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2

3 **Title: Drug reaction with eosinophilia and systemic symptoms (DRESS) may occur**  
4 **within two weeks of drug exposure: a retrospective study.**

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36 media, carbamazepine, lamotrigine, allopurinol

37

38 **Capsule summary**

- 39 - Drug reaction with eosinophilia and systemic symptoms (DRESS) is thought to  
40 occur between 2 and 8 weeks after drug exposure.
- 41 - DRESS may occur within 2 weeks of exposure, depending on the medications  
42 involved. Rapid onset of symptoms should not exclude the diagnosis of DRESS.
- 43
- 44

45 **Abstract**

46  
47 **Background**

48 Diagnosing DRESS is challenging. Some clinicians reject this diagnosis when the delay of onset  
49 is less than 15 days after drug intake.

50 **Objectives**

51 To assess the delay of DRESS occurrence and culprit drugs.

52 **Methods**

53 All patients with a 1<sup>st</sup> occurrence of DRESS hospitalized in 3 dermatology departments, for  
54 which a drug was highly suspected were included in this retrospective study. Based on the delay  
55 in DRESS occurrence, cases were classified into two groups: a rapid-onset group ( $\leq 15$  days  
56 after exposure) and a delayed-onset group ( $> 15$  days).

57 **Results**

58 41 patients with DRESS were included; 14 in the rapid-onset and 27 in delayed-onset groups.  
59 In the rapid-onset group, antibiotics (n = 6/14) and iodinated contrast media (n = 5/5) were the  
60 predominant culprits. Carbamazepine (n = 4/4), lamotrigine (n = 6/6), allopurinol (n = 8/8) and  
61 sulfasalazine (n = 2/2) were exclusively found in the delayed-onset group.

62 **Limitations**

63 The retrospective nature, the limited number of subjects, and lack of detailed information on  
64 previous exposure to sensitizing drugs in some instances.

65 **Conclusions**

66 DRESS is frequently related to drugs introduced  $\leq 15$  days before the occurrence of cutaneous  
67 adverse reactions. The time of onset of DRESS may differ depending on the medications  
68 involved.

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74 **Abbreviations**

75 CMV: Cytomegalovirus

76 DHIS: Drug-induced hypersensitivity syndrome

77 DRESS: Drug reaction with eosinophilia and systemic symptoms

78 EBV: Epstein-Barr virus

79 HHV-6: Human herpes virus-6

80 ICM: Iodinated contrast media

81

82

83 **Text**

84 **Background**

85 DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome is characterized by  
86 widespread skin involvement, fever, and lymphadenopathy with at least one instance of visceral  
87 involvement associated with biological abnormalities (eosinophilia, mononucleosis-like  
88 atypical lymphocytes). Viral infection or reactivation also plays a role. The diagnosis of  
89 DRESS, especially in the early stages, remains challenging due to the heterogeneous clinical  
90 presentation of this condition and the complex natural course with different patterns depending  
91 on the causal drug<sup>1</sup>. Because of difficulties in classification, standardized retrospective data,  
92 *i.e.*, clinical, biological and histological diagnosis criteria for DRESS, have been established by  
93 the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) group <sup>2</sup>. It is  
94 sometimes difficult at an early stage to differentiate between DRESS, viral infections, and other  
95 drug eruptions. DRESS can be life threatening and cause severe, potentially chronic sequelae  
96 <sup>3-5</sup>; for these reasons, it seems important to diagnose DRESS as early as possible.

97 The acronym DRESS was proposed in 1996 by Bocquet *et al.* <sup>6</sup>. Previously, many clinical terms  
98 had been used, including drug-induced hypersensitivity syndrome (DIHS)<sup>7</sup>, hypersensitivity  
99 syndrome and mononucleosis-like syndrome. A DRESS diagnosis validation score was  
100 proposed by the RegiSCAR group <sup>2</sup> in 2007. The delay in the occurrence of DRESS is the time  
101 latency between the beginning of drug use and the onset of the first symptoms of DRESS. In  
102 Europe, it is conventionally accepted that this delay is between 2 and 8 weeks <sup>4,6,8</sup> after the  
103 initiation of the offending medication. The delay parameter is often used as a diagnostic  
104 criterion, although this parameter is not included <sup>2,9</sup> in the RegiSCAR scoring system <sup>2,9</sup>. Some  
105 clinicians reject the diagnosis of DRESS when the delay of onset after initiating the inciting  
106 drug is less than 15 days.

