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Review Article

Generalized pustular psoriasis: Clinical management and update on autoinflammatory aspects

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Abstract

Generalized pustular psoriasis (GPP) is a chronic, systemic inflammatory disease accompanied by high fever and general malaise. Diffuse erythema and swelling of the extremities occur with multiple sterile pustules all over the body in GPP patients. GPP often relapses over the lifetime and can be life-threatening. Recent discoveries of the underlying molecular genetic basis of many cases of this disorder have provided major advances to clinicians and researchers towards an understanding of the pathomechanism of GPP. However, the therapeutic management of GPP still faces many challenges and much uncertainty, and an evidence-based review summarizing the available clinical data on the management of this heterogeneous disease is needed. The present review addresses challenges regarding the precise clinical diagnosis and evaluation of clinical symptoms in GPP. In addition, we update and briefly summarize the current understanding of molecular pathomechanisms behind GPP as an autoinflammatory keratinization disease. Recent publications have clarified the genetic backgrounds of patients with GPP and ethnic differences in predisposing factors. Although there are ethnic differences in the prevalences of these pathogenic alleles, from the recent reports, at most 60.5% (*IL36RN*), 5.9% (*CARD14*) and 10.8% (*AP1S3*) of GPP patients have the mutations/variations of these genes. All the reported biologics studied seemed effective and relatively safe. Although it is difficult to evaluate therapeutic efficacy from studies on just a few cases, recent findings suggest that biologics can be a useful, powerful tool for controlling skin and systemic inflammation in GPP and for improving the quality of life of GPP patients.

Key points

Generalized pustular psoriasis patients frequently have *IL36RN* mutations and occasionally have *CARD14 or AP1S3* variants/mutations.

58 Generalized pustular psoriasis cases with *IL36RN*, *CARD14* or *AP1S3* mutations/variants are
59 included in autoinflammatory keratinization diseases (AiKD).
60 Biologics are promising treatments for generalized pustular psoriasis.
61

1. Introduction

1.1 Background

Generalized pustular psoriasis (GPP) is traditionally classified as the most severe form of pustular psoriasis (Table 1), although some reports have proposed that GPP alone can be treated as a distinct etiology because it differs strikingly from psoriasis vulgaris and pustular psoriasis in terms of its clinical, histological and genetic backgrounds [1, 2]. Diffuse erythema and swelling of the extremities occur with multiple sterile pustules all over the body in patients with GPP (Fig. 1a). GPP is a chronic, systemic inflammatory disease accompanied by high fever and general malaise. GPP often relapses over the lifetime, and fatal outcomes have been reported [3]. Various findings indicate that the GPP pathogenesis involves a combination of autoinflammation and T-cell mediated mechanisms, although these mechanisms would not normally seem related and might even seem contradictory [4]. In 2011, *IL36RN* mutations were reported as causative genetic defects in several GPP cases, suggesting deficiency of the IL-36 receptor antagonist [5, 6]. Moreover, we and another group reported that *CARD14* mutations/variants are associated with GPP [7-9]. Proinflammatory genetic variants in *CARD14* and *APIS3* found in GPP promote NF-κB activation [10]. Thus, discovering the underlying molecular genetic basis of many cases has given clinicians and researchers major advances in their understanding of GPP pathomechanisms.

However, the therapeutic management of GPP still faces many challenges and much uncertainty, and an evidence-based review summarizing the available clinical data on the management of this heterogeneous disease is warranted. This review addresses challenges regarding the precise clinical diagnosis and presentation of GPP and the issues surrounding them. We focus on evaluating the short-term and long-term safety, efficacy and tolerability of treatments available for GPP. In addition, we briefly update the current understanding of molecular pathomechanisms behind GPP as an autoinflammatory keratinization disease (AiKD).

