

IN-DEPTH REVIEW

Drug Reaction with Eosinophilia and Systemic Symptoms: A Review of Treatment Options

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ABSTRACT

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a life-threatening condition with an estimated mortality of 5-10%. Multiple therapeutic regimens are routinely used, but literature comparing their effectiveness and safety remains limited.

Objective: To evaluate the effectiveness of commonly used treatments for DRESS, focusing on mortality, duration of treatment, and adverse effects.

Methods: We conducted a PubMed literature review for articles published between 2005 and 2022, including peer-reviewed publications with at least two DRESS patients treated with supportive care, systemic corticosteroids (SCS), intravenous immunoglobulin (IVIG), and/or cyclosporine. We excluded articles that did not clearly delineate the number of patients that received each treatment type and/or respective outcome. We extracted and analyzed data including patient demographics, implicated drugs, treatment regimens, and outcomes.

Results: We included 19 studies encompassing 427 patients, dividing patient data into four groups by the treatment received: supportive care (92), SCS alone (276), SCS with IVIG (44), or cyclosporine (15). The mortality was 5.4% for supportive care, 8.0% for SCS, 13.6% for SCS with IVIG, and 0% for cyclosporine. Overall mortality was 7.7%. Adverse effects were most often attributed to SCS, including opportunistic infections and DRESS recurrence.

Conclusion: Supportive care may be appropriate for mild DRESS cases. While SCS are commonly used, their effectiveness and safety remain a concern. IVIG, though typically used in severe cases, revealed higher mortality. Cyclosporine had favorable outcomes and could be a more suitable DRESS treatment. Prospective, randomized trials are needed to further evaluate treatment efficacy and guide clinical decision-making.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome, is a severe cutaneous adverse reaction characterized by diffuse rash, fever, lymphadenopathy, hematologic

abnormalities, and multi-organ dysfunction.¹⁻

³ Mortality is routinely between 5% and 10% but estimates have been as high as 20%.^{1,2}

Cause of death is most often due to internal organ involvement, primarily hepatic and/or renal failure.¹⁻³ Importantly, neither internal organ involvement nor disease severity necessarily corresponds with cutaneous findings, and an absent rash does not

automatically rule out diagnosis.⁴ Although the constellation of clinical manifestations may create difficulty in establishing a diagnosis, the scoring system proposed by the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) helps to reconcile clinical and laboratory findings to determine disease likelihood: definite DRESS (≥ 6), probable DRESS (4-5), possible DRESS (2-3), and no DRESS (< 2).^{5,6}

In managing DRESS, immediate cessation of the implicated drug(s) is paramount.⁴ Some patients may then recover with supportive care alone, but, in many instances, immunomodulatory agents such as systemic corticosteroids (SCS), intravenous immunoglobulin (IVIG), and cyclosporine are used to attenuate the disease course, particularly in more severe presentations.^{2,3} SCS are considered first-line—a practice largely informed by convention of treating other immune-mediated diseases.³ However, their effectiveness has been questioned, and prospective, randomized trials comparing the efficacy of different therapies do not exist.^{3,7}

To help clinicians better evaluate the effectiveness of different treatment options, we reviewed the literature to describe the overall mortality and adverse effects seen in DRESS patients who received either supportive care only, SCS alone, SCS with IVIG, or cyclosporine alone.

METHODS

A PubMed database search was performed in November 2022 for articles published between 2005 and 2022 using combinations of the following: “drug reaction with eosinophilia and systemic symptoms,” “DRESS,” “drug-induced hypersensitivity syndrome,” “DIHS,” “drug hypersensitivity,”

“corticosteroids,” “intravenous immunoglobulin,” “IVIG,” “cyclosporine,” and “treatment.” The search term “NOT dressing” was included to eliminate extraneous results. We performed title and abstract screening implementing the following inclusion criteria: peer-reviewed publications, English-language abstracts, and studies of all designs with ≥ 2 patients with DRESS treated with any combination of supportive care, SCS, IVIG, and/or cyclosporine. DRESS diagnosis was based on the discretion of the authors for each study; no restrictions were made based on use/reporting of standardized diagnostic criteria (e.g. RegiSCAR scores). Articles were excluded if there was insufficient information to delineate the number of patients receiving each type of treatment and/or survival by treatment received.

