Dupilumab as Effective Therapy for Corticosteroid-Dependent/Resistant Type 2 Inflammation-Related Cutaneous Adverse Reactions

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High-grade cutaneous adverse effects during drug administration are major concerns for clinicians. Although systemic corticosteroids are generally effective, they may be affected by resistance or subject to contraindications for long-term use in certain complex cases. As most drug hypersensitivity reactions manifest with maculopapular rash and severe pruritus—indicating the involvement of a type 2 inflammatory response—targeting IL-4Rα with dupilumab promises to be a safe alternative. We administered dupilumab to a patient with drug rash with eosinophilia and systemic symptoms (DRESS) syndrome who experienced persistent itching and skin eruption. The patient's symptoms improved, and values for T_H2 cells producing IL-4 and IL-13 cytokines in peripheral blood returned to normal. Additionally, we reviewed the literature on the use of dupilumab in controlling corticosteroid-dependent or -resistant drug rash characterized by type 2 inflammation with the intention of identifying new treatment options for affected patients. The patient gave her permission for her data to be published.

We report the case of an 18-year-old woman diagnosed with DRESS syndrome at an external hospital after taking buspirone and oxcarbazepine intermittently over the previous 3 months. The patient had no history of atopy, and her symptoms included fever (>39°C), diffuse pruritic morbilliform rash, and facial swelling. Laboratory examination revealed eosinophilia of 1140/μL, alanine transaminase of 1757 U/L, elevated anti–Epstein-Barr virus antibody titer, pleural effusion, and enlarged lymph nodes at various sites, including the neck and groin. According to the RegiSCAR criteria [1], the patient was diagnosed with DRESS syndrome (score, 6). She discontinued all potentially offending medications. Most symptoms improved after 1 week of treatment with prednisone 500 mg/d, immunoglobulin 20 g/d, and a single dose of

adalimumab 80 mg (Figure, A), followed by corticosteroid tapering (oral prednisolone 30 mg/d for 1 week, and tapering by 5 mg/wk), although the rash and itching persisted. The patient's skin symptoms responded well to further treatment with corticosteroids (intravenous dexamethasone 10 mg/d for 8 days), although she experienced a severe relapse during dose reduction (oral prednisolone 20 mg/d for 4 days). Moreover, she developed moon face (Supplementary Figure 1, a), as well as residual rash on her back (Supplementary Figure 1, b) and was admitted to our hospital.

Upon admission, the patient received a further 2 weeks of treatment with methylprednisolone 40 mg/d (equivalent to prednisone 50 mg/d), which significantly reduced the area of the rash, although the pruritus numerical rating scale (NRS) score remained at 9 (Figure, B). In the immunological evaluation, the eosinophil count decreased to normal levels (37.0/μL) (Supplementary Figure, 2), while the total IgE level remained high at 3127 kU/mL. The total T-cell count ($CD3^+CD19^-$) in serum was increased (3282.52/μL [normal range, 955-2860/μL]), with an increase in $CD4^+$ T cells ($CD3^+CD19^-CD4^+$) as the main population (2017.57/μL [normal range, 550-1440/μL]). Of note, in this case of DRESS syndrome, the amount of $CD4^+$ T cells that generate IL-4 and IL-13 was significantly higher than for healthy controls (Supplementary Figure, 3). Moreover, no increase was observed in levels of IL-5 and IL-31 produced by $CD4^+$ T cells (Supplementary Figure, 3).

IL-5 is considered to play a key role in the pathogenesis of eosinophilia-related diseases by promoting the differentiation and maturation of eosinophils [2,3]. The normalization of the IL-5 level and eosinophil count in the present case could be the result of previous treatments with systemic corticosteroids. IL-4 is associated with the activity of DRESS syndrome, mainly by triggering the production of thymus and activation-regulated chemokine [4], and $IL\text{-}13^+CD4^+$ T cells steer the core pathology, especially in cutaneous lesions [5]. Therefore, dupilumab was administered (600 mg loading dose followed by 300 mg every 2 weeks), starting 2 weeks after admission. With the help of the biologics, intravenous methylprednisolone was tapered to oral prednisone tablets 40 mg/d, and the

