Original Article

Successful Intravenous Immunoglobulin Treatment in Pediatric Severe DRESS Syndrome

Nufar Marcus, MD[a,b,c,*], Keren Smuel, MD[a,*], Moran Almog, MD[a], Dario Prais, MD[c,d], Rachel Straussberg, MD[c,e], Daniel Landau, MD[a,c], and Oded Scheuerman, MD[a,c] *Petach Tikva and Tel Aviv, Israel*

What is already known about this topic? Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe cutaneous and systemic delayed drug reaction. The treatment consists of withdrawal of the offending drug, and in severe cases, corticosteroids are added. The treatment of steroid-resistant cases is unclear.

What does this article add to our knowledge? We describe 7 pediatric patients with severe DRESS syndrome who were treated successfully with intravenous immunoglobulin (IVIG) with minimal side effects.

How does this study impact current management guidelines? IVIG treatment may hasten recovery in pediatric patients with severe DRESS syndrome, especially in patients with a severe course not responding to steroid treatment.

BACKGROUND: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening delayed drug-induced hypersensitivity reaction. The most frequently reported drugs causing DRESS are aromatic antiepileptic agents. Prompt withdrawal of the offending drug and administering systemic corticosteroids is the most widely accepted and used treatment. The treatment of severe DRESS not responsive to systemic corticosteroids is uncertain.

OBJECTIVE: The objective of this study was to describe a case series of pediatric patients with DRESS who were treated successfully with intravenous immunoglobulins (IVIGs).

METHODS: A retrospective review of all children hospitalized in a tertiary care children's hospital with severe DRESS syndrome who received IVIG in addition to offending drug withdrawal and systemic corticosteroids during 1999-2017 is performed.

RESULTS: Seven severe DRESS patients (4 males, age: 9.5 ± 5.7 years) are described. The offending drugs were antiepileptics in all but one case. Clinical findings included fever, rash, lymphadenopathy, dyspnea, anasarca, and hepatic involvement. After IVIG treatment (total dosage: 1-2 g/kg), fever resolved within a median time of 1 (range, 0-5) day, rash disappeared after 6.3 ± 1.6 days, and liver enzymes substantially improved after 3.8 ± 1.6 days. Patients were discharged 6.1 ± 2.7 days after IVIG commencement. There was no mortality.

CONCLUSION: The addition of IVIG in DRESS syndrome resistant to regular drug withdrawal and systemic corticosteroid therapy may hasten disease recovery. © **2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *DRESS syndrome; Pediatric; Intravenous immunoglobulins*

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening delayed drug-induced hypersensitivity reaction.[1] Symptoms include skin eruptions and systemic symptoms of fever, malaise, and lymphadenopathy. Additional symptoms are related to visceral involvement such as altered liver function, nephritis, and pneumonitis. Hematologic abnormalities may include leukocytosis with eosinophilia, thrombocytopenia, and atypical lymphocytosis.[1,2] The most frequently reported offending drugs are aromatic antiepileptic agents, antibiotics, and allopurinol. Other common drugs associated with DRESS are ibuprofen[3] and griseofulvin.[4] The syndrome usually begins within 2 months (but more often within 2 to 6 weeks) after drug introduction. The symptoms relapse soon after drug re-administration.[1] Reactivation of herpesviruses has also been shown to play a role in the pathogenesis of DRESS syndrome, especially human herpesvirus-6 (HHV-6) but also cytomegalovirus, Epstein-Barr virus (EBV), and HHV-7.[1,2,5] Mortality rates of up to 10% have been reported, most commonly after fulminant hepatitis with hepatic necrosis.[1]

[a]Department of Pediatrics B, Schneider Children's Medical Center of Israel, Petach Tikva, Israel
[b]Kipper Institute of Immunology, Schneider Children's Medical Center of Israel, Petach Tikva, Israel
[c]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[d]Pediatric Pulmonology Institute, Schneider Children's Medical Center of Israel, Petach Tikva, Israel
[e]Pediatric Neurology Unit, Schneider Children's Medical Center of Israel, Petach Tikva, Israel
No funding was received for this work.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication July 26, 2017; revised September 14, 2017; accepted for publication October 12, 2017.
Available online ■■
Corresponding author: Oded Scheuerman, MD, Department of Pediatrics B and Pediatric Infectious Diseases Unit, Schneider Children's Medical Center of Israel, Petach Tikva 4920235, Israel. E-mail: odedshv@clalit.org.il.
* These authors contributed equally to this work.
2213-2198

https://doi.org/10.1016/j.jaip.2017.10.016

Abbreviations used
DRESS- Drug reaction with eosinophilia and systemic symptoms
EBV- Epstein-Barr virus
HHV-6- Human herpesvirus-6
IVIG- Intravenous immunoglobulin
TARC- Thymus and activation-regulated chemokine