Data extracted from each study included patient age, sex, implicated drug, RegiSCAR score, organ involvement, human herpes virus six (HHV6) testing, therapeutic regimen (agent, dose, mean treatment duration), previous treatments (if applicable), adverse effects, and causes of death. Patients were divided into four groups: supportive care alone, SCS alone, SCS with IVIG, or cyclosporine alone. Treatment effectiveness was evaluated by treatment duration and overall mortality, including both patients that died from disease progression and/or adverse effects of treatment.

DISCUSSION

Study selection and overall patient characteristics

Our initial search and title/abstract screening yielded 28 non-duplicate articles meeting inclusion criteria. Nine articles were removed based on exclusion criteria. We ultimately

included 19 studies, representing 427 patients.⁸⁻²⁶

Demographic features, minimum RegiSCAR scores, implicated drugs, internal organ involvement, and treatments used in this study are summarized (**Table 1**). Mean patient age was 47.3 years. The cohort included 201 females (47%) and 178 males (42%), but sex was not reported for the remaining 48 patients (11%).⁸⁻²⁶ Minimum RegiSCAR scores for inclusion in the studies were most often ≥ 6 (30%), followed by 4 or 5 (23%), and 2 or 3 (14%).^{8-10,13,15-25} For the remaining 33% of patients, the RegiSCAR scores for patient inclusion were not reported or there was no mention of whether diagnostic scores were used at all.^{11,12,14,26} The most implicated drugs were anticonvulsants (38%), antimicrobials (29%), and allopurinol (22%). Regarding internal organ involvement, the liver was most often affected (84%), followed by the kidneys (31%), lungs (13%), cardiac and/or skeletal muscle (7%), pancreas (5%), spleen (2%) and nervous system (<1%).⁸⁻²⁶ Laboratory investigations for HHV-6 infection and/or reactivation were performed in 10% of patients and were positive in 40% of them.^{8,11-13,16,17,21,24,25} Patients most often received SCS alone (65%), followed by supportive care only (22%), IVIG in addition to SCS (10%), and cyclosporine (4%).⁸⁻²⁶

Overall, 33 (7.7%) patients died.^{8,11,12,14-16,19,21,23-26} Allopurinol was the offending agent in 18 (55%) of these patients.^{8,11,12,16} Demographic information was included for 31 patient deaths: 14 were female (45%), 15 were male (55%), and mean age was 58.5 years.^{8,11,12,15,16,19,23-25} Of all fatal cases, seven had no significant underlying health conditions, seven others had no reported information of baseline health, and the remaining 19 (58%) had varying combinations of co-morbid conditions

including chronic kidney disease (12), hypertension (7), heart disease (6), diabetes mellitus (4), tuberculosis infection (2), and/or chronic bronchitis (1).^{8,11,12,15,16,19,21,23-26}

Supportive care alone

Characteristics of the 92 patients who received supportive care alone are summarized (**Table 2**).^{8,11,12,14,18,21,23} No rationale was provided for the decision to withhold systemic therapy in greater than half (49) of these patients.^{11,21,23} For the remainder, reasons included contraindications to corticosteroids (19) and less severe disease (24) defined in articles as less extensive rash, no visceral organ involvement, and/or lack of concerning hematologic abnormalities.^{8,12,14,18}

Supportive care consisted of varying combinations of the following: topical corticosteroids, topical antipruritic agents, antihistamines, and oral non-steroidal anti-inflammatory drugs.^{8,11,12,14,18,21,23} Mean duration of supportive care was 16.9 days.^{4,21}

Adverse reactions to supportive care were not reported in any patient nor were there any reported instances of treatment being escalated to systemic therapy.^{8,11,12,14,18,21,23} Still, there were five (5.4%) deaths: one attributed to an upper gastrointestinal bleed and four attributed to sepsis (two from pneumonia, one with renal failure, and one with multi-organ involvement).^{8,11,12}

