Eur J Clin Pharmacol (2011) 67:463–470
DOI 10.1007/s00228-011-1005-8

PHARMACODYNAMICS

Risk factors associated with DRESS syndrome produced by aromatic and non-aromatic antipiletic drugs

Nahuel Pereira de Silva · Paulo Piquioni · Silvia Kochen · Patricia Saidon

Received: 13 September 2010 / Accepted: 21 January 2011 / Published online: 26 February 2011

Abstract
Purpose DRESS (drug reaction with eosinophilia and systemic symptoms) is an idiosyncratic entity associated with the use of drugs. Its pathophysiology is not known, but is associated with immunological or genetic factors. The incidence is 0.4 cases per 1,000,000 general population. The syndrome usually develops at the beginning of treatment and is characterized by the presence of rash, fever, eosinophilia and systemic manifestations. The aim of our study was to describe the clinical manifestation and treatment of patients with DRESS associated with antiepileptic drugs (AEDs).
Methods This is a descriptive study with the aim of describing the clinical manifestation and treatment associated with DRESS produced by aromatic and non-aromatic AEDs.
Results Eight patients treated with AEDs developed DRESS between January 2007 and May 2010 at our hospital. All had dermatological manifestations, eosinophilia and systemic (haematological and hepatic) manifestations that could be attributed to treatment with aromatic AEDs (carbamazepine, 2 patients; lamotrigine, 3 patients; phenytoin, 3 patients). Therapeutic management included removal of the drug from the therapeutic regime, symptomatic management, life support and use of corticosteroids. There was no mortality associated with the syndrome. Reversion of systemic manifestations was very slow: between 1 and 6 months.
Conclusions DRESS is a severe cutaneous reaction, with high morbidity and mortality, whose development seems to be associated with individual susceptibility, type of antiepileptic drug used (more common with aromatic drugs), titration rate and concomitant medications.

N. Pereira de Silva (✉) · P. Piquioni · S. Kochen · P. Saidon
Epilepsy Section, Neurology Division,
José María Ramos Mejía Hospital,
Urquiza 609 (1221),
Buenos Aires, Argentina
e-mail: nahuelpereira@gmail.com

Keywords Epilepsy · Antiepileptic drugs · Adverse effects · Hipersensitivity · DRESS syndrome

Abbreviations

ADRs	Adverse drug reactions
AEDs	Antiepileptic drugs
CBZ	Carbamazepine
DPH	Phenytoin
DRESS	Drug reaction with eosinophilia and systemic symptoms
HHV 6	Human herpes virus 6
HHV 7	Human herpes virus 7
LMT	Lamotrigine
OXC	Oxcarbacepine
Pb	Phenobarbital
SCARs	Severe cutaneous adverse reactions
VPA	Valproic acid
TPM	Topiramate

Introduction

Adverse drug reactions (ADRs) are defined as any harmful manifestation, either clinical or biological, produced by a drug that appears with usual doses supplied to human beings for prophylaxis, diagnosis or disease treatment, or to modify physiological functions. ADRs produced by antiepileptic drugs (AEDs) are quite common, and up to 61% of patients treated with AEDs present some adverse event; 40% of treatment withdrawals are due to ADRs caused by AEDs [1].

Five types of ADR associated with AEDs have been described: (1) those related to the mechanism of action of the drug, which are dose dependent and usually reversible; (2) idiosyncratic, due to a particular susceptibility; (3) those related to chronic use; (4) those produced by teratogenic and carcinogenic effects; (5) those produced by drug interactions [1]. Idiosyncratic effects represent just 6–10% of ADRs. However, they are an important cause of morbidity, and even of mortality, due to toxicity associated with the drugs. Severe cutaneous adverse reactions (SCARs), which require hospitalization and specific cares due to their severity, fall within this category. These reactions include, among others, drug reaction with eosinophilia and systemic symptoms (DRESS) [2–4].

DRESS is an idiosyncratic entity associated with drug use and was first described by Bouquet in 1996 [5]. Its physiopathology is unknown, but it is associated with immunological and/or genetic factors [2, 3]. Its clinical manifestations usually develop at the start of the treatment, between the second and eighth week, depending on the different drug, and it is characterized by rash, fever, eosinophilia and systemic manifestations.

