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REVIEW

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The systemic treatments for drug reaction with eosinophilia and systemic symptoms (DRESS) beyond corticosteroids

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DiHS), is a severe type of cutaneous adverse reaction. The gold standard therapy for DRESS involves the discontinuation of the culprit drug, supportive therapies, and administration of corticosteroids. However, in cases of primary treatment failure or suboptimal response, there arises an urgent need for alternative interventions. This review focuses on exploring alternative systemic therapies for patients with steroid-resistant DRESS, steroid-dependent DRESS, or refractory DRESS, encompassing immunosuppressive agents, intravenous immunoglobulin, plasmapheresis, biologics, and small molecule drugs, with an emphasis on their clinical efficacy and the underlying mechanisms in the treatment of DRESS. Furthermore, this review provides a summary of potential management strategies and laboratory workup during the treatment of DRESS.

Keywords: Drug reaction with eosinophilia and systemic symptoms, Drug-induced hypersensitivity syndrome, Corticosteroid, Cyclosporine, IL-5/IL-5R inhibitors

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS), also referred to as drug-induced hypersensitivity syndrome (DiHS), typically manifests 2–8 weeks after exposure to the offending agent, with an incidence ranging from 1/1000 to 1/10,000 depending on the culprit drug and an estimated mortality rate of 10%, which represents a potentially life-threatening type IV T-cell-mediated delayed drug hypersensitivity reaction characterized by a combination of exanthema, fever, hematologic abnormalities, and multi-organ involvement.[1] The complex interplay between drugs, viruses, and the immune systems primarily mediated by T-cells is believed to underpin the pathogenesis of DRESS[2] and cellular immunopathogenesis of DRESS is intricate, involving $CD4^+$ T cells, $CD8^+$ T cells, dendritic cells (DCs), and monocytes.[3] During early-stage DRESS, $CD8^+$ cytotoxic T cells predominate, while in late-stage DRESS, $CD4^+$ helper T cells, including Th1 and Th2 cells, become more prevalent.[4] Thymus and activation-regulated chemokine (TARC/CCL17) secreted by CD11c + dermal DCs and interleukin-33 (IL-33) secreted by type 2

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innate lymphoid cells can enhance the Th2 immune response, leading to eosinophil activation and recruitment.[2] Subsequently, activated eosinophils release granules, resulting in tissue damage. Meanwhile, Th1/Th2 imbalance and drift contribute to viral reactivation and the development of DRESS. During the resolution stage, an intensified Th1 response may aid in viral elimination, and T-reg exhaustion corresponds to a shift toward Th17 cells.[5]

It is worth noting that due to the inherent challenges in treating DRESS, there is a dearth of randomized studies to evaluate specific therapies and a recognized consensus or guideline for DRESS is lacking.[6] Withdrawal of the offending medication immediately and supportive therapy are essential components of management. Systemic corticosteroids are generally considered to be the gold standard pharmacotherapy for moderate and severe DRESS, with significant relief of clinical symptoms often observed shortly after initiation. Nevertheless, rapid reduction of steroids can lead to severe or fatal flares or relapses. Therefore, it's recommended that DRESS patients should start at a dose of prednisolone or an equivalent of 0.5–1.0 mg/kg/day with a gradual tapering over 2–3 months.[7,8] However, some patients with DRESS and severe organ involvement do not respond well to systemic corticosteroids, called steroid-resistant DRESS, and some experience relapses during steroid tapering (even after adding steroids to a higher dose, relapses could not be well controlled), called steroid-dependent DRESS. In such cases and patients with contraindications of systemic steroids or with severe steroid-related adverse effects, or when a prolonged course of steroids is not ideal, effective add-on or alternative systemic therapies of steroids are urgently considered. Hence, this review provides a summary of available immunosuppressive agents, intravenous immunoglobulin (IVIG), biologics, small molecule drugs, and plasmapheresis when confronted with the conditions above, emphasizing their underlying mechanisms and establishing a foundation for future treatments of DRESS. Furthermore, this review raises the prospect of a potential clinical pathway and laboratory workup of DRESS during treatments, serving as a basis for future clinical management of DRESS.

IMMUNOSUPPRESSIVE AGENTS

Cyclosporine

Cyclosporine, a calcineurin inhibitor, selectively targets T cells with the main impact on helper T cells.[9] This has been linked to the inhibition of IL-2 production by T cells, which is crucial for full T-cell activation, and the suppression of IL-5, essential for eosinophil activation in DRESS (See Fig. 1).[10] Previous reports, mainly from case studies and retrospective analyses with small sample sizes (summarized in Table 1 and Table 2), have explored the use of cyclosporine alone or in combination with steroids or IVIG for treating DRESS. Through Table 1, a dose of 2–5 mg/kg per day of cyclosporine as monotherapy has shown responsive action, with an average treatment duration of approximately 16.8 days. On average, fever resolution and rash improvement occurred approximately 4.1 days after starting cyclosporine, demonstrating effective outcomes, although its role in preventing viral reactivations and relapses requires further investigation.[11,12] A retrospective case-control study revealed a mean treatment duration with cyclosporine of 12.5 days versus 48.5 days with systemic steroids. Hospitalization duration was also shorter with cyclosporine (8.1 days) than with systemic corticosteroids (16.2 days).[13] However, a retrospective 20-year single-center study in South Korea comparing cyclosporine with corticosteroids showed no statistically significant differences in hospitalized days (17.7 days versus 14.94 days), treatment period (21.96 days versus 20.41 days), and time to normalization from clinical manifestations while the cyclosporine group experienced relatively fewer adverse effects.[14] The varied treatment duration with cyclosporine in these retrospective studies, longer than in case reports, highlights the need for researchers to elucidate the specific course and remission time of cyclosporine monotherapy in DRESS patients without prior corticosteroid administration.[11,15]

In Table 2, it is noted that most DRESS cases are initially treated with systemic corticosteroids, followed by a switch to cyclosporine as a steroid-sparing agent or as replacement therapy for patients resistant to steroids. The typical dose ranges from 3 to 5 mg/kg/d, with lower doses of 1–3 mg/