Systemic corticosteroids alone

Characteristics of the 276 patients who received SCS alone are summarized (**Table 3**).^{8,9,11-16,18,19,21-24,26} Types of SCS included: oral prednisone/prednisolone, intravenous methylprednisolone, intravenous or intramuscular dexamethasone, and intravenous hydrocortisone. Two studies specified that methylprednisolone and dexamethasone were reserved for the most

Table 1. Demographic and clinical factors of our study population

Characteristics	Overall (N=427)
Mean age, years	47.3
Sex	
Male	178 (42)
Female	201 (47)
NR	48 (11)
Minimum RegiSCAR score for inclusion	
2 or 3	61 (14)
4 or 5	99 (23)
≥6	128 (30)
NR	139 (33)
Reported culprit drug/drug classes	
Anticonvulsants	164 (38)
Antimicrobials	125 (29)
Allopurinol	95 (22)
Anti-inflammatory/NSAIDs	17 (4)
Other/Unknown cause	25 (6)
Internal organs affected	
Liver	358 (84)
Kidney	134 (31)
Lungs	56 (13)
Cardiac/skeletal muscle	30 (7)
Pancreas	21 (5)
Spleen	9 (2)
Nervous system	3 (<1)
HHV-6 testing results	
Positive	17 (4)
Negative	27 (6)
NR or not performed	383 (90)
Treatments	
Supportive care alone	92 (22)
Systemic corticosteroids only	276 (65)
Systemic corticosteroids with IVIG	44 (10)
Cyclosporine	15 (4)
Patient deaths	33 (7.7)

Data presented as number (%). NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; IVIG, intravenous immunoglobulin

Table 2. Patients who received supportive care alone

Author	Year	Study method	No.	Mean age (years)	Minimum RegiSCAR score for inclusion	Mean duration of treatment (days)	Deaths No. (%)
Chiou ¹²	2007	Retrospective chart review	7	51	NR	NR	2 (28%)
Chen ¹¹	2010	Case series	10	51	NR	NR	1 (10%)
Pereira de Silva ¹⁸	2010	Retrospective chart review	2	30.8	5	30-180	0
Um ¹⁴	2010	Retrospective chart review	22	59.8	NR	14.4	0
Nam ²¹	2014	Retrospective chart review	35	57.6	2	18.4	0
Lee ⁸	2017	Retrospective chart review	12	53	4	NR	2 (16.7%)
Pozzo-Magaña ¹⁶	2022	Retrospective chart review	4	36.5	6	NR	0

NR, not reported; RegiSCAR, Registry of Severe Cutaneous Adverse Reaction

Table 3. Patients treated with systemic corticosteroids only

Author	Year	Study method	No.	Mean age (years)	Minimum RegiSCAR score for inclusion	Therapeutic regimen description	Mean duration of treatment (days)	Deaths No. (%)
Chiou ¹²	2007	Retrospective chart review	22	51	NR	IV hydrocortisone later changed to oral prednisolone	NR	1 (4.5%)
Chen ¹¹	2010	Case series	43	51	NR	Either IV methylprednisolone (40-120 mg/d) or oral prednisolone (30-60 mg/d)	NR	4 (9%)

SKIN

Pereira de Silva ¹⁸	2010	Retrospective chart review	6	30.8	5	Oral prednisone 30-60 mg/day	30-180	0
Um ¹²	2010	Retrospective chart review	16	52.3	NR	Unspecified systemic corticosteroid regimens	31.1	1 (6.2%)
Botelho ¹³	2011	Retrospective chart review	10	45.7	5	Oral prednisone 1mg/kg/day	NR	2 (20%)
Nam ²¹	2014	Retrospective chart review	10	57.6	2	Unspecified systemic corticosteroid regimens	46	1 (10%)
Sasidharanpillai ²⁴	2014	Prospective cohort	26	37.3	4	Prednisolone 1 mg/kg/day or equivalent dose of dexamethasone in patients with severe presentation	39.8	1 (3.8%)
Sultan ²⁶	2015	Retrospective chart review	17	29	NR	Injectable dexamethasone was used until fever/rash resolved, followed by a course of oral prednisolone taper	29.1	1 (5.9%)
Ocampo-Garza ²²	2015	Retrospective chart review	9	35.3	3	IV Dexamethasone 4mg/every 6-8 hours or oral prednisone 1 mg/kg/day	NR	0