1.2 Comorbidities of GPP

Choon et al. reported 102 Malaysian patients with adult-onset GPP [11]. In their paper, comorbidities of adult-onset GPP included obesity (42.9%), hypertension (25.7%), hyperlipidemia (25.7%) and diabetes mellitus (23.7%) [11]. Additionally, nine cases with ischemic heart disease (8.8%, 9/102) and four with hepatitis B infection (3.9%, 4/102) were reported [11]. Borges-Costa et al. noted that abnormalities in liver enzymes were present in 47% of patients [12]. In a comparison between groups of patients with versus without liver abnormalities, a male preponderance and higher leukocyte counts were found in the former, with a positive correlation between the absolute neutrophil count and total bilirubin also being observed [12]. Although the actual prevalence and long-term outcome of neutrophilic cholangitis is currently unknown in patients with GPP, neutrophilic cholangitis is also known as a complication of GPP [13]. Moreover, around 30% of patients are eventually affected with polyarthritis [14, 15]. In terms of oral lesions, an association between GPP and geographic tongue was identified. A higher prevalence of geographic tongue was reported in both a GPP cohort (83.9%, 47/56) and a family member cohort (47.8%, 32/67), versus the control cohort (0/168) or previous reports (ranging from 0.2 to 14.29%) [16, 17]. The lips may become red and scaly, and superficial ulceration may occur [15]. Although the comprehensive frequencies have not been reported, other possible comorbidities are hypoalbuminemia, hypocalcemia (a consequence of hypoalbuminemia), renal tubular necrosis (as a result of hypovolemia) and secondary infectious diseases. Hypoparathyroidism has also been reported in association with GPP [18, 19]. On other rare occasions, the disease is followed by pulmonary capillary leakage, pulmonary emphysema, jaundice and renal failure [15].

2. Diagnostic criteria and differential diagnosis

2.1 Diagnostic criteria for GPP

Fujita et al. summarized the primary parameters for the diagnosis of GPP in the Japanese therapeutic guidelines for GPP [20]. The four primary features are (i) systemic symptoms (e.g., high fever and fatigue), (ii) systemic or extensive flush accompanied by multiple sterile pustules that sometimes merge to form lakes of pus, (iii) neutrophilic subcorneal pustules histopathologically characterized by Kogoj's spongiform pustules, and (iv) the repeated recurrence of the above clinical and histological features [20]. They assessed the sensitivity of the four primary features with reference to 41 patients with GPP, as summarized in Table 2. These four primary parameters can be assessed in most dermatology clinics, because no special techniques are required. The current clinical diagnostic parameters for patients with GPP may benefit clinicians when they evaluate patients in the early stage, by enabling accurate diagnostic data that can have immediate clinical relevance to patient diagnosis and management [20].

2.2 Diagnostic methods

Skin biopsies may show hyperkeratosis with neutrophilic microabscesses in the epidermis (Fig. 1b). The formation of subcorneal pustules and spongiform pustules of Kogoj is characteristic of GPP. In addition, neutrophilic and lymphocytic infiltration is often seen in the upper dermis. A combination of the clinical features, histological observations and DNA sequencing of *IL36RN*, *CARD14* and *AP1S3* is the best way to establish the diagnosis of GPP. Although there are ethnic differences in the prevalences of these pathogenic alleles, from recent reports, at most 60.5% (*IL36RN*) [21-25], 5.9% (*CARD14*) [21] and 10.8% (*AP1S3*) [21] of GPP patients have the mutations/variations of these genes.

2.3 Differential diagnoses for GPP

Clinically, a number of inflammatory diseases should be excluded for the accurate diagnosis of GPP, and these are described here.

2.3.1 Infectious diseases

Differential diagnoses for GPP include various infectious diseases, such as acute generalized pustular bacterid, bullous or non-bullous impetigo, and multiple sweat gland abscesses in infants caused by bacterial infections. In general, these infectious diseases do not show the edematous erythema that is a characteristic eruption of GPP patients. Repeated cultures for microorganisms and Gram-staining of blood/skin samples are useful for diagnosing these infectious diseases.

2.3.2 Other types of pustular psoriasis and pustular diseases

Among other types of pustular psoriasis and pustular diseases, circinate and annular forms of pustular psoriasis, subcorneal pustular dermatosis, and localized pustular psoriasis must be excluded, although they may share certain clinical and histopathological features with GPP (Table 1).

2.3.3 Systemic autoinflammatory diseases and drug eruptions

Various forms of systemic autoinflammatory diseases should be considered as differential diagnoses, although the presence of pustulosis is the differential and specific feature of GPP. Most conventional autoinflammatory diseases/syndromes are known to have skin symptoms. Their various skin manifestations include urticarial eruptions, erythema nodosum-like lesions and pustular acne [26].

Differential diagnoses from other drug-induced eruptions (e.g. acute generalized exanthematous pustulosis (AGEP), or pustular-type drug eruptions) are made. A first flare of GPP is particularly difficult to differentiate from AGEP in some cases. Similarly to GPP, some AGEP cases are associated with mutations in *IL36RN* and have clinical and histopathological features that overlap with those of GPP [27, 28]. A detailed drug history of the patient might be useful information for

differentiating between GPP and AGEP. In addition, AGEP tends to have a more favorable prognosis than GPP has, with AGEP patients typically recovering more quickly, in about 10 days [27, 28].

3. Treatments

The application of several biologics has demonstrated how dramatically these new treatments can improve the quality of life as well as skin symptoms of patients with GPP. However, controlling the disease severity of GPP remains challenging. Due to the overall rarity of GPP, it is not easy to establish standard treatments. This review focuses on updates of GPP treatments involving several biologics.