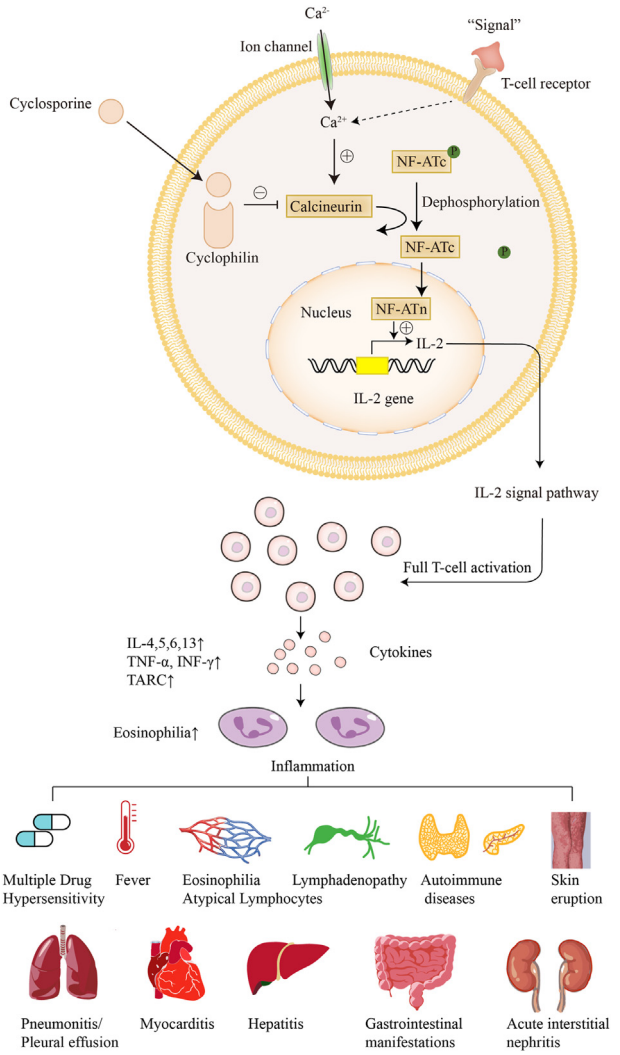

Fig. 1 The schematic mechanisms of cyclosporine on T cells. Figure notes: First, cyclosporine A forms a complex in the cytoplasm by binding to its immunophilin, cyclophilin A. Following this interaction, the complex effectively inhibits the activity of the Ca^{2+}-dependent phosphatase calcineurin, which is characterized by its serine/threonine phosphatase activity. Consequently, the cytoplasmic component of the nuclear factor of activated T cells (NF-ATc) fails to be dephosphorylated due to the absence of calcineurin phosphatase activity. Thereby NF-ATc fails to transport from the cytoplasm to the nucleus and bind to the nuclear component of the nuclear factor of activated T cells (NF-ATn). NF-ATn is responsible for binding to the promoter region of the interleukin 2 (IL-2) gene, consequently initiating IL-2 production. Therefore, T cells are unable to produce IL-2, which is essential for full T-cell activation.[9] Abbreviations: IL-2, interleukin 2; NF-ATc, the cytoplasmic component of the nuclear factor of activated T cells; NF-ATn, the nuclear component of the nuclear factor of activated T cells

kg/d also showing good effectiveness, possibly due to previous long-term corticosteroid immunocompromise and concomitant corticosteroid.[16] In comparison to cyclosporine monotherapy in Table 1, the average duration of cyclosporine for steroid-dependent and steroid-resistant DRESS is 41.6 days, indicating a longer duration with a slower tapering process. These observational research and cases suggest the potential use of cyclosporine in DRESS management and provide further evidence that cyclosporine may offer an effective alternative or adjunct to systemic corticosteroid therapy. Nevertheless, this treatment option for DRESS remains inconclusive with low evidence to support the application, and to evaluate the efficacy of cyclosporine therapy in treating DRESS, further prospective, randomized controlled studies are warranted.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive agent that selectively targets lymphocytes, inhibiting antibody formation and reducing the adhesion of lymphocytes and monocytes to endothelial cells, thereby hindering the recruitment of leukocytes to areas of inflammation.[17] Meanwhile, compared to other immunosuppressives, MMF is well-tolerated and has fewer nephrotoxic, hepatotoxic, and neurotoxic effects.

Although it is not frequently reported, MMF has been used in the treatment of DRESS. For instance, a 28-year-old African-American woman with fulminant myocarditis as a late sequela of DRESS was successfully treated with high-dose intravenous methylprednisolone (1 gm/day), IVIG (1 gm/kg/day × 2 doses), and MMF during hospitalization, followed by MMF along with lower doses of prednisone for maintenance therapy for a year.[18] Additionally, a 14-year-old girl with DRESS was effectively treated with MMF at a dose of 500 mg twice daily as a corticosteroid-sparing agent.[19] In a case of minocycline-induced DRESS with persistent lymphocytic myocarditis, MMF, 1500 mg twice daily, along with prednisone, 15 mg per day, was used for maintenance therapy following remission from the acute stage.[20]

Thus, these instances suggest that MMF could serve as an adjunctive option and a maintenance agent during remission in DRESS. Common side effects during MMF treatment involve the gastrointestinal, hematological, and genitourinary systems, such as diarrhea (most common), nausea,

Patient	Age Sex	Culprit drug	RegiSCAR score	Prior systemic steroid exposure	Cyclosporine dose	Cyclosporine duration	Days to resolution[a]	Relapse	Reference
1	40s F	Carbamazepine	> 5	No	100 mg BID	7 days	NA	No	[15]
2	30s M	Minocycline	4 or 5	No	5 mg/kg QD	3 days	2 days	No	[15]
3	25 F	Lamotrigine	NA	No (patient decline)	3 mg/kg QD	7 days	NA	No	[11]
4	88 F	Vancomycin	6	No (patient decline)	3 mg/kg QD	7 days	NA	No	[11]
5–9	43(mean age) 4F and 1 M	Vancomycin 2; Sulfasalazine 1; Captopril 1; Diltiazem 1	NA	No (contraindications)	3–5 mg/kg QD for 7 days; tapered to 1.5-2.5 mg/kg QD for 7 days	14 days	2 days	NA	[13]
10	19 F	Phenytoin or oxcarbazepine	2	No	2.5 mg/kg BID	5 days	9 days	NA	[12]
11	22 F	Phenytoin	3	No	2.5 mg/kg BID	7 days	1 days	NA	[12]
12	75 M	Phenytoin	4	No	1.5 mg/kg BID	3 days	2 days	NA	[12]
13	75 M	Phenytoin	2	No	2 mg/kg BID	7 days	1 days	NA	[12]
14	43 F	Vancomycin	6	No	0.667 mg/kg Q12h iv	5 days	3 days	NA	[12]
15	75 M	Vancomycin	3	No	2.5 mg/kg BID	5 days	2 days	NA	[12]
16	50 M	Vemurafenib	5	No	2 mg/kg BID	5 days	1 days	NA	[12]
17	59 F	Vemurafenib	2	No	2 mg/kg BID	2 days	No resolution	NA	[12]

18–44	54.9(mean age) 16F and 11 M	Antibiotics (10); anticonvulsant (6); anti-tuberculosis (5); NSAIDs (2); allopurinol (2); herbs (1); β-blocker (1)	4-5(23); > 5(4)	No	2–3 mg/kg/day divided twice daily for 1 week, and subsequently tapered to 1–1.5 mg/kg/day for an extended treatment period (totally 21.96 ± 23.66 days).	4.68 days (average)	NA	14