In a study of DRESS among a Chinese population, the proportion of hospitalization due to DRESS was reported to be 0.06:1.000, and the proportion of DRESS occurrence in hospitalized patients to be 0.01:1.000 [4]. The prevalence of SCARs was 0.32:1.000 and the prevalence of DRESS was 0.07:1.000. The authors estimated DRESS incidence to be no lower than 0.4 cases per million general population, with a slightly higher representation of men and patients with an average age between 21 and 40 and between 61 and 70 years [4]. Recently, the RegiSCAR Project reported incidence rates ranging from 1:1000 to 1:10,000 [6].

A number of AEDs are among the drugs associated with DRESS onset. In a study carried out by Tennis and Stern, DRESS occurred with an incidence of 2.3-4.5:10.000 patients exposed to phenytoin (DPH) and 1.0-4.1:10.000 patients exposed to carbamazepine (CBZ) [7]. Roujeau reported a higher DRESS incidence with aromatic AED use [8]. Isolated cases have been reported with lamotrigine (LMT), whose manifestations are similar to those with other AEDs, but with a more severe rash and a lower frequency of eosinophilia and lymphadenopathies [2, 9].

The aim of our study was to describe the clinical manifestations and treatment in patients with DRESS associated with AEDs.

Material and methods

This was a descriptive study with the aim of describing the clinical manifestation and treatment associated with DRESS development produced by aromatic AEDs, namely, CBZ, oxcarbacepine (OXC), DPH, phenobarbital (Pb), primidone, LMT and zonizamide, and non-aromatic AEDs, namely, valproic acid (VPA), vigabatrin, gabapentin, pregabalin, levetiracetam, topiramate (TPM) and felbamate. It was carried out at Ramos Mejía Hospital (Buenos Aires, Argentina) in patients with a confirmed diagnosis of epilepsy. This study was reviewed and approved by the Hospital Ethics Committee.

DRESS diagnosis was based on the criteria of Kardaun and colleagues for the RegiSCAR study group [6, 10] and includes:

1. Hospitalization
2. Reaction suspected to be drug related
3. Acute skin rash
4. Fever above 38°C
5. Enlarged lymph nodes at, at least, two sites
6. Involvement of at least one internal organ
7. Blood count abnormalities:
   a. Lymphocyte level above or below the laboratory limits
   b. Eosinophil level above the laboratory limits (in percentage or absolute count)
   c. Platelet level below the laboratory limits

The following factors were evaluated: (1) aromatic ring presence in AED used; (2) monotherapy or polytherapy; (3) dose; (4) titration; (5) exposure period from drug prescription to symptoms; (6) history of drug skin reaction; (7) comorbidities (liver disease and renal disorder); (8) concurrent medication.

Results

Between January 2007 and May 2010, we identified eight patients treated with AEDs and diagnosed with DRESS according to the RegiSCAR classification. Seven of these presented a maculopapular rash with desquamation, which had started on the upper and lower arm, thighs and legs in a bilateral way, progressively involving the anterior and posterior trunk, neck and head with facial edema, and ultimately covering 82% of the body surface area. Four patients had pruritus and one of these also presented mucosa commitment. The remaining patient presented a generalized exanthema from the beginning, with an involvement of 100% of the body surface area. A skin biopsy on three patients suggested a skin drug reaction diagnosis. In all cases, resolution was longer than 15 days.

All eight patients presented fever of ≥38º5 that disappeared within 2 days of treatment initiation as well as generalized adenopathies >2 cm in diameter.

No patient presented transaminase values in the hepatitis range (more than tenfold the normal value). However, the values for liver enzymes were abnormal in six patients (75%). Of these six patients, five had sustained serum glutamate pyruvate transaminase (SGPT) values at least double normal ones (85–408 UI/l) between days 2 and 7 day of treatment, and one of these also had abnormal values of conjugated bilirubin (CB) (2.77 UI/l). The sixth patient had abnormal values of alkaline phosphatase (ALP) (406 UI/l) and gamma glutamyl transpeptidase (GGT) (178 UI/l), but not fulfill the RegiSCAR criteria.

One patient had pancreas involvement with an amylase value of 173 UI/l. Of the patients, 87.5% presented eosinophilia at $\geq 1500 \times 10^9\ l^{-1}$ (range 1584–3800 $\times 10^9\ l^{-1}$). One patient did not present eosinophilia, however his hematological evaluation showed atypical lymphocytes and thrombocytopenia ($54{,}000 \times 10^9\ l^{-1}$). Serological tests for for hepatitis A, B and C viruses (HAV/HBV/HCV), blood culture and antinuclear antibody were negative for all patients.