3.1 Effective treatments for the acute phase (short-term)

Systemic management and drug therapies are essential parts of GPP treatment because the direct cause of death is often cardiorespiratory failure [20]. Additionally, the management of respiratory failure and of infectious diseases and the discontinuation of aggravating drugs with the concurrent systemic administration of corticosteroids are effective [20]. Many other systemic therapies (etretinate, cyclosporin, methotrexate, biologics (see below: “3.3 Newly developed systemic treatments involving biologics” and Table 4) and granulocyte and monocyte adsorption apheresis have been reported as effective for the acute phase; however, the evidence for each is insufficient. The selective depletion of increased granulocytes and monocytes by adsorptive apheresis is proven to alleviate GPP symptoms and related disorders [29].

3.2 Conventional medications for long-term management

Fujita et al. [20] analyzed 2010 data from the Japanese national clinical database, involving 1350 patients with GPP, and found that etretinate accounted for 35.6% of all oral medications, with an efficacy rate of 87.1%, while the usage and corresponding efficacy rates were 37.8% and 87.6% for cyclosporin, 6.4% and 84.9% for methotrexate, and 16.6% and 83.5% for corticosteroids, respectively. Efficacy was evaluated by each clinician who provided information to the database. For topical medications, the usage and efficacy rates were 84.2% and 87.8% for corticosteroids, 65.7% and 86.6% for activated vitamin D3, 11.0% and 74.5% for phototherapy, and 2.1% and 78.6% for an ultraviolet light therapy called “psoralen plus ultraviolet light-A therapy”, respectively [20].

3.3 Newly developed systemic treatments involving biologics

The literature has described the efficacy and safety of various biologics for GPP patients. We performed a literature search in MEDLINE to identify all relevant studies on the use of biologics for GPP (from January 2016 to August 2019). We identified five open clinical trials involving at least five GPP patients each, not including case reports (Table 3; we define “open clinical trials” as open trials not single- or double-blinded). However, as GPP is an extremely rare disease, clinical trials are difficult to perform. Most clinical trials involving GPP patients have been reported from Japan. From countries other than Japan, only a few case reports have been published. Although a methodology for the assessment of efficacy against GPP has not been sufficiently established, all the biologics studied seemed to be effective and relatively safe (Table 3) [30-34]. We summarize the biologics from anti-TNF biologics to anti-IL17 pathway biologics briefly, as follows.

As observed in clinical practice, skin inflammation is a predominant feature of GPP and high TNF-α levels may be responsible for the signs and symptoms of the disease [35, 36]. Esposite et al. reported that their GPP case series demonstrated favorable and persistent control of signs and

symptoms of the disease during treatments with the TNF-α inhibitor etanercept, a fusion protein containing human TNF-α receptor [35]. TNF-α-blocking agents, including infliximab, adalimumab and etanercept, were early biologics approved as treatments for psoriasis vulgaris and were the first applied for off-label use against GPP [37]. In fact, several TNF-α inhibitors have been reported to cure GPP successfully [38], while sometimes inducing generalized pustular eruptions [39]. From France, Viguier M. et al. reported the efficacy and safety of TNF inhibitors in a series of patients with GPP (two out of 11 GPP patients had mutations in *IL36RN*) [40]. In their report, the immediate efficacy of TNF inhibitors in controlling acute GPP attacks was evaluated in 16 flares (infliximab, 10; adalimumab, 3; and etanercept, 3) [40]. In the 10 patients who received infliximab, clinical remission was obtained in 8 flares (80%), with a median time for pustule clearance of 2 days (range: 1-8 days) [40]. Thus, TNF inhibitors appeared to provide great help in the control of the acute phase of GPP [40].

The strong expression of IL-17A has been consistently observed in skin specimens of GPP patients [41, 42]. A few open clinical trials with IL-17A antagonists (secukinumab [30], ixekizumab [31]) or an IL-17RA antagonist (brodalumab [32]) have been performed in Japan. These studies showed good efficacy for each compound, and IL-17 antagonists have been approved for the treatment of GPP in Japan [41]. Seven GPP patients treated with IL-17A antagonists (six with secukinumab and one with ixekizumab) were reported from Germany, all of whom showed a good or excellent clinical response without severe adverse events [41]. Anti-IL-17A therapy was well tolerated and ongoing in all patients after an average therapy duration of 12.9 months [41].