Table 1. DRESS patients treated with cyclosporine but without prior systemic steroid exposure. *Abbreviations: RegiSCAR score, the European Registry of Severe Cutaneous Adverse Reactions score; M, male; F, female; NA, not appliable; QD, once per day; BID, twice per day; DRESS, drug reaction with eosinophilia and systemic symptoms; NSAIDs, nonsteroidal anti-inflammatory drugs.* [a]*"Days to resolution" refers to days after starting cyclosporine to resolution of fever and rash improvement.*

vomiting, abdominal cramps, leukopenia, anemia, thrombocytopenia, urgency, frequency, dysuria, and sterile pyuria. In light of the immunosuppressive effects of MMF, infectious side effects and malignancy potential are worth carefully monitoring if long-term high-dose administration is required.[21]

Cyclophosphamide

Cyclophosphamide, an alkylating drug capable of slowing or stopping the cell growth of lymphocytes and polymorphonuclear leukocytes, has shown efficacy in various autoimmune diseases.[22] Low-dose cyclophosphamide not only decreases cell number but leads to decreased functionality of regulatory T cells (Tregs), and cyclophosphamide may contribute to changes in the ratio of $CD4^+/CD8^+$ T cells as well as decreased cytokines.[23]

To the best of our knowledge, there are only a few cases showing the efficacy of cyclophosphamide in severe DRESS, since its sensitivity is greater in B cells than in T cells. One is a 48-year-old white woman with multi-visceral DRESS, especially along with dialysis-dependent acute kidney failure, who was successfully treated with 1 intravenous pulse of cyclophosphamide (750 mg/m^2), relayed by oral cyclophosphamide for 6 months when there was resistance to prolonged corticosteroid therapy.[24] Another is a male DRESS patient with refractory eosinophilic myocarditis and concurrent thyroiditis, who responded only temporarily to multiple courses of high-dose pulse corticosteroids but was successfully cured by a 6-month course of monthly intravenous 1500 mg cyclophosphamide plus 300 mg mepolizumab.[25]

Therefore, as an alternative treatment for DRESS resistant to steroid therapy, cyclophosphamide deserves to be deliberately considered, especially in cases involving severe kidney failure or potentially life-threatening refractory myocarditis. Significantly, side effects of cyclophosphamide, including hemorrhagic cystitis, susceptibility to infection, potential infertility, and increased individual lifetime risk for transitional cell carcinoma of the bladder and hematologic malignancies, which is proportional to the cumulative dose, should be considered.[26]

Patient	Age Sex	Culprit drug	RegiSCAR score	Prior systemic steroid exposure	Cyclosporine dose	Cyclosporine duration	Days to resolution[a]	Relapse	Reference
1	37 F	Phenytoin	NA	Yes (steroid-resistant; iatrogenic Cushing's syndrome)	4 mg/kg QD	6 months	Improvement	No; stable 9 months later	[76]
2	45 F	Vancomycin	NA	Yes-14 days (steroid-resistant)	100 mg BID	5 days	7 days	No; stable 20 months later	[77]
3	29 F	Celecoxib and ethambutol	NA	Yes (relapse)	100 mg QD iv x 1 month with methylprednisolone 60 mg QD	Exacerbation	NA	NA	[78]
4	60 M	Bortezomib	NA	Yes-14 days (steroid-dependent)	5 mg/kg with prednisone	Improvement	NA	No	[79]
5	56 F	Sulfasalazine	NA	Yes	High-dose dexamethasone with cyclosporine	No resolution	NA	NA	[80]
6	31 F	Celecoxib	NA	Yes	Along with steroids and IVIG	NA	NA	Myocarditis as a late sequela of DRESS after 4 months	[18]
7	48 M	Mexiletine	6	Yes-15 days	5 mg/kg QD	7 days; gradually tapered and 41 days total duration	3 days	No; stable 6 months later	[81]
8	59 M	Trimethoprim/ Sulfamethoxazole	NA	Yes	5 mg/kg QD	7 days	3 days	No	[82]

9	59 M	Sulfasalazine	6	Yes-2 months (steroid-dependent)	3 mg/kg QD	NA	Continuing to have intermittent flares	NA	83
10	NA F	Vancomycin	9	Yes-1 days	1.5 mg/kg BID	4 days	Continuing to worsen; resolution after switch to corticosteroids	NA	84
11	66 M	Trimethoprim-sulfamethoxazole	6	Yes (steroid-resistant)	1.5 mg/kg BID with steroids	6 months	3 days	No; stable 1 year later	85
12	45 M	Cotrimoxazole	NA	Yes-27 days (steroid-dependent)	2.47 mg/kg QD	90 days	NA	No; stable 3 months later	16
13	15 M	Amoxicillin	NA	Yes-30 days (steroid-dependent)	0.53 mg/kg QD	84 days	2 weeks	No; stable 3 months later	16
14	39 F	Etodolac	NA	Yes-24 days (steroid-dependent)	1.92 mg/kg QD	111 days	3 weeks	No; stable 3 months later	16
15	40 F	Amoxicillin	NA	Yes-29 days (steroid-dependent)	1.66 mg/kg QD	18 days	2 weeks	No; stable 3 months later	16
16	75 M	Zonisamide	NA	Yes-47 days (steroid-dependent)	2.21 mg/kg QD	75 days	NA	No; stable 3 months later	16
17	35 M	Dapsone	NA	Yes-21 days (steroid-dependent)	2.63 mg/kg QD	90 days	3 weeks	No; stable 3 months later	16
18	43 F	Sulfasalazine	NA	Yes-23 days (steroid-dependent)	1.49 mg/kg QD	114 days	NA	No; stable 3 months later	16
19	21 F	Amoxicillin	NA	Yes-22 days (steroid-dependent)	1.66 mg/kg QD	27 days	2 weeks	No; stable 3 months later	16

(continued)

Patient	Age Sex	Culprit drug	RegiSCAR score	Prior systemic steroid exposure	Cyclosporine dose	Cyclosporine duration	Days to resolution[a]	Relapse	Reference
20	15 F	Valproic Acid	9	Yes-8 days	100 mg BID	3 days	1 days	Recurrence after 1 week	86
21	35 M	Leflunomide	2	Yes-along with cyclosporine	2.5 mg/kg BID	2 weeks	1 days	NA	87
22	77 F	Icodextrin	5	Yes-3 weeks	NA	6 weeks and then discontinued as she had abdominal infections with no DRESS recurrence	4 weeks	NA	88
23	30s F	Sulfasalazine	4 or 5	Yes	5 mg/kg QD with steroid	2 months	NA	No; stable 6 months later	89
24	21 M	Carbamazepine	3	Yes-4 days	2 mg/kg BID	7 days	1	NA	12
25	49 M	Carbamazepine	3	Yes-13 days	2.5 mg/kg BID	5 days	3	NA	12
26	48 F	Dabrafenib	2	Yes-1 days	2 mg/kg Q12h iv	5 days	1	NA	12
27	22 M	Phenytoin	5	Yes-5 days	2.5 mg/kg BID	3 days	10	NA	12
28	47 M	Phenytoin	4	Yes-4 days	2.5 mg/kg BID	5 days	1	NA	12
29	38 F	Empagliflozin/ Metformin HCl tablets (Synjardy)	3	Yes-3 days	2.5 mg/kg BID	7 days	NA	NA	12
30	56 F	Vancomycin	5	Yes-2 days	2.5 mg/kg BID	7 days	1 days	NA	12