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Avancin j ¹⁹	2016	Retrospective chart review	27	36	6	Prednisone 1 mg/kg/day then increased to 1.5 mg/kg/day if no improvement was observed	122	1 (4%)
Lee ⁸	2017	Retrospective chart review	11	55.9	4	Either IV methylprednisolone (30mg/kg/day) or oral prednisone (1mg/kg/day)	25	1 (9%)
Han ¹³	2019	Retrospective chart review	10	11.2	4	Varying regimens: Oral prednisolone or hydrocortisone (0.27-2 mg/kg/day) with or without initial 3-day course of methylprednisolone (30 mg/kg/day)	65	0
Liu ¹⁶	2019	Systematic review	34	56	6	Unspecified systemic corticosteroid regimens	NR	8 (23.5)
Nguyen ⁹	2020	Retrospective case-control	21	44.5	6	IV methylprednisolone 1-2 mg/kg/day with variable taper	45.5	0
Pozzo-Magaña ^{a23}	2022	Retrospective chart review	14	52.9	6	Unspecified doses of prednisone, methylprednisolone, or hydrocortisone	6.9	1 (7%)

IV, intravenous; NR, not reported; RegiSCAR, Registry of Severe Cutaneous Adverse Reaction

severe cases with defining characteristics including multiple organ dysfunction, a 10-

fold increase in transaminase levels, and/or hyperbilirubinemia.^{8,24} When reported,

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corticosteroids were initiated between the 5th and 15th day of hospitalization.^{9,13} Mean treatment duration was 51.5 days.^{8,9,12-14,19,21,23,24,26}

Adverse events were reported in 26 (9%) patients. Ten experienced systemic infections: two were opportunistic and thought to be secondary to treatment-related immunosuppression and eight occurred during hospitalization (authors did not specifically attribute these to corticosteroid use).^{8,11,14-16,21} The remaining 16 had DRESS recurrence after discontinuing or tapering of therapy.^{13,15,18,20,24}

There were 22 (8%) deaths: nine from multiple organ dysfunction syndrome (MODS), four from sepsis, two from hepatic failure, two from sepsis with hepatic failure, one from sepsis with MODS, one from rhabdomyolysis with acute renal failure, one from cardiogenic shock, and one from an unknown form of shock.^{8,11,12,14-16,19,21,23,26} Lastly, one patient prematurely discontinued steroid therapy after discharge and subsequently developed toxic epidermal necrolysis two weeks later, dying from acute renal failure on day five of readmission.²⁴

Systemic corticosteroids and IVIG

There were 44 patients who received both SCS and IVIG (**Table 4**).^{8,11,16,17,23,25} Lack of improvement with corticosteroids alone was the reason for initiating IVIG in 25 (57%) patients.^{8,17,25} When reported, that decision was made after a mean of 5.9 days of steroid monotherapy.^{17,25} One patient was started on IVIG and corticosteroids concomitantly, and another began IVIG three days before starting corticosteroids; the rationale for neither decision was provided.¹⁷ Regarding the remaining 17 patients, timing of IVIG administration and rationale for its addition were not reported.^{11,16,23}

Mean dose of IVIG was 1.9 g/kg/day.^{17,25} The dose and type of concurrent corticosteroids were seldom provided, but the mean duration of corticosteroid therapy, including time before and after IVIG administration, was 31.4 days.^{8,11,17,23,25} Twenty-five (57%) patients had improvement within an average of 1.4 days of IVIG administration; this was defined by decreasing fever, eosinophilia, aminotransferases, extent of rash and/or improved anasarca.^{17,25} For the remaining 19 patients, time from IVIG administration to improvement was not provided.^{8,11,16,23}

Reported adverse effects attributed to IVIG administration included: two patients with facial flushing and head pain, one with fever, and one with transient hyponatremia.^{17,23,25} Six (13.6%) patients died: two from MODS, one from respiratory failure, one from sepsis, one from respiratory and cardiac arrest, and one from DRESS progression attributed to failure to remove the offending agent.^{11,16,25}