The presence of mycoplasma, chlamydia, cytomegalovirus (CMV) and Epstein–Barr virus (EBV) was not tested for, but the effects these viruses were considered to be negligible given the negative results above. A skin patch test or a lymphocytic transformation test/lymphocyte stimulation test was also not performed, and neither was viral reactivation ([human herpes virus (HHV) 6, HHV 7, CMV or EBV] search carried out.

All eight patients met at least three of the above diagnostic criteria for DRESS. In the scoring system for classifying the patients, four patients had a final score between 6 and 7 and classified as definitive cases; the other four had final score of 5 and were classified as probable cases.

These results are summarized in Table 1.

The demographic characteristics and medication history of the eight patients are summarized in Table 2. Seven patients (87.5%) were women. The average age was of 30.8 years (range 15–59 years).

Based on an analysis of the chemical structure of the AEDs, all patients receiving aromatic AEDs [CBZ (2 patients), DPH (3),LMT (3)] presented with DRESS. Four patients were in monotherapy and the other four were receiving treatment with at least a second AED. The drug dose was in all cases within the recommended dose rages. Titration was the recommended drug administration procedure for five patients and was faster in three of these (LMT increase at the rate of 50 mg per week). The average exposure period from drug prescription to symptoms was of 28.5 days (range 9–72 days). One patient (12.5%) had a history of a probable skin drug reaction to another AED (CBZ) and a second patient (12.5%) presented history of hepatic injury (one patient had had a HAV infection). No patients presented a history of renal or any other disorder.

Concomitant drug use, dose and exposure time to AEDs are given in Table 2. Three patients presented DRESS associated with LMT use, and all had been receiving VPA as a long-term concomitant treatment. The clinical manifestations had remitted with LMT withdrawal. In the context of a bacterial meningitis treated with ceftriaxone and ampicillin, one patient had a status epilepticus and received an intravenous loading dose of DPH. Within a period of 9 days this patient developed DRESS. Clinical manifestations remitted only when DPH treatment was suspended. Another patient developed DRESS after beginning CBZ treatment. He received amoxicillin for 7 days. Again, clinical manifestation remitted only when CBZ treatment was suspended. We did not tried to rechallenge the suspected drug responsible for DRESS in any of the patients.

The therapeutic approach included suspension of the drug considered likely to be associated with DRESS, treatment of symptoms and possible use of corticoids and histamine antagonists. Reversion of the systemic manifestations was slow: between 1 and 6 months. Four patients received diphenhydramine, and one received loratadine. Six patients received prednisone treatment at a dose between 30 and 60 mg per day; three of these patients received prednisone concomitantly with antihistamines.

The length of the treatment was 1–6 months, dependent on when there was remission of symptoms. One patient presented a syndrome relapse associated with corticoid withdraw, which remitted when the corticoids were rechallenged and their use extended. This patient had had previous drug skin rash associated with CBZ use.

There was no mortality associated with the DRESS syndrome.

Discussion

Many immune-mediated reactions to AEDs are delayed hypersensitivity (type IV) mediated by different T-cell populations. Histopathologically, a predominance of CD4+ cells has been identified at the dermis, and of CD8+ at the epidermis, including, curiously, Th1 phenotypes with an apparent protector role in allergies. Many immune-mediated reactions occur only when a critical threshold dose of antigen is reached. In reactions mediated by T-cells, dendritic cells may be able to facilitate or inhibit the immunogenic responses depending on the dose of antigen [11, 12]. T-cells with special reactivity to CBZ and LMT have also been discovered in the blood of patients with hypersensitivity to the corresponding drug [13, 14].

Table 1 Scoring system for classifying HSS/DRESS cases as definite, probable, possible or no case

