

Early Temporal Dissociation between C-reactive Protein and Neutrophil Counts after Spesolimab Treatment in Generalized Pustular Psoriasis

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Generalized pustular psoriasis (GPP) is a rare and severe inflammatory disease characterized by widespread sterile pustules and systemic manifestations. In addition to cutaneous symptoms, GPP is associated with systemic inflammation, as reflected by fever, elevated white blood cell (WBC) and neutrophil counts, increased serum C-reactive protein (CRP) level and decreased serum albumin level. Since GPP can be life-threatening, rapid control of systemic inflammation is essential. Spesolimab, a monoclonal antibody targeting the interleukin (IL)-36 receptor, has demonstrated efficacy in GPP flares (1), and our previous real-world study showed rapid clinical improvement, particularly in pustular lesions (2). However, day-to-day changes in systemic inflammatory markers after spesolimab treatment remain unclear. Therefore, we aimed to evaluate the early effects of spesolimab on systemic inflammatory markers during the first 14 days of treatment in patients with GPP.

MATERIALS AND METHODS

This study included patients with GPP accompanied by systemic inflammation who were treated with spesolimab in our department between February 2023 and August 2025. Systemic inflammation was defined according to the Japanese guidelines for GPP as meeting all of the following criteria (3): body temperature (BT) ≥ 37.0 °C, WBC count $\geq 10 \times 10^9$ cells/L, serum CRP ≥ 0.3 mg/dL and serum albumin level < 3.8 g/dL; and at least one of the following: BT ≥ 38.5 °C, WBC count $\geq 15 \times 10^9$ cells/L, CRP ≥ 7.0 mg/dL and serum albumin < 3.0 g/dL. Patients with conditions that could affect inflammatory markers, such as active infections,

were excluded. Data were retrospectively collected from medical records. BT was assessed daily up to day 14 relative to baseline values. Since WBC count, neutrophil count, CRP and serum albumin were not measured daily in most patients, mean values over 2–3 consecutive days were calculated and used for analysis. This study was approved by the ethics committee of Teikyo University (24-087) and was conducted in accordance with the Declaration of Helsinki.

RESULTS

Seven patients with GPP accompanied by systemic inflammation (4 females and 3 males) were included in the analysis. The mean (standard deviation) age was 53.1 (13.0) years. Six patients received etretinate and 5 received ixekizumab before or after spesolimab initiation (**Table I**). On the day of initiating spesolimab (day 0), the mean BT was 37.7 (0.98) °C, the mean WBC count was $15.9 (8.5) \times 10^9$ cells/L, the mean neutrophil count was $13.1 (7.4) \times 10^9$ cells/L, the mean CRP level was 15.1 (7.1) mg/dL, and the mean serum albumin level was 2.4 (0.88) g/dL. During the 14 days after spesolimab initiation (**Fig. 1**), BT values significantly decreased at days 10–11, whereas neither the absolute nor percentage changes from baseline reached statistical significance. The WBC count significantly decreased at days 10–11 in both absolute and percentage changes. The neutrophil count significantly decreased at days 12–14 in both absolute and percentage changes. CRP levels significantly decreased as early as days 2–3 in percentage change and days 4–5 in absolute change from baseline. Serum albumin levels gradually increased over time, although these changes did not reach statistical significance.

Table I. Demographics and clinical characteristics of generalized pustular psoriasis patients with systemic inflammation treated with SPE

No.	Age (years)	Sex	Biologic treatment prior to this episode	Concomitant systemic therapy ^a	Day of GMA initiation ^b	Additional SPE dose at day 7
1	38	F	Naïve	-	4	-
2	79	M	Naïve	ETR (+1 d)	-	+
3	47	F	Naïve	ETR (-1 d), IXE (+5 d)	-	-
4	49	M	Naïve	ETR (-1 d), IXE (+2 d)	-	+
5	47	F	Naïve	ETR (-5 d), IXE (-4 d)	0	+
6	56	M	Naïve	ETR (-3 d), IXE (-2 d)	-1	+
7	56	F	Naïve	ETR (-4 d), IXE (-4 d)	-1	+
Mean $\pm$ SD	53.1 $\pm$ 13.0	F:4, M:3			+0.5 $\pm$ 2.38	

^aTime of its initiation, relative to the day of initiating SPE. ^bRelative to the day of initiating SPE.

