

Successful Intravenous Immunoglobulin Treatment in Pediatric Severe DRESS Syndrome



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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 2018;6:1238-42)

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 ibuprofen³ 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

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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-CD₃, 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 1.

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

TABLE 1. 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		Respiratory distress	Anasarca	Eosinophils-max (cells/ μ L)*	Atypical Lymphocytes (%)	AST-max (U/L)	Bilirubin (mg/dl)	DRESS RegiSCAR score ¹⁷	
1	13.5/M	Carbamazepine	4.5	N	C	Y	N	400	3	907	4.7	4	
2	6/M	Phenytoin, Phenobarbital	2.5	Y	C, SO	N	Y	1224	4	55	0.1	7	
3	16/F	Phenobarbital	3	N	N	N	N	100	2	152	0.5	3	
4	3.5/F	Phenobarbital	1.5	Y	A, C, SO, SM, I	N	Y	200	11	326	0.8	7	
5	10/M	Lamotrigine, valproic acid	4	N	C	Y	Y	5100	38	1313	1.4	8	
6	15.7/F	Phenytoin	2	Y	C	N	Y	100	—	43	0.3	4	
7	2.1/M	Ceftriaxone, clindamycin	1.7	N	C, I	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.

¹⁷DRESS RegiSCAR score¹⁷ is defined as follows: <2: no case; 2-3: possible; 4-5: probable; >5: definite.

TABLE II. Treatment protocol and response to IVIG treatment

Treatment				Response to IVIG treatment			
Patient no.	Corticosteroid dose (mg/kg/d)	Corticosteroid days before IVIG	IVIG dose (g/kg)	Corticosteroid days after IVIG	Days to defervescence	Days to liver enzyme improvement	Days to anasarca resolution
1	2	0	2	D3-D8	5	5	—
2	2	5	2	D1-D30	1	3	3
3	1	0	1	D1-D8	1	6	—
4	30	1	2	D1-D17	1	3	1
5	2	9	2	D1-D40	1	2	1
6	2	2	2	D1-D14	0	ND	—
7	1	2	2	D1-D54	0	—	2

D, Day of IVIG administration; ND, not done; IVIG intravenous immunoglobulin.

different potentially offending drugs, including phenobarbital (3), phenytoin (2), carbamazepine, lamotrigine, valproic acid, and ceftriaxone/clindamycin. The mean time between drug exposure and beginning of symptoms was 2.7 ± 1.2 weeks. The mean time from admission to clinical suspicion in DRESS was 1.7 ± 2.4 days. All patients presented with fever and rash. Three patients had a maculopapular rash, 2 had erythrodermia, and 2 presented with erythema multiforme; 1 patient with erythema multiforme also presented with a vesicular rash. Three patients had oral mucosal involvement and 2 of those patients also had conjunctival involvement. Six patients presented with lymphadenopathy, 4 patients had severe anasarca, and 6 patients had elevated liver enzymes (aspartate transaminase and alanine aminotransferase). Hepatomegaly was associated with significantly elevated liver enzymes and mild elevation in bilirubin in 2 patients. Renal function was normal in all patients. Only 4 patients had eosinophilia. Atypical lymphocytosis was marked in 6 patients. Of the 3 patients tested for HHV-6 infection, 2 were found positive. The symptoms of DRESS in order of appearance were fever (at admission), rash (0-2 days), lymphadenopathy (0-8 days), mucosal involvement (3-6 days), and anasarca (2-7 days).

Treatment regimens and response to IVIG treatment

All 7 patients were treated with IVIG, either as an initial or add-on therapy to steroid treatment. Treatment regimens and response to IVIG treatment are summarized in Table II.

Withdrawal of the causative drug was initiated as soon as diagnosis was made for all patients. Because all patients had severe disease, they were treated with systemic corticosteroids. Five patients were treated first with corticosteroids, but because there was no improvement (ie, fever and rash continued and there was no laboratory improvement), IVIG treatment was added within a median time of 2 days from the beginning of corticosteroids. One patient started IVIG treatment and corticosteroids simultaneously and 1 patient received IVIG treatment before corticosteroids (which were added subsequently 3 days later). Six patients received an IVIG dose of 2 g/kg and 1 patient received 1 g/kg.

Rapid improvement in well-being was noted 24 hours after IVIG treatment in 6 patients. The last patient improved after 48 hours. Fever resolved after a median of 1 day (range, 0 to 5 days) after IVIG administration. Rash disappeared after 6.3 ± 1.6 days. Anasarca improved after 1 day in 2 patients and after 2-3 days in the other patients. Liver enzyme values improved (at least 50% reduction in hepatic enzymes) after 3.8 ± 1.6 days. Patients were discharged after 6.1 ± 2.7 days. One patient had

fever during IVIG administration; another patient had significant transient hyponatremia (121 mEq/L), which could also be attributed to the combination of anasarca and hypoalbuminemia.

