Research letter

Risk assessment of drug-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a disproportionality analysis using the French Pharmacovigilance Database

DOI: 10.1111/bjd.14649

Dear Editor, Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe cutaneous drug-induced reaction with a mortality rate that can reach 10%.[1] This syndrome was first described for anticonvulsant drugs (carbamazepine, phenytoin and phenobarbitone), and the same symptoms were subsequently observed with a variety of other drugs.[2,3] DRESS is a very rare adverse drug reaction (ADR), such that it is difficult to estimate its true incidence for each drug. There is only one study reporting estimates of DRESS incidence, and the values are in the range of 1 case per 1000 to 10 000 drug exposures.[4] Prospective studies would provide better estimates, but might take too long to be feasible. Because there are too few cases to calculate the true incidence of DRESS for any single drug, we sought to use disproportionality measures[5,6] (also called the case–noncase method) to categorize the risk of DRESS syndrome according to the drug involved.

The aims of this study were to identify those drugs most frequently associated with DRESS syndrome spontaneously reported in France and to compare the risk of DRESS syndrome between these drugs.

For this study, we collected all ADRs recorded in the French Pharmacovigilance Database (FPVD)[7] during 3 years from 1 September 2007. Reports of the reaction of interest (DRESS) were scored as cases and all other reports were considered to be noncases.

Cases were included only if sufficient data were available to calculate a RegiSCAR score[8] ≥ 2. The causal relationship between an ADR and one or more drugs was evaluated by applying the French causality assessment method[9] based on seven causality levels divided into two groups: chronological criteria (time to onset and evolution) and semiological criteria (mechanism of action, specific test and other cause). For each case, on the basis of the World Health Organization criteria, drugs involved in the DRESS syndrome were classified by one of us (A.P.J.B.) as suspect (drug with the highest chronological and semiological score) or other (drug with the lowest chronological and semiological score). Exposure in cases and noncases was thus defined according to the presence of the culprit drug in the report.

For each drug of interest, the association with DRESS syndrome was assessed by calculating an ADR reporting odds ratio (ROR)[10] with its 95% confidence interval (CI) (two-by-two contingency table, Table 1). This ADR ROR provided an estimate of the risk of DRESS syndrome occurrence with the index drug relative to that with the reference drug(s). By comparing the ROR obtained, we could classify the drugs involved in the occurrence of DRESS into three levels of risk: very high, high and moderate. To test the validity of this case–noncase method, we used a negative control (acetaminophen), defined *a priori* as not being associated with DRESS syndrome.

Of the 73 732 reports of ADR recorded in the FPVD during the 3 years, we reviewed 409 reports coded DRESS (0·5% of all reports) and then included 312 cases (162 drugs involved) that meet the inclusion criteria. For 173 (55%) cases of DRESS, only one drug was involved (i.e. with the higher imputability score), and for 139 cases, two or more drugs were involved (i.e. with the same imputability score). The median age was 57 years (interquartile range 40–73) and 164 cases (52·6%) were in women (sex ratio 0·9). The median time to DRESS onset after the start of administration of the suspected drug was 22 days (interquartile range 13–31). The outcome was classified as favourable in 213 cases (68·3%), continuing improvement at the time of notification in 74 cases (23·7%), recovered with sequelae in four cases (1·3%), fatal in 17 cases (5·4%) and unknown for four cases (1·3%).

Table 1 Two-by-two contingency table for a combination 'drug of interest' and 'DRESS syndrome'

	Number of cases of DRESS syndrome	Number of cases of other ADRs	
Drug of interest	a	b	a + b
Other drugs	c	d	c + d
	a + c	b + d	N = a + b + c + d

(a) Number of exposed cases (DRESS with drug of interest); (b) number of unexposed cases [all other adverse drug reactions (ADRs) with drug of interest]; (c) number of exposed controls (DRESS with other drugs); (d) number of unexposed controls (all other ADRs with other drugs). Reporting odds ratio = (a/c)/(b/d) = ad/bc. DRESS, drug reaction with eosinophilia and systemic symptoms.

Table 2 Characteristics of cases of drug reaction with eosinophilia and systemic symptoms (DRESS) according to the suspected drug

Drug	No. DRESS cases	n[a]	Time of onset (days), median (IQR)	Age (years), median (IQR	Deaths, % (95% CI)
Allopurinol	69	35	24 (10·5–33·5)	70 (57–78)	11 (2–28)
Carbamazepine	33	22	25 (20–38·5)	32·5 (19–54)	0 (0–15)
Sulfasalazine	20	12	22 (13·5–25)	50 (39–55)	11 (0–48)
Lamotrigine	10	9	32 (29–39)	56 (52–70)	13 (0–53)
Vancomycin	38	9	26 (14–31)	56 (49–58)	0 (0–35)
Sulfamethoxazole/ trimethoprim	20	7	11 (8–21)	45 (37–64·5)	0 (0–63)
Minocycline	8	7	22·5 (17–48)	17 (16·5–28)	0 (0–39)
Fluindione	11	6	23 (15–31)	60·5 (51–74)	0 (0–53)
Amoxicillin	10	6	3 (1·2–4·7)	61 (55·5–65)	0 (0–39)
Amoxicillin/clavulanic acid	7	5	6 (3–8)	59 (55–77)	0 (0–63)
Strontium ranelate	8	5	46 (29–50)	80 (77–87)	33 (1–91)

IQR, interquartile range; CI, confidence interval. [a]Cases of DRESS for which only one drug was suspected.