107 We analyzed a large series of patients with DRESS hospitalized in 3 French dermatology  
108 departments with well-defined criteria according to the RegiSCAR scoring system. We used  
109 this data to determine the timing of DRESS after the initiation of the suspected causative drug  
110 and looked for associations with the types of drugs involved and patients' clinical  
111 characteristics.

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113

## 114 **Materials and methods**

### 115 *Case selection*

116 We retrospectively included all cases recorded between 2010 and 2018 in three French  
117 departments of dermatology (Hôpital Saint André, Bordeaux, Hôpital Hôtel Dieu, Nantes and  
118 Hôpital Tenon, Paris).

119 The inclusion criteria were adult patients ( $\geq 18$  years) with a diagnosis of DRESS made by a  
120 dermatologist as defined by the RegiSCAR scoring system<sup>2</sup>. All patients had the following: 1-  
121 first occurrence of DRESS hospitalized/ retrospectively explored; 2- a RegiSCAR score  $>5$  with  
122 definite (final score:  $>5$ ) DRESS; and 3- the use of a highly suspected causal drug (positive  
123 drug patch test and/or single suspected and/or highly attributable drug). The first day of DRESS  
124 was defined as the first day of skin involvement.

125 The exclusion criteria were multiple drugs suspected (multiple sensitization to several drugs  
126 from the patch test results and/or several suspected drugs) and a RegiSCAR score  $\leq 5$ .

### 127 *Data collection*

128 All medical records of the patients included were analyzed retrospectively. The epidemiological  
129 (*i.e.*, age, sex, time to DRESS occurrence) and clinical characteristics were recorded, and the  
130 RegiSCAR score was calculated using the RegiSCAR scoring system. The delays of DRESS  
131 occurrence after the introduction of the culprit drug and the drug classes were recorded.

132 According to the delay of DRESS occurrence after the introduction of the culprit drug, the  
133 patients were classified into two groups: the “rapid-onset” group with a time latency  $\leq 15$  days  
134 and the “delayed-onset” group with a latency of more than 15 days.

135

### 136 *Statistical analysis*

137 Continuous variables are reported as the means (SDs) or medians and interquartile ranges  
138 (IQR), when appropriate. Discrete variables are described as counts and percentages. Groups  
139 were compared by analysis of variance for continuous variables and Fisher exact tests for  
140 discrete variables.

## 141 **Results**

### 142 *Patients, clinical and biological findings*

143 Among the 70 patients included in the database, we included all patients with definite DRESS  
144 (RegiSCAR score >5). Forty-one patients were retrospectively included; fourteen patients were  
145 classified in the rapid-onset group ( $\leq 15$  days), and twenty-seven were classified in the delayed-  
146 onset group (Table 1).

147 The mean delay of DRESS occurrence was 7.3 days ( $\pm 4.0$ ) and 29.4 days ( $\pm 8.4$ ) in the rapid-  
148 onset and delayed-onset groups, respectively ( $p < 0.001$ ). Concerning the clinical manifestations,  
149 the only significant difference found between the 2 groups was the presence of  
150 lymphadenopathy ( $p = 0.03$ ), which occurred in 8 (57%) patients in the rapid-onset group and  
151 24 patients (92%) in the delayed-onset group.

152 No significant differences between the 2 groups were observed in terms of demographics (*i.e.*,  
153 age, sex), other clinical characteristics (*i.e.*, facial edema in 10 and 18 patients in the rapid-onset  
154 and delayed-onset groups, respectively), biological characteristics (*i.e.*, eosinophilia with  $2070$   
155 and  $2540/\mu$  in the rapid-onset and delayed-onset groups, respectively), organ involvement,  
156 cutaneous features, and herpes virus viral replication (Table 1). Concerning DRESS therapies,  
157 no significant differences between local or systemic steroid use were noted between the two  
158 groups; local and systemic steroids were used in 8 and 7 patients in the rapid-onset group

159 compared to 13 and 11 patients in the delayed-onset group, but data were not available for 2  
160 and 6 patients in the rapid-onset and delayed-onset groups, respectively.

#### 161 *Culprit drugs and delay of DRESS occurrence*

162 The culprit drugs were significantly different between the 2 groups ( $p=0.002$ ) (Table 1).  
163 Antibiotics were the main class of culprit drugs and were involved in 10 cases (24%); among  
164 these cases, 8 were due to beta-lactams (BLs), including 6 patients (43%) in the rapid-onset  
165 group and 4 (15%) in the delayed-onset group (Tables 1, 2). Anticonvulsants were the culprit  
166 drugs in 10 cases, including 6 patients who received lamotrigine and 4 who received  
167 carbamazepine. Interestingly, all cases of DRESS due to anticonvulsant drugs were in the  
168 delayed-onset group. Allopurinol and sulfasalazine were implicated in 8 and 2 cases,  
169 respectively, in the delayed-onset group. Iodinated contrast media (ICM) was implicated in 5  
170 cases, all in the rapid-onset group. Other cases were due to antifungal drugs ( $n=1$ ), antiretroviral  
171 drugs ( $n=2$ ), neuroleptics (1), anticoagulants ( $n=1$ ) and vemurafenib ( $n=1$ ) (Table 2).

