Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Evaluating Baricitinib for Severe Paediatric Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) with Single-Cell Sequencing

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Purpose: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe type of drug reaction that has significant mortality rate. Traditional treatments, including glucocorticoids and immunosuppressants, are sometimes insufficient. We present a case of severe paediatric DRESS unresponsive to conventional therapies, in which baricitinib, guided by single-cell RNA sequencing (scRNA-seq), led to clinical improvement. Single-cell transcriptomics is a revolutionary technology that allows scientists to measure the activity of all genes in individual cells on a large scale and has emerged as a tool for personalized therapeutic targeting.

Patient and Methods: A 3-year-old male with DRESS triggered by phenobarbital presented with fever, skin rash, impaired liver function, eosinophilia, and cytomegalovirus infection. After failing high-dose corticosteroids, intravenous immunoglobulin, and etanercept, baricitinib was initiated. Peripheral blood mononuclear cells and skin biopsy samples underwent scRNA-seq to identify dysregulated pathways and potential therapeutic targets.

Results: Baricitinib treatment led to resolution of skin lesions, normalization of eosinophil counts and liver function, and successful tapering of corticosteroids. Single-cell RNA sequencing uncovered that clusters of CD4+ and CD8+ T cells contain JAK2.

Conclusion: Our findings suggest that baricitinib, a JAK1/2 inhibitor, is a safe and effective salvage therapy for corticosteroid-refractory paediatric DRESS. scRNA-seq can guide targeted treatment decisions in DRESS.

Keywords: baricitinib, drug reaction with eosinophilia and systemic symptoms syndrome, severe type, treatment, single-cell RNA sequencing analysis

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) is a severe type of drug reaction with significant morbidity and mortality and the potential for long-term sequelae.[1–3] DRESS is characterised by haematologic changes, such as eosinophilia, heterogeneous lymphocytes, impaired liver and kidney function, reactivation of Human Herpesvirus-6 (HHV6), enlarged lymph nodes, and fever.[4] Patients with DIHS/DRESS are at a risk for systemic autoimmune sequelae after several months or even years of rash remission.[3] The first step in management is discontinuation of the culprit drug. Systemic glucocorticoids (1 mg/kg/day) remain first line, up to 30% of cases show inadequate response.[3,4] Refractory cases pose a therapeutic challenge, especially in paediatrics were

https://doi.org/10.2147/JIR.S576383
Received: 3 November 2025
Accepted: 12 March 2026
Published: 2 May 2026

prolonged high-dose corticosetroids carry risk of growth suppression, metabolic disturbances and opportunistic infections.[5]

Single-cell transcriptomics is a revolutionary technology that allows scientists to measure the activity of all genes in individual cells on a large scale and has emerged as a tool for personalized therapeutic targeting.[6]

Janus Kinase inhibitors (JAKi) have emerged as a potential alternative due to their ability to broadly suppress cytokine signalling involved in DRESS pathogenesis.[5–8] Previous case reported adult patients with DRESS have been successfully treated with JAK inhibitors.[6–8] While the paediatric DRESS patient in JAK inhibitors have not be reported. This research aims to describe the clinical course, therapeutic rationale, and scRNA-seq findings in a corticosteroid-refractory paediatric patient treated with baricitinib.

Materials and Methods

Patient's Information

A 3-year-old male patient and his parents visited the dermatology department. More than 1 month prior, the patient had developed epilepsy combined with an upper respiratory tract infection. Red papules appeared on the face without obvious itching after oral medication, accompanied by fever of approximately 40°C, which was diagnosed as a "viral rash". One weeks later, erythema and papules gradually appeared on the trunk, limbs, and neck partly fused into pieces, accompanied by itching. The patient was diagnosed as drug eruption and prescribed with methylprednisolone and the rash gradually disappeared, and the body temperature returned to normal. The culprit drug is phenobarbital. One week prior, large erythematous patches and papules with itching appeared on the trunk, limbs, and scalp. Ulceration of the lips with exudation. These findings supports the DRESS diagnosis.

Ethics Statements

This study was conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. The patient's parents consented to the treatment plan and publication of his medical history. We followed the CARE checklist guidelines during writing the manuscript.