Table 3 Drug reaction with eosinophilia and systemic symptoms (DRESS) risk according to drug involved in seven cases or more of DRESS syndrome

Drug	No. of DRESS (a)	No. of other ADRs (b)	No. of DRESS with other drugs (c)	No. of other ADRs with other drugs (d)	ROR (95% CI)	Risk level
Sulfasalazine	20	94	292	73 326	53·4 (32·5–87·7)	Very high
Allopurinol	69	435	243	72 985	47·6 (35·8–63·2)	Very high
Minocycline	8	45	304	73 375	42·9 (20·1–91·8)	Very high
Carbamazepine	33	432	279	72 988	20·0 (13·8–29·0)	High
Vancomycin	38	623	274	72 797	16·2 (11·4–23·0)	High
Strontium ranelate	8	204	304	73 216	9·4 (4·6–19·3)	Moderate
Lamotrigine	10	360	302	73 060	6·7 (3·5–12·7)	Moderate
Co-trimoxazole	20	928	292	72 492	5·3 (3·4–8·4)	Moderate
Acetaminophen (control)	3	2896	309	70 524	0·24 (0·08–0·75)	

ADR, adverse drug reaction; ROR, reporting odds ratio (see Table 1); CI, confidence interval.

The characteristics of the cases (time to onset, age and outcome) for the 11 drugs most frequently involved in DRESS are described in Table 2. Significant RORs were found for eight drugs (Table 3), confirming that DRESS is more frequently associated with the suspected drug than with the other drugs in the database. Significant RORs were also found for colchicine (7·0, 95% CI 3·6–13·7), rifampicin (3·7, 95% CI 2·0–7·0) and ciprofloxacin (3·3, 95% CI 1·7–6·4), but they became nonsignificant when considering cases with only one drug involved. Finally, we used the ROR to classify the drugs involved in DRESS into three levels of risk: 'very high' for ROR > 20, 'high' for ROR 10–20 and 'moderate' for ROR < 10 (Table 3).

For this study, we collected 312 reports of DRESS syndrome notified to the French pharmacovigilance centres over a period of 3 years (about 100 cases per year). The drugs most frequently involved in DRESS were allopurinol, vancomycin, carbamazepine, co-trimoxazole and sulfasalazine. These findings are consistent with those of the RegiSCAR study.[11] Nevertheless, our results highlight treatments for which a few cases have been published.

To appreciate the risk of DRESS with a given drug, the number of published cases is generally used. Thus, Cacoub *et al.*[3] state that the most causative drugs for DRESS are carbamazepine (47 of 172 published cases, 27%) and allopurinol (11%). However, the absolute number of cases reported depends on the extent of the use of a drug. In our study, the drug most frequently involved was allopurinol, ROR 47·6 (95% CI 35·8–63·2), which ranks it among drugs with 'very high' risk of DRESS. This is in agreement with the large number of reports of DRESS with allopurinol. Conversely, for minocycline, the risk seems to be high in our study (ROR 42·9, 95% CI 20·1–91·8), considering the small number of published cases (only three).[3] The same applies to vancomycin (ROR 16·2, 95% CI 11·4–23·0), but with only four published cases. For these two drugs, the risk of DRESS syndrome is greater than would be expected from the literature. For strontium ranelate, the risk is moderate (ROR 9·4, 95% CI 4·6–19·3); however, two publications[12,13] summarize at least 47 cases, and we found a similar risk of DRESS as for lamotrigine and co-trimoxazole.

The weaknesses of disproportionality analyses are well documented.[5] Indeed, a true quantification of risk is not

possible because not all cases are reported in the FPVD, although in the case of a severe effect, notification is mandatory. Even if the incidence is underestimated, it is possibly similar for all drugs; this facilitates the identification of important drug–adverse event pairs, as they emerge from comparisons of their frequency with respect to others within the same data source.[14] The ROR may also be artificially decreased if another reaction, specific to the drug, is better reported, thereby diluting the association by increasing the presence of the drug among the noncase reports (e.g. haemorrhage with fluindione, for which the ROR was nonsignificant).

Proportionality analysis can be used to compare the risk of ADR between some drugs, but it is limited by the difficulty of excluding various biases, particularly those due to unequal ADR reporting between different drugs (for example due to ADR notoriety) and to the overrepresentation of specific ADRs for some drugs.

In conclusion, this study is the first to categorize the risk of DRESS syndrome according to drugs among the French population. Sulfasalazine, allopurinol and minocycline are associated with a higher risk of DRESS than other drugs that induce DRESS syndrome. For carbamazepine, vancomycin and strontium ranelate, the risk of DRESS syndrome is lower, but higher than expected on the basis of data in the literature.

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Funding sources: none.

Conflicts of interest: none declared.