31	65 M	Vancomycin	2	Yes-45 days	2 mg/kg BID	5 days	3 days	NA	12
32	45 M	Vemurafenib	4	Yes-3 days	2 mg/kg BID	5 days	2 days	NA	12
33	51 M	Vemurafenib	3	Yes-4 days	2 mg/kg BID	7 days	2 days	NA	12
34	53 F	Vemurafenib	3	Yes-5 months	2 mg/kg Q12h iv; 2 mg/kg PO BID	3.5 days; 1.5 days (respectively)	3 days	NA	12
35	34 F	Rifampin, isoniazid, pyrazinamide, or levofloxacin	7	Yes (with peri-myocarditis)	Cyclosporine with systemic steroids	NA	Improvement	No	90
36	17 F	Itraconazole	5	Yes-4 days (steroid-resistant)	5 mg/kg QD	5 days	Improvement	No; stable 10 months later	91

Table 2. (Continued) DRESS patients treated with cyclosporine after prior systemic steroid exposure. *Abbreviations: RegiSCAR score, the European Registry of Severe Cutaneous Adverse Reactions score; M, male; F, female; NA, not appliable; QD, once per day; BID, twice per day; DRESS, drug reaction with eosinophilia and systemic symptoms.* [a]*"Days to resolution" refers to days after starting cyclosporine to resolution of fever and rash improvement.*

Other immunosuppressive agents

Apart from these mentioned immunosuppressive agents, others such as methotrexate, azathioprine, and tacrolimus, have been utilized in the management of some DRESS case reports. A 48-year-old man with azithromycin-induced DRESS and hypersensitivity myocarditis was treated with high-dose corticosteroids and azathioprine for 2 weeks but unfortunately, later sepsis led to his death.[27] A patient with imedeen-induced DRESS was treated with corticosteroids and methotrexate and achieved complete recovery after nearly 4 months.[28] Moreover, a lamotrigine-induced 20-year-old DRESS patient experienced recrudescence of liver injury on initial oral 60 mg prednisone taper and then was treated with a 9-week-long prednisone taper in addition to a 37-week-long oral 1.5 mg twice a day tacrolimus cross-taper.[29] However, these other immunosuppressive options are mostly used as add-on therapies to corticosteroids or as adjuvant methods during corticosteroid tapering, with little evidence supporting their applications in DRESS. It's important to note that the use of these agents in DRESS cases should be carefully monitored due to their potential side effects and the lack of strong evidence supporting their efficacy in this specific condition. Each case should be evaluated individually, and the benefits and risks of using these agents should be carefully considered in the context of the patient's overall health and the severity of their DRESS symptoms.

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

IVIG, a preparation of polyclonal serum IgG pooled from thousands of blood donors, is increasingly applied to the treatment of severe drug eruptions.[30] Although the mechanisms of IVIG in treating DRESS have not been fully elucidated, immunomodulatory, anti-inflammatory activity, and neutralization of the virus may be involved.[31] Several cases have supported the use of IVIG at a dose of 0.4–1 g/kg/d for 3–5 consecutive days in addition to systemic corticosteroids for the treatment of corticosteroid-refractory DRESS in adults to rapidly improve clinical symptoms and help steroid taper.[31,32] Additionally, a DRESS patient was successfully treated with IVIG monotherapy at a dose of 0.4 g/kg/d for 5 successive days because of the severe infection, a steroid's contraindication.[33] A retrospective study presented that a series of pediatric patients with severe DRESS were treated successfully with IVIG in addition to systemic corticosteroids with favorable outcomes and lower side effects in comparison with the data published in adult patients.[34]

However, previous research containing 10 DRESS patients with the treatment of 200 mg/kg/d IVIG monotherapy for 5 consecutive days showed only 1 patient achieved the primary endpoint, 5 patients experienced severe adverse events, and 4 patients had to be treated with oral corticosteroids because of IVIG adverse effects or uncontrolled DRESS, which didn't support a beneficial effect of IVIG monotherapy in DRESS.[35] Interestingly, the timing of IVIG may play a crucial role in the treatment of DRESS. During the early and acute stages of DRESS, non-corticosteroid therapy is associated with the subsequent generation of autoantibodies against epidermal proteins and the development of autoimmune diseases, which is significantly lower in the corticosteroid-treated group,[36,37] and at the peak of severe liver damage, IVIG administration could further accelerate the rapid recovery of B cells, thereby contributing to the subsequent expansions of autoreactive B cells with the specificity to a variety of epitopes.[38] Based on these findings, it seems that monotherapy of IVIG in patients with DRESS might be not recommended, the timing of IVIG administration is controversial, and it may be a useful adjunctive therapy concomitantly treated with steroids or immunosuppressive agents to help replenish low immunoglobulin levels, relieve symptoms, and steroid taper, especially not during the acute stage of DRESS patients with high risk of autoimmune syndrome.[38]

In terms of adverse effects associated with IVIG, the common ones are headaches, flushing, and chills, which are related to infusion, and thromboembolic events are the most serious complications, especially in patients with old age, diabetes, and a history of prior thromboembolic events. Moreover, IgA deficiency is the contraindication of IVIG.[39]

BIOLOGICS

IL-5/IL-5R inhibitors

IL-5, in synergy with other chemokines, such as IL-33, TARC, transforming growth factor β (TGF-β), and thymic stromal lymphopoietin, plays a central and profound role in eosinophil chemoattraction, activation, proliferation, and infiltration, contributing to sequential eosinophilic inflammation and tissue damage.[40] Consequently, a therapeutic strategy to suppress eosinophils has been considered, and the blockade of the IL-5/IL-5 receptor axis is illustrated in Fig. 2. A total of 16 cases have been examined, including 7 treated with mepolizumab (anti-IL-5), 7 with benralizumab (anti-IL-5R), 1 with reslizumab (anti-IL-5), and 1 switched from benralizumab to mepolizumab during the DRESS disease course or DRESS-induced sequelae, as documented in Supplemental Table 1. According to Supplemental Table 1, it is evident that the efficacy of a single dose or repeated doses of reslizumab,