Diagnosis of DRESS

Japanese consensus group in 2006, laid down seven mandatory features for DiHS.[9] The validated European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system was used for diagnosis (score ≥6 indicates definite DRESS).[9,10] Features included fever >38.5 °C, rash >50% body surface, eosinophilia, atypical lymphocytes, hepatitis, and lymphadenopathy. The risk stratification of the DIHS/DRESS cases based on the early score was 3.[11]

Therapy

The patient was hospitalised for systemic treatment (Figure 1). Initially, prednisone acetate (20 mg/day) was prescribed for three days; however, it was ineffective. Therefore, the treatment was changed to methylprednisolone 100 mg/day for three days, and IVIG 5g for five days. However, the skin lesions did not improve. Therefore, 150 mg/day

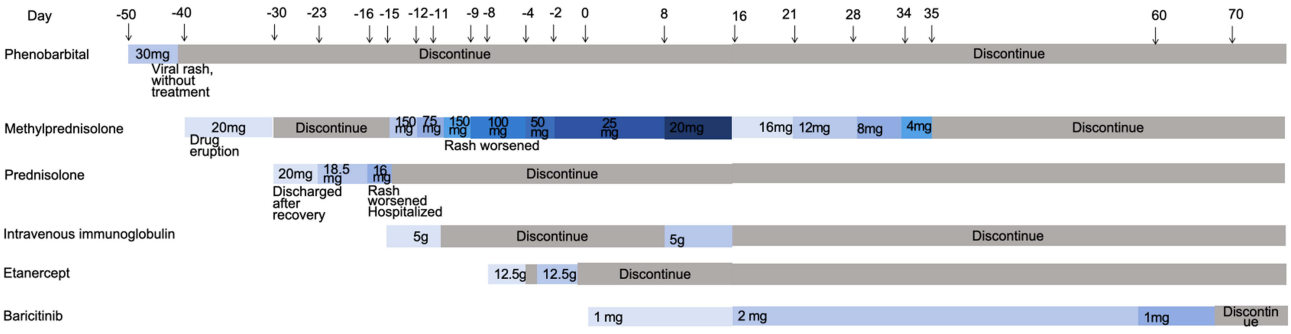

Figure 1 The time course of clinical treatment. Day 0 is the time when baricitinib is started.

https://doi.org/10.2147/JIR.S576383

methylprednisolone was administered as a shock treatment for two days. After two days, the dosage was reduced to 100 mg/day. However, the effect of the glucocorticoid reduction was unsatisfactory. Then, etanercept (12.5 mg) was administered twice a week and discontinued after two injections. Intravenous ganciclovir 70 mg/day was administered for 10 days to treat the cytomegalovirus (CMV). Liver-protecting drugs were also administered to improve liver function. With ongoing progression, baricitinib was selected with the full informed consent from the family. After 17 days hospitalisation (day 0), baricitinib was initiated at an initial dose of 1 mg/day. The dose of methylprednisolone was reduced to 25 mg/day; however, the skin lesions did not ameliorate. After 16 days, baricitinib was added at a dose of 2 mg/day. Methylprednisolone was reduced at the slowest rate to 4 mg/week and discontinued after two months. Baricitinib was tapered over 3 months and stopped by Day 70.

Next Generation Sequencing

Next-generation sequencing (NGS) of plasma identified cytomegalovirus (CMV) DNA, prompting antiviral therapy.

Single-Cell RNA Sequencing

Single-cell RNA analysis guides treatment of DiHS/DRESS.[6,12] The patient's blood and skin biopsies were sent into a single-cell suspension, and single-cell RNA sequencing (scRNAseq) analysis was performed.

The experimental process was as following:

1. Cell preparation: Single-cell suspension were inspected and counted, and the cell survival rate was 85%. Before the test, the qualified cells were washed and re-suspended to prepare the appropriate cell concentration of 700–1200 cells/μL for the 10x Genomics Chromium™ system.
2. GEM generation and labelling: According to the expected number of target cells, Gel Bead in Emulsion (GEMs) were constructed for single-cell separation according to the expected number of target cells. After normal formation, GEMs were collected for reverse transcription using a PCR instrument to achieve labelling.
3. Post-GEM-RT purification and cDNA amplification: GEMs oil-breaking treatment, purification, and enrichment of a strand of cDNA with magnetic beads, followed by cDNA amplification and quality inspection.
4. Library construction and quantification: Qualified cDNA was constructed for the second-generation sequencing library, and the quantitative quality of the library was finally determined through the experimental processes of fragmentation, sequencing connection, and sample Index PCR.
5. Computer sequencing: The Illumina HiSeq or NovaSeq platform and PE150 sequencing mode were used for complete library sequencing. It is recommended that the sequencing quantity should reach 50k read pairs/ cells or above.

scRNAseq Analysing

Data Processing of Single-Cell RNA-Seq from Chromium System

Mapping to GRCh38 human genome, quality control and read counting of Ensembl genes was performed by Cellranger software with default parameter (v6.1.1).

