

Intravenous Immunoglobulin May Be Beneficial as an Add-on Therapy in DRESS



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DRESS, Drug Reaction (Rash in the original description) with Eosinophilia and Systemic Symptoms, is a delayed drug-induced hypersensitivity reaction with specific clinical-laboratory features. Patients characteristically have rash, fever, lymphadenopathy, malaise, and may have multiorgan involvement such as hepatitis, nephritis, pneumonitis, and myocarditis. Hematologic abnormalities may include leukocytosis, eosinophilia, atypical lymphocytosis, and thrombocytopenia.¹⁻³ Given that approximately 20% of the patients do not present eosinophilia, this syndrome is also called drug-induced hypersensitivity syndrome, as suggested by the Japanese researchers.² DRESS is one of the Severe Cutaneous Adverse Reactions (SCARs), and it is associated with high morbidity and mortality rates up to 10%, most commonly due to fulminant hepatitis. Morbidity includes the preclusion to use the culprit drug, which is in many cases the first-line therapy for the patient.^{2,3}

The more that is known about a disease, the more specific will be its treatment (Figure 1). DRESS is a syndrome that has an intriguing pathophysiology and can be an interesting model in which to study the immune system function. Two major events mediate the immunopathophysiology of DRESS, the drug-specific immune response and the virus reactivation.^{2,4} The typical immune response of this syndrome is a delayed hypersensitivity reaction type IVb, a T-cell-mediated immune response against the culprit drug with eosinophils as the major effector cells. The most frequent offending drugs are aromatic anticonvulsants, dapsone, sulfasalazine, antibiotics, and allopurinol. Three mutually nonexclusive models have been developed to explain how a small-molecule, nonprotein drug may elicit a specific T-cell immune response: the hapten/prohapten model, the pharmacologic interaction model, and the altered peptide repertoire model.⁵

Virus reactivation has been reported in up to 60% of patients with DRESS, but many important questions remain unanswered. Why and when does the reactivation occur? Is it the primary driving force in the immunopathophysiology of this syndrome, or a secondary impulse, or even a bystander event?

Most scientific evidence suggests an initial drug reaction inducing activation, proliferation, and dysregulation in the immune system. The capacity of stimulated lymphocytes to reactivate and release viruses is well established. In addition, studies have shown that regulatory T cells decrease in parallel with patients' clinical deterioration, and B-cell lymphocyte counts and immunoglobulin levels may also decrease in DRESS. As a consequence, several viruses of the herpes group may reactivate characteristically human herpesvirus 6 (HHV6), but also HHV7, Epstein Barr virus, and human cytomegalovirus. The HHVs are ubiquitous pathogens that are notable for their ability to establish lifelong infection and cellular latency. They induce massive expansion of cross-reactive memory T-cell populations with polyspecific TCRs that are capable of recognizing multiple peptides (heterologous immunity). Under this model, the T-cell response would be primarily generated by the initial encounter with pathogen antigen and then boosted by drug exposure.^{2,4-6}

The harmful immune response established in DRESS has a type 2 profile with T cells that cross-react with both the drug and the virus, and virus reactivation explains the prolonged evolution and relapses observed during the illness, even after months of drug withdrawal. It remains unknown if, and to what extension, virus cytopathic effects contribute to the clinical manifestations of DRESS. Another question is if the administration of systemic steroids in these patients contributes to an immunodeficiency state and further virus proliferation.^{2,4-6} Future studies should clarify the clinical consequences of virus reactivation, and there may be 2 DRESS phenotypes, the syndrome with and without virus reactivation.

Rapid diagnosis and prompt withdrawal of the culprit drug is the mainstay of DRESS management. The diagnosis is based on clinical and laboratorial findings, which compose 2 scoring systems: from the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR)⁷ and from the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR)⁸ (Table I). Systemic corticosteroids have been the most widely used pharmacotherapy to treat the syndrome, particularly for the severe cases. Although there are no randomized trials assessing their use in DRESS, scientific evidence supports the corticosteroid therapy. Most patients present clinical and laboratorial improvement after onset of therapy, and they often get worse if rapid corticosteroid tapering is done, needing several weeks, sometimes months, of medication. In addition to the acute benefits in the treatment of DRESS, systemic corticosteroid therapy may reduce the risk of subsequent development of autoimmune diseases, which are among the long-term complications of this syndrome. However, some patients do not respond to corticosteroids, and patients with DRESS could be divided into 2 other phenotypes: responsive and resistant to corticosteroids. Intravenous immunoglobulin has been used in

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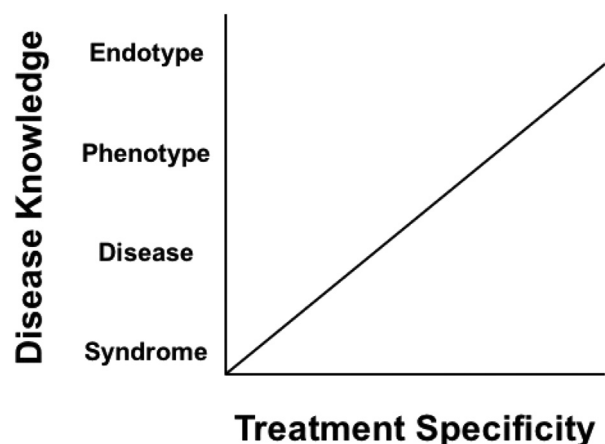


FIGURE 1. Correlation between disease knowledge and treatment specificity.