DISCUSSION

We describe here the largest series, to our knowledge, of pediatric patients with severe DRESS syndrome who were treated successfully with IVIG in addition to systemic corticosteroids. All patients recovered promptly compared with the clinical course reported in the literature.² The rapid defervescence and improvement in systemic symptoms after IVIG initiation were striking in most patients. Four of our patients had a severe deteriorating course despite high dose steroid therapy and responded dramatically to the addition of IVIG.

DRESS syndrome is life threatening with up to 10% mortality rate, and therefore early diagnosis is crucial. Diagnosis might be delayed when symptoms mimic infectious diseases and other allergic reactions. The treatment of DRESS syndrome is discontinuation of the culprit drug and systemic corticosteroids if visceral involvement exists.

The pathogenesis of DRESS syndrome is not fully understood, but unique immunological alternations were found: an expansion of memory T cells that crossreact with both the drug and virus (eg, HHV-6)¹⁸ or an increase in cytokine secretion, particularly TNF and IL-6, which are both proinflammatory cytokines. Regulatory T cells are initially increased in the blood and skin, but subsequently decrease in parallel with the functional deterioration of different organs and systems.^{19,20} B-cell lymphocyte counts and immunoglobulin levels may also decrease. This was found in association with HHV-6 reactivation and the subsequent onset of DRESS.²¹ Some reports describe hypergammaglobulinemia.¹⁶ Thymus and activation-regulated chemokine (TARC) recruits Th2-polarized T lymphocytes into local inflammation sites, thus leading to a Th2-type immune reaction. Serum TARC levels are elevated preferentially in patients with DRESS, reflecting a Th2-type immune response in these patients. Serum TARC may be a prognostic biomarker of severity of inflammation in drug eruptions.²²

Although the beneficial mechanisms of IVIG treatment in DRESS as well as other severe adverse drug reactions are not fully elucidated, its immunomodulatory and anti-inflammatory activity may be significant.²³ One possible mechanism is that IVIG preparations contain antiviral neutralizing antibodies that help clear the viral infection/reactivation found to be important in the pathophysiology of DRESS syndrome. Galvão et al¹⁶

reported an improvement of DRESS syndrome after IVIG treatment in a patient that was associated with EBV viremia clearance. The patient they described had hypergammaglobulinemia, but they suggested that the antibodies were not effective in clearing the infection and therefore the patient benefited from IVIG therapy.¹⁶ In cases presenting with decreased immunoglobulin levels, IVIG may help neutralize HHV-6 reactivation.²⁴

A few cases of successful treatment with IVIG have been described in the literature, mostly in adult patients. In these cases, IVIG was given in addition to systemic corticosteroids^{11,12,14} or as a monotherapy.¹³ However, there is a controversy regarding IVIG treatment in adults with DRESS, and a recent study of 6 adult patients with severe DRESS syndrome did not support a beneficial effect of IVIG; 5 of 6 patients experienced severe adverse effects.¹⁵ In our cohort, transient fever during treatment with IVIG was noted in 1 patient. Transient hyponatremia observed in another patient might have been caused by severe anasarca. No other adverse reactions were observed.

The favorable outcome and lower side effects we observed in our study in comparison with the data published in adult patients may have several explanations. The IVIG regimen was of continuous 2 g/kg protocol unlike some of the adult 5-day regimen. Furthermore, in our study, all patients were treated with systemic corticosteroids in addition to IVIG. The study in adults described severe adverse reactions to IVIG that were not seen in our population. Previous reports have suggested that children may tolerate IVIG with less side effects.²⁵ Another possible explanation for the difference is the relatively early diagnosis of DRESS in our patients (1.7 days from admission).

There were a few case reports of children with DRESS who were treated successfully with corticosteroids and IVIG.²⁶⁻²⁹ Our results also suggest that IVIG treatment can hasten recovery and has an additive value in patients who are resistant to corticosteroid therapy, that is, fever and rash continuation, eosinophilia despite corticosteroid therapy and anasarca.

This study is limited as it is retrospective and there is no control group. Severe DRESS is a rare clinical syndrome. Due to its rarity and the positive experience in our institution with IVIG add-on treatment for severe DRESS, we could not find patients with severe DRESS who were not treated with IVIG. One of our patients had a possible diagnosis of DRESS according to RegiSCAR, but his overall clinical course did fit a diagnosis of DRESS and therefore he was included. In addition, 3 patients did not have eosinophilia, but, as mentioned, this is not an obligatory DRESS criterion, as tissue eosinophilic infiltration may not always be associated with circulating eosinophilia.

In conclusion, DRESS syndrome continues to be a therapeutic challenge in pediatric patients. Early diagnosis and treatment are crucial even if symptoms are still evolving. The current treatment relies mainly on offending drug withdrawal and systemic corticosteroids. Our results suggest an important role of IVIG, especially in patients with a severe course not responding to steroid treatment.

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