ETR: etretinate; F: female; GMA: granulocyte and monocyte adsorption apheresis; IXE: ixekizumab; M: male; SD: standard deviation; SPE: spesolimab.

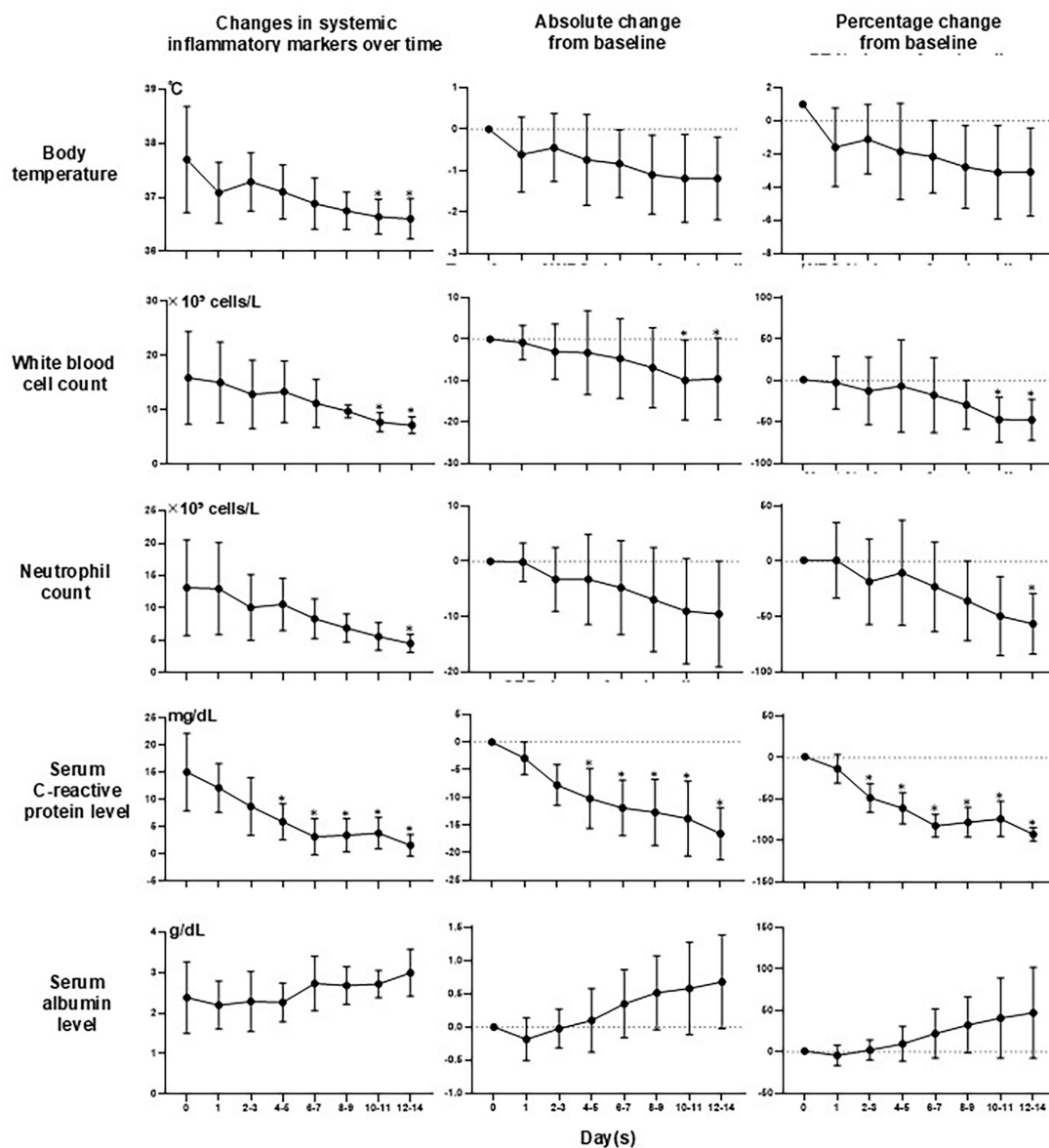


Fig. 1. Changes in body temperature and laboratory parameters in 7 patients with generalized pustular psoriasis accompanied by systemic inflammation before and after the first spesolimab treatment. Absolute and percentage changes from baseline are also shown. Values are expressed as mean $\pm$ standard deviation. Normality was assessed using the Shapiro-Wilk test, followed by Dunnett's multiple comparisons test to compare each time point with baseline. Statistical significance was defined as p -value < 0.05 (* $p < 0.05$).