172 In 9 cases, the delay of DRESS occurrence was less than or equal to 7 days; among these cases,  
173 3 cases were related to beta-lactam antibiotics, including 2 cases due to amoxicillin, 1 case due  
174 to ceftriaxone, 1 case due to olanzapine and all 5 cases related to iodinated contrast media. In 3  
175 cases, the delay of DRESS occurrence was very short; DRESS occurred within 2 days of the  
176 initial exposure in 2 cases due to iohexol and in 1 case due to iomeprol (Table 2).

#### 177 *RegiSCAR scoring and delay of DRESS occurrence*

178 No significant differences between the 2 groups were observed in terms of RegiSCAR scores  
179 <sup>2</sup>; 10 and 4 patients had scores of 6 and 7 in rapid-onset group, respectively, and 11, 9, 6 and 1  
180 patients had scores of 6, 7, 8 and 9 in delayed-onset group, respectively, according to  
181 RegiSCAR system ( $p=0.15$ ) (Table 3).

182

## 183 Discussion

184 The diagnosis of DRESS, especially in the early stages, remains challenging due to the  
185 heterogeneous clinical presentation of this condition and complex natural course with different  
186 patterns depending on the causal drug <sup>1</sup>.

187 Here, we report a retrospective series of 41 patients who had a diagnosis of DRESS according  
188 to a RegiSCAR score > 5. Nearly one-third of the cases occurred less than 15 days following  
189 exposure. In addition, there appears to be a link between the timing of onset and the class of  
190 drugs involved. There was a statistically significant difference between the drugs involved in  
191 the rapid-onset DRESS group compared to those implicated in the delayed-onset group.

192  
193 In terms of epidemiological and clinical characteristics, this series was similar to other  
194 previously published series or to literature reviews <sup>4,5,9,10</sup> The mean age of 51.9 years was  
195 similar to that in other published series (40.1<sup>5</sup>, 48<sup>9</sup>, 51<sup>4</sup>, and 64<sup>10</sup> years old). The percentage  
196 of women was slightly over 50% in previous reports (51% to 56.6%), as was also observed in  
197 our series (52.3%). Likewise, organ involvement was reported in 91% of the 117 cases in the  
198 study from Kardaun *et al.* <sup>9</sup>, and liver dysfunction was the main manifestation of visceral  
199 involvement between 89 and 100% of the cases. Lymphadenopathy was noticed in 80% of our  
200 patients, which is higher than the figure previously found (54%<sup>9</sup>, 31%<sup>4</sup>, or 65% of the  
201 probable/definite cases in an overview of DRESS <sup>5</sup>). This difference could be explained by a  
202 more systematic search for lymphadenopathy that was possible after the publication of a review  
203 of 172 cases<sup>5</sup>, which reported that lymphadenopathy was much more common in  
204 probable/definite cases than in no/possible cases of DRESS.

205 Iodinated contrast media was involved in cases of rapid-onset DRESS that occurred very early,  
206 less than 2 days after the initial exposure. To explain such short and very rapid onset delays,  
207 there are several possible assumptions. First, we can hypothesize that a particular property of

208 some drugs is to activate the immune system very quickly, such as iodinated contrast media.  
209 Second, it is possible that patients had a previous exposure to the drug before DRESS with a  
210 previous asymptomatic or pauci-symptomatic sensitization phase. DRESS would then  
211 correspond to the revelation phase of drug hypersensitivity in previously sensitized patients or  
212 to a rechallenge with a more rapid onset of a more severe cutaneous adverse drug reaction, as  
213 previously reported <sup>11,12</sup>.