Unsupervised Clustering and Visualization

The single-cell data were integrated with a published dataset for analysis. Unsupervised clustering was performed with R (Seurat pack age version 4). Cells with 200–6000 genes, <10% mitochondrial genes and <10% red blood cell genes were further processed. Putative doublets were identified and removed from the single-cell RNA-seq dataset using the Scrublet package. Then, variation coefficient of genes was calculated with Seurat. Multi-dataset integration and batch correction were conducted with the Harmony algorithm. Dimensionality reduction of data was performed by using principle component analysis based on the first 2000 highest variable genes. A k-nearest neighbor graph was constructed from Euclidean distances in the space of the first 20 significant principal components. Louvain Modularity optimization algorithm was utilized to cluster the cells in the graph and clustering results were visualized by using t-distributed

Stochastic Neighbor Embedding(tSNE) project. Cells expressing high levels of genes encoding hemoglobin were discarded.

Marker Gene Identification and Cell-Type Annotation

Differential expression of each cluster was calculated using the "bimod" test as implemented in Seurat FindMarkers function. Genes with a log2 average expression difference 0.585 and $P < 0.05$ were identified as marker genes. Cell clusters were annotated using canonical markers of known cell types.

Seurat-Bimod statistical test was used to find differentially expressed genes between each group of cells and other groups of cells (FDR <= 0.05 and |log2 Fold Change| ≥ 1.5). Gene ontology enrichment analysis for these significant differentially expressed genes was performed by TopGO R package and the KEGG pathway enrichment analysis was performed using the Hypergeometric test in R. Significantly enriched GO terms and KEGG pathways were selected by a threshold FDR (adjusted P-value) ≤ 0.05.

The annotation of cell clusters was based on the Cellmaker2.0 website and relevant references.[13–21]

Laboratory Testings

Routine blood examinations and biochemical tests (including, liver function, renal function, electrolytes, blood lipids, and blood glucose) were performed to monitor and assess the patient's condition. Dynamic changes in eosinophil counts are of great concern. The alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels and total bilirubin levels were used to assess liver function. Procalcitonin (PCT) + interleukin-6 (IL6)+ C-reactive protein (CRP) combined with detection and infantile antibodies were used to assess infection. Upper-abdomen ultrasound was performed on the patient.

Results

Laboratory Testings

Eosinophilia peaked at 1.84×10^9/L after 33 days (Day 7 post-baricitinib), then declined to 0.09×10^9/L after 8 months (Figure 2). ALT and AST were elevated during hospitalisation. The ALT dropped from 1236 IU/L to 19 IU/L after 6 months. The AST decreased from 617 IU/L to 31 IU/L (Figure 3). The total bilirubin was 23.6 μmol/L in first day and

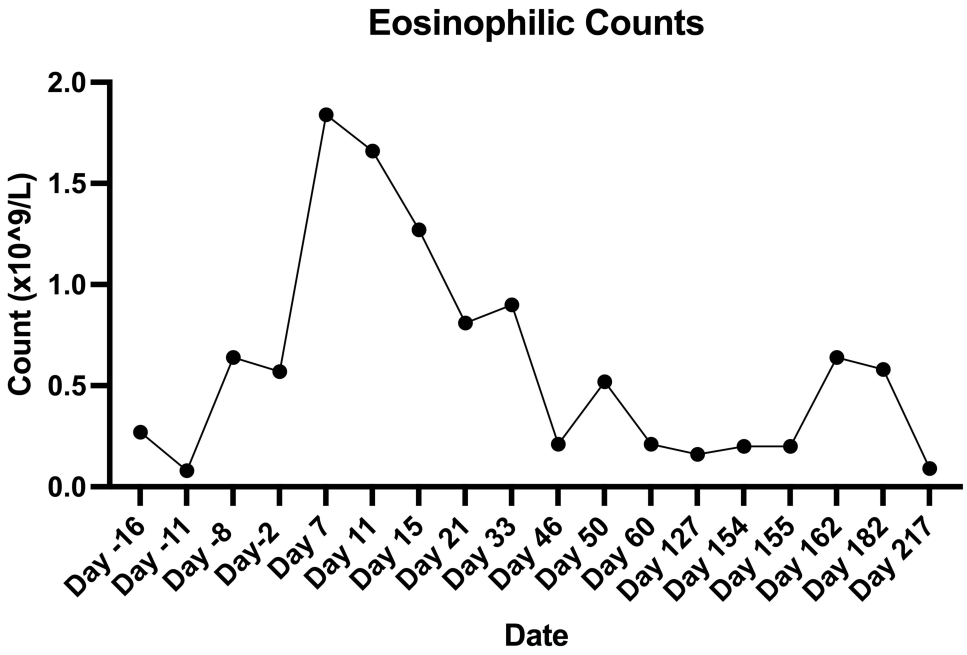

Figure 2 The eosinophilic counts showed dynamic changes. The highest is 1.84×10^9/L at Day7. After 33 days it drops to 0.09×10^9/L.