Cyclosporine

There were 15 patients who received cyclosporine (**Table 5**).^{9,10,20} For eight (53%) patients, cyclosporine was initiated after recurrence of DRESS while tapering steroids after a mean of 28 days.¹⁰ The remaining 7 (47%) patients received cyclosporine without preceding corticosteroids.^{9,20} In three patients, this was due to contraindications to steroids.⁹ In the remaining 4, no rationale was provided for the decision.^{9,20}

Cyclosporine was administered either orally or intravenously, and doses ranged from 1.5-5.0 mg/kg/day.^{9,10,20} Mean treatment duration was 45.5 days. Notably, higher doses of cyclosporine were associated with faster clinical improvement and shorter required treatment courses. The 7 patients who received doses ranging from 3-5 mg/kg/day had a mean treatment duration of less than two weeks.^{9,20} In contrast, the eight patients

Table 4. Patients treated with corticosteroids and IVIG

Author	Year	Study method	No.	Mean age (years)	Minimum RegiSCAR score for inclusion	Previous treatment regimen	Therapeutic regimen description	Mean duration of treatment (days)	Deaths No. (%)
Chen ¹¹	2010	Case series	2	51	NR	NR	Either IV methylprednisolone, (40-120 mg/day) or oral prednisolone (30-60 mg/day) + IVIG	NR	1 (50%)
Lee ⁸	2017	Retrospective chart review	2	62	4	NR	Either IV methylprednisolone (30mg/kg/day) or oral prednisone (1mg/kg/day) + IVIG in patients with an initial poor response to steroids	24	0
Marcus ¹⁷	2017	Retrospective chart review	7	9.5	3	5 treated with SCS alone for mean of 3.8 day with no improvement	Unspecified systemic corticosteroid regimens + IVIG 1-2 g/kg	24	0
Liu ¹⁶	2019	Systematic review	14	56	6	NR	Unspecified systemic corticosteroid regimens + IVIG	NR	4 (28.6%)
Sim ²⁵	2021	Retrospective chart review	18	54	4	All treated with SCS alone for mean of 6.5 days with no	Unspecified systemic corticosteroids + IVIG added after 6.5 days of	36.5	1 (5.5%)

						improvement	no improvement		
Pozzo-Magaña ²¹	2022	Retrospective chart review	1	59	6	NR	Unspecified systemic corticosteroids + IVIG	5	0

IVIG, intravenous immunoglobulin; NR, not reported; RegiSCAR, Registry of Severe Cutaneous Adverse Reaction

Table 5. Patients treated with cyclosporine

Author	Year	Study method	No.	Mean age (years)	Minimum RegiSCAR Score for Inclusion	Previous treatment regimen	Therapeutic regimen description	Mean duration of treatment (days)	Deaths No. (%)
Kirchhoff ²⁰	2016	Case series	2	NR	4	None	Oral cyclosporine 5mg/kg/day divided twice daily	5	0
Nguyen ⁹	2020	Retrospective case-control	5	43	6	None	IV or oral cyclosporine (3-5 mg/kg divided into twice daily for 7 days, taper to 1.5-2.5mg/kg divided twice daily for 7 days)	12.5	0
Su ¹⁰	2021	Retrospective chart review	8	39.1	6	Mean of 27.9 days of methylprednisolone with no improvement	Cyclosporine 1.7 mg/kg/day	76.1	0

IV, intravenous; NR, not reported; RegiSCAR, Registry of Severe Cutaneous Adverse Reaction

who received a mean dose of 1.7 mg/kg/day had a treatment duration averaging 76.1 days.¹⁰

Two (13%) patients experienced unspecified adverse effects that were reversed following the resolution of DRESS and discontinuation of cyclosporine.⁹ No deaths were reported.^{9,10,20}

DISCUSSION

To our knowledge, this is the most recent review of DRESS that focuses on comparing the effectiveness of different therapies. In our analysis of studies published between 2005 and 2022 meeting inclusion/exclusion criteria, the overall mortality for patients with DRESS was determined to be 7.7%, largely consistent with the commonly cited values between 5% and 10%.^{1,2,4,27,28} Interestingly, there has been an improvement in DRESS mortality in recent years with estimates between 1.2% and 6.1%.²⁹

