate identification of those at risk, and thus help avoid unnecessary drug withdrawal and incorrect labeling of AED hypersensitivity. Optimal management will not only prevent unjustified treatment restriction but also reduce health care costs.

2. Hypersensitivity; an idiosynchratic side effect

Cutaneous reactions are reported in between 1 to 8% of individuals on prescribed medication [8]. A minority of these are caused by true allergies. Hypersensitivity is an immune-mediated reaction, classified as a type B or *'idiosynchratic side effect'*. When suspected, patients must be assessed for 'red flag' features. If they have clinical signs of severe cutaneous hypersensitivity, or are at high risk of this, the offending drug must be withdrawn and avoided in the future. Re-exposure in this group carries unacceptably high risk of exacerbating the previously seen immune response. Reports addressing risk in males and females are conflicting. Multivariate analysis in large group of patients from the UK and Europe report no difference between sexes [4]. Smaller studies on patients with learning difficulty [3] and those from China found higher risk in females (2:1; androgens protective [7]). Hypersensitivity is more common in those with pre-existing immune or dermatological conditions, and at the extremes of life. Several genetic associations have already been identified (see HLA data below).

Immediate reactions evolve from minutes to hours after exposure. They are rapidly progressive IgE or histamine mediated medical emergencies. Anaphylaxis is more frequent in children, often after intravenous (IV) AED administration. Caution is advised, as rarely anaphylaxis may also occur, when a drug previously taken and tolerated orally is weeks or months later administered IV. Urticaria and angioedema have both been reported after exposure to aromatic AEDs. Isolated bronchospasm is rarely seen in patients with epilepsy, but a few cases have been described after IV PHT treatment [9]. While PHT is the most likely to cause immediate reactions, these are rarely anaphylactic. For patients at risk, safe and structurally different drugs are available for rapid iv administration in the acute setting, such as levetiracetam (LEV) and sodium valproate (VPA). Note that VPA as a liver enzyme inhibitor affects metabolism of several AEDs including PHT, fosphenytoin, LTG, PB and PRM. Bruni et al. [10] describe a complex interaction with PHT; VPA displaces protein bound fraction, thus increasing active PHT levels. This process may temporarily aggravate allergic reaction even after PHT discontinuation. Above interactions must be considered when VPA administered to patient diagnosed or at risk of AED hypersensitivity.

Immediate reactions often have a clear temporal relationship between administration of the offending drug and the allergic response, thus diagnosis is rarely in doubt. In these cases repeated exposure, or desensitisation is best avoided (high risk-benefit ratio). Mortality after re-challenge increases if a patient with an immediate reaction suffered additional cardiovascular or respiratory symptoms. In carefully selected cases skin prick testing and immediate intradermal testing (IDT) may be helpful, and if negative reintroducing the drug should always utilize a hospital based graded challenge format as detailed below.

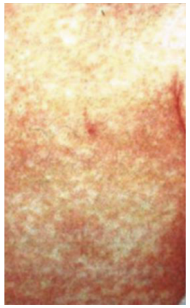
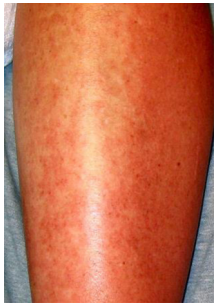
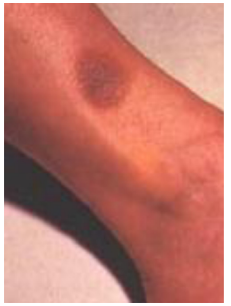
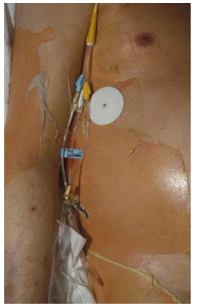
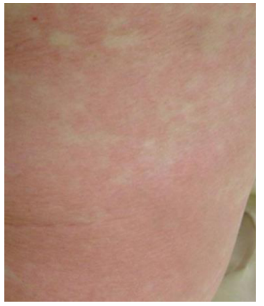
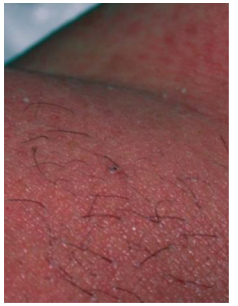
Delayed, mostly T cell mediated cutaneous reactions evolve from 12 h to days or weeks after the first AED dose was taken. The clinical picture may be varied, from a low risk isolated skin rash to severe systemic and multiorgan diseases such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). The clinical picture and skin rash is often non-specific at the onset, but may rapidly evolve from a blanching maculopapular rash with absent to mild systemic symptoms to the more widespread severe, often non-blanching/blistering/pustular rash with systemic upset in those developing the more severe reactions. Regular clinical assessment is critical and targeted investigations will identify patients at risk and inform choice of alternative future AEDs (see Table 1). In general, patients with simple maculopapular rashes without systemic symptoms and abnormal blood investigations (FBC, U&E, CRP, LFTs) tend not to progress to the more serious syndromes even if the offending drug is continued. This relates to the different immune mechanisms that underlie these reactions (see below).