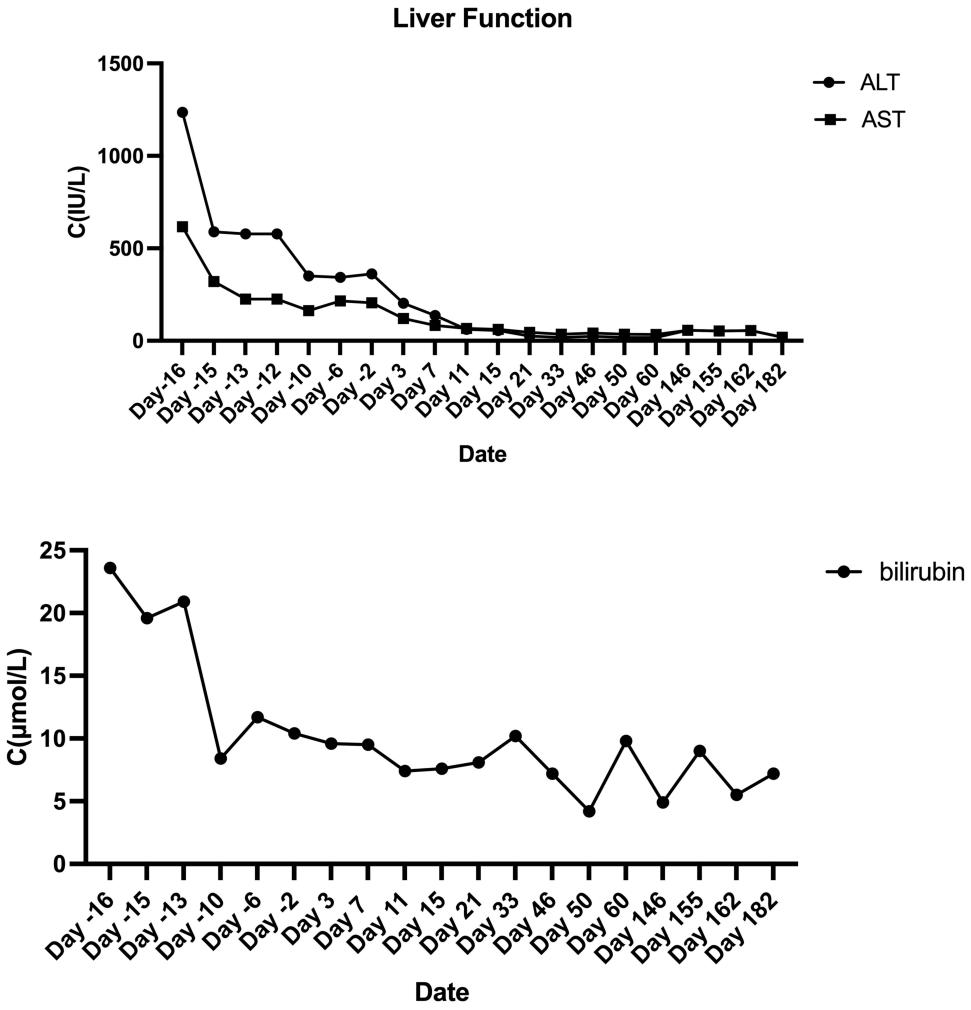

Figure 3 Liver function showed dynamic changes. The ALT and AST was high at Day-11 (The day before the treatment of baricitinib). The ALT is 1236 IU/L and the AST is 617IU/L; The total bilirubin at Day −16 was high. The total bilirubin is 23.6 μmol/L.

after six months it was 7.2μmol/L (Figure 3). The Infantile antibodies against rubella virus IgM 6.3 AU/mL, rubella virus IgG 164.7 IU/mL, cytomegalovirus IgG 648.8 AU/mL. The IL6 is 32.21 pg/mL (Figure 4). Upper-abdomen ultrasound indicated that liver and spleen were slightly enlarged.

Clinical Response

The patient was treated with high-dose oral corticosteroids, intravenous methylprednisolone shock, five rounds of IVIG, two subcutaneous injections of etanercept. These medications did not effectively control the disease and seriously threatened the life of patient. Hence, baricitinib was used, which was eventually successfully tapered and cured (Figure 1).

After one year of follow-up, the child's vital signs were normal, with no skin or visceral damage or recurrence of seizures were observed. Skin lesions were recorded at the beginning of baricitinib treatment and on the ninth day, half a month, one month, two months and stopped baricitinib after two months (Figure 5). No relapse occurred during 12-month follow-up. No adverse events occurred.

Next Generation Sequencing

CMV DNA was detected. Ganciclovir (70 mg/day) was administered intravenously for 10 days.

