

## ONLINE FIRST

### Poor Benefit/Risk Balance of Intravenous Immunoglobulins in DRESS

**D**rug reaction with eosinophilia and systemic symptoms (DRESS), sometimes called hypersensitivity syndrome, is a severe drug-induced reaction with visceral involvement and blood abnormalities associated with reactivations of viruses of the herpes family: human herpesvirus (HHV)-6, HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV).<sup>1</sup> Our research group<sup>2</sup> recently reported that the immune response in DRESS, previously thought to be directed against drug components, is in fact mediated by tumor necrosis factor (TNF)- and interferon- $\gamma$  (INF- $\gamma$ )-secreting CD8<sup>+</sup> T lymphocytes, which are directed against previously quiescent HHVs reactivated by the drug and home to the skin and visceral organs.<sup>2</sup> Oral corticosteroid treatment is often proposed for severe DRESS, but oral corticosteroids might favor a relapsing course of the syndrome. Some researchers,<sup>3,4</sup> based on the presence of antiviral IgGs in intravenous immunoglobulins (IVIGs) and their numerous immunologic effects, have suggested that IVIGs might be effective in a few patients with DRESS, although these patients were concomitantly treated with systemic corticosteroids. The aim of the present study was to evaluate the safety and efficacy of IVIGs in patients with DRESS and to assess the evolution of immunologic and virologic parameters after treatment.

**Methods.** Ten patients with severe DRESS<sup>2</sup> were considered for enrollment in this multicenter prospective open study, which was approved by the Northwest France ethics committee and registered as NCT00505648. Six patients were ultimately enrolled. Study patients were treated with IV infusions of Tegeline (LFB Biomedicaments), 200 mg/kg/d for 5 consecutive days. The primary end point was the disappearance of fever and disease progression by day 7 after treatment and complete remission without corticosteroids by day 30. The study was prematurely stopped by the ethics committee for safety reasons. To assess the role of IVIGs on viral reactivations and immunologic parameters, blood samples were collected at baseline and at days 5 (end of IVIG treatment), 10, and 30. Viral DNA from EBV, HHV-6, HHV-7, and CMV was quantified by real-time polymerase chain reaction in patients' serum and peripheral blood mononuclear cells.<sup>2</sup>

**Results.** Six patients with severe DRESS (2 men and 4 women), mean (SD) age 58 (15) years, were included in the study (**Table**). All patients had an extensive eruption and facial swelling. According to the RegiSCAR scale,<sup>5</sup> the patients' median severity score was 7 (range, 6-7) on a scale ranging from 1 to 9, meaning that the diagnosis of DRESS was certain in all patients. Patients were treated

after a median delay of 12.5 days (range, 7-24 days) after the onset of DRESS. Two patients experienced severe malaise during the infusion, one with hypertension and the other with hypotension, and so infusion was stopped by the investigators. One patient had a pulmonary embolism at day 9.

Four patients required rescue oral corticosteroid treatment, the 2 patients with initial malaise and 2 others owing to the occurrence of hemophagocytic syndrome during the follow-up period. These 4 patients dropped out of the study, according to the study protocol (ie, rescue corticosteroid treatment). Only 1 of 6 patients achieved the primary end point. This patient was in partial remission at day 30 and achieved complete remission by day 120.

Viral reactivations were observed at baseline in all 6 cases and were still observed after treatment in 3 of the 3 cases tested (**Table**). Immunologic analyses showed a slight decrease in TNF and INF- $\gamma$  serum levels from baseline to day 30 in the 2 patients who achieved partial or complete remission with IVIG treatment alone, whereas the number of TNF- and INF- $\gamma$ -producing CD8<sup>+</sup> T lymphocytes paradoxically increased despite the regression of DRESS symptoms in these patients.