DISCUSSION

In this study, CRP decreased significantly by days 2–3, whereas WBC and neutrophil counts decreased later, at days 10–11 and 12–14, respectively. These findings suggest that biochemical and circulating cellular inflammatory indices may not improve in parallel during the early phase after IL-36 receptor blockade.

CRP can respond rapidly to changes in cytokine-driven inflammation, whereas circulating leukocyte and neutrophil counts are also influenced by bone marrow output, peripheral redistribution, and tissue recruitment. Thus, suppression of inflammatory signalling may precede normalization of circulating cellular inflammatory indices.

The discrepancy between cutaneous and circulating neutrophil responses is also noteworthy. Spesolimab rapidly improved pustular lesions in our previous study (2), while EFFISAYIL 1 showed reduced neutrophil infiltration in lesional skin as early as week 1 after spesolimab treatment (4). In contrast, peripheral neutrophil counts decreased significantly at days 12–14 in the present study. Although these findings cannot be directly compared across studies, they raise the possibility that suppression of neutrophil accumulation in lesional skin may precede normalization of circulating neutrophil counts.

This temporal dissociation may have clinical implications. Persistent leukocytosis or neutrophilia

during the first several days after spesolimab initiation may not necessarily indicate an insufficient therapeutic response when accompanied by clinical improvement and declining CRP. Serial assessment of biochemical and cellular markers may therefore help avoid premature treatment modification based solely on persistently elevated leukocyte counts.

Our previous study suggested relatively rapid improvement in leukocyte-related markers with ixekizumab-containing treatment (5). Although direct comparison is not possible because of differences in study design, patient characteristics, and concomitant therapies, early inflammatory marker kinetics may differ according to therapeutic target. Further standardized studies are needed to determine whether the observed dissociation is characteristic of IL-36 receptor blockade.

This study has several limitations. First, the sample size was small, reflecting the rarity of GPP. Second, the study was retrospective, and laboratory assessments were not performed daily in all patients; therefore, mean values over 2–3 consecutive days were used for analysis. Third, concomitant etretinate, ixekizumab, GMA, and additional spesolimab may have influenced inflammatory marker kinetics. Etretinate may have contributed to overall improvement but is unlikely to fully explain changes within the first several days. Ixekizumab-containing treatment and GMA can also improve systemic inflammatory markers in GPP; in our GMA study, BT improved rapidly, whereas early reductions in CRP and WBC were not significant (6). Additional spesolimab administered from day 7 may have affected the later course but cannot explain the early CRP decline. Thus, the findings should be interpreted as real-world observations after initiation of spesolimab-containing treatment rather than as effects attributable solely to spesolimab, and the contribution of each therapy could not be determined in this small retrospective cohort.

In conclusion, CRP and leukocyte-related parameters showed different early temporal patterns after initiation of spesolimab treatment in GPP, with CRP declining early whereas WBC and neutrophil counts improved more gradually. These findings highlight the importance of time-resolved assessment of multiple systemic inflammatory markers when evaluating early treatment

responses in GPP. Further standardized studies are warranted to validate these early kinetics and to compare temporal response patterns across biologic treatments for GPP.

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Previous presentations: This study has been accepted for presentation as an e-Poster at the EADV Congress 2026, Vienna, Austria, 30 September–3 October 2026.

Data Availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

IRB approval status: This study was approved by the ethics committee of Teikyo University (24-087), and was carried out under the principles of the Declaration of Helsinki.

Patient consent statement: Informed consent was obtained through an opt-out procedure on the institutional website. Patients who declined participation were excluded from the study.

Conflict of interest: M.K. received honoraria for lectures from LEO Pharma. Y.T. received honoraria for lectures and grants for research irrelevant to this study from LEO Pharma.

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