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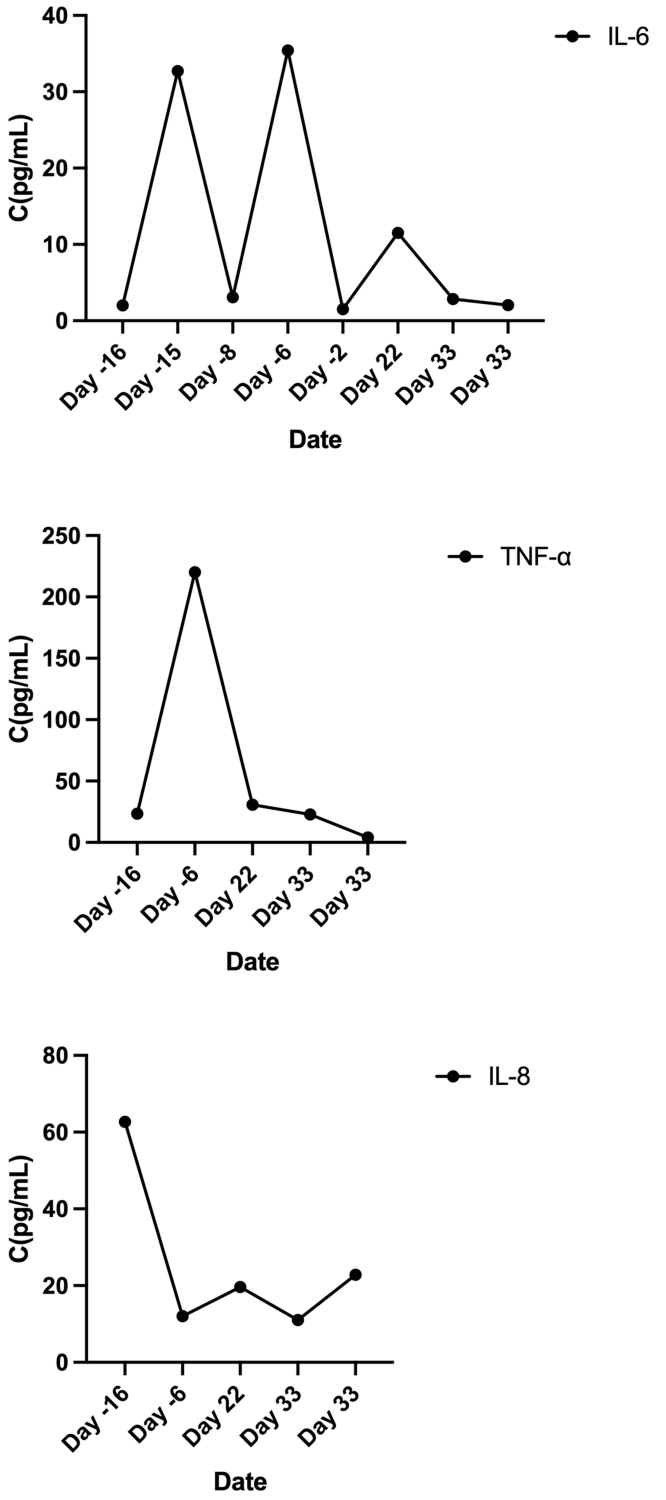

Figure 4 Changes in cytokines during the course of the patient's illness.

scRNAseq Data Analysis

After quality control, twenty-one clusters (Supplementary Table 1 Clusters' markers with annotation) were manually annotated and identified according to the following categories (Figure 6).

The skin and PBMC of the patient were compared with healthy control of skin and PBMC (from Nat Med. (GSE132802)) in the UMap. Considering cluster 1 comprises $CD4^{+}$T cells and cluster 6 and cluster 21 comprises