Most AED induced allergic reactions are the result of delayed cell mediated hypersensitivity. These are insidious, may occur up to several weeks after commencement of new treatment, making it especially difficult to implicate a specific drug in patients prescribed various medications. This appears to suggest a direct drug induced T cell reactivity and with likely involvement of the HLA class I and sometimes class II proteins [11]. HLA-A*31:01 association has been most consistently identified for CBZ induced reactions ([12], see below). AED binding to specific parts of certain HLA molecules would then oligoclonally stimulate specific types of T cells as has been suggested in the case of the antiretroviral, abacavir induced reactivity in HLA-B*57:01 positive patients [13]. It is likely that there is also a reduction in more general T helper type 1 (Th1) function. This allows previously acquired viruses such as HHV6 (human herpes virus 6) and to a lesser degree HHV7 (human herpes virus 7), Epstein Barr Virus (EBV) and cytomegalovirus to reactivate [14–16]. The final clinical features of the AED induced skin reaction are therefore a composite of direct immune response and viral reactivation with features of infection by one or more of the above viruses. Symptomatically, the latter may be associated with fatigue, headache, myalgia, fever, sore throat with cervical lymphadenopathy, raised liver function tests. Clinical assessment and targeted investigations will identify patients at risk and inform management (see Table 1 and Fig. 2)

3. Management of AED induced rash

Neurologists as well as general practitioners, psychiatrists and pain management specialists may receive messages from their patients about a skin rash following initiation of an aromatic AED. If symptoms started within 8 weeks after taking first dose, and other causes (co-medication, contact chemical/cosmetic, known or new skin conditions) have been considered and excluded, a symptom based clinical risk assessment is

Table 1
Clinical characteristics of common cutaneous skin reactions informing differential diagnosis - a structured review. AGEP = Acute generalized exanthematous pustulosis, CBZ = Carbamazepine, HLA = human leukocyte antigen, LTG = Lamotrigine, PB = Phenobarbital, PHT = Phenytoin.

Reaction	maculopapular	Urticaria	Fixed Drug reaction	SJS/TEN	DRESS	AGEP
Picture						
Incidence	Some data suggests 1.7/100,000 of the total population. Of these 0.05/100,000 from antiepileptics.	Some data suggests 1.7/100,000 of the total population. Of these 0.01/100,000 from antiepileptics.	No good statistics on incidence.	Around 0.1/100,000 of the total population. For incidence among new users of CBZ, LTG, PB, PHT, the incidence is around 0.1-0.01%	Good data is lacking, however estimated to be 0.1-0.01% of patients exposed to potentially causative drugs.	0.1-0.5/100,000 of the total population.
Risk Factors	Commonly associated with CBZ and PHT CFHR4 has an association with Phenytoin induced maculopapular exanthema. HLA-A*3101 has an association with CBZ induced maculopapular exanthema.	Most common in children and young adults, and in those with a history of allergy or atopy	HLA-B*22	Rapid titration. Genetic risk factors include; HLA-B*1502, and HLA-A*2402 in Han Chinese populations. HLA-A*3101 for CBZ in European populations.	HLA-A*3101	More frequent in women. Genetic risk factors include IL-36RN
Rash onset	Under 2 weeks	Days	Days	2-8 weeks	2-8 weeks	Within 11 days
Preceding features	Usually none, however some complain of malaise	Usually no preceding symptoms	Usually no preceding symptoms	Fever, headache, rhinitis and myalgia, preceding exposure by 1-3 days	Fever over 38.5, in 90% of patients. Also dysphagia, Lymphadenopathy, puritis and pain.	Preceding symptoms are vague with malaise and sometimes low grade fever.
Associated features	Itch (excoriation)	Lesions fluctuate, may be confluent and itchy	Locally pruritis, burning and pain. Systemic symptoms are uncommon.	Mucosal blistering, fever, fatigue, flu-like symptoms desquamation and bullae	Eosinophilia, abnormal liver function tests, gastrointestinal and pulmonary involvement	Oedema of the face, sometimes mild oral mucous membrane involvement, fever and leucoytosis.
Resolution	Under 2 weeks	Rarely lasts more than a few days, chronic urticaria if over 6 weeks.	Days to weeks	Re-epithelialisation occurs within 3 weeks. Further complications take longer to resolve	May begin to resolve within 1 month, but still at risk of complications after several months	Days
Differential diagnoses	Measles, scarlet fever, viral exanthema.	Eczema, maculopapular, erythema multiforme, pityriasis rosea.	Spider bite, bullous pemphigoid	Staphylococcal scalded skin syndrome, disseminated fixed bullous drug eruption, graft vs host disease, EMM	At onset it may be difficult to differentiate from maculopapular exanthema or AGEP.	AGEP, corneal pustular dermatosis, IgA pemphigus, Bullous Impetigo.
Treatment	Purely symptomatic. Some prescribe topical corticosteroids or oral antihistamines.	Antihistamines or oral Steroids.	Top steroid, oral treatment rarely required	Supportive care, consult dermatology, burn unit if over 25% BSA involve	Supportive therapy, including antipyretics, antihistamines, topical corticosteroids. If internal organ involvement, corticosteroids, can be considered	Admission, and treatment with moisturisers, topical corticosteroids, oral antihistamines.
Desensitize / re-challenge	Desensitisation possible	Desensitisation possible	Desensitisation possible.	No	No	Possible with caution
mortality	N/A	Rare unless angioedema develops	N/A	Up to 30%	10%	4%

required. The offending drug must be withdrawn if the patient cannot be monitored safely (cognitive problems, elderly, lack of carer etc.). It is important to characterize the rash; when hemorrhagic, blistering, pustular, confluent or involving mucus membranes, the risk of a severe allergic reaction is high. Further 'red flags' are the presence of systemic symptoms, such as malaise, fever, lymphadenopathy. When in doubt, a blood test (FBC, CRP, LFT, U&E) and urine dipstick for blood and protein will add further information. For a comprehensive assessment and management pathway see Fig. 2.