	Patient (score)															
	1		2		3		4		5		6		7		8	
Fever ≥38.5°C	Yes	0	Yes	0	Yes	0	Yes	0	Yes	0	Yes	0	Yes	0	Yes	0
Enlarged lymph nodes	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1
Eosinophils (leucocytes $>4.0\times10^9$ l^{-1})	2342	2	1606	2	1584	2	3184	2	0		1419	1	3800	2	1310	1
Atypical lymphocytes	No	0	No	0	No	0	No	0	Yes	1	No	0	No	0	No	0
Skin involvement																
Skin rash extent (% body surface area)	>50%	1	>50%	1	>50%	1	>50%	1	>50%	1	>50%	1	>50%	1	>50%	1
Skin rash suggesting DRESS	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1	Yes	1
Biopsy suggesting DRESS	No	−1	No	-1	Yes	0	No	−1	No	−1	Yes	0	Yes	0	No	−1
Organ Involvement																
Liver	Yes	1	No	0	No	0	Yes	1	Yes	1	No	0	Yes	1	Yes	1
Kidney	No	0	No	0	No	0	No	0	No	0	No	0	No	0	No	0
Lung	No	0	No	0	No	0	No	0	No	0	No	0	No	0	No	0
Pancreas		0		0	Amylase 173	1		0		0		0		0		0
Resolution ≥15 days	Yes	0	Yes	0	Yes	0	Yes	0	Yes	0	Yes	0	Yes	0	Yes	0
Evaluation of other potential causes		1		1		1		1		1		1		1		1
Antinuclear antibody	–		–		–		–		–		–		–		–	
Blood culture	–		–		–		–		–		–		–		–	
Serology for HAV/HBV/HCV	–		–		–		–		–		–		–		–	
Chlamydia/mycoplasma	Unk		Unk		Unk		Unk		Unk		Unk		Unk		Unk	
EBV/CMV	Unk		Unk		Unk		Unk		Unk		Unk		Unk		Unk	
Total score	6		5		7		6		5		5		7		5	

HSS/DRESS, Hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; Unk, unknown; HAV/HBV/HCV, hepatitis A, B, C virus, respectively; EBV/CMV, Epstein–Barr virus/cytomegalovirus

Another proposed mechanism to the delayed hypersensitivity reactions is the "p-I concept", which is an interaction between a drug and immune receptors. Thus, naive T-cells are not involved, but memory T-cells with cross-reactivity to previously used drugs are [2]. Cross reactivity between different aromatic AEDs is frequent and occurs in about 40–58 to 80% of cases involving AED use; it also occurs more frequently when the patient has a previous history of DRESS. Moreover, DRESS cases have been reported upon reintroduction of a previously well-tolerated drug [15, 16].

The positive rate of patch tests to CBZ have been reported to be relatively high, from 70 to 100%, and positive results in DPH-induced hypersensitivity were much lower (30–60%). Moreover, it is not yet known accurately how many of the patients on anticonvulsants have had a previous positive patch test [15].

Santiago et al. studied 56 patients with skin patch testing and found that 33 of these were on AEDs; 32.1% had positive test results, with 30.35% due to AEDs. CBZ was responsible in 76.5% of cases [17]. Despite this, the diagnostic accuracy of the patch test in DRESS syndrome is uncertain. We did not perform any skin patch test in our patients.

Metabolic, immunological and inflammatory factors are part of DRESS pathogenesis. Aromatic AEDs are metabolized into non-toxic hydroxylated metabolites in the cytochrome P450 system. An alteration of the cytochrome structure could produce an excess of toxic arena-metabolites that in turn would cause an immune cellular reaction by acting as haptens (hapten theory), or it could cause cellular oxidative damage that would promote the production of cytokines (danger signal theory) in organs where this cytochrome is found [3, 15, 18].

In 1998, both Toyama et al. and Suzuki et al. suggested an association between the reactivation of the infection by HHV 6 and 7 and DRESS [19, 20], particularly in those cases in which clinical symptoms persist for a long time, and in recurrence without drug reexposition [15, 18]. This association may arise because AEDs may be able to produce a reactivation of the herpes simplex virus (HSV) as well as and an unspecific immune-inflammatory response, which in turn produce sensibility to other drugs.

Descamps et al. reported high concentrations of anti-HHV 6 immunoglobulin (Ig) G and M and HHV 6 DNA copies in the serum of five patients with DRESS due to CBZ, supporting some association with DRESS [21]. Hashimoto described increases in IgG titles anti-HHV 6