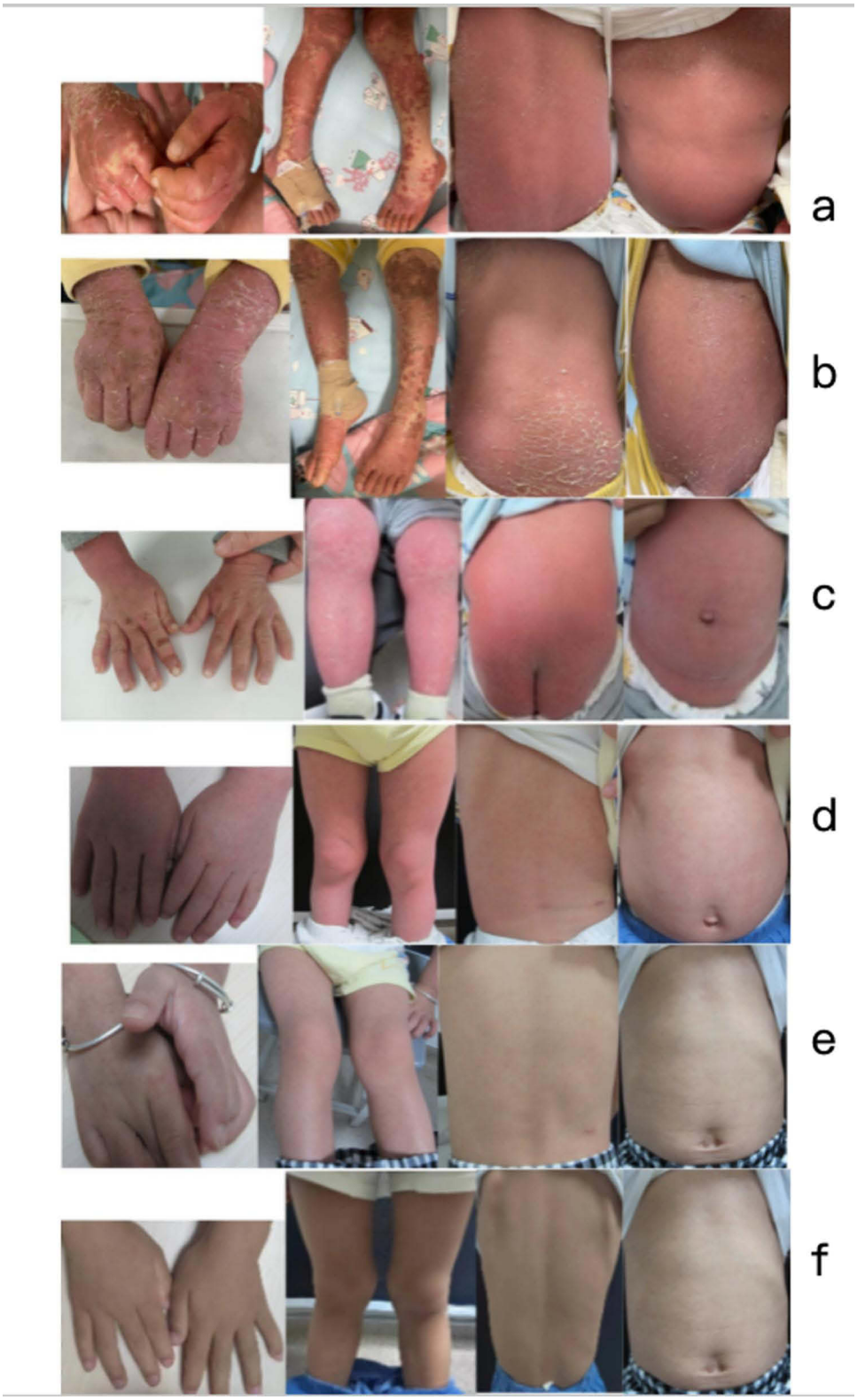

Figure 5 Patient's skin lesions improved and were captured at following time: (**a**) Baricitinib treatment day 0; (**b**) Baricitinib treatment day 9; (**c**) Baricitinib treatment day 15; (**d**) Baricitinib treatment day 30; (**e**) Baricitinib treatment day 60; (**f**) Baricitinib treatment stopped day 112.