If the rash is non-confluent, maculopapular, limited to skin and in a systemically well patient, it is safe to reduce the dose of the offending AED and monitor patient. If required, an antihistamine may be started. After symptoms resolved, dose may be escalated at a slower rate. Morbilliform rashes are the most frequent and are usually mediated by CD4 Th1 cells. Systemic symptoms are few and the role of viral reactivation in the aetiology of the reaction is unclear. Thus, quite often viral titers and copy numbers are only evident many days after the onset of the reaction. Atopy patch testing (APT) involving the application on intact forearm skin of a very small quantity of the suspected drug mixed in white soft paraffin or normal saline and assessed after 48–72 h may be helpful in determining the AED responsible for the reaction and appears to have only a low risk.

In case of high risk or confirmed diagnosis of severe hypersensitivity an alternative and safe AED must be sought. As Hirsch et al. [17] reported prescribing another aromatic AED also carries a risk. For example, a patient allergic to OXC or PB has an estimated 70% risk of a similar reaction to CBZ (Fig. 1). This risk reduces with slow titration or desensitization regimen. Caution is advised when switching treatment from LTG, PB, PRM or PHY to VPA, as if it is started before the offending AED is fully metabolized and excreted, VPA may transiently increase levels and worsen hypersensitivity.

4. Delayed hypersensitivity syndromes and desensitization

Exact description and onset of symptoms, rash pattern, character and distribution with any additional systemic symptoms will secure an accurate diagnosis of AED reactivity (Table 1). This is critical for determining the mechanism of drug reaction [18]. Especially important is onset of the reaction in regard to the first drug dose administration. In certain types of delayed reactivity, APT [19,20] and delayed reading intradermal testing (IDT) is helpful. However, this needs to be performed several weeks after the disappearance of all features of the reaction. Determining the 'non-irritant' concentration of the offending AED is a challenge, as this has not been conclusively ratified for many AEDs [21]. Unfortunately, the risk of an accelerated drug induced reaction with re-exposure is significant and may sometimes be accompanied by systemic symptoms. In some cases, continuation of AED treatment may be possible; perhaps with steroid and anti-viral medication to reduce symptoms, many caused by viral reactivation. The latter is considered to involve one or more of the common herpes viruses such as HHV6, EBV, HHV7 etc which are released from immune control by a drug induced immune dysfunction. While routine non-toxic anti-viral medication against these viruses is not generally available, a trial of acyclovir or valaciclovir in full anti-varicella-zoster dosage is worth considering alongside carefully utilized steroids as both have at least activity against these agents [22,23].

In the case of Drug reaction with eosinophilia and systemic symptoms (DRESS) a T helper lymphocyte (Th) type 2 pattern of cellular reactivity is evident, although the reaction can be acute and occasionally life-threatening. The Th2 cytokines interleukin (IL) 4 and IL5 appear critical and the typical DRESS reaction is associated with a fever, sore and mildly itchy flat to mildly bumpy rashes and systemic symptoms. The latter often comprise lymphadenopathy, abnormal liver function, interstitial nephritis, lung and heart infiltrates and several haematological abnormalities: especially eosinophilia and atypical lymphocytes. The AEDS most frequently associated with DRESS are PHT and CBZ. Other drugs that are implicated in causing dress include allopurinol, minocycline and sulphonamides. The diagnosis is often not in doubt with the typical syndrome but IDT with reading of the test at 24, 48 and 72 h can be used with a very high dilution of the most likely causative drug. When test positive, redness, swelling and scaling may be evident although sometimes blistering can also be seen. The value of lymphocyte transformation responses (LTR) remains unclear although they have been informative in some cases [24]. In the case of DRESS, Cabañas et al. [25] recently reported LTR sensitivities and specificities of 73% and 82% in 41 patients with DRESS secondary to β lactams, contrast media and AEDs, all assessed during the recovery phase. These figures were 100% in the case of AEDs.

Acute generalised pustulosis (AGEP) is considered the result of T helper 17 mediated reactivity in which pustules are seen in several parts of the body but especially on the chest and upper back. Here drug