Table 2 Demographic characteristics and medication history

	Patient							
	1	2	3	4	5	6	7	8
Gender/age (years)	F/44	F/32	F/43	F/59	F/18	F/21	F/15	M/15
Current treatment	DPH	LMT VPA TPM	CBZ	DPH	CBZ	LMT VPA	LMT VPA Clobazam	DPH Pb
Suspected drug	DPH	LMT	CBZ	DPH	CBZ	LMT	LMT	DPH
Dose	300 mg tid	200 mg bid	600 mg tid	300 mg tid	400 mg qd	100 mg qd	75 mg bid	75 mg bid
Titration	Proper	50 mg per week	Proper	1400 mg qd	Proper	50 mg per week	50 mg per week	Proper
Exposure period (days)	12	45	23	9	19	18	30	72
Previous adverse events	No	No	No	No	No	Rash by CBZ	No	No
Renal and Hepatic	No	No	Hepatitis A	No	No	No	No	No
Indication	Epilepsy	Epilepsy	Epilepsy	B. Meningitis S. Epilepticus	Epilepsy	Epilepsy	Epilepsy	Epilepsy
Concomitant drug (exposure period in days)	AAS 200 mg qd (30)	VPA 1600 mg bid (540) TPM 125 mg bid (540) CNZ 2 mg bid (5475) Risperidone 3 mg bid (years)	Amoxicillin 500 mg qd (7) Magnesium (30)	Ceftriaxone 4 g bid (9) Ampicillin 2 g × 6 (2) Acyclovir 2100 mg tid (2) Ranitidine 200 mg qid (33) Metoclopramide 30 mg tid (9) Morphine 30 mg qd (7)	CNZ 2 mg qd Vitamin B	VPA 1600 mg bid (4745) CNZ 2.5 mg tid	VPA 1000 mg bid (1095) Clobazam 10 mg qd (1095)	Pb 200 mg bid (7)

F, Female; M, male; DPH, phenytoin, LMT, lamotrigine; VPA, valproic acid, TPM, topiramate, CBZ, carbamazepine, Pb, phenobarbital; CNZ, clonazepam; qd, four times daily; bid, twice daily; tid, three times daily; B. meningitis, Bacterial meningitis; S. epilepticus, Status epilepticus; figures in parenthesis correspond to exposure period in days

copies, preceded by the detection of HHV 6 DNA, in cases of slow resolution of DRESS symptoms [22]. Apart from testing for HAV, HBV and HCV, we did not carry out any further viral reaction search in our patients.

Previous studies [4, 23, 24] have reported predominance of male patients with SCARs, including DRESS. We found a greater predominance of women. However our small number of patients precludes the drawing of any conclusion on a gender association.

In a study on SCAR epidemiology, Li and Ma [4] described two peaks of DRESS manifestation with respect to age: between 21 and 40 years, and between 61 and 70 years. The average age of our patients was 30.8 years old; seven were between 21 and 40 years of age and one was between 61 and 70 years of age.

The average exposure time to different drugs was 28.5 days, which is within the period of 2–8 weeks described for DRESS development.

Skin lesions, the most commonly reported sign of DRESS, have been reported in 73–100% of patients. Such lesions progress a non-specific erythema to a diffuse maculopapular inflammatory rash and erythroderma. Since the clinical pattern of skin lesions is quite variable and nearly infinite, no clear relationship seems to exist between the causative drug and the clinical subset of cutaneous lesions [10, 25]. All of our patients had skin lesions that could be related to DRESS. Patients without skin lesions could be miss-diagnosed.

All our cases were associated to aromatic AEDs, and none of the patients who developed DRESS were taking non-aromatic AEDs. This result is in agreement with data reported in the literature showing a greater incidence of DRESS secondary to the use of aromatic AEDs [8], and a greater incidence of cross reactions between different aromatic AEDs [15, 16]. However, the small number of patients in our study does not allow further analysis.

Canevini et al. recently pointed out that the development of adverse events is independent of the quantity of AEDs supplied, and it is related to individual susceptibilities [26]. Mono or polytherapy is not related to DRESS.

We used recommended dosing schedules; titration was high in three patients that received LMT. Three were receiving VPA treatment (2 of whom presented DRESS with LMT use and one by CBZ use). VPA inhibits LMT glucuronidation by metabolizing it to its oxide intermediate metabolite, which may explain the greater risk of developing hypersensitivity reactions with this drug [3].

High doses of AEDs and a fast titration is particularly relevant in other SCARs, although not for DRESS, especially when there is a previous history of hypersensitivity and the patients receive drugs such as LMT and VPA that can have interactions. In the Glaxo-Wellcome Lamictal Advisory Board Briefing Document of 1997 [27], of the cases of possible severe skin rashes, 85% of the patients were receiving doses of LTG that were higher than recommended and 83% were receiving LTG with concomitant VPA; the risk was 1.5% in adults receiving VPA compared with 0.2% in adults not receiving VPA [28]. The relationship between the initial dose, titration rate and the incidence of skin reactions is particularly evident for LTG. In one study, the skin eruptions occurred in 6.1% of patients when the dose in the first week of treatment was <31 mg/day, and 20.5% when the dose was between 62.5 and 125 mg/day [29]. These results were verified in subsequent studies [30–32].