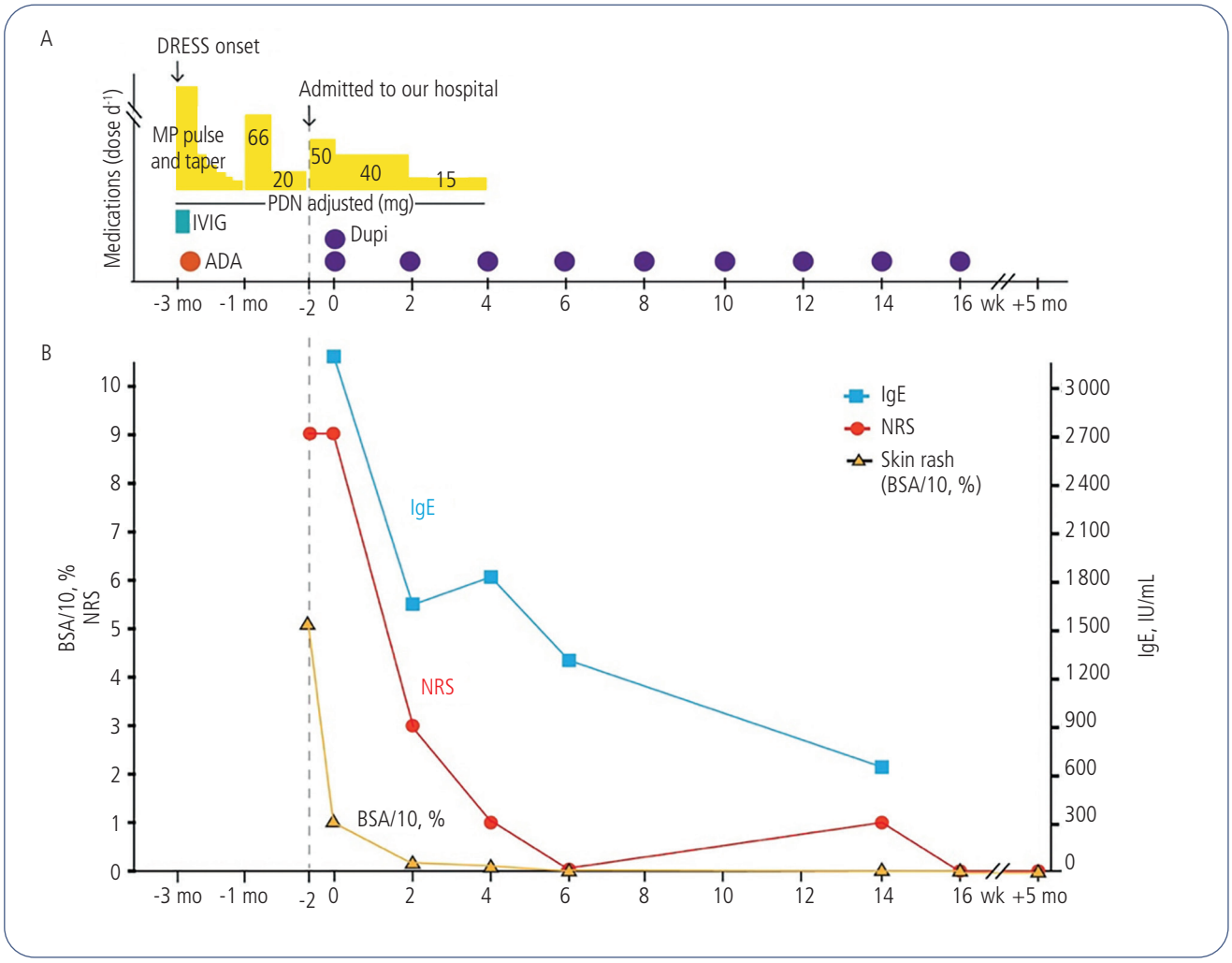

Figure. Timeline, strategy, and clinical indicators for the therapeutic process. DRESS indicates drug rash with eosinophilia and systemic symptoms; MP, methylprednisolone; PDN, prednisone; IVIG, intravenous immunoglobulin; ADA, adalimumab; Dupi, dupilumab; IgE, immunoglobulin E; NRS, numerical rating scale; BSA, body surface area.

patient's rash had completely disappeared by the second week (Supplementary Figure 1, c), with the NRS score decreasing to 3 (Figure, B). By the fourth week, oral prednisone had been discontinued, and the patient's skin lesions and itching were under control. She received a total of 16 weeks of dupilumab injections before treatment was complete. No relapses were recorded during the 5-month follow-up period. Laboratory examination showed that the patient's IgE level had decreased to 645 kU/mL after 3 months of treatment with dupilumab. The IL-4^{+} and IL-13^{+} T_H2 subsets declined rapidly from the second week and remained at normal levels in the 2 subsequent follow-ups (Supplementary Figure, 2).