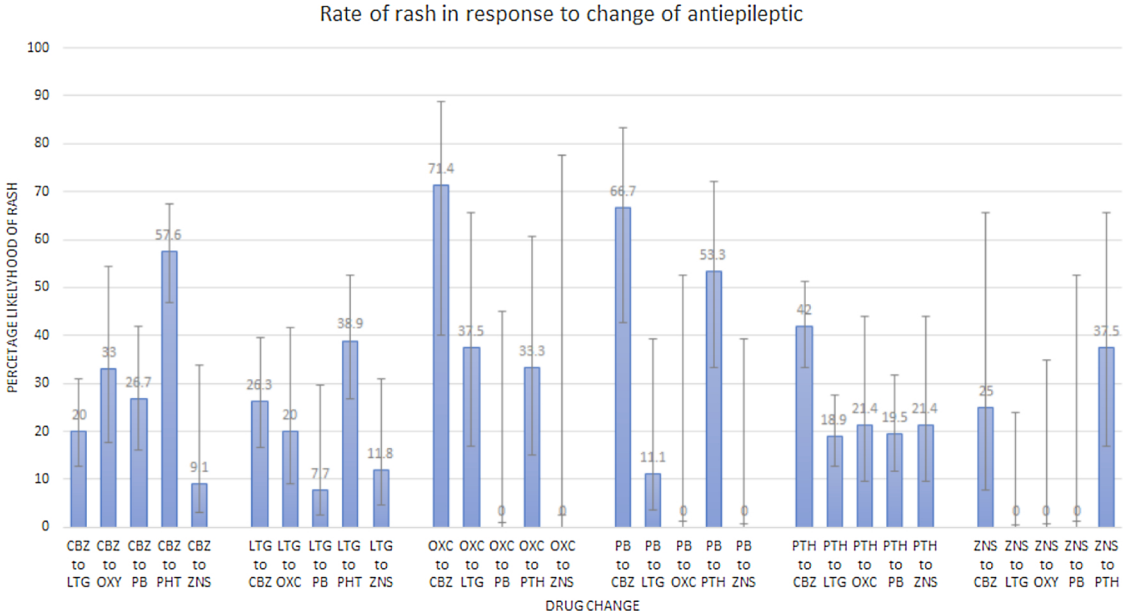


Fig. 1. Risk of allergic rash / hypersensitivity with new AED in patients with history of skin reaction to previous medication. Note confidence interval high in columns with low number of patients in group. Created using data from [17].

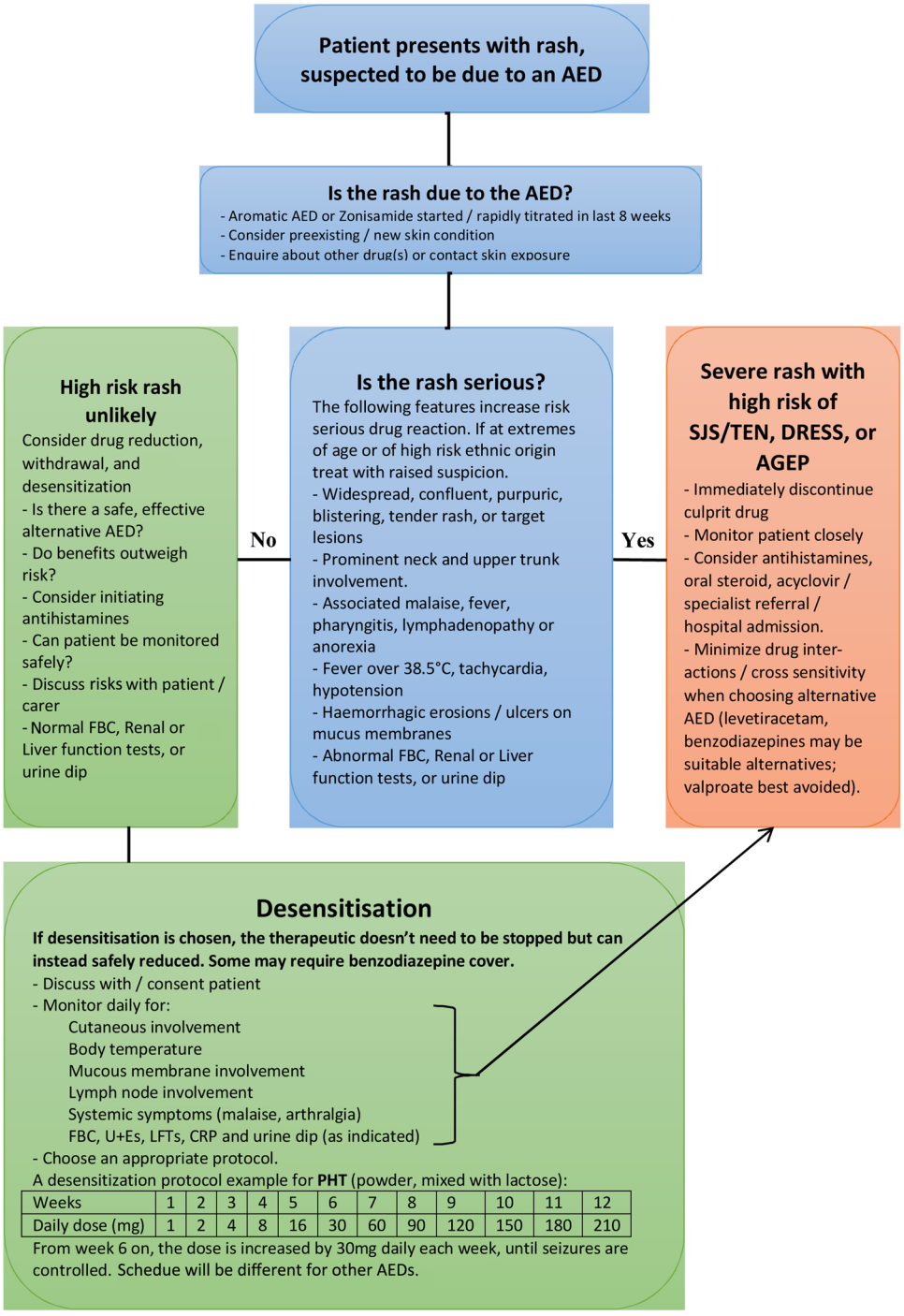


Fig. 2. Management pathway for patients presenting with AED related skin reaction summarising red flag signs of high risk hypersensitivity.

mediated stimulation of excessive interleukin 8 (IL8) secretion leads to recruitment of T cells and neutrophils to the skin and systemic symptoms that include cutaneous itching/soreness, fever and fatigue [26]. Both APT and delayed reading ID has been considered helpful in confirming specific drug involvement.