The Federal Drug Administration has also issued a warning about skin rashes and LMT use: “Severe and potentially life-threatening skin rashes requiring hospitalization have been reported; Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash associated with lamotrigine. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of lamotrigine with valproate, (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose escalation for lamotrigine. However, cases have been reported in the absence of these factors” [33].

Even though the association of these mentioned risk factors with DRESS is not clear, it would be advised to take them into account.

None of our patients showed renal or hepatic abnormalities, apart one with a medical history of a HAV infection.

Two of our patients received ceftriaxone, one received ampicillin and one other patient received amoxicillin treatment. Even if sulfonamides and other antibiotics are related to DRESS development [4, 18], it would not seem to be related with DRESS in our patients because the clinical manifestations only remitted when treatment with the involved AED was suspended. Suspending involved AED is the main therapeutic measure to take [18]. Even though no histamine release has ever been demonstrated, antihistamines are commonly used to treat skin rashes. Glucocorticoid use is controversial. Some experts suggest that its use is unadvisable because of the reactivation of latent viral infections that could be associated with DRESS manifestation. However, glucocorticoid use in patients with systemic commitment or very severe rash does help their recovery [2, 18].

Only two of our patients did not receive corticoids. Corticoids were prescribed according to the severity of rash and associated systemic commitment (hepatic, pancreatic and/or hematological).

According to our experience, DRESS patients should be hospitalized for better management, the use of the AED should be suspended as main therapeutic measure and, in severe cases, treatment with corticoids should be initiated.

Peyrière at al. reported up to 10% mortality, even though the mortality rate does seem to be lower [25]. There was no mortality related to DRESS in our patients. Given the small number of patients, this may have occurred by chance. In addition, the average age of our patients was 30.8 years; as such, they were young and relatively healthy in terms of mortality. Nevertheless, early detection and appropriate treatment are very important in the management DRESS.

Conclusion

DRESS is a severe cutaneous drug reaction with high morbidity and mortality. Its development seems to be associated to an individual susceptibility, chemical structure of the AED used (more frequent with aromatic drugs), titration and concomitant drugs. The suitable selection of the antiepileptic treatment and the doctor's skills are still the most important factors in the prevention of this syndrome and other adverse events. Future studies should focus on elucidating the pathogenesis, genetic basis, and possible associated risk factors of DRESS.

Acknowledgments Nation Health Ministry. National Commission "Salud Investiga".

Buenos Aires University. Medicine School.

Conflict of interest None.