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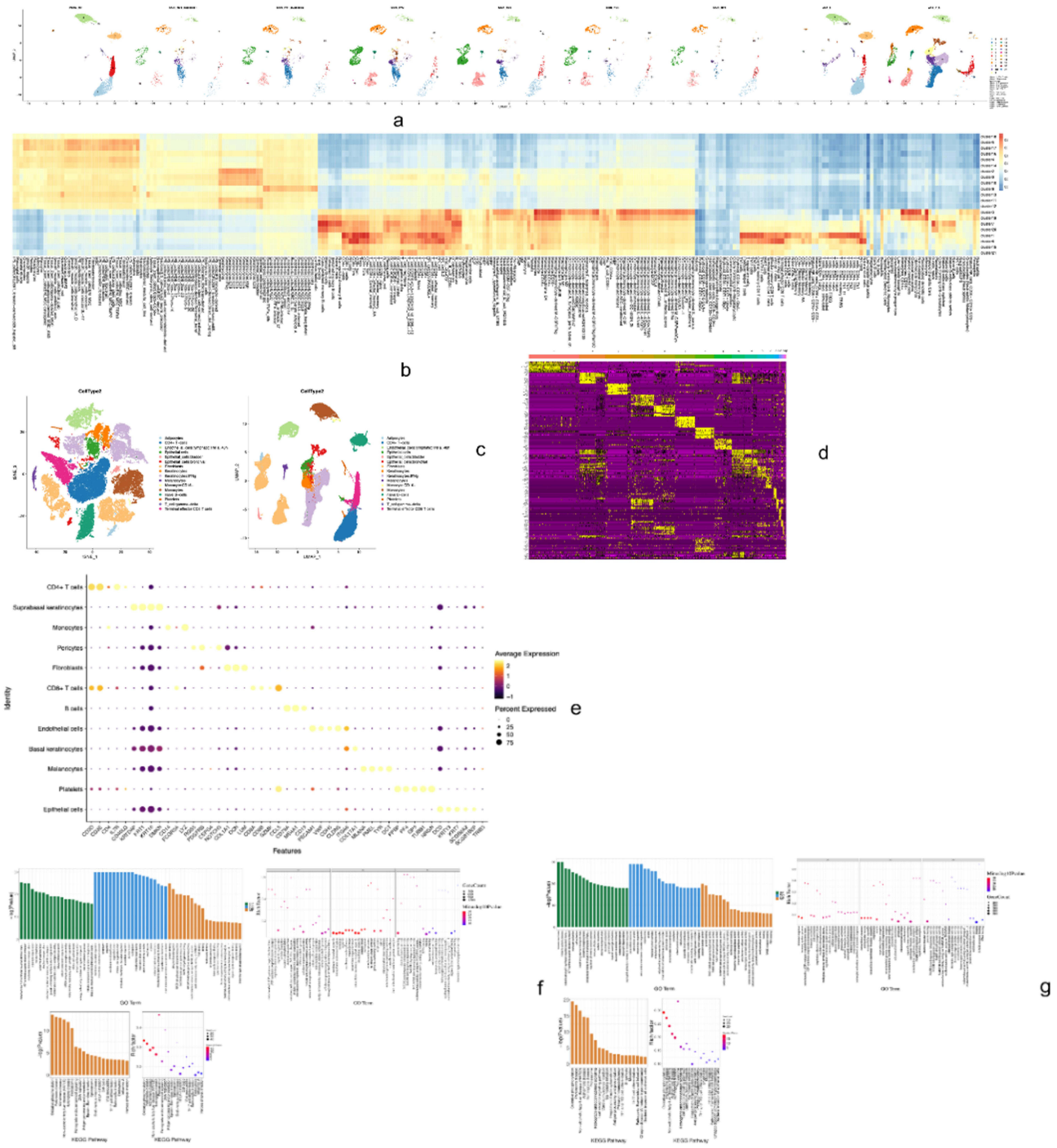

Figure 6 The results of Single cell RNA-seq. Healthy control of skin and PBMC from Nat Med.(GSE132802). ZXY_5 is the PBMC sample of patient. ZXY_P_5 is the skin sample of patient. (**a**) scRNAseq UMAP analysis of DiHS/DRESS skin and PBMC with healthy control (HV). (**b**) Heatmap of celltype by Fine Label. (**c**) TSNE and UMAP By CellType Fine Label. (**d**) Heatmap of the top-ten genes. (**e**) markers dotplot. (**f**) GO TERM and KEGG upregulated of skin $CD4^{+}$T cells. (**g**) GO TERM and KEGG upregulated of skin CD8+ T cells.

$CD8^{+}$T cells, the GO Biological Processes did not reveal the Janus kinase and signal transducer and activator of transcription (JAK-STAT) pathways, but found interferon gamma signalling. (Figure 6).

Discussion

The acronym DRESS was first introduced by Bocquet in 1996 to describe a drug rash with eosinophilia and systemic symptoms.[1] Corticosteroid-refractory cases are a clinical problem, and approximately 30% of patients with DiHS/DRESS

Table 1 Literature Review with Other Medications with DRESS

Drug	Dose	Article Type	Ref
Cyclophosphamide	750 mg/m^2 intravenously once; approximately 2 wk later, begin 100 mg orally daily for 6 mo	Case report	[35–38]
Mycophenolate mofetil	1500 mg twice daily; without dose	Case report	[39–41]
Rituximab	4-day course and 1-month course of weekly	Case report	[41]
Tofacitinib	From 10 mg twice daily to 5 mg twice daily;10 mg in the morning and 5 mg at night.	Case report	[6–8]
Mepolizumab	100mg-600 mg; single dose or monthly	Case report; Original Research	[42]
Reslizumab	Initial dose 100 mg i.v. 2 weeks later, a second dose of 200 mg i.v.	Case report	[42]
Benralizumab	30 mg single dose to 3 doses	Case report; Original Research	[42–45]
Tocilizumab	8mg/kg single dose	Case report	[45]
Infliximab	5mg/kg Single dose	Case report	[45]
Etanercept	First dose doubled (50 mg) and then 25 mg, total 5 injection	Case report	[46]

develop complications, including infections and inflammation/autoimmune disorders.[4,6,22,23] Doyoung Kim et al (2020) first used scRNA-seq to analyze skin and blood samples from a refractory DRESS patient, uncovering the activation of the JAK-STAT signalling pathway.[6] Our study extends this approach to paediatric and highlights baricitinib as a viable alternative. Spatial proteomics in toxic epidermal necrolysis (TEN) has also uncovered the JAK/STAT and interferon signalling pathways, which identified JAKi as a treatment.[24]

