Dupilumab as an 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 important concerns for clinicians. Although systemic corticosteroids are generally effective, there may be resistance to steroid treatment or contraindications for long-term use in certain complex cases. As most drug hypersensitivity reactions manifest with maculopapular rashes and severe pruritus, which indicates the involvement of Type 2 inflammatory response, thus targeting IL-4Rα with dupilumab promises to be a safe alternative. We applied dupilumab in a drug rash with eosinophilia and systemic symptoms (DRESS) patient who had persistent itching and skin eruption, which resulted in the improvement of clinical symptoms, as well as the normalization of Th2 immune cells producing IL-4 and IL-13 cytokines in peripheral blood. Additionally, we reviewed literature on the use of dupilumab in controlling steroid-dependent or resistant drug rashes showing Type 2 inflammation, hoping to provide new treatment option for these patients.

We here reported an 18-year-old female patient who was diagnosed with DRESS at an external hospital after intermittently taking buspirone and oxcarbazepine during the past three months. The patient had no history of atopy, and her symptoms included

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fever (>39°C), diffuse pruritic morbilliform rash with facial swelling. Laboratory examination results revealed eosinophilia of up to 1140/μL, alanine transaminase level of up to 1,757 U/L, elevated anti-Epstein-Barr virus antibody titer, pleural effusion and enlarged lymph nodes at sites including the neck and groin. According to RegiSCAR criteria [1], the patient was diagnosed as DRESS syndrome with a score of 6. She discontinued all potentially offending medications. After one week of treatment with prednisone 500 mg/day, immunoglobulin 20 g/day, and adalimumab 80 mg for single dose (Figure 1, a), followed by corticosteroid tapering (oral prednisolone 30 mg/day for 1 week, and tapering by 5 mg per week), most symptoms improved, but the rash and itching persisted. The patient's skin symptoms responded well to steroid retreatment (intravenous dexamethasone 10 mg/day for 8 days), but there was a severe relapse during dose reduction (oral prednisolone 20 mg/day for 4 days). Moreover, the patient developed moon face (Supplementary Figure 1, a) as well as the residual rash on the back (Supplementary Figure 1, b), and was admitted to our hospital.

Upon admission, the patient received another two weeks of treatment with methylprednisolone 40 mg/day (equivalent to prednisone 50 mg/day), which significantly reduced the rash area, but the pruritus numerical rating scale (NRS) score remained at 9 (Figure 1, b). In the immunological evaluation, the eosinophil count has decreased to normal (37.0/μL) (Supplementary Figure, 2), while the total IgE level remained elevated up to 3,127 kU/mL. The total T-cell ($CD3^+CD19^-$) count in the serum was increased (3,282.52/μL, normal range: 955-2,860/μL), with an increase in $CD4^+$ T

cells ($CD3^+CD19^-CD4^+$) as the main population (2,017.57/μL, normal range: 550-1,440/μL). Notably, in this DRESS patient, $CD4^+$ T cells that generate IL-4 and IL-13 cytokines were significantly raised compared to healthy controls (Supplementary Figure, 3). Notably, no increase in levels of IL-5 and IL-31 produced by $CD4^+$ T cells was observed (Supplementary Figure, 3).

IL-5 is typically 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 this patient could be a result of previous treatments with systemic steroids. IL-4 primarily links to DRESS activity by triggering the production of thymus and activation-regulated chemokine (TARC) [4], and $IL\text{-}13^+CD4^+$ T cells steer the core pathology, especially in the cutaneous lesion [5]. Therefore, dupilumab was administrated to this patient (600 mg loading dose followed by 300 mg every two weeks), starting two weeks after her admission. With the help of the biologics, intravenous methylprednisolone were tapered down to 40 mg/day oral prednisone tablets, and by the second week, the patient's rash had completely disappeared (Supplementary Figure 1, c), with the NRS score decreasing to 3 (Figure 1, b). By the 4th week, oral prednisone was smoothly discontinued, and the patient's skin lesions and itching remained effectively managed. She received a total of 16 weeks of dupilumab injections before the treatment was terminated. And during the 5-month follow-up period, there was no relapse. Laboratory examination showed that the patient's IgE level decreased to 645 kU/mL after three months of dupilumab treatment.

The IL-4^+ and IL-13^+ Th2 subsets rapidly declined from the second week and remained at normal levels in the two subsequent follow-ups (Supplementary Figure, 2).

We reviewed literatures on the successful treatment of corticosteroid-dependent/resistant drug eruptions using dupilumab (Supplementary Table). Corticosteroid-resistant/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, IL-17 and IL-23 molecular inhibitors [6]. The rash generally manifested as widespread pruritic maculopapular rash or bullous pemphigoid-like lesions, which suggested the primarily Th2 cell-driven immunopathological mechanism [7]. This was further supported by laboratory findings, showing eosinophil involvement and increase in Th2-related molecules in skin lesions or peripheral blood. Due to varying degrees of resistance and adverse reactions to systemic steroids, 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 cases smoothly reduced or stopped corticosteroid use, and some even began to resume the culprit drug use. Of note, no safety issues related were reported in all cases.

It is worth noting that most offending drugs are indispensable for treating either fatal malignancies or lifelong chronic diseases, making drug discontinuation a rather

difficult decision [8]. Additionally, long-term use of high-dose corticosteroids in these patients added to their serious consequences [9]. TNF-α or IL-17 inhibitors have been proposed for severe skin adverse reactions [10]. However, dupilumab, which possesses dual advantages in terms of both efficacy and safety, has been largely underestimated. Nevertheless, 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

None declared.

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Figure 1. Time line, strategy and clinical indicators for the therapeutic process. DRESS, 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; mo, month; wk, week.