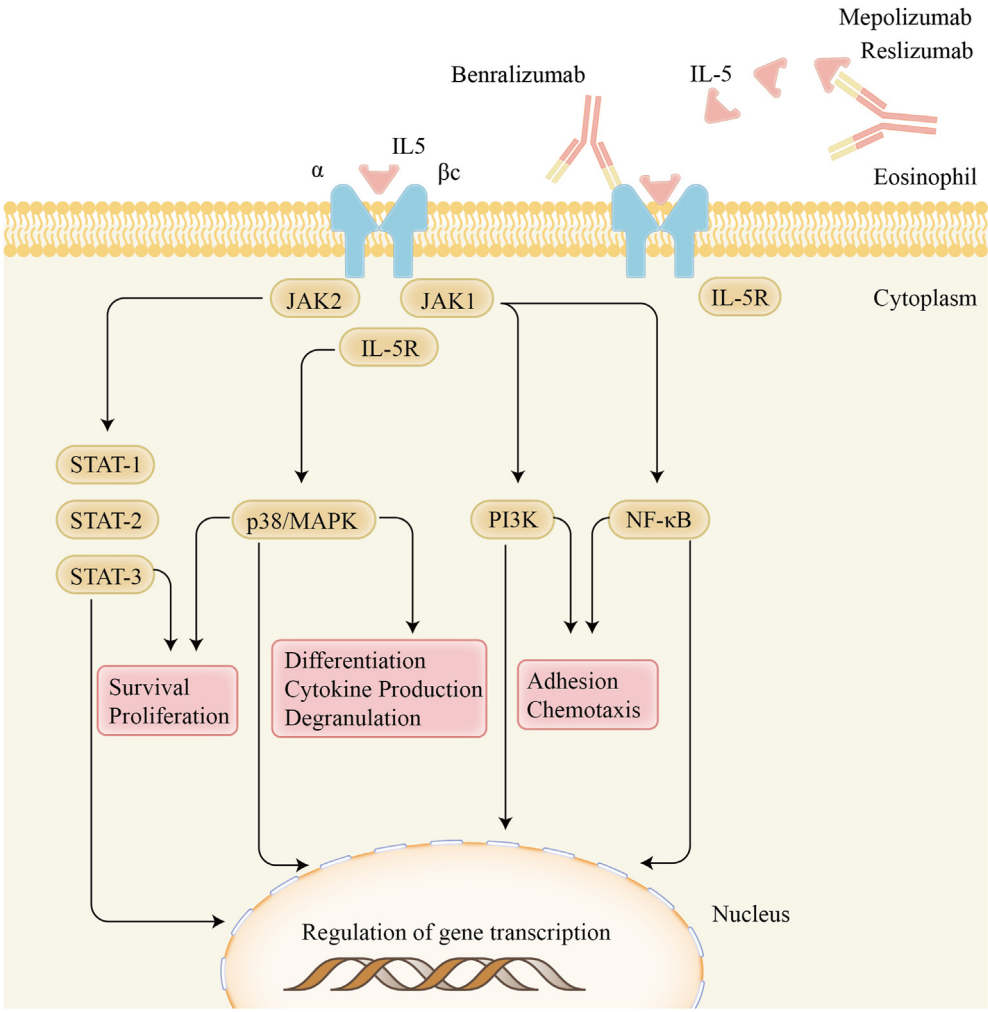

Fig. 2 The schematic mechanisms of IL-5/IL-5R inhibitors and their downstream signal pathways.[75] Figure notes: Mainly derived from T cell and mast cell, interleukin-5 (IL-5) acts on eosinophils and closely related basophil lineages in humans. In eosinophils, IL-5 can bind to its membrane receptor composed of a ligand-specific α subunit (IL-5Rα) and a nonspecific signaling βc subunit and thereby triggers downstream signal transduction probably via dimerization of the cytoplasmic domain. The activated signaling pathways involve several transducing enzymes, mainly including Janus kinases (JAK), JAK/signal transducer and activator of transcription (STAT), mitogen-activated protein kinase (MAPK), the extracellular signal-regulated kinases (ERK1 and ERK2), Lyn tyrosine kinase, phosphoinositide 3-kinase, and nuclear factor κB (NF-κB), which play a vital role in eosinophil differentiation, proliferation, and survival. Mepolizumab is an IgG1κ antibody against interleukin-5 (IL-5), while reslizumab is an IgG4κ antibody against IL-5, and hence they exhibit differences in their Fc biologic activity. Benralizumab targets and binds to the α subunit of IL-5R, preventing eosinophil signal transduction. Abbreviations: IL-5, interleukin-5; IL-5R, interleukin-5 receptor; ERK, extracellular signal-regulated kinases; JAB, JAK-binding protein; JAK, Janus kinases; MAPK, mitogen-activated protein kinase; MEK, MAP or ERK kinase; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; Raf-1, v-raf-1 murine leukaemia viral oncogene homologue 1; Ras, Ras GTPase; STAT, signal transducer and activator of transcription

mepolizumab, and benralizumab in treating DRESS patients is inconclusive, with a lower occurrence of adverse effects compared to steroids and other systemic immunosuppressants. Furthermore, a recent retrospective European multicentric study has revealed 4 DRESS cases with the treatment of anti-IL-5 biologics.[41] Concerning safety, a systematic review of seventeen studies involving approximately 7600 participants concluded there were no excess serious adverse events with any anti-IL-5 treatment and even a reduction in such events with benralizumab. Meanwhile, compared to placebo, there was no difference in adverse events leading to discontinuation with mepolizumab or reslizumab, but significantly more discontinued benralizumab than with placebo.[42]

Thus, anti-IL-5/anti-IL-5R biologics potentially offer a novel therapeutic modality for steroid-resistant and steroid-dependent DRESS patients as well as those with steroid-related contraindications, especially in the presence of a significant increase in eosinophils. After summarizing DRESS patients treated with anti-IL-5 agents, Gschwend et al have recommended the administration of an IL-5/IL-5R blockade in the early use in the course of severe DRESS requiring intensive care medicine treatment, with no clinical improvement even using high-dose corticosteroids, with severe concomitant infectious disease, with additional immunosuppressive drugs despite the initiation of high-dose corticosteroids, or with severe and life-threatening organ damage.[43] More importantly, to further implement IL-5/IL-5R inhibitors in DRESS, a specific selection of reslizumab, mepolizumab, or benralizumab with a single dose or repeated doses as well as their efficacy still needs to be investigated in future research.