3.4 Published or ongoing clinical trials of treatments for GPP

We searched the Clinicaltrials.gov database (https://clinicaltrials.gov/) using ‘generalized pustular psoriasis’ as the search term in the field ‘Condition or disease’ (September 2019). After

filtering out the results for PPP, we identified quite a few completed or ongoing clinical studies for drugs. BI 655130 (Spesolimab), which is a monoclonal antibody against the interleukin-36 receptor, is being used in phase 2 and phase 3 clinical trials. The published preliminary results from a phase 1 study revealed that the inhibition of the interleukin-36 receptor with a single dose of BI 655130 might reduce the severity of GPP over a 20-week period [43]. The efficacy of BI 655130 regardless of the presence of the IL36RN mutation suggests that the interleukin-36 pathway may play a pathogenic role in patients with GPP who have different genetic backgrounds, including those without target mutations [43]. ANB019, another humanized monoclonal antibody for the interleukin-36 receptor, is also in clinical trials for patients with GPP and pustular psoriasis.

Patients with GPP have been enrolled in clinical trials of risankizumab (a humanized monoclonal antibody targeting IL-23A), certolizumab pegol (a PEGylated anti-TNFα biologic) and anakinra (a human interleukin-1 receptor antagonist). However, the results have not been published. Recently, Papp K, et al. reported that the selective inhibition of tyrosine kinase 2 (TYK2) with the oral agent BMS-986165 at doses of 3 mg daily or higher resulted in greater resolution of psoriasis than did the placebo over a 12-week period [44]. TYK2 inhibitors, such as BMS-986165, might also be useful for patients with GPP. Although longer durations and larger sample sizes are needed to evaluate efficacy and safety in actual clinical use, these new medications may be able to change treatments for GPP patients dramatically in the near future.

4. GPP as a representative disorder of AiKD

Recently, we proposed the new disease concept of AiKD to encompass inflammatory keratinization disorders with autoinflammatory pathogenic mechanisms [45, 46]. AiKD have main inflammation sites in the epidermis and the upper dermis, and the inflammation leads to

hyperkeratosis. In the pathogenesis of AiKD, primary genetic causative factors associated with the hyperactivation of innate immunity (autoinflammation) play important roles, mainly in the epidermis and the upper dermis. AiKD includes several diseases [47], such as GPP associated with *IL36RN* and *CARD14* mutations/variants.

4.1 GPP associated with *IL36RN* mutations

IL36RN mutations were reported as causative genetic defects in several GPP cases [5, 6]. *IL36RN* encodes the interleukin 36-receptor antagonist (IL36Ra), which is an anti-inflammatory cytokine. Deficiency of IL36Ra and aberrant IL36Ra structure and function lead to up-regulated signal transduction of IL-1 family cytokines, resulting in the unregulated secretion of inflammatory cytokines and GPP. Patients who develop GPP are not limited to those with homozygous or compound heterozygous mutations in *IL36RN*, but include those with heterozygous mutations in that gene [20, 23, 48]. In this study, patients were classified as ‘‘positive’’ if they carried at least one mutation in *IL36RN* (Table 4). The prevalence of *IL36RN* mutations was significantly high in patients with GPP (Table 4). Importantly, most GPP cases without preceding psoriasis vulgaris had mutations in *IL36RN* [23, 24, 49]. Setta-Kaffetzi et al. noted that disease severity did not differ significantly in patients with a single heterozygous mutation in *IL36RN* from those with a homozygous mutation or compound heterozygous mutations in *IL36RN* [50, 51]. However, Hussain et al. reported that *IL36RN* mutation-positive patients manifested a more severe clinical phenotype characterized by an earlier age of onset and an increased risk of systemic inflammation compared to those in the *IL36RN* mutation-negative patients [51, 52].

It has not been well studied whether such mutations in *IL36RN* influence therapeutic responses to drugs. No clear influence on the therapeutic response has been identified [41]. In the literature, patients successfully treated with ustekinumab [53] or with IL-17A antagonists have been