214 Conversely, a long delay with some drugs, such as allopurinol or anticonvulsants, could  
215 correspond to active sensitization then revelation phases following the introduction of the  
216 culprit drug. Moreover, some drugs, such as carbamazepine and lamotrigine, have been shown  
217 to activate drug-specific T cells through cytokine production (interferon-gamma, interleukine-  
218 5) upon drug stimulation, leading to immune activation that predisposes the patient to DRESS  
219 <sup>12</sup>. Overall, activation of the immune system during DRESS involves complex and probably  
220 various mechanisms depending on the responsible drug. Previously, in a retrospective series of  
221 60 cases of DRESS, the delay in DRESS occurrence was significantly longer with allopurinol  
222 (mean delay: 27 days) than with phenytoin (14.3 days) or other drugs (19.1 days) ( $p=0.04$ ) <sup>4</sup>.  
223 The median time interval between the first intaking the inducing drug and DRESS occurrence  
224 seemed to be shorter for abacavir, lamotrigine and nevirapine than for other drugs, which has  
225 been reported in other series <sup>1,9</sup>. Unusually long delays of occurrence, over 3 months, have been  
226 reported with carbamazepine and allopurinol <sup>1</sup>. Only one case of abacavir-induced DRESS was  
227 observed in the rapid-onset group, whereas all the cases due to lamotrigine ( $n=6$ ),  
228 carbamazepine ( $n=4$ ) and allopurinol ( $n=8$ ) were in the delayed-onset group.

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232 For Japanese teams, typical DIHS is characterized by a delay of occurrence ranging from 3  
233 weeks to 3 months after introducing the culprit drug. The delay in occurrence is included in the

234 Japanese scoring system for DHIS/DRESS and must be longer than 3 weeks to ensure a  
235 DIHS/DRESS diagnosis.

236 These differences between the two classifications could partly explain why some drugs, such  
237 as antibiotics or ICM, were less reported than anticonvulsant drugs or allopurinol; the  
238 requirement of a time delay longer than 3 weeks in the Japanese scoring system for  
239 DIHS/DRESS potentially excludes potential DIHS/DRESS cases related to drugs associated  
240 with short delays before the first symptoms occur. Moreover, some HLA haplotypes predispose  
241 individuals to DIHS/DRESS in Asiatic populations.

242  
243 Our study suffers from some limitations, in particular its retrospective nature, the limited  
244 number of subjects from three centers, and the lack of detailed information on previous  
245 exposure to sensitizing drugs in some instances. Moreover, due to the descriptive nature of this  
246 study, no attempts were made to adjust for known and unknown confounders. As such, these  
247 data are ultimately hypothesis-generating and need confirmation in larger, population-based  
248 cohorts to obtain sufficient longitudinal patient-level data for multivariate analyses.

249 Nonetheless, the data collection was particularly thorough, as all participating centers were  
250 specifically interested in studying DRESS.

## 251 **Conclusion**

252 This retrospective series of 41 definite DRESS cases suggests that a diagnosis of DRESS should  
253 not be rejected when the delay of onset after introducing the responsible drug is less than 15  
254 days if the other diagnostic criteria are met. Some of the drugs involved are by themselves  
255 associated with shorter delays of onset. However, prospective studies are needed to confirm  
256 these results.

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259

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293 **Table Legends**

294

295 **Table 1.** Clinical and biological characteristics of the patients according to the delay of DRESS  
296 occurrence.

297 Values are expressed as the mean ( $\pm$  SD) or number (percentage), y: years, d: days, <sup>a</sup>Epstein-  
298 Barr virus (EBV) replication in 4 cases; <sup>b</sup>human herpes virus-6 (HHV-6) in 5 cases, Epstein-  
299 Barr virus (EBV) replication in 2 cases, and 1 patient had concomitant CMV and EBV  
300 replication; <sup>c</sup>data were not available for 2 and 6 patients in the rapid-onset and delayed-onset  
301 groups, respectively; <sup>d</sup>some patients had successively topical and systemic steroids.

302

303 **Table 2.** Culprit drug according to the occurrence of DRESS.

304 d: days, \*: mean (and range) or delay when only 1 case was reported with the drug

305

306 **Table 3.** RegiSCAR scores according the delay of DRESS occurrence.

307 Values are expressed as numbers (percentages).

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311 **Table 1.** Clinical and biological characteristics of the patients according to the delay of DRESS occurrence.