TNF-α inhibitors

As a pro-inflammatory mediator, tumor necrosis factor (TNF)-α, is involved in cell differentiation, mitogenesis, cytotoxic responses, inflammation, immunomodulation, and wound healing. It has been reported that the serum levels of TNF-α are significantly higher in DRESS patients with HHV-6 reactivation compared to those without, indicating its role in the reactivation of HHV-6 and the exacerbation of DRESS.[44] In 2017, Leman et al first presented a case of DRESS associated with lithium carbonate that successfully recovered after a total of 5 injections of TNF-α inhibitor (the first dose doubled (50 mg) and then 25 mg thereafter), leading to a rapid decline of serum aminotransferase levels.[45] However, it is worth noting that the pruritus in this case continued to persist during the treatment and didn't completely disappear until the end of treatment possibly owing to no inhibition on the eosinophil infiltration. Later, a vemurafenib-related severe, rapidly worsening DRESS case without remission even after the treatment of prednisone 2 mg/kg/day, showed a dramatic improvement of skin lesions and mucositis after receiving a single dose (5 mg/kg) of infliximab. This was accompanied by the maintenance of therapeutic infliximab blood concentrations, allowing an early switch to other therapeutic drugs.[46]

Interestingly enough, a recent case of corticosteroid-induced DRESS was successfully treated with 50 mg weekly subcutaneous injection of etanercept (total 4 times), and 3 days later, the patient's vital signs were stabilized, along with a dramatical improvement of the skin rash.[47] Moreover, in the complicated therapeutic setting of transition from DRESS to toxic epidermal necrolysis (TEN), etanercept possibly is lifesaving after multiple previous unsuccessful therapies (high dose steroid, human immunoglobulins, and cyclosporine).[48]

IL-4/IL-13 inhibitors

A Th2-type response, characterized by the elevation of abundant cytokines such as IL-4, IL-5, and IL-13, is observed in DRESS.[49] Dupilumab, a fully human monoclonal antibody, can block the shared receptor component for IL-4 and IL-13. Two DRESS cases depict the successful clinical application of dupilumab (600 mg as a loading dose→300 mg as a maintenance dose) without hospitalization and readmission, and their cutaneous symptoms and eosinophilia count improve within 7 days. One patient initially responded well to corticosteroids with recurrence 5 days after prednisone cessation and then achieved remission after the administration of dupilumab as monotherapy. The other patient's symptoms continued to deteriorate despite the use of prednisone but rapidly improved after the initiation of dupilumab,

combined with the rapid discontinuation of prednisone. However, both patients experienced mild rebounding rash within 2 months after discontinuing dupilumab treatment, but with the reinitiation of dupilumab, their symptoms resolved with a sustained remission for more than 4 months.[50] Another patient, experiencing a severe relapse during corticosteroid dose reduction and exhibiting adverse effects of corticosteroid therapy, manifested elevated levels of IgE and pronounced pruritus. Subsequently, the initiation of dupilumab for 16 weeks effectively facilitated corticosteroid tapering and induced a sustained decline in IgE levels without recurrence.[51] To refrain from DRESS recrudescence, prolonged duration of dupilumab with or without increasing dose intervals for a minimum of 6 months may be necessary and its indications should be better explored.

Throughout various clinical trials, the overall safety profile of dupilumab was generally comparable to that of the placebo. The most frequently reported adverse effects (injection-site reactions and conjunctivitis) tended to occur more frequently at the initiation of dupilumab treatment and gradually subsided over time. It is worth mentioning that a small number of patients experienced a temporary rise in eosinophil count following treatment with dupilumab with uncertain clinical relevance.[52]

Other biologics

Given that severe pruritus is a primary manifestation of DRESS, the potential therapeutic effect of omalizumab, an anti-IgE monoclonal antibody, has been proposed for the management of DRESS. This could be attributed to its modulation of the Th2 pathway via IL-33 signaling or its impact on the histamine 1 receptor. A recent retrospective study enrolled 14 patients with corticosteroid low response, each of whom was treated with omalizumab every 2 weeks for 6 weeks (300 mg per injection). Remarkably, all cases demonstrated a positive response, enabling corticosteroid tapering in all patients within 1 month of initiating omalizumab therapy.[53]

Rituximab, an anti-CD20 monoclonal antibody, can eliminate B cells in the peripheral blood, making it suitable for conditions with high autoantibody count and diseases where B cells are implicated in the pathogenesis.[54] There is only a reported case of minocycline-induced DRESS that has successfully improved with rituximab and plasmapheresis despite the prior use of high-dose steroids.[20] On the one hand, this patient was treated in combination with rituximab and plasmapheresis. On the other hand, since B cells and immunoglobulins are reduced in the early stages of DRESS, further investigation is needed to understand the specific therapeutic mechanisms of the anti-CD20 antibody in DRESS and the timing of this targeted therapy.

IL-6 and TGF-β play a role in the development of Th17 cells, and whether Th17 cells or Tregs emerge as the dominant phenotype: high IL-6 levels along with low TGF-β levels could shift the Treg/Th17 balance towards a Th17 response.[55] In the resolution stage of DRESS, where impaired Tregs and increased Th17 cells sustain the inflammatory responses, anti-IL-6 antibody might have a beneficial effect.[55] In a vemurafenib-related DRESS case where a patient's condition worsened despite the use of prednisone 2 mg/kg/day, a single 8 mg/kg dose of tocilizumab (a humanized monoclonal antibody that acts as an IL-6 receptor antagonist) initiated to interrupt capillary leakage of fluid in the interstitial space, leading to an obvious improvement of body weight, edema, blood pressure, and renal function.[46] Therefore, based on the detection of IL-6 and TGF-β, anti-IL-6 antibodies could be considered for refractory DRESS patients.

CD134, or OX40, a member of the TNF receptor superfamily, has been identified as a specific entry receptor for HHV-6. It is suggested that HHV-6 might latently infect monocytes in vivo, and during the early phase of DRESS, latent HHV-6-infected monocytes could be reactivated, leading to virus replication and infection of $CD4^+$ T cells via CD134.[56] Moreover, in patients with DRESS, the percentage of CD134-expressing $CD4^+$ T cells has been proven to be positively correlated with the serum thymus and activation-regulated chemokine level and eosinophil count, which are the laboratory parameters linked to Th2-type immune responses.[57] From a therapeutic point of view, since CD134 might function as both an HHV-6 receptor and a driver of Th2-type immune responses, targeting CD134 might be efficient for

the treatment of DRESS and the prophylaxis of HHV-6 reactivation.

The utilization of biologics in managing steroid-refractory, steroid-resistant, or steroid-dependent DRESS relies predominantly on evidence from case reports or limited retrospective case series. It is noteworthy to highlight that no biologics have an indication approved by a regulatory agency for the management of DRESS. Consequently, despite the challenges associated with conducting prospective trials, there is an urgent imperative for their initiation.