Rapid diagnosis and prompt withdrawal of the offending drug is the mainstay of treatment in patients with DRESS.[6] Skin eruption and visceral involvement resolve gradually within 6 to 9 weeks after drug withdrawal.[2] Patients without evidence of visceral involvement can be treated symptomatically, with only supportive care and topical corticosteroids.[7,8] Although there is still a significant mortality rate in DRESS, the therapeutic arsenal is quite limited. Systemic corticosteroid therapy is currently the most widely accepted and used treatment for DRESS with severe organ involvement. The use of systemic corticosteroids for the treatment of DRESS with severe organ involvement has not been evaluated in randomized trials.[2,9] Various treatment options have been described in the treatment of severe/refractory DRESS, including plasmapheresis, cyclophosphamide, cyclosporine, interferon, muromonab-CD_3, mycophenolate mofetil, and Rituximab.[10] Most studies on these interventions are anecdotal and involve adults with severe disease. Intravenous immunoglobulin (IVIG) treatment was described, especially in adults, in several anecdotal cases with varying results.[11-15] Although the mechanisms of action of IVIG in DRESS have not been fully elucidated, immunomodulatory and anti-inflammatory activity may be involved.[16] The aim of the present study was to describe a series of pediatric patients who were diagnosed with severe DRESS syndrome and successfully treated with IVIG.

METHODS

The study group included all pediatric patients with severe DRESS syndrome during 1999-2017 admitted to Schneider Children's Medical Center of Israel (a large pediatric tertiary care hospital), who had received IVIG in addition to systemic corticosteroids along with withdrawal of the offending drug. The diagnosis of DRESS syndrome was made according to DRESS RegiSCAR score.[17] DRESS RegiSCAR score is based on clinical and laboratory findings, which define DRESS. Patients receive a score of (−1), 0, 1, or 2 based on the presence of fever, lymphadenopathy, skin rash, internal organ involvement, resolution within 15 days, and the presence of eosinophilia or atypical lymphocytosis. Based on the score, DRESS diagnosis is defined as follows: <2 cases excluded; 2-3 possible cases; 4-5 probable cases; and >5 definite cases. Data were retrieved from the patient's files and included demographics, clinical presentation, laboratory findings, treatment protocols, and outcome.

The study was approved by the local institutional review board. The need for patient consent was waived owing to the retrospective nature of the study.

RESULTS

Clinical presentation and laboratory results

Seven patients were included in this study, 4 males and 3 females. The mean age at presentation was 9.5 ± 5.7 years (range, 2.1-16 years). Clinical presentation and laboratory results are summarized in Table I.

Six patients presented with convulsive disorder and 1 patient with severe acute pleuropneumonia. Patients were exposed to

TABLE I. Clinical and laboratory presentation

Clinical features									Laboratory results				
Patient no.	Age (y)/sex	Suspected medications	Time from drug exposure to symptoms onset (wk)	Mucosal involvement	Lymphadenopathy	Hepatomegaly	Resp. distress	Anasarca	Eosinophils-max (cells/μL)*	Atypical Lymphocytes (%)	AST-max (U/L)	Bilirubin (mg/dl)	DRESS RegiSCAR score†
1	13.5/M	Carbamazepine	4.5	N	C	Y	Y	N	400	3	907	4.7	4
2	6/M	Phenytoin, Phenobarbital	2.5	Y	C, SO	N	N	Y	1224	4	55	0.1	7
3	16/F	Phenobarbital	3	N	N	N	N	N	100	2	152	0.5	3
4	3.5/F	Phenobarbital	1.5	Y	A, C, SO, SM, I	N	N	Y	200	11	326	0.8	7
5	10/M	Lamotrigine, valproic acid	4	N	C	Y	Y	Y	5100	38	1313	1.4	8
6	15.7/F	Phenytoin	2	Y	C	N	Y	N	100	–	43	0.3	4
7	2.1/M	Ceftriaxone, clindamycin	1.7	N	C, I	N	N	Y	1600	6	24	0.4	4

AST, Aspartate transaminase; *A*, axillary; *C*, cervical; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *I*, inguinal; *SM*, submandibular; *Resp*, respiratory; *SO*, suboccipital.
Patients 2, 3, 6 were published as case reports.[27,28]
*Normal <800.
†DRESS RegiSCAR score[17] is defined as follows: <2: no case; 2-3: possible; 4-5: probable; >5: definite.