Worse survival outcomes were observed when allopurinol was the offending drug as it accounted for 55% of patient deaths yet was only implicated in 22% of total cases in our study. This difference likely signals that allopurinol-induced DRESS has a poorer prognosis compared to DRESS caused by other agents. This association, as suggested in previous studies, may be explained by the higher likelihood of renal and hepatic involvement in allopurinol-induced DRESS.¹ Patients who died were often older with a mean age of 58.5 years, compared to the overall study population's mean age of 47.3 years. Chronic co-morbid conditions were observed in at least 58% of fatal cases, most often chronic kidney disease and/or hypertension. Presence of these co-morbidities, along with advanced age and/or causation by allopurinol, may necessitate more vigilant management. While patient age and baseline health are closely tied to prognosis in many other conditions, further research could help clinicians better understand why these specific factors may confer a poorer prognosis. Additionally, development of a standardized set of prognostic criteria for DRESS could improve medical decision making, as determination of

severity is largely subjective and at the discretion of the treating physician. Several additional clinical factors have been suggested to convey higher severity/poorer prognosis, such as presence of viral reactivation, extent of serum creatinine elevation, and various derangements of leukocyte counts.^{30,31} However, data on prognostic factors remains limited.

Organized by treatment group, mortality was 5.4% for supportive care alone, 8% for SCS, 13.6% for IVIG with SCS, and 0% for cyclosporine (**Table 6**). Supportive care alone has been proposed as suitable for mild cases of DRESS.³ Thus, the improved survival of patients receiving only supportive care, compared to those receiving SCS, could reflect less severe disease at baseline. Indeed, this was the rationale to forgo systemic treatment in at least 26% of patients in this group.^{14,18}

Lower mortality in the supportive care group might also be explained by the side-effect profile observed with SCS. High-dose corticosteroids can worsen existing infections and/or increase susceptibility to opportunistic infections, and sepsis was a common cause of death amongst the SCS-treated group.³² Additionally, recurrence of DRESS upon tapering/discontinuation of treatment was a complication unique to patients receiving SCS. A previous systematic review revealed that recurrent DRESS has particularly unfavorable outcomes, including greater risk of disease sequelae and an overall mortality of 29%.³³ Of note, eight patients in the cyclosporine group initially received SCS as a monotherapy. In addition to recurrence of DRESS upon SCS tapering, each of these patients experienced adverse effects to SCS including peptic ulcers, adrenal insufficiency, weakness, and hyperglycemia.¹⁰

Table 6. A comparison of observed mortality, mean duration of treatment, and causes of death across the four treatment groups

Treatment	Number of patients	Mean duration of treatment (days)	Deaths No. (%)	Causes of death
Systemic corticosteroids	276	51.5	22 (8%)	MODS (9), sepsis (4), hepatic failure (2), sepsis + hepatic failure (2), sepsis + MODS (1), cardiogenic shock (1), other form of shock (1), rhabdomyolysis + acute renal failure (1), acute renal failure after recurrence and progression to TEN (1)
IVIg with systemic corticosteroids	44	31.4	6 (13.6%)	MODS (2), sepsis (1), respiratory failure (1), cardiac & respiratory arrest (1), failure to remove implicated drug (1)
Cyclosporine	15	45.5	0 (0%)	
Supportive care	92	16.9	5 (5.4%)	Sepsis + pneumonia (2), sepsis + renal failure (1), sepsis (1), upper gastrointestinal bleed (1)

IVIg, intravenous immunoglobulin; MODS, Multiple organ dysfunction syndrome; TEN, toxic epidermal necrolysis

Regarding IVIG with SCS, although this group had the highest mortality in our study, it is important to consider that these patients may have had more severe disease than those treated with SCS alone. IVIG was often added when no improvement was observed after a mean of 5.9 days of SCS monotherapy.^{8,17,25} Furthermore, four of the six deaths were from DRESS caused by allopurinol,¹⁶ a culprit drug thought to be associated with a poorer prognosis, as previously mentioned. Of the two remaining deaths, one was observed in a patient who refused to surgically remove the suspected culprit drug of vancomycin-loaded bone cement,²⁵ and the other occurred from septic shock after the patient developed pancytopenia.¹¹ These factors of the fatal cases in this group carry potential to confound mortality. Nevertheless, IVIG should generally not be used as monotherapy given the current level of evidence.^{2,34} While IVIG may benefit patients failing SCS therapy in some instances, clinicians might also

consider choosing an alternative therapy, such as cyclosporine, based on available data.