JANUS KINASE (JAK) INHIBITORS

Activation of the Janus kinase-signal transducer and activator of transcription proteins (JAK-STAT) pathways leads to the production of JAK-STAT-dependent cytokines such as IL-5, IL-6, IL-10, and IL-13, playing a role in DRESS pathogenesis and signaling, which could be simultaneously targeted using JAK inhibitors. There have been 3 reported severe DRESS patients with myocardial involvement successfully treated with the JAK 1/3 inhibitor tofacitinib monotherapy. Within 24 h of tofacitinib initiation, levels of IL-5, IL-6, IL-13, C–C motif chemokine ligand 1 (CCL1), CCL17, CCL22, and eosinophil count sharply dropped or even normalized.[58]

Kim et al reported a refractory DRESS patient who didn't respond to high-dose prednisone, 1 dose of etanercept, high-dose IVIG, cyclosporine at 400 mg/day, and MMF at 2 g/day in succession. Thus, using single-cell RNA sequencing analyses, both skin sample and peripheral blood mononuclear cells from this patient showed excessive proliferation of T cells, overexpression of chemokine receptors, and up-regulation of JAK-STAT signaling pathway, while HHV6b DNA was highly enriched in $CD4^+$ central memory T cells. Further lymphocyte transformation test found that all tested concentrations of tofacitinib completely inhibited $CD4^+$ T cell proliferation and genes associated with the JAK-STAT pathway, while ganciclovir inhibited $CD4^+$ T cell proliferation in a dose-dependent manner. Based on these findings, tofacitinib (5 mg/day→10 mg/day) plus ganciclovir was administrated in the patient with complete clearance of skin lesions, reduction of corticosteroids, and successful discontinuation of immunosuppressive agents.[59] The rapid clinical and molecular responses after the initiation of JAK inhibitor show its potential application in DRESS patients, and the single-cell omics-based approaches and diagnostic tests in vitro might be powerful approaches for targeted therapy in patients with complex pathophysiology. In addition to tofacitinib, whether other JAK inhibitors, such as baricitinib, upadacitinib, and abrocitinib, can be administered in DRESS needs to be further studied.

OTHER SYSTEMIC TREATMENTS FOR DRESS

Plasmapheresis

Since the pathophysiology of DRESS includes cytokine storm in response to a complex immune reaction, plasmapheresis, also known as plasma exchange, has emerged as a potential treatment modality for DRESS. While the evidence is limited and the specific mechanism is not fully understood, there are increasing cases of plasmapheresis as an add-on therapy for critical DRESS. In 1 report, a 14-year-old patient with a life-threatening DRESS showed a dramatic and sustained clinical response to plasmapheresis performed every other day for a total of 4 procedures after failure to high-dose steroids.[60] Another case described a patient with minocycline-induced DRESS and persistent lymphocytic myocarditis who significantly improved after a 4-day course of plasmapheresis and rituximab despite the prior use of high-dose corticosteroids and the addition of cyclosporine, mycophenolate, and OKT3.[20] Additionally, with 4 times of plasmapheresis, a 53-year-old DRESS patient with 2 times of relapses despite 2 sessions of steroid pulse therapy successfully reduced the activity of DRESS and the dose of corticosteroids.[61] Plasmapheresis appears promising for the management of life-threatening DRESS complicated by acute renal failure and multi-organ dysfunction.[62] However, the American Society for Apheresis guidelines have not specified the role of plasmapheresis in DRESS,[63] and more studies should be carried out to explore the timing and application of plasmapheresis in DRESS.

Given the critical condition of the DRESS patient, complications and adverse events of plasmapheresis, such as hypotension, syncope,

urticaria, chills, fever, arrhythmia, asystole, fluid and electrolyte imbalance, nausea, and vomiting, require close observation and evaluation of hemodynamic stability and toleration is necessary before administration.

N-acetylcysteine

N-acetylcysteine (NAC) replenishes glutathione by acting as a donor of cysteine, which helps maintain redox balance in cells, detoxify reactive oxygen species (ROS) produced by the culprit drug, and reduce specific T cell stimulation, and is effective only when given early.[64] Besides, NAC has demonstrated anti-inflammatory effects by decreasing the levels of TNF-α, IL-1β, IL-6, and nuclear factor-kappa B.[65] A phenytoin-induced DRESS patient immediately improved clinically and biochemically after receiving 2 g per 6 h of intravenous NAC.[66] Another phenytoin-induced DRESS patient showed rapid progress of elevated liver enzymes (>3000 UI/L) even after initiation of steroids, and then a combination of NAC and IVIG was administered with a markable improvement over the next 2 days.[67] There are also reports of co-administration of corticosteroids and NAC for DRESS.[68] However, reviews and guidelines on the management of DRESS often don't mention NAC as a treatment option. Thereafter, NAC in conjunction with steroids or IVIG rather than NAC alone might be a promising option especially when patients are under extremely high levels of ROS and liver enzymes.

LABORATORY WORKUP DURING TREATMENTS FOR DRESS

Laboratory tests (Supplemental Figure 1) are indispensable for not only the diagnosis and severity grading of DRESS but also the monitoring of the condition change during treatments. When a patient with suspected DRESS attends the hospital, a comprehensive diagnostic workup should be performed, including 3 main parts: basic workup, complementary organ-specific and exclusive workup, and workup on the virus reactivations.[69] The first part comprises the complete differential blood count (including platelets and search for atypical lymphocytes), peripheral blood smear, urinalysis, liver function tests, kidney function tests, erythrocyte sedimentation rate, C-reactive protein, ultrasound of superficial lymph nodes, and electrocardiogram.[1] The second part consists of different evaluations of potentially affected organs and exclusions of alternative diagnoses, including coagulation tests, serum cytokine levels, antinuclear antibodies, serology for viral hepatitis, chlamydia/mycoplasma antigens, blood culture, swabs from lesions sent for virology and bacterial culture, lesional biopsy, lymph node biopsy, liver biopsy, myocardial enzymes, brain natriuretic peptide (BNP)/proBNP, transthoracic echocardiogram, pancreatic enzymes, chest imaging (CT/radiograph), pulmonary function tests, bronchoscopy, brain imaging (CT/MRI), and lumbar puncture.[69] The third part includes serum polymerase chain reaction (PCR) for human herpes virus 6 (HHV-6), HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) or their serum IgM and IgG.[70] Once antiviral treatments are initiated, viral load tests should be performed weekly to determine the antiviral duration.