References

1. Perucca E, Meador KJ (2005) Adverse effects of antiepileptic drugs. Acta Neurol Scand 112(Suppl 181):30–35
2. Zaccara G, Franciotta D, Perucca E (2007) Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia 48(7):1223–1244
3. Criado PR, Fachini Jardim Criado R, Vasconcellos C, de Oliveira Ramos R, Gonçalves AC (2004) Severe cutaneous adverse drug reactions - relevant aspects to diagnosis and treatment—Part II. An Bras Dermatol 79(5):587–601, set./out
4. Li L-F, Ma C (2006) Epidemiological study of severe cutaneous adverse drug reactions in a city district of China. Clin Exp Dermatol 31:642–647
5. Bouquet H, Bagot M, Roujeau JC (1996) Drug induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinphilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg 1:250–257
6. Guidelines for the RegiSCAR Study. September 2009. Available at: http://regiscar.uni-freiburg.de/
7. Tennis P, Stern RS (1997) Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology 49:542–546
8. Roujeau J-C, Stern RS (1994) Severe adverse cutaneous reaction to drugs. N Engl J Med 10:1272–1285
9. Schlienger RG, Knowles SR, Shear NH (1998) Lamotrigine-associated anticonvulsant hypersensitivity syndrome. Neurology 51:1172–1175
10. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, Roujeau JC (2007) Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 156(3):609–611
11. Roncarolo MG, Gregori S, Battaglia M, Bacchetta R, Fleischhauer K, Levings MK (2006) Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. Immunol Rev 212:28–50
12. Girolomoni G, Gisondi P, Ottaviani C, Cavani A (2004) Immunoregulation of allergic contact dermatitis. J Dermatol 31 (4):264–270
13. Naisbitt DJ, Britschgi M, Wong G, Farrell J, Depta JP, Chadwick DW, Pichler WJ, Pirmohamed M, Park BK (2003) Hypersensitivity reactions to carbamazepine: characterization of the specificity, phenotype, and cytokine profile of drug-specific T cell clones. Mol Pharmacol 63:732–741
14. Naisbitt DJ, Farrell J, Wong G, Depta JP, Dodd CC, Hopkins JE, Gibney CA, Chadwick DW, Pichler WJ, Pirmohamed M, Park BK (2003) Characterization of drug-specific T cells in lamotrigine hypersensitivity. J Allergy Clin Immunol 111:1393–1403
15. Kim C-W, Choi G-S, Yun Chang-Ho, Kim Deok-In (2006) Drug hypersensitivity to previously tolerated phenytoin by carbamazepine-induced DRESS syndrome. J Korean Med Sci 21:768–772
16. Klassen BD, Sadler RM (2001) Induction of hipersensitivity to a previously tolerated antiepileptic drug by a second antiepileptic drug. Epilepsia 42(3):433–435
17. Santiago F, Gonçalo M, Vieira R, Coelho S, Figueiredo A (2010) Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). Contact Dermat 62(1):47–53
18. Cervigón GI, Sandín SS, Pérez HC, Bahillo MC, Vélez PC, García Almagro D (2006) Síndrome de DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) por sulfonamidas. Med Cutan Iber Lat Am 34(3):120–126
19. Tohyama M, Yahata Y, Yasukawa M et al (1998) Severe hypersensitivity syndrome due to sulfalazine associated with reactivation of human herpesvirus 6. Arch Dermatol 134:1113–1117
20. Suzuki Y, Inagi R, Aono T, Yamanishi K, Shiohara T (1998) Human herpesvirus 6 infection as a risk factor for the development of severe drug induced hypersensitivity syndrome. Arch Dermatol 134:1108–1112
21. Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B, Beilachs S, Crickx B (2001) Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol 137:301–304
22. Hashimoto K, Yasukawa M, Tohyama M (2003) Human herpesvirus 6 and drug allergy. Curr Opin Allergy Clin Immunol 3:255–260
23. Pitche P, Padonou CS, Kombate K et al (2005) Stevens–Johnson syndrome and toxic epidermal necrolysis in Lome (Togo). Evolutional and etiological profiles of 40 cases. Ann Dermatol Venereol 132(6–7 Pt 1):531–534
24. Schopf E, Stuhmer A, Rzany B et al (1991) Toxic epidermal necrolysis and Stevens–Johnson syndrome. An epidemiologic study from West Germany. Arch Dermatol 127:839–842
25. Peyrière H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac J-P, Buys DH (2006) Variability in the clinical pattern of cutaneous side effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Therapeutics 155:422–428
26. Canevini MP, De Sarro G, Galimberti CA, Gatti G, Licchetta L, Malerba A, Muscas G, La Neve A, Striano P, y Perucca E, SOPHIE Study Group (2010) Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy. Epilepsia 51(5):797–804
27. Centre for Drug Evaluation and Research (CDER) (1997) Glaxo-Wellcome Lamictal Advisory Board Briefing Document, October 23. Glaxo-Wellcome
28. Guberman A, Besag F, Brodie M, Dooley J, Duchowny M, Pellock J, Richens A, Stern R, Trevathan E (1999) Lamotrigine-

associated rash: risk benefit considerations in adults and children. Epilepsia 40(7):985–999, I
29. Messenheimer J, Mullens EL, Giorgi L, Young F (1998) Safety review of adult clinical trial experience with lamotrigine. Drug Saf 18:281–296
30. Anderson GD (2002) Children versus adults: pharmacokinetic and adverse-effect differences. Epilepsia 43(Suppl 3):53–59
31. Hirsch LJ, Weintraub DB, Buchsbaum R, Spencer HT, Straka T, Hager M, Resor SR Jr (2006) Predictors of Lamotrigine-associated rash. Epilepsia 47:318–322
32. Fitton A, Goa KL (1995) Lamotrigine: an update of its pharmacology and therapeutic use in epilepsy. Drugs 50:691–713
33. Federal Drug Administration. Available at: http://www.fda.com