The most serious of the delayed drug reactions seen with the AEDs is severe erythema multiforme (EM) at the mild end of the spectrum and SJS/Toxic Epidermal Necrolysis (TEN) at the severe end. Here CD8 T cells secrete perforins, granzymes and other factors that directly damage epidermal and mucosal cells. In the past skin testing, and intradermal testing in particular, has been considered dangerous and with a significant risk to reactivate skin inflammation. However, testing using very low amounts of the drug may be undertaken safely and 0.001% of the dose that was considered causative of the reaction is suggested. If the result is positive, then the drug is definitely avoided. The problem arises with a negative result and whether the drug should be offered even in a desensitization regime as described below.

As yet, pre-treatment atopy patch testing (APT) has not been investigated as means of predicting potential reactivity in several of the delayed severe T cell mediated AED sensitivities. Clearly the danger is that the testing may stimulate potential reactivity which was previously absent. In the case of T cell mediated penicillin hypersensitivity, negative delayed reading skin tests has provided an excellent negative prediction for non-reactivity to a carbapenem [27]. In the case of AEDs, once a reaction has occurred, skin prick test (SPT) may be helpful for acute IgE mediated reactions accompanied by urticaria and angioedema with or without

cardiorespiratory symptoms. For the delayed reactions including DRESS, APT [20,28] may be helpful. In the case of AGP and SJS/TENS IDT with delayed reading of the test at 24, 48 and 72 h may be useful. In these latter cases a 0.1% solution is suggested for the testing as this is very unlikely to produce a recurrence of the reaction.

The gold standard in establishing specific drug reactivity is provocation testing. For certain types of reactions such as SJS/TENS this is extremely hazardous and carries a very significant risk of reactivating muco-cutaneous inflammation and blistering. However, where there is doubt as to the cause of type 1 reactions and morbilliform rashes and SPT has been negative or equivocal, provocation testing may be undertaken utilizing a graded challenge at specific time intervals. For the type 1 reactions a 0.1% dose followed by a 1% dose 3 h later and then 10% dose 3 h subsequently and finally 100% dose 3 h after this is suggested. Clearly an IV line and emergency facilities should be available. In the case of the delayed onset morbilliform rashes, the same doses should be offered at 24 h intervals and the patient may be allowed home between the exposures.

The alternative to provocation testing in the case of patients with mild type 1 reactions without cardiorespiratory compromise and mucocutaneous inflammation is an active desensitization process [29]. This may also be employed in those with morbilliform rashes and possibly AGEP. Here parallels may be drawn with general penicillin allergy, piperacillin/tazobactam, ceftazidime, meropenem and aztreonam allergy in cystic fibrosis [30] and cotrimoxazole hypersensitivity in HIV infection [31]. The precise regime to be employed with AED desensitization should be based on the immune basis of the AED reactivity. Notwithstanding, the aim is to increase blocking drug specific IgG4 antibodies, decrease the auto-reactive Th1, Th2, Th17 cells and/or increase the number of T regulatory cells that can keep drug specific T cells under control [32]. Interestingly, an increase in the latter was noted after allopurinol desensitisation for a fixed drug eruption by Teraki and Shiohara [33]. However, more specific evidence in those with AED reactivity is lacking.

In terms of desensitization for AED induced reactions, three types of regime may be utilized although intermediate patterns can be used and varied according to time constraints and facilities for inpatient stay. For the immediate type 1 IgE mediated reactions confirmed by SPT, several regimes are available. The first involves an inpatient 'rush' exposure to the chosen AED. It is initially introduced at a 0.1% dose and the amount doubled at 2 hourly intervals until the desired dose is reached. Facilities for cardiorespiratory resuscitation should be available although in the case of penicillin and insect venom desensitization this type of regime is considered very safe. The second regime involves an initial 0.1% dose of the drug being offered and the doubling interval being every 24 h. In the third regime, the 0.1% initial dose is taken daily for a week and the dose doubled at weekly intervals. In the authors view this perhaps the safest of the three regimes but only possible where there are no time constraints. Unfortunately, this is not often available in patients with epilepsy. Regardless, regular contact with the patient/carer is clearly critical in the case of the regimes used on an outpatient basis. In the case of morbilliform rashes and AGEP, the second and third patterns of desensitization may be used with doubling increments daily or weekly. In terms of using prophylactic anti-histamines and/or steroids there is no consensus on their use in any type of desensitization [29].

There is little or no research in the use of AED desensitization in patients suffering SJS/TENS and DRESS and even those returning negative skin testing. There is a clear risk of reactivating the original reaction as there are high numbers of T memory cells that are long lived and reactivate quickly on drug re-exposure. Overall, we would not recommend desensitization in patients whose AED sensitivity is associated with this type of reactivity and especially if there are alternatives available.

5. Aromatic AEDs

5.1. Lamotrigine

LTG is a relatively well tolerated AED, with a wide spectrum of efficacy, including focal, generalized as well as tonic-clonic seizures and Lennox-Gastaut syndrome. It is also prescribed as a mood stabiliser in bipolar disease. Pregnancy outcome data is also encouraging; LTG is one of few low risk choices for women of childbearing age with idiopathic generalised epilepsy.

A rash is a common side effect of LTG treatment, occurring in 8.3%, with half of these withdrawing medications as a consequence [34]. This may be an over cautious measure, as separate studies have found that only 0.04% of new users develop SJS/TEN, and less than 0.1% develop DRESS [35]. Many clinicians are aware of appearance or aggravation of acne in those staring lamotrigine, however literature on this is sparse [36].

The risk of a severe rash from LTG is reduced by over 10 fold with slow titration schedule such as 25 mg fortnightly increments [34]. The risk of rash is increased when LTG is prescribed with VPA, as it competitively inhibits LTG glycoxidation in the liver, increasing half-life. When the offending aromatic anticonvulsant is exchanged for another aromatic AED, there is up to 60% risk of rash reoccurrence ([17]; Fig. 1).

