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HAL Authorization

1 **Topical versus oral corticosteroids in moderate drug reaction with eosinophilia**
2 **and systemic symptoms (DRESS): a multicenter randomized clinical trial**

3 **Short title: DRESS CODE study**

4

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57 controlled trial.

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60 Severity of drug reaction with eosinophilia and systemic symptoms (DRESS) may vary
61 from mild to severe life-threatening forms.¹⁻⁴ Treatment includes high-potency topical
62 corticosteroids (TCS) for mild cases, and high-dose systemic corticosteroids (SCS) in
63 severe forms.^{3,5} There is no consensus for moderate DRESS. We conducted a randomized
64 controlled trial (RCT) which aimed to demonstrate both the non-inferiority of TCS
65 compared to SCS for the control of visceral involvements and the superiority of TCS for
66 the remission of skin involvement.

67

68 This academic open label multicenter RCT (NCT01987076), conducted from October
69 2013 to December 2017, included adults with mild severity DRESS (**Table 1**). Patients
70 received either clobetasol propionate (TCS group) 30 g/day for 30 days, tapered over 5
71 months or oral prednisone (SCS group) 0.5 mg/kg/day for 30 days, tapered over 6
72 months. If occurrence of severe DRESS (**Table 1**), considered as failure, patients were
73 treated according to the investigator's decision. We assessed the skin involvement
74 severity with a scale ranging from 0 to 15.

75 The primary outcome was the rate of patients with organ involvement cleared at day 30
76 (D30, non-inferiority objective), and with complete healing of skin involvement at D30
77 (superiority objective).

78 We used an alpha risk of 2.5% for each objective. Assuming a success rate of 90% in the
79 patients of both groups, we estimated that a sample size of 112 patients would give the
80 trial 80% power to show non-inferiority of TCS (margin of 20 percentage points).

81

82 The trial was stopped prematurely owing to poor recruitment. Fifty-two patients
83 underwent randomization, 26 in each group (**Table 2, Supplemental Figure 1**). After a
84 consent withdraw, 25 SCS patients were available for the main analysis.

85 At D30, for the main analysis, 14/26 patients (53.8%) of the TCS group had remission of
86 visceral involvement, compared to 18/25 (72.0%) of the SCS group, -18.2% difference,
87 97.5%CI [-43.7; 11.5]. At D30, 15/26 patients (57.7%) of the TCS group showed cleared
88 skin involvement, compared to 17/25 (68.0%) of the SCS group, -10.3% difference,
89 97.5%CI [-37.0; 18.8].

90 At D30, 69.6% in the TCS group showed remission of all involvements, versus 82.6% in
91 the SCS group, -13.0% difference, 95%CI [-36.0; 11.7]. Before D30, in the TCS group, 6
92 patients (23.1%) showed a worsening of the DRESS, rescued with high doses of SCS,
93 compared to no patients in the SCS group. Two patients died (one in each group, not
94 related to the trial treatment). Among 92 AEs, 20 (21.7%) were related to the treatment
95 without difference among groups, 4 (4.3%) were severe but not related to the treatment.

96

97 Due to the early stop of the trial, we lacked power to demonstrate both the non-
98 inferiority of high-dose TCS for the control of organ involvement, and their superiority
99 for the remission of skin lesions. DRESS worsened in 23.1% of patients with TCS, but the
100 switch to high-dose SCS was effective. Long-term SCS have AEs, while TCS may be
101 expensive in some countries. We propose two strategies for first-line treatment of
102 moderate DRESS: either low-dose SCS or high-potency TCS, subject to in-patient
103 monitoring.

104

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107

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127 **Supplemental Figure 1:** Flow chart of the study.

129 **Table 1: Criteria for moderate and severe DRESS used in our RCT**

<u>Criteria for moderate severity DRESS</u>
At least one visceral involvement of intermediate severity according the following criteria:
- Liver: transaminases between 4 and 15 folds above the normal values (N), alkaline phosphatase between 3 and 5 N and Factor V >50%
- Kidney: organic kidney insufficiency with sudden increase of creatininemia over 26.4 µmol/L or 1.5 N or oliguria < 0.5 mL/kg/h
- Blood cell count: hemoglobin between 7 and 10 g/dL and/or neutrophils between 500 and 1500/mm ³ and/or platelets between 50,000 and 100,000/mm ³
- Lungs: interstitial pneumonia with PaO ₂ 60-75mmHg, without rest dyspnoea
AND no cardiac, neurological, or digestive life-threatening involvement
<u>Criteria for severe DRESS*</u>
At least one of the following criteria:
- Liver: transaminases >15 folds above the normal values (N), alkaline phosphatase >5 N and Factor V <50%
- Kidney: rapidly progressive organic kidney or oligo-anuria
- Lungs: interstitial pneumonia with PaO ₂ <60mmHg
- Myocarditis, neurological, digestive involvement, pancytopenia, multi-organ failure, hemophagocytosis

130 **In our study, patients who worsened and achieved criteria of severe DRESS were treated according to the*
131 *investigator decision. In routine practice, at the time of the study, treatment of severe DRESS could include*
132 *high doses of corticosteroids (1 mg/kg/day), intravenous immunoglobulins, and/or antiviral agents.*

133

134 **Table 2: Main epidemiological, clinical and biological characteristics of patients at**
 135 **baseline**

Group by randomization	TCS (n ₁ =26)	SCS (n ₂ =26)
Patient characteristics		
Age (years)	53.0 ± 20.0	58.6 ± 18.4
Male sex, n (%)	12 (46.1)	11 (42.3)
Transfer from emergency department or other hospital, n (%)	19 (73.1)	19 (73.1)
Temperature, (°C) (n ₁ =26, n ₂ =25)	38.1 (1.1)	38.0 (1.2)
Enlarged lymph nodes, n (%) (n ₁ =25, n ₂ =26)	16 (64.0)	17 (65.4)
Score of the skin involvement / 15 (n ₁ =25, n ₂ =24)	6.7 (1.7)	7.3 (2.1)
Eosinophilia (Giga/L) (n ₁ =25, n ₂ =26)	2.4 (3.7)	1.8 (1.1)
Lymphocytosis (Giga/L,) (n ₁ =25, n ₂ =26)	4.1 (3.6)	3.5 (3.1)
Creatininemia (µmol/l) (n ₁ =25, n ₂ =26)	120.5 (76.9)	125.3 (79.5)
Rate of liver enzymes		
ALAT (UI/l) (n ₁ =25, n ₂ =26)	212.1 (158.6)	245 (209.5)
ASAT (UI/l) (n ₁ =25, n ₂ =26)	149.6 (110.3)	146 (105.6)
Gamma-GT (UI/l) (n ₁ =25, n ₂ =25)	287.7 (263.1)	333.8 (308.2)
Alkaline phosphatase (UI/l) (n ₁ =25, n ₂ =26)	246.9 (215.9)	263.5 (198.6)
Blood viral PCR (N positive / N performed)		
HHV6	6/15	0/14
EBV	3/16	1/17
CMV	0/16	5/18

136 *TCS = topical corticosteroids; SCS = systemic corticosteroids; PCR = polymerase chain reaction*

137 *Values are mean (SD) or number (percentage)*

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