reported in patient subgroups with and without *IL36RN* mutations [41]. Significant contributions of IL-17A, TNF, IL-1, IL-36, and interferons to the pathogenesis of psoriasis vulgaris and GPP have been reported, although the GPP lesions showed higher IL-1 and IL-36 and lower IL-17A and IFN-g mRNA expressions than psoriasis vulgaris lesions showed [54]. Thus, the IL-1/IL-36 inflammatory axis might be a potent driver of disease pathogenesis in GPP [54]. Arakawa et al. reported that unopposed IL-36 signaling promotes antigen-driven and likely pathogenic T-helper type 17 responses in GPP [4]. They revealed that $CD4^+$ T cells in the peripheral blood and skin lesions of GPP patients were characterized by intense hyperproliferation, the production of the GPP key mediator IL-17A, and highly restricted TCR repertoires with identical T-cell clones in the peripheral blood and skin lesions, indicating antigen-driven T-cell expansions [4]. Recently, Campbell J. et al. reported CCR6 and CXCR2 as novel targets for a mechanistically distinct therapeutic approach for inflammatory skin diseases with dysregulated IL-36 signaling, such as GPP [55]. They found that the immune cells infiltrating in the IL-36a-injected mouse skin showed a dramatically different composition from those of infiltrating cells in imiquimod-treated skin [55]. Ligands for chemokine receptors CCR6 and CXCR2 were increased in both GPP and IL-36a-treated skin [55]. Additionally, an optimized small-molecule antagonist (CCX624, targeting CCR6 and CXCR2) significantly reduced the infiltration of T cells, neutrophils, and inflammatory dendritic cells in IL-36a-treated skin and was more effective at reducing inflammatory symptoms than saturating levels of anti-IL-17RA monoclonal antibodies was [55].

4.2 GPP associated with *CARD14* mutations/variants

Gain-of-function mutations in *CARD14*, which encodes caspase recruitment domain family member 14 (CARD14), were identified as the cause of familial psoriasis vulgaris and familial PRP in 2012 [56, 57]. CARD14 is mainly expressed and localized in epidermal keratinocytes. CARD14 is regarded as a scaffold protein regulating the signaling pathway of NF-kB, and it

contributes to inflammatory responses within the epidermis [56-58]. Shao S. et al. [59] reported that neutrophils isolated from patients with GPP induced the up-regulated expression of inflammatory genes including *IL-1b*, *IL-36G*, *IL-18*, *TNF-a*, and C-X-C motif chemokine ligands in keratinocytes more than normal neutrophils did. Moreover, neutrophils from patients with GPP secreted more exosomes than controls did, and these neutrophils were then rapidly internalized by keratinocytes, increasing the expression of these inflammatory molecules by activating the NF-κB and MAPK signaling pathways [59].

We and another group reported that *CARD14* variants are associated with GPP and palmoplantar pustular psoriasis [7, 8]. In addition, we reported the first autosomal dominant familial GPP pedigree associated with *CARD14* mutations [9]. Clinically, *CARD14* mutations are observed in only a minority of GPP cases [21]. Our group and Li et al. reported that GPP with psoriasis vulgaris and GPP without psoriasis vulgaris have different genetic backgrounds in terms of *CARD14* mutations/variants [2, 7].

4.3 GPP associated with *AP1S3* mutations

Adaptor-related protein complex 1 (AP-1) is an evolutionary conserved heterotetramer that promotes vesicular trafficking between the trans-Golgi network and the endosomes [10]. In 2014, Setta-Kaffetzi et al. reported two founder mutations in *AP1S3*, the gene encoding AP-1 complex subunit sigma-3, in 15 unrelated individuals with severe pustular psoriasis, including GPP [10]. AP1S3 expression is distinctively elevated in keratinocytes [60]. *AP1S3* silencing in their generated *AP1S3*-knockdown cell lines disrupts the endosomal translocation of the innate pattern-recognition receptor TLR-3 and results in a marked inhibition of downstream signaling [10]. In addition, Mahil et al. reported that *AP1S3* knockout in several cell lines disrupts keratinocyte autophagy, causing the abnormal accumulation of p62, an adaptor protein mediating NF-κB activation, and as a consequence, *AP1S3*-deficient cells up-regulate IL-1 signaling and

overexpress IL-36α [60]. To date, there are fewer mutational reports on *AP1S3* than on *IL36RN* or *CARD14*. However, we hypothesize that pustular psoriasis associated with *AP1S3* mutations may be possibly categorized as an AiKD.

5. Conclusion

One of the limitations of this review is that it includes only studies with small sample sizes and retrospective designs, biased mostly to the Japanese population. As we mentioned above, mutations in *IL36RN* and *CARD14* have been identified as prevalent predisposing factors for GPP. These facts have provided new insights into the pathogeneses of GPP. At the same time, recent reports have clearly revealed the genetic background of patients with GPP and ethnic differences in predisposing factors (Table 4). In recent years, various cytokines have been considered to be involved in the pathogenesis of GPP, similarly to how they have been associated with the pathogeneses of skin and systemic lesions in psoriasis vulgaris. Although it is difficult to evaluate the efficacy of biologics from the small number of cases, recent findings suggest that biologics can be a useful, powerful tool for controlling skin and systemic inflammation in GPP and for improving the quality of life of GPP patients. However, few safe, effective therapies have been established for this disorder, especially for infantile GPP.

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Figure legends

Figure 1. Characteristic clinical and histological features of GPP.