For selected ethnic groups a genetic predisposition has been identified: HLA-B*15:02 in Han Chinese (odds ratio 4.98, 95% confidence interval 1.43–17.28), HLA-B*44:03 and HLA-B*38:01 alleles as a probable risk factor for SJS/TEN in the Korean population [37,38,39]. HLA-A*24:02 was recently confirmed as a shared risk factor for SJS/TEN after exposure to aromatic AEDs, including LTG [40]. Pre-treatment screening for HLA-B*15:02 and HLA-A*24:02 is indicated in Han Chinese and future studies are expected to confirm other ethnic groups at risk.

Further risk factors for LTG induced hypersensitivity include infection with human immunodeficiency virus (HIV), co-administration of antiviral drugs, liver disease, advanced age, and concomitant use of immunosuppressive agents. LTG titration may also coincide with the appearance of an unrelated skin condition, such as rosacea, acne etc [41]. Our clinical experience suggests this is more likely in women.

Several publications suggest, if LTG related cutaneous reaction is without red flag signs, it is safe to either treat through with or without antihistamine cover, or lower the dosage until resolution and re-challenge with slower titration regimen [29,42,43]. Serious adverse cutaneous reactions are rare, with only 0.3% of those with a rash requiring hospitalization. Rechallenge should only be attempted if patient can be safely monitored in the Community and benefits of continuing treatment outweigh risks. To make this decision, clinicians should consider the necessity of LTG treatment and the availability of suitable, safe and effective alternative drugs with acceptable risk of cross reactivity (Fig. 1). Rechallenge is successful in 87% (n = 48) of those in whom it is attempted [42]. A starting dose of 5 mg or 12.5 mg daily is recommended for the first 2 weeks, and then increased to 25 mg once a day for a fortnight. Additional 25 mg fortnightly increments are then added until the target dose is reached. Cautious titration using a re-challenge regimen may also be appropriate if the individual previously developed a non-serious skin reaction to other aromatic AEDs (CBZ, OXC etc). After LTG induced SJS/TEN, DRESS, or other serious hypersensitivity rechallenge must not be attempted. If in doubt, and further assessment of LTG treatment risk is indicated, referral for skin testing may be appropriate.

5.2. Carbamazepine

CBZ is an aromatic voltage dependent sodium channel inhibitor, with a wide range of uses. As an AED it is first line agent for focal onset seizures in monotherapy. It's also key in the treatment of trigeminal neuralgia, kinesogenic dyskinesia, bipolar disorder, prescribed unlicensed for alcohol withdrawal and diabetic neuropathy. Between 1–10% of patients develop a cutaneous reaction; over 85% of these are mild maculopapular reactions. SJS/TEN is estimated to occur in less than 0.06% of adults started on CBZ, 0.04% or fewer develop DRESS [44].

The mechanism of CBZ induced skin reaction remains unknown. Theories propose abnormalities in drug metabolism producing toxic by-products (arene oxides), or major histocompatibility complex presentation of metabolites to T-cells which are found in skin lesions of DRESS and SJS/TEN. HHV 6 and 7 reactivation was shown to play a part, and when present may worsen prognosis [45].

The HLA-B*1502 allele (both hetero- and homozygous) was first described as a risk factor for SJS/TEN, however not DRESS, in the Southeast Asian population. This allele is most prevalent (15%) in Hong Kong, Malaysia, Thailand and the Philippines. In Caucasians this antigen is largely absent. It is estimated to have a 98.3% sensitivity, 97% specificity, a 7.7% positive predictive value and a 100% negative predictive value, for developing SJS/TEN on CBZ [46]. Guidelines for screening CBZ naïve patients are in place in UK (BNF), US (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/016608s098.020712s029.021710_ClinRev.pdf), Canada and the Netherlands (https://www.ncbi.nlm.nih.gov/books/NBK321445/pdf/Bookshelf_NBK321445.pdf).

HLA-A*3101 positivity increases the risk of SJS/TEN, DRESS and maculopapular eruptions. This marker is prevalent in 15% of Japanese, South Indians and Native Americans, in 10% of Europeans, South Koreans and Han Chinese. Those positive have a 0.89% risk of developing DRESS when exposed to CBZ, which is over five times less than in those carrying HLA-B*1502).

HLA-B*1511 is a risk factor for SJS/TEN in Japan, Korea and central China, also in those negative for HLA-B*1502. This allele is seen in around 1% of this population. Patients positive for HLA-B*1511 have a 0.27–0.73% risk of developing SJS/TEN. Other HLA markers have also been investigated as potential markers of CBZ hypersensitivity with data at present inconclusive [47]. Screening for these and other less studied markers is currently not recommended in the UK.

When the at risk population is identified and no acceptable alternative to CBZ / OXC treatment is available, close monitoring and slow titration using a desensitization regimen, will reduce the risk of hypersensitivity. Warning signs and symptoms, alongside risks and benefits must be discussed with patients if this management is chosen. Any patient positive for the above markers and tolerating CBZ without adverse effects for over 3 months is at low risk of hypersensitivity to this AED.

In the case of a CBZ induced rash with red flags for DRESS or SJS/TEN, medication must be immediately discontinued. Early hospitalisation and steroids are important in the management of DRESS. Some authorities recommend IVIG and plasma exchange. If there's doubt about the culprit drug, patch testing has been safely used to determine whether there is a reaction to CBZ, with positive patch tests in 62.5% of those after SJS/TEN reactions, and in 70% of those after DRESS reactions [48]. It can also be used to check for cross-reactivity if the decision is made to discontinue CBZ. In our opinion, APT should be used first and if this is negative then SPT using a 0.001% amount of the daily drug dosage is undertaken. If both are negative and the clinical suspicion for drug reactivity is low then a graded challenge may be considered.