TABLE I. Scoring systems for the diagnosis of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Criterion	RegiSCAR*	J-SCAR†
Characteristic maculopapular rash	+	+
Fever	+	+
Lymphadenopathy	+	+
Leucocyte abnormalities (eosinophilia, atypical lymphocytosis)	+	+
Organ involvement (liver or other)	+	+
Prolonged resolution	+	+
Human herpesvirus 6 reactivation	–	+
Tests for differential diagnosis	+	–

+ Present; – absent.

*Scoring system for classifying DRESS cases as definitive, probable, possible, or no case from the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR). Each criterion receives a score from –1 to 2. Final score: <2, no case; 2–3, possible case; 4–5, probable case; >5, definitive case.⁷

†Diagnosis criteria for drug-induced hypersensitivity syndrome from the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR). The diagnosis is confirmed by the presence of the 7 criteria (typical drug-induced hypersensitivity syndrome [DIHS]) or of 5 criteria, excluding lymphadenopathy and human herpesvirus 6 reactivation (atypical DIHS).⁸

the treatment of DRESS in children and adults, and several anecdotal cases with successful outcomes have been reported.^{2,3,9}

In the current issue of *JACI: In Practice*, Marcus et al⁹ describe the largest case series of pediatric patients with severe DRESS syndrome who were treated successfully with intravenous immunoglobulin (IVIG), in addition to systemic corticosteroids. Although the study is retrospective and the therapeutic intervention is not controlled, it shows a dramatic and immediate response to IVIG in all children, some of whom had not responded to corticosteroid therapy.⁹ Their results corroborate a previous study reporting a case series of 4 adolescents who improved with IVIG administration.¹⁰ On the contrary, another study did not support a beneficial effect of IVIG in adults with DRESS. However, the 6 adults in that case series did not take systemic corticosteroids at the beginning of their treatment and received only IVIG, which was associated with an unusually high rate of severe adverse effects.¹¹

In addition to its formal use as replacement therapy in immunodeficiencies, IVIG has been used as an immunomodulatory

agent in several immune and inflammatory disorders. The immune-regulatory and anti-inflammatory properties of immunoglobulins may be mediated by the Fab or Fc portion of the antibody and have been attributed to the following different mechanisms: (1) neutralization of autoantibodies by anti-idiotypic antibodies; (2) neutralization of cytokines, toxins, and T-cell superantigens; (3) suppression of antibody-dependent cell-mediated cytotoxicity; (4) saturation of the Fc receptors in the cells of the immune system, blocking the clearance of opsonized target cells; (5) action of Fc fragments containing sialic acid on macrophages inducing the expression of the inhibitory FcIII receptor; (6) inhibition of the complement system.¹²

Marcus et al. reported in their study that all their patients with DRESS responded well to IVIG treatment, although the mechanism of its immunomodulatory effect remains unknown.⁹ Because other SCARs, including Steven-Johnson syndrome and toxic epidermal necrolysis (TEN), also may respond to IVIG treatment, it is reasonable to assume that the same mechanism(s) may be operating in DRESS as well. For instance, in TEN, it was shown that IVIG inhibited Fas-Fas ligand and caused blockade of CD95.¹³ However, DRESS has its unique clinical presentations as well. Besides the beneficial effects of IVIG described above, specific immunomodulatory mechanisms may be operating in DRESS and its effect may differ, depending on the phenotype of the patient. Because eosinophilia is commonly noted in DRESS, blockage of IL-5 could be one mechanism operating among the responders to IVIG treatment. Another possible mechanism is the presence of antiviral neutralizing antibodies in IVIG preparations that could help to clear reactivated virus. We reported a patient with DRESS syndrome, who, in spite of having hypergammaglobulinemia, improved with IVIG in parallel with virus clearance.¹⁴

In the era of precision medicine, phenotyping of patients and personalizing their treatment is essential. Intravenous immunoglobulin is becoming a good option in the treatment of severe DRESS cases who are nonresponsive to systemic corticosteroids alone. Further studies should help to better determine who should receive IVIG in the treatment of DRESS syndrome.

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