(a) An 18-month-old male. Pustules and scaly hyperkeratosis are seen on erythrodermic skin of the legs. (b) Hematoxylin-eosin staining reveals the accumulation of neutrophils under the stratum corneum, and neutrophilic infiltration within the spongiotic epidermis and the upper dermis. Scale bar = 200 μm.

366 **Table 1. Clinical classification of pustular psoriasis**

	Invasive area	Subtypes
Generalized	Generalized pustular psoriasis	Acute (von Zumbusch)
		Generalization of acrodermatitis continua of Hallopeau
		Infantile (early-onset) generalized pustular psoriasis
		Impetigo herpetiformis
	Circinate and annular forms of pustular psoriasis	
Localized	Localized pustular psoriasis	
	Palmoplantar area	Palmoplantar pustulosis
		Acrodermatitis continua of Hallopeau

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Table 2. Primary parameters for the diagnosis of GPP

	Parameter	Sensitivity (evaluated for 41 patients with GPP)
a	Systemic symptoms (e.g. high fever and fatigue)	83%
b	Systemic or extensive flush accompanied by multiple sterile pustules that sometimes merge to form lakes of pus	95%
c	Neutrophilic subcorneal pustules histopathologically characterized by Kogoj's spongiform pustules	95%
d	Repeated recurrence of the above clinical and histological features (a-c)	87%

A definitive diagnosis of GPP can be made in patients with all four parameters above, and GPP would be suspected in those with two or three parameters [20].

Abbreviations: GPP, generalized pustular psoriasis.

Table 3. Summary of the efficacy and adverse events of each biologic treatment for GPP (only open-label, multicenter, phase 3 clinical trials (at least 52 weeks of observation) in Japan)

Drug	Dose	Number of patients enrolled	Assessment point (number of patients assessed as of week 52)	Overall efficacy described in the paper	PASI 50/75/ 90/100 (%)	All/ severe adverse events (%)	Adverse events
Adalimu-mab [33]	80 mg at week 0 and then 40 mg/ 2 weeks from week 2. Dose escalation (80 mg) allowed from week 8.	10	52 weeks (n=10)	Seven patients (70%) achieved the primary efficacy endpoint of CR at week 16. CR rates reached 50% at week 2 and remained approximate ly stable thereafter through week 52.	80/60/ 60/NA	90/30	Bacterial enterocolitis and worsening of pustular psoriasis in one patient; chronic sinusitis in one patient; dehydration, cardiac failure and renal failure in one patient.
Ixekizu-mab [31]	160 mg at week 0 and then 80 mg/ 2 weeks (from week 2 to week 12), 80 mg/ 4 weeks (from week 13 to week 52).	5	52 weeks (n=5)	All patients had a GIS of resolved or improved from Week 12 onwards. By Week 64 (Retreatmen t Week 12), 2/5 patients had a GIS of resolved and 3/5 patients had a GIS of improved.	NA/N A/NA/ NA	100/0	Not described.

Secukinu-mab [30]	150 mg once weekly at weeks 0, 1, 2, 3 and 4, and then every 4 weeks until week 52. Two patients were up-titrated to 300 mg at weeks 8 and 24, respectively.	12	52 weeks (n=9)	Treatment success was achieved by 83.3% (n=10) of patients at week 16 with CGI evaluated as “very much improved” (n=9) and “much improved” (n=1). The improvements were sustained throughout 52 weeks.	NA/72.7/63.6/27.3	100/25	Bowen’s disease and cellulitis, drug-induced liver injury, upper gastrointestinal hemorrhage, hypoglycemia and abnormal hepatic function.
Brodalu-mab [32]	140 mg at week 0 and then 140 mg/ 2 weeks (n=9) or 210 mg/ 2 weeks (dose escalation, n=3) from week 2.	12	52 weeks (n=12)	At week 52, CGI remission or improvement was achieved in 91.7 % (11/12) of patients with GPP.	NA/83.3/83.3/58.3	91.7/25	Lumbar vertebral fracture, exacerbation of pustular psoriasis, hepatocellular carcinoma.
Guselku-mab [34]	50 mg at weeks 0, 4, 12, and then 50 mg/ 8 weeks (n=5) or 100 mg/ 8 weeks (dose escalation, n=5) from week 20.	10	52 weeks (n=8)	At week 16, the proportion of GPP patients achieving treatment success was 77.8% (7/9). Guselkumab treatment demonstrated efficacy in Japanese patients with GPP through week 52.	NA/NA/NA/NA	100/10	Squamous cell carcinoma.