5.3. Oxcarbazepine

OXC is structurally similar (keto-analogue) to CBZ launched in the UK almost 20 years ago, with comparable licensed indications. The incidence of skin reactions and hypersensitivity is lower than seen with CBZ, it is described as a side effect in 3% of 2436 patients [49]. This is below 50% of that seen on CBZ. In the same population two cases of exfoliative dermatitis and three of erythema multiforme were identified. When those with previous CBZ hypersensitivity are excluded from recruitment, rates are lower: from 521 patients prescribed add-on oxcarbazepine, none were reported to suffer a rash / allergies [50]. The British National Formulary (BNF) advises caution when starting OXC in patients with historic CBZ hypersensitivity. Hirsch et al. [17] using retrospective data and routine drug titration regimens, reports the risk of a rash after OXC exposure in those previously sensitive to CBZ 33% (n = 15). Interestingly in the reverse situation (prescribing CBZ to those previously allergic to OXC), the risk increases to 71% (note n = 11). Drug titration using desensitization regimens is expected to reduce these numbers.

A paediatric case series (n = 20) of successful OXC desensitization have been published [51]. Asian children selected for the procedure previously suffered only mild cutaneous adverse reactions to the drug; those with severe hypersensitivity (SJS/TEN, DRESS) were excluded.

HLA-B*1502 association has also been recognized as a risk factor (positive predictive value: 0.73% versus 7.7% for CBZ) for OXC induced SJS/TEN (n = 26; [52,53]). Reactions are described as less severe than those seen this CBZ. The BNF and 2017 guidelines for Clinical Pharmacogenetics Implementation Consortium [47] recommend screening and avoiding exposure to OXC in HLA-B 51:02 positive patients. An exception may be made in those who had previous exposure to OXC for 3 months or longer with benefit and without signs of allergy.

5.4. Eslicarbazepine

ESL is the most recently (10 years ago) launched carboxamide derivative licensed for focal onset seizures in the UK. The drug is given as acetate which is rapidly metabolized to the same though mainly active S isomere metabolite as oxcarbazepine, licarbazepine (monohydroxycarbazepine). Up to 2.6% of patients report ESL related adverse skin reactions. Less than a third stops the medication as a consequence [54]. The lower incidence of skin reactions may be due to the absent toxic epoxide metabolite when compared to CBZ. More severe skin reactions are in the form of case reports: erythema multiforme major is reported 25 days after ESL treatment started [55]. In 2018 Finelli et al. [56] describe a case of purpuric maculopapular rash associated with systemic symptoms (not satisfying diagnostic criteria for DRESS) 10 days after ESL exposure. This patient's skin patch test was later positive for ESL.

Due to the structural similarities with CBZ, as for OXC, the BNF recommends pretreatment HLA-B*1502 screening in Han Chinese or Thai origin. In positive patients the risk of SJS is considered high, and where possible, an alternative AED is recommended. A desensitization protocol has not been published for ESL.

5.5. Phenytoin

This aromatic AED has been available in the UK to treat focal onset seizures and status for over 60 years. It is also licensed for postsurgical/post head injury seizure prophylaxis. Cutaneous reactions seen in 5% of patients limit its use. The incidence of SJS/TEN is reported 69/100,000, and 23/100,000 for DRESS. Numbers are several folds higher in Asia: 240/100,000 and 210/100,000 respectively [57]. Risk factors for PHT related hypersensitivity include a history of allergic reaction to other aromatic AEDs and reactivation of latent viruses, such as HHV, EBV, or CMV. Cranial irradiation for malignancy is associated with SJS in patients taking PHT, first cutaneous symptoms appear at the site of radiation exposure, spreading from there [58].

As for CBZ and OXC, presence of HLA-B*1502 allele increases the risk of SJS/TEN in south Asian population (p = 0.0041; [53]). The BNF carries a warning: unless essential, PHT should be avoided in patients positive for HLA-B*1502. Other HLA subtypes were studied in Thailand [57]. Patients (n = 36; versus 100 PHT tolerant controls) harbouring HLA-B*1301 or HLA-B*5602 and HLA-B*5604 variants were found to be at increased risk of DRESS and drug hypersensitivity syndrome. The sensitivity of combined screening is 66.7% in this population. Shi et al. [40] showed HLA-A*2404 allele increases the risk of SJS when exposed aromatic AEDs, including PHT (p = 0.027) in those with Southern Chinese ancestry. A small Spanish study reports PHT induced SJS/TEN harbouring the HLA-A*02:01/Cw*15:02 allele combination in Caucasians (n = 9, one South American; [59]). When interpreting these

findings, keep in mind: the study investigated numerous outcome measures. McCormack et al. [60] found no association of HLA-A*3101 and maculopapular eruptions in the UK. Note only one patient with SJS was recruited for this study.

McCormack et al. [12] identified a novel, complement factor H related 4 gene in patients developing maculopapular rash on PHT ($p = 4.5 \times 10^{-11}$). This association was confirmed for those with European descent (n = 259), but not Han Chinese (n = 116) and not controls tolerant of 3 aromatic AEDs (n = 1321). No HLA associations were detected.