Regarding cyclosporine, this group observed the lowest mortality compared to all other treatment groups. Similar to IVIG, cyclosporine has not been considered first-line for DRESS and has classically been reserved in practice for refractory cases.^{2,35} Eight patients in the cyclosporine group were initially treated with SCS alone, but experienced DRESS recurrence upon tapering.¹⁰ Despite the increased morbidity and mortality associated with recurrent DRESS, each of these patients had notable clinical improvement within three weeks of beginning cyclosporine (mean dose of 1.7 mg/kg/day), and experienced complete remission within three months of treatment.^{10,33} The remaining seven patients in the cyclosporine group were given higher doses (ranging from 3-5 mg/kg/day) without prior SCS therapy and had faster clinical

improvement, requiring shorter durations of treatment.^{9,20}

The favorable survival of patients receiving cyclosporine could be attributed to a publication bias, especially given the small number of patients in this group. Nevertheless, two retrospective studies published in 2023 demonstrated outcomes in line with our own.^{35,36} Kwon et al compared 27 DRESS patients treated with oral cyclosporine (2-3 mg/kg/day for one week, followed by 1-1.5 mg/kg/day) for a mean of 22 days, and 53 DRESS patients treated with methylprednisolone (1-1.5 mg/kg/day for one week, followed by variable tapering) for a mean of 20.4 days.³⁵ Study authors found no significant differences in treatment durations between groups, but adverse effects were more common in those treated with corticosteroids (51% vs 19%).³⁵ In Zita et al, 19 DRESS patients received either oral or intravenous cyclosporine at an average dose of 4.6 mg/kg divided twice daily with a mean treatment duration of 5.3 days.³⁶ Seventeen (89%) had disease resolution, one was lost to follow-up, and one required switching to prednisone.³⁶ Data from these studies demonstrate both high effectiveness of cyclosporine and dose-associated time to disease resolution.

Cyclosporine inhibits the synthesis of interleukin-2 leading to impairment of T lymphocytes.³⁵ While DRESS pathophysiology is not fully elucidated, cytotoxic T cells have been implicated in the downstream effects of the disease.³⁷ Cyclosporine's mechanism of action may simply be more appropriate for DRESS management and have lower propensity for adverse effects than the broader immune and hormonal modulation seen with SCS.

Importantly, cyclosporine is not universally effective. In addition to the patient reported

by Zita et al, there are two other cases of cyclosporine failing to improve DRESS, requiring rescue with steroids and/or IVIG.^{35,38,39} There are also two cases of fatal DRESS whereby cyclosporine was used in combination therapy with systemic steroids and/or IVIG.^{40,41}

Limitations

In addition to the aforementioned limitations, our review was limited by the largely retrospective nature of included articles. Data regarding age, patient comorbidities, implicated drugs, and extent of internal organ involvement were rarely available for individual patients, preventing us from better assessing for differences in baseline patient and disease factors between treatment groups. Lastly, several larger studies could not be used in our analysis based on our exclusion criteria, which could potentially limit the generalizability of our findings.

CONCLUSION

SCS are often utilized for the treatment of DRESS. However, their efficacy has yet to be investigated in prospective, randomized trials and their side-effect profiles remain a source of concern. Our review provided further support for the use of supportive care alone in properly selected patients with less severe disease. Existing data regarding administration of IVIG with SCS demonstrated a worse mortality compared to corticosteroids alone. However, it may still be reasonable to consider IVIG as an adjuvant for more severe, steroid-refractory cases. While limited data exists, we have also highlighted how cyclosporine may be a more suitable option for DRESS considering its favorable mortality and safety profile. Still, a prospective trial is needed to further guide clinical decision-making.

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