377 Abbreviations: GPP, generalized pustular psoriasis; CR, clinical response, defined as remission

378 (total skin score, 0) or reduction of 1 point or more if the baseline total skin score was 3, or 2

379 points or more if the baseline total skin score was 4 or more; CGI, clinical global impression;
380 GIS, global improvement score; PASI, Psoriasis Area and Severity Index; NA, not analyzed.
381

382 **Table 4. Frequencies of *IL36RN* mutations in GPP patients reported around the world**

Nation/ ethnicity	European	European (mostly German)	East Asian	South Asian	Malaysian	Chinese (Sichuan region)	Japanese
Frequency of *IL36RN* mutation-positive patients*	34.7 %	29.4 %	28.8 %	0 %	11.5 %	60.5 %	45.2 %
Allele frequency of *IL36RN* mutations in GPP patients	NA	24.5 %	NA	0 %	8.5 %	55.8 %	43.5 %
Reference	[21]	[25]	[21]	[21]	[21]	[22]	[23, 24]

383 *Patients were classified as *IL36RN*-positive if they carried at least one mutation.

384 Abbreviations: NA, not analyzed.

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REFERENCES

1. Ohkawara A, Yasuda H, Kobayashi H, Inaba Y, Ogawa H, Hashimoto I, et al. Generalized pustular psoriasis in Japan: two distinct groups formed by differences in symptoms and genetic background. Acta Derm Venereol. 1996 Jan;76(1):68-71.
2. Li L, You J, Fu X, Wang Z, Sun Y, Liu H, et al. Variants of CARD14 are predisposing factors for generalized pustular psoriasis (GPP) with psoriasis vulgaris but not for GPP alone in a Chinese population. Br J Dermatol. 2019 Feb;180(2):425-6.
3. Yamamoto M, Imai Y, Sakaguchi Y, Haneda T, Yamanishi K. Serum cytokines correlated with the disease severity of generalized pustular psoriasis. Dis Markers. 2013;34(3):153-61.
4. Arakawa A, Vollmer S, Besgen P, Galinski A, Summer B, Kawakami Y, et al. Unopposed IL-36 Activity Promotes Clonal CD4(+) T-Cell Responses with IL-17A Production in Generalized Pustular Psoriasis. J Invest Dermatol. 2018 Jun;138(6):1338-47.
5. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med. 2011 Aug 18;365(7):620-8.
6. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet. 2011 Sep 9;89(3):432-7.
7. Sugiura K, Muto M, Akiyama M. CARD14 c.526G>C (p.Asp176His) is a significant risk factor for generalized pustular psoriasis with psoriasis vulgaris in the Japanese cohort. J Invest Dermatol. 2014 Jun;134(6):1755-7.
8. Berki DM, Liu L, Choon SE, David Burden A, Griffiths CE, Navarini AA, et al. Activating CARD14 Mutations Are Associated With Generalized Pustular Psoriasis but Rarely Account for Familial Recurrence in Psoriasis Vulgaris. J Invest Dermatol. 2015 Jul 23.
9. Takeichi T, Kobayashi A, Ogawa E, Okuno Y, Kataoka S, Kono M, et al. Autosomal dominant familial generalized pustular psoriasis caused by a CARD14 mutation. Br J Dermatol. 2017 Oct;177(4):e133-e5.
10. Setta-Kaffetzi N, Simpson MA, Navarini AA, Patel VM, Lu HC, Allen MH, et al. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. Am J Hum Genet. 2014 May 1;94(5):790-7.
11. Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2014 Jun;53(6):676-84.
12. Borges-Costa J, Silva R, Goncalves L, Filipe P, Soares de Almeida L, Marques Gomes M. Clinical and laboratory features in acute generalized pustular psoriasis: a retrospective study of 34 patients. Am J Clin Dermatol. 2011 Aug 1;12(4):271-6.