During the treatment stage, basic workup and complementary organ-specific workup according to the initial organ involvement should be regularly monitored to observe condition changes and timely adjust the therapeutic regimen. After discharge, regular follow-up consultations are necessary during the period of steroids or immunosuppressive agents tapering. For diagnosis of causal drugs in DRESS, skin tests, such as drug patch tests and intradermal tests in vivo, which are avoided during the acute and resolution phases, and lymphocyte transformation tests in vitro, which are suggested to be performed within 5–8 weeks after in patients with DIHS/DRESS are available.[71] A thorough investigation of the progression to autoimmune disease and sequelae is needed, including thyroid dysfunction, type I diabetes mellitus, autoimmune hepatitis, autoimmune hemolytic anemia, and visceral organ failure.[72]

MANAGEMENT OF DRESS

The potential management of DRESS is depicted in Fig. 3. Following the discontinuation of the responsible drug, the provision of supportive care, and the appropriate use of topical corticosteroids for symptomatic relief, mild DRESS patients may

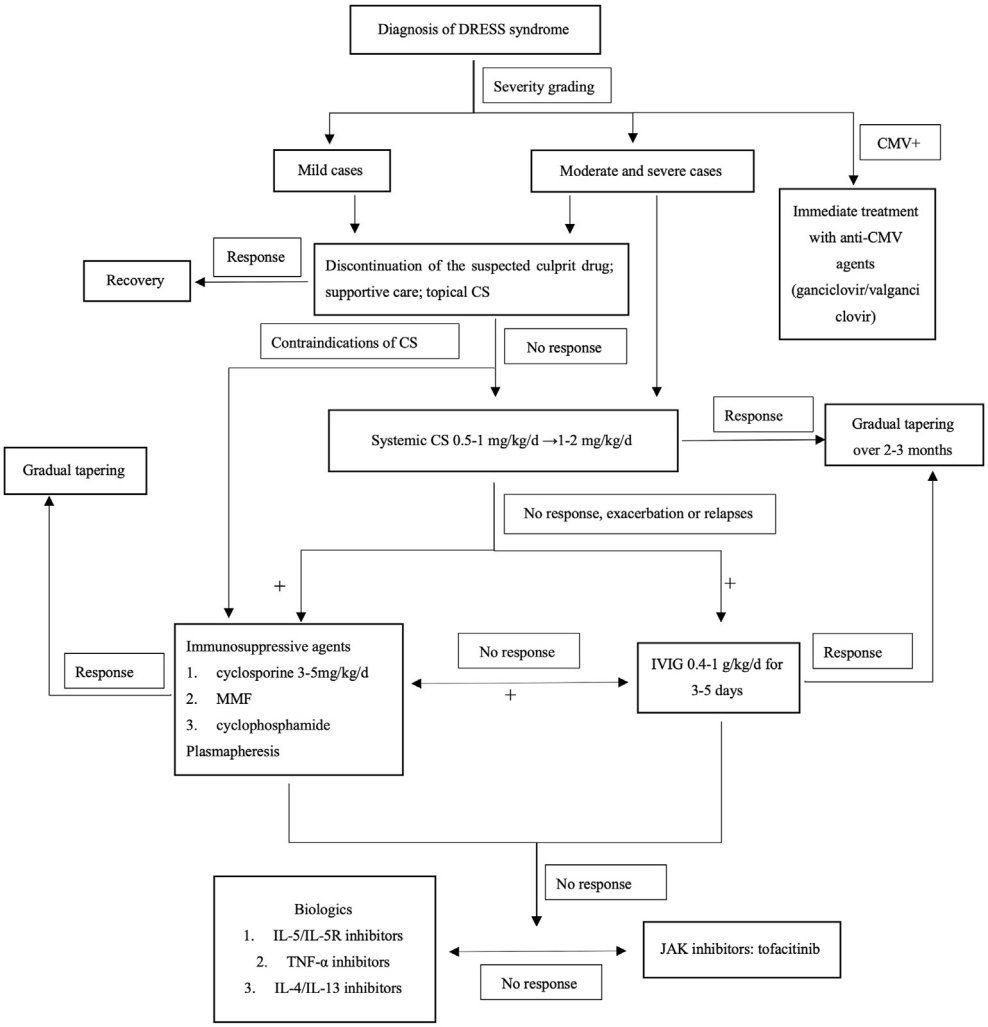

Fig. 3 Management of DRESS patients based on current scientific evidence. Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; CS, corticosteroid; CMV, cytomegalovirus; MMF, mycophenolate mofetil; IVIG, intravenous immunoglobulin

experience gradual recovery without the need for systemic corticosteroids or other immunosuppressive agents, and corticosteroids should be tapered over 6 weeks to 3 months.[69] For patients with moderate or severe DRESS, especially if life-threatening visceral involvement is present, systemic steroid treatment is advised, with a common initial dose of 0.5–1.0 mg/kg/day of prednisolone or an equivalent, gradually tapered over 2–3 months.[7,8] In cases with limited efficacy or exacerbation of symptoms, the dose may be increased to 1–2 mg/kg/day, and pulsed-dose intravenous methylprednisolone can be considered, whose outcomes and adverse effects are controversial.[73] However, accurate evaluation of DRESS severity at admission is challenging, and as demonstrated in a multicenter retrospective analysis in the US, 84% of 391 DRESS inpatients received either IV or oral corticosteroids.[73] Apart from the Japanese scoring system for DRESS in Supplemental Table 2, a recent Delphi-based international consensus on the management of adult DRESS patients has proposed DRESS severity grading, which divided DRESS into 3 grades (mild, moderate, and severe) based on the blood test, renal function, hepatic function, and other organ failures.[69]

Here, for patients with contraindications to systemic steroids, severe steroid-related adverse effects, refractory relapses during steroid tapering, or lack of improvement after high-dose steroid usage, alternative treatments are recommended. Based on the currently available evidence, we

recommend that: 1.) cyclosporine, JAK inhibitors, IL-4/13 inhibitors, and IL-5 inhibitors show great potential; 2.) IVIG is indicated for the high risk of infection in combination with corticosteroids; and 3.) the application of immunosuppressive agents other than cyclosporine, plasmapheresis, and other biologics needs to be analyzed case by case. Simultaneously, if major viral reactivations have been confirmed and there's a high serum viral load, antiviral treatments, such as ganciclovir and valganciclovir, can be considered for at least 1 week.[74]

However, the level of evidence supporting alternative steroid-sparing therapies for DRESS is mainly derived from case reports and case series, most of which are level III (evidence from nonexperimental descriptive studies), with only 1 at level IIB (evidence from at least 1 other type of experimental study).[73] Therefore, more robust and high-level evidence from controlled studies, including randomized controlled trials, is required. Along with time, advancements in new therapeutic targets through gene expression profiling and multiomic analysis might open the door to personalized medicine in DRESS.

Abbreviations

BNP, brain natriuretic peptide; CCL1, C-C motif chemokine ligand 1; DCs, dendritic cells; DiHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; HHV-6, human herpes virus 6; IL-33, interleukin-33; IVIG, intravenous immunoglobulin; JAK-STAT, the Janus kinase-signal transducer and activator of transcription proteins; MMF, mycophenolate mofetil; NAC, N-acetylcysteine; RegiSCAR score, the European Registry of Severe Cutaneous Adverse Reactions score; TARC/CCL17, thymus and activation-regulated chemokine; TEN, toxic epidermal necrolysis; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor-α.

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Data sharing and data accessibility

No datasets were used for the current study.

Author contributions

All authors declare that they have contributed substantially to the conception and design, literature review, drafting the article, and revising it critically for important intellectual content.

Ethics approval

Ethics approval does not apply to this work given that this is a literature review, and no patient information is disclosed.

Submission declaration

All authors approved the final manuscript as submitted, consented to publication, and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors declare no conflicts of interest in relation to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100935.

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