In view of the patient's age, we reviewed relevant literature to find evidence of previous experience using the drug in children.[25,26] Baricitinib was chosen to treat this patient because of the indications associated with its use for the treatment of COVID-19 patients.[26] ScRNA-seq data analysis revealed that the symbols of JAK2 were evident. The US Food and Drug Administration (FDA) has granted an Emergency Use Authorisation (EUA) to allow baricitinib for the treatment of COVID-19 in hospitalised adult and paediatric patients aged 2 years or older.[26,27] There are different recommended doses for patients aged 2–18 years: 4 mg/day for 9 years and older and 2 mg/day for 2–9 years old patients.[25,28] For patients who are unable to swallow whole tablets, baricitinib can be dispersed tablets in water, which make it easier for children to take medicine.[29] These support the treatment we administrated to a 3-year-old patient.

WHO strongly recommends that baricitinib for the treatment of severe and critically ill COVID-19 patients has both antiviral and anti-inflammatory effects on COVID-19, and can inhibit signal transduction associated with viral infection, including IL-2, IL-6, IL-10, IFN-γ, and G-CSF.[29] Thus, it can reduce the excessive inflammatory response in the early stages of infection and effectively inhibit the storm of inflammatory factors,[28] which effectively block interferon and IL-6 signalling implicated in DRESS. Moreover, baricitinib is used to treat moderate-to-severe alopecia areata in pre-adolescent children.[30]

Although the use of systemic corticosteroids in the treatment of DRESS has not been studied in randomised trials, the recommended dose is 0.8–1 mg/kg/day.[31] Another expert opinion on systemic corticosteroids suggests a usual dosing of 40–60 mg orally daily, followed by a prolonged tapering over 6–8 weeks.[32,33] Another recommended dose is 1–2 mg/kg/day.[34] When there is a lack of control or a contraindication for corticosteroids, cyclosporine (CsA) is recommended at 4–5 mg/kg/day for 5 days.[31] The IVIG is 2 g/kg for 5 days.[31] Plasmapheresis is frequently used to remove pathogenic cytokines.[31,35,36] Other medications are listed in (Table 1).

Limitations include the single-case design and lack of control samples from the same patient post-treatment. Larger prospective studies are warranted to validate scRNA-seq as a guiding tool and to establish dosing and safety of JAKi in paediatric DRESS.

Conclusion

In corticosteroid-refractory paediatric DRESS, baricitinib may be an effective salvage therapy. Single-cell RNA sequencing can uncover dysregulated pathways and guide targeted treatment. Future studies should explore JAKi as early intervention in severe DRESS to reduce corticosteroid exposure and improve outcomes.

https://doi.org/10.2147/JIR.S576383

Supplementary Material

The 21 clusters with markers and annotations were uploaded as Supplementary Table 1 Clusters' markers with annotation.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data associated with this article can be found in the online version at doi:10.6084/m9.figshare.28028537.

Ethics Statement

This study was carried out in accordance with provisions of the Declaration of Helsinki and International Conference on Harmonization guidelines for Good Clinical Practice. The patient's parents gave their written informed consent to the publication of this study to the treatment plan and the publication of his medical history. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (reference number: 2024lunshen071).

Consent for Publication

The patient's written informed consent was given by the patient's parents for the publication of the patient's photos.

Acknowledgments

We thank the patient and his parents for providing his medical history and lesions' graphs for research aims.

Author Contributions

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Danyang Yang: Writing- Original draft, supervision, software, investigation and formal analysis, Xin Liu: Writing- Original draft and data curation, Wenwen Jing: Writing- Original draft and validation, Xu Feng and Canying Lai: Writing- Original draft and software, Chenyue Liu: Writing- Original draft and formal analysis, Zhigang Xu: Writing- Original draft, data curation and funding acquisition, Yangang Zhang and Jiayi Han: Writing- Original draft and methodology, Songmei Geng: writing – review & editing and conceptualization, Ruilian Li and Dan Li: writing – review & editing and investigation, Boyi Cheng and Yufei Wu: Writing- Original draft and visualization, Zhuokun Liu, Jialin Lian and Zhenghui Wang: Writing- Original draft, visualization and project administration, Xiaoli Li and Yale Liu: Funding acquisition, writing – review & editing, formal analysis and resources. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (no. 30901297), the Doctoral Fund of Youth Scholars of Ministry of Education of China (no. 20090201120074), Shaanxi Province She Fa (2020SF-177), Shaanxi Administration of Traditional Chinese Medicine (no. 2021-01-ZZ-004), Shaanxi Real World Research Center of Chinese medicine clinical branch (no. SZY-ZSSJ-20210721TZ-F9), the Key Research and Development Program (no. 2022SF-025).

Disclosure

All the authors have declared that no conflict of interest exists.

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