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

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%. 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. 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 10 000 drug exposures. 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 (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) 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 ≥ 2. The causal relationship between an ADR and one or more drugs was evaluated by applying the French causality assessment method 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) 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: high, very 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%), resolving at the time of notification in 74 cases (23.7%), recovered with sequelae in four cases (1.3%) and fatal in 17 cases (5.4%) and unknown for four cases (1.3%).

<table>
<thead>
<tr>
<th>Drug of interest</th>
<th>Number of cases of DRESS syndrome</th>
<th>Number of cases of other ADRs</th>
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<tbody>
<tr>
<td>a</td>
<td>b + c</td>
<td>a + b</td>
</tr>
<tr>
<td>Other drugs</td>
<td>c</td>
<td>d</td>
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<tr>
<td>a + c</td>
<td>b + d</td>
<td>N = a + b + c + d</td>
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(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.
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. Nevertheless, our results highlight treatments for which a few cases have been published.
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.\(^1\)\(^4\) 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 the data in the literature.

References


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