**Comments.** This study does not support a beneficial effect of IVIG treatment in patients with DRESS, since 5 of 6 patients experienced severe adverse events, and 4 patients had to be treated with oral corticosteroids because of IVIG adverse effects (n=2) or uncontrolled DRESS (n=2). This absence of beneficial effect of IVIGs is in accordance with the persistence of multiple viral reactivations after treatment, which was previously reported in a patient with DRESS treated with IVIGs,<sup>4</sup> and with the absence of significant modification of immunologic parameters in patients who did not receive oral corticosteroids. Our observations suggest that IVIGs must not be used as a single treatment in DRESS.

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**Table. Clinical, Biologic, and Virologic Parameters at Baseline and After Treatment in the 6 Patients With DRESS Treated With IVIGs**

Characteristic	Study Patient					
	1	2	3	4	5	6
<b>Baseline Clinical and Biologic Parameters</b>						
Sex/age, y	M/34	F/76	F/53	F/52	F/69	M/62
Ethnicity	Nonwhite	White	White	White	White	Nonwhite
Delay between first symptoms and treatment, d	9	11	14	7	24	14
Culprit drug(s) (delay from start of drug treatment to the onset of DRESS, d)	Phenytoin (23)	Vancomycin (9) Ciprofloxacin (35)	Spiramycin (8) Metronidazole (8)	Vancomycin (53) Trimethoprim-sulfamethoxazole (53)	Allopurinol (13)	Allopurinol (29)
Temperature (°C)	39.3	Ticarcillin (22) 39.0	Azithromycin (29) 39.0	Gabapentin (38) 40.2	37.9	39.5
Lymph node sites involved, No.	0	2	4	4	1	0
Visceral involvement	Hepatitis	Hepatitis	Hepatitis	Hepatitis	Hepatitis pneumonitis	Hepatitis
Severity score <sup>a</sup>	6	7	7	6	7	7
Blood eosinophil count, cells/ $\mu$ L <sup>b</sup>	700	1970	41 300	34 200	6100	3000
<b>Clinical Evolution After IVIG Treatment</b>						
Severe adverse events	Pulmonary embolism	None	Hemophagocytic syndrome	Hemophagocytic syndrome	Severe malaise	Severe malaise
Response to IVIG	PR	CR	Failure	Failure	Dropped out	Dropped out
Rescue corticosteroid treatment <sup>c</sup>	No	No	Yes	Yes	Yes	Yes
<b>Virologic And Immunologic Parameters at Baseline (Day 0) and After IVIG Treatment (Day 30)</b>						
EBV reactivation	+→+	+→+	+→ND	+→+	→ND	→ND
CMV reactivation	→→+	→→+	→→ND	→→+	→→ND	→→ND
HHV-6 reactivation	→→-	→→-	→→ND	+→+	+→ND	+→ND
HHV-7 reactivation	→→-	→→+	→→ND	→→+	→→ND	+→ND
INF- $\gamma$ serum level, pg/mL	9.6 → 2.3	4.2 → 1.2	7.9 → ND	2.1 → 23.0	ND → ND	ND → ND
TNF serum level, pg/mL	56.3 → 14.8	53.4 → 29.4	20.8 → ND	29.2 → 7.9	ND → ND	ND → ND
INF- $\gamma$ -producing CD8 <sup>+</sup> T lymphocytes, %	16 → 55	14 → 19	ND → ND	ND → 24	4 → ND	19 → ND
TNF producing CD8 <sup>+</sup> T lymphocytes, %	20 → 54	24 → 62	ND → ND	ND → 21	14 → ND	13 → ND

Abbreviations: CMV, cytomegalovirus; CR, complete response (absence of clinical and biologic signs at day 30); DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; HHV, human herpesvirus; INF, interferon; IVIGs, intravenous immunoglobulins; ND, not determined; PR, partial response (presence of clinical and/or biologic signs at day 30); TNF, tumor necrosis factor; -, negative; +, positive; →, evolved to.

SI conversion factor: To convert eosinophils to number of cells  $\times 10^9/L$ , multiply by 0.001.

<sup>a</sup>Severity score was assessed according to the RegiSCAR study.<sup>5</sup>

<sup>b</sup>Maximum count.

<sup>c</sup>Assessed at day 30 after IVIG treatment.

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