We reviewed the literature on the successful treatment of corticosteroid-dependent or -resistant drug eruptions using dupilumab (Supplementary Table). Corticosteroid-resistant or -dependent drug eruptions were defined as recurrent maculopapular rash with pruritus caused by an offending drug that did not resolve with systemic corticosteroids or recurred at least once during corticosteroid tapering. To our surprise, we found that culprit drugs involve many immune-modulating agents, represented by immune checkpoint inhibitors and IL-17 and IL-23 inhibitors [6]. The rash generally manifests as widespread pruritic maculopapular rash or bullous pemphigoid-like lesions, suggesting a primarily T_H2 cell–driven immunopathological mechanism [7]. This was further supported by laboratory findings showing involvement of eosinophils and an increase in T_H2-related molecules in skin lesions or peripheral blood. Given the varying degrees of resistance and adverse reactions to systemic corticosteroids, all reported cases, including ours, began targeted therapy for type 2 inflammation with dupilumab on a routine basis. After 2 months of treatment, more than half of the patients were able to gradually reduce or stop corticosteroids, and some even began to resume therapy with the culprit drug. No related safety issues have been reported.

It is worth noting that most offending drugs are indispensable for treating either fatal malignancies or lifelong chronic diseases, making discontinuation difficult [8]. Additionally, long-term use of high-dose corticosteroids in affected patients added to their serious consequences [9]. TNF-α and IL-17 inhibitors have been proposed for severe adverse skin reactions [10]. However, dupilumab, which possesses dual advantages in terms of both efficacy and safety, has been largely underestimated. Future clinical evidence and mechanistic studies on the use of dupilumab to treat these refractory drug eruptions are still needed.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169:1071-80.
2. Truong K, Kelly S, Bayly A, Smith A. Successful mepolizumab treatment for DRESS - induced refractory eosinophilic myocarditis and concurrent thyroiditis. BMJ Case Rep. 2021;14:e242240.
3. Schmid-Grendelmeier, Steiger P, Naegeli MC, Kolm I, Cécile Valérie LC, Maverakis E, et al. Benralizumab for severe DRESS in two COVID-19 patients. J Allergy Clin Immunol Pract. 2021;9:481-3.e2.
4. Catherin J, Roufosse F. What does elevated TARC/CCL17 expression tell us about eosinophilic disorders? Semin Immunopathol. 2021;43:439-58.
5. Yuichi T, Tomoo F. Skin-homing IL-13-producing T cells expand in the circulation of patients with Drug Rash with Eosinophilia and Systemic Symptoms. Dermatology. 2017;233:242-9.
6. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol. 2021;39:4073-126.
7. Takamura S, Teraki Y. Treatment of bullous pemphigoid with dupilumab: dupilumab exerts its effect by primarily suppressing T-helper 2 cytokines. J Dermatol. 2022;49:845-50.
8. Nikolaou VA, Apalla Z, Carrera C, Fattore D, Sollena P, Riganti J, et al. Clinical associations and classification of immune checkpoint inhibitor-induced cutaneous toxicities: a multicentre study from the European Academy of Dermatology and Venereology Task Force of Dermatology for Cancer Patients. Br J Dermatol. 2022;187:962-9.
9. Phillips GS, Wu J, Hellmann MD, Postow MA, Rizvi NA, Freites-Martinez A, et al. Treatment outcomes of immune-related cutaneous adverse events. J Clin Oncol. 2019;37:2746-58.
10. Dougan M, Luoma AM, Dougan SK, Wucherpfennig KW. Understanding and treating the inflammatory adverse events of cancer immunotherapy. Cell. 2021;184:1575-88.

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