In addition, cytochrome P450 polymorphism (CYP2C9) is also expected to increase the probability of severe cutaneous adverse reactions (SCARs), in both DRESS and SJS/TEN [61]. CYP2C9 is known to be involved in the clearance of PHT; polymorphs are likely to cause the accumulation of toxic arene oxides. Similar mechanism is suspected when PHT is used with an enzyme inhibitor, such as VPA.

Desensitization can be attempted several weeks after non-seriouscutaneous reactions have resolved. A successful published PHT desensitization regimen (PHT power mixed in lactose) is detailed in Fig. 2 [62].

5.6. Phenobarbitone

This drug is a well-established AED, infrequently prescribed in the UK today. In many other and most developing countries it remains first line treatment for epilepsy. Rash and other severe allergic reactions are quoted as rare when administered, a Cochrane review of monotherapy studies found an incidence of 2.25% (n = 754; [63]). The risk of SJS/TEN in new users is somewhat higher than for PHT, estimated 82/100,000 [64], this compares unfavourably with VPA at 5/100,000. Intravenous application and previous SCARs to other aromatic AEDs will increase this risk.

Data on genetic predisposition informing pre-exposure screening is very limited. Small studies on children from Thailand suggest an association of CYP2c19*2 and HLA-B*13:01 alleles [65].

5.7. Lacosamide

Publications on rashes induced by LCM, a recently licensed AED are limited. As it harbours an aromatic ring, we include this agent in our review. Pivotal studies [5] reported a rash in 2.9% of 1308 patients, 0.2% discontinued the drug as a consequence. The risk was not significantly different from the 3% incidence observed in those taking a placebo. No cases of SJS/TEN were seen. When administered intravenously, one of 47 children suffered a skin reaction in a US intensive care unit [66]. A case report documents a rash after rapid oral titration of LCM starting 50 mg BD for a week, doubling the dose after. Patient history is relevant for past LTG skin reaction. HLA association and additional risk factors remain to be explored.

A single published case of DRESS in a Chinese man developed weeks after a previous adverse cutaneous reaction to phenobarbitone [67]. He also suffered a rash on PHT four years prior. In other cases angioedema is reported after intravenous administration [68].

6. Non-aromatic AEDs

Undoubtedly the above discussed aromatic AEDs carry the highest risk of a rash and hypersensitivity. A Cochrane review of selected AED side effects [63] summarised adverse skin reactions in several AEDs with a different chemical structure. In monotherapy the risk with levetiracetam was reported 13.1% (n = 948), gabapentin 9.3% (n = 1209), ZNS 10.9% (n = 282), VPA 2% (n = 2303), and topiramate 8.5% (n = 1898). These numbers were extracted from selected adult and pediatric monotherapy trails, without a placebo arm. Rash was not reported amongst the common side effects in levetiracetam add on, placebo controlled licensing studies [69]. However, statistical analysis of matched cases of 480 validated SJS/TEN reported no casual association with VPA, gabapentin, pregabalin and clobazam [70]. There were no cases observed after initiating levetiracetam, clonazepam or topiramate. Note, case reports of SJS/TEN after exposure to gabapentin, levetiracetam and clobazam have been published. In these, AEDs were taken in combination with other potentially causative agents, such as antibiotics or started in high doses after previous hypersensitivity to one or more aromatic AEDs. Other immune mediated side effects have also been described. For example, levetiracetam effects CD4 T cell function, leading to increased incidence of viral upper respiratory tract infections [71].

DRESS syndrome on non-aromatic AEDs (excluding ZNS, see below) is also rare. Six case reports document DRESS after levetiarcetam treatment, some of these in monotherapy. Small trials of HLA association as a risk factor for levetiracetam hypersensitivity thus far could not be identified. Case reports of VPA induced DRESS are also known, mostly in combination with lamotrigine, questioning direct causation.

6.1. Zonisamide

ZNS is considered a safe AED with intermediate withdrawal rates in post-marketing retention trials [72]. Structurally ZNS is sulphonamide derivative incorporating an aromatic ring, with metabolism similar to aromatic AEDs. Hydroxylation breaks the molecule down into toxic arene oxides, increasing risk of allergic reactions. The risk of a rash is estimated at around 2% when ZNS is prescribed as an add-on AED. Case reports exist on ZNS induced SJS as well as DRESS. The latter occurred when patient was re-challenged with unknown dose of ZNS months after discontinuing the drug for unpublished reasons.

A promising method of assessing risk of ZNS allergy in drug naïve patients is in vitro lymphocyte toxicity essay [72]. Twenty patients with history of CBZ, PB or PHT hypersensitivity (1) were recruited and compared to sulphonamide allergic (2) and control populations (3). Test was negative in first and third and positive in second group, predicting the highest risk of a rash on ZNS exposure in the latter. There is no data on the outcome of ZNS exposure in individuals studied, and this screening method is not routinely recommended at present.

ZNS was first marketed in Korea and Japan, thus early reports relate to non-caucasian populations [73]. Analysis of HLA types of 12 Japanese patients with ZNS induced SJS/TEN, found five patients to have HLA-A*02:07 allele compared to 6.8% of controls (p = 0.0176).

7. Summary

Our current understanding informs the cost effective pretreatment screening only for selected epilepsy patients. Findings, however point to the possibility of genomic markers used more widely in the future to predict hypersensitivity and other sinister adverse reactions. In addition, new diagnostic tests (such as serum interleukin 15 levels and microRNA miR 122) are expected to aid differential diagnosis of allergic skin rash from low risk cutaneous side effect in the acute setting. Until these become available, targeted clinical assessment is required to prevent mislabeling patients with unconfirmed allergy and/or miss early sings of serious hypersensitivity.

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