	All n=41	Delay ≤15 days n=14	Delay >15 days n=27	P-value
Age, y	51.9 (±17.9)	54.8 (±15.5)	50.3 (±19.1)	0.46
Female	20 (49)	7 (50)	13 (48)	0.59
Eosinophilia, /μL	2380 (±2632)	2070 (±1809)	2540 (±2990)	0.59
DRESS duration, d	41.9 (±31.2)	50.4 (±37.6)	37.4 (±27.0)	0.21
Delay of DRESS occurrence, d	21.9 (±12.8)	7.3 (±4.0)	29.4 (±8.4)	<0.001
Organ involvement	40 (98)	14 (100)	26(96)	0.66
Hepatic involvement	38 (93)	14 (100)	24 (89)	0.27
Renal involvement	14 (34)	5 (36)	9 (33)	0.57
Pulmonary involvement	8 (19.5)	1 (7)	7 (26)	0.15
Pancreatic involvement	3 (7)	1 (7)	2 (7)	0.74
Fever	35 (85)	12 (86)	23 (85)	0.74
Lymphadenopathy	32 (80)	8 (57)	24 (92)	<b>0.03</b>
Pustulosis and/or vesicles	7 (17)	2 (14)	5 (18.5)	0.55
Facial edema	28 (70)	10 (71)	18 (69)	0.34
Mucosal involvement	6 (15)	1 (7)	5 (18.5)	0.32
Viral replication	12 (29)	4 (29) <sup>a</sup>	8 (30) <sup>b</sup>	0.96
DRESS therapy <sup>c</sup>				
<i>Local steroids</i>	21 (51)	8 (57) <sup>d</sup>	13 (48) <sup>d</sup>	0.70
<i>Systemic steroids</i>	18 (44)	7 (50) <sup>d</sup>	11 (41) <sup>d</sup>	0.57
<i>Recurrence after steroids decrease</i>	5 (12)	2 (14)	3 (11)	0.20
Culprit drug				<b>0.002</b>
<i>Antibiotics</i>	10 (24)	6 (43)	4 (15)	
<i>Iodinated contrast media</i>	5 (12)	5 (36)	0 (0)	
<i>Anticonvulsants</i>	10 (24)	0 (0)	10 (37)	
<i>Allopurinol</i>	8 (19.5)	0 (0)	8 (30)	
<i>Sulfasalazine</i>	2 (5)	0 (0)	2 (7)	
<i>Antiretroviral therapies</i>	2 (5)	1 (7)	1 (4)	
<i>Others</i>	4 (10)	2 (14)	2 (7)	

313 Values are expressed as the mean ( $\pm$  SD) or number (percentage), y: years, d: days, <sup>a</sup>Epstein-Barr virus (EBV)  
314 replication in 4 cases; <sup>b</sup>human herpes virus-6 (HHV-6) in 5 cases, Epstein-Barr virus (EBV) replication in 2 cases,  
315 and 1 patient had concomitant CMV and EBV replication; <sup>c</sup>data were not available for 2 and 6 patients in the rapid-  
316 onset and delayed-onset groups, respectively; <sup>d</sup>some patients had successively topical and systemic steroids.

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324 **Table 2.** Culprit drug according to the occurrence of DRESS.  
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<b>Classes of culprit drugs</b>	<b>Delay ≤15 days (n)</b>	<b>Mean (range) or delay<sup>a</sup>, d</b>	<b>Delay &gt;15 days (n)</b>	<b>Mean (range) or delay<sup>a</sup>, d</b>
<i>Antibiotics</i>	Amoxicillin (4) Ceftriaxone (2)	8.25 (6-11) 10.5 (6-15)	Ceftriaxone (1) Isoniazid (1) Piperacillin-tazobactam (1) Vancomycin (1)	17 20 27 23
<i>Iodinated contrast media</i>	Iohexol (2) Iomeprol (1) Ioversol (2)	2 (2) 2 6.5 (6-7)	-	-
<i>Uric acid inhibitor</i>	-	-	Allopurinol (8)	31.4 (21-45)
<i>Anticonvulsants</i>	-	-	Carbamazepine (4) Lamotrigine (6)	29.7 (21-36) 33.3 (20-50)
<i>Intestinal anti-inflammatory</i>	-	-	Sulfasalazine (2)	35 (24-46)
<i>Antifungal</i>	-	-	Fluconazole (1)	24
<i>Neuroleptic</i>	Olanzapine (1)	6 (6)	-	-
<i>Antiretroviral therapies</i>	Abacavir (1)	10	Etravirine (1)	21
<i>Anticoagulant</i>	-	-	Fluindione (1)	22
<i>Protein kinase inhibitor</i>	Vemurafenib (1)	13	-	-

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327 d: days, <sup>a</sup>: mean (and range) or delay when only 1 case was reported with the drug

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336 **Table 3.** RegiSCAR scores according the delay of DRESS occurrence.

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		<b>All n=41</b>	<b>Delay ≤15 days n=14</b>	<b>Delay &gt;15 days n=27</b>	<b>P-value</b>
<b>RegiSCAR score</b>	<b>6</b>	21 (51)	10 (71)	11 (41)	0.15
	<b>7</b>	13 (32)	4 (29)	9 (33)	
	<b>8</b>	6 (15)	0 (0)	6 (22)	
	<b>9</b>	1 (2)	0 (0)	1 (4)	

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Values are expressed as numbers (percentages).