13. Bachelez H. Pustular psoriasis and related pustular skin diseases. Br J Dermatol. 2018 Mar;178(3):614-8.
14. Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. Br J Dermatol. 1968 Dec;80(12):771-93.
15. Umezawa Y, Ozawa A, Kawasima T, Shimizu H, Terui T, Tagami H, et al. Therapeutic guidelines for the treatment of generalized pustular psoriasis (GPP) based on a proposed classification of disease severity. Arch Dermatol Res. 2003 Apr;295 Suppl 1:S43-54.
16. Furlanetto DL, Crighton A, Topping GV. Differences in methodologies of measuring the prevalence of oral mucosal lesions in children and adolescents. Int J Paediatr Dent. 2006 Jan;16(1):31-9.
17. Liang J, Huang P, Li H, Zhang J, Ni C, Wang Y, et al. Mutations in IL36RN are associated with geographic tongue. Hum Genet. 2017 Feb;136(2):241-52.
18. Knuever J, Tantcheva-Poor I. Generalized pustular psoriasis: A possible association with severe hypocalcaemia due to primary hypoparathyroidism. J Dermatol. 2017 Dec;44(12):1416-7.
19. Guerreiro de Moura CA, de Assis LH, Goes P, Rosa F, Nunes V, Gusmao IM, et al. A Case of Acute Generalized Pustular Psoriasis of von Zumbusch Triggered by Hypocalcemia. Case Rep Dermatol. 2015 Sep-Dec;7(3):345-51.
20. Fujita H, Terui T, Hayama K, Akiyama M, Ikeda S, Mabuchi T, et al. Japanese guidelines for the management and treatment of generalized pustular psoriasis: The new pathogenesis and treatment of GPP. J Dermatol. 2018 Nov;45(11):1235-70.
21. Twelves S, Mostafa A, Dand N, Burri E, Farkas K, Wilson R, et al. Clinical and genetic differences between pustular psoriasis subtypes. J Allergy Clin Immunol. 2019 Mar;143(3):1021-6.
22. Li Z, Yang Q, Wang S. Genetic polymorphism of IL36RN in Han patients with generalized pustular psoriasis in Sichuan region of China: A case-control study. Medicine (Baltimore). 2018 Aug;97(31):e11741.
23. Sugiura K, Takemoto A, Yamaguchi M, Takahashi H, Shoda Y, Mitsuma T, et al. The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. J Invest Dermatol. 2013 Nov;133(11):2514-21.
24. Takeichi T, Togawa Y, Okuno Y, Taniguchi R, Kono M, Matsue H, et al. A newly revealed IL36RN mutation in sibling cases complements our IL36RN mutation statistics for generalized pustular psoriasis. J Dermatol Sci. 2017 Jan;85(1):58-60.
25. Mossner R, Wilsmann-Theis D, Oji V, Gkogkolou P, Lohr S, Schulz P, et al. The genetic basis for most patients with pustular skin disease remains elusive. Br J Dermatol. 2018 Mar;178(3):740-8.
26. Tripathi SV, Leslie KS. Autoinflammatory diseases in dermatology: CAPS, TRAPS, HIDS, FMF, Blau, CANDLE. Dermatol Clin. 2013 Jul;31(3):387-404.
27. Kardaun SH, Kuiper H, Fidler V, Jonkman MF. The histopathological spectrum of acute generalized exanthematous pustulosis (AGEP) and its differentiation from generalized pustular

459 psoriasis. J Cutan Pathol. 2010 Dec;37(12):1220-9.
460 28. Navarini AA, Simpson MA, Borradori L, Yawalkar N, Schlapbach C. Homozygous missense
461 mutation in IL36RN in generalized pustular dermatosis with intraoral involvement compatible with
462 both AGEP and generalized pustular psoriasis. JAMA Dermatol. 2015 Apr;151(4):452-3.
463 29. Fujisawa T, Suzuki S, Mizutani Y, Doi T, Yoshida S, Ogura S, et al. Granulocyte and
464 Monocyte Adsorption Apheresis for Generalized Pustular Psoriasis: Therapeutic Outcomes in Three
465 Refractory Patients. Ther Apher Dial. 2015 Aug;19(4):336-41.
466 30. Imafuku S, Honma M, Okubo Y, Komine M, Ohtsuki M, Morita A, et al. Efficacy and safety
467 of secukinumab in patients with generalized pustular psoriasis: A 52-week analysis from phase III
468 open-label multicenter Japanese study. J Dermatol. 2016 Sep;43(9):1011-7.
469 31. Okubo Y, Mabuchi T, Iwatsuki K, Elmaraghy H, Torisu-Itakura H, Morisaki Y, et al. Long-
470 term efficacy and safety of ixekizumab in Japanese patients with erythrodermic or generalized
471 pustular psoriasis: subgroup analyses of an open-label, phase 3 study (UNCOVER-J). J Eur Acad
472 Dermatol Venereol. 2019 Feb;33(2):325-32.
473 32. Yamasaki K, Nakagawa H, Kubo Y, Ootaki K, Japanese Brodalumab Study G. Efficacy and
474 safety of brodalumab in patients with generalized pustular psoriasis and psoriatic erythroderma:
475 results from a 52-week, open-label study. Br J Dermatol. 2017 Mar;176(3):741-51.
476 33. Morita A, Yamazaki F, Matsuyama T, Takahashi K, Arai S, Asahina A, et al. Adalimumab
477 treatment in Japanese patients with generalized pustular psoriasis: Results of an open-label phase 3
478 study. J Dermatol. 2018 Dec;45(12):1371-80.
479 34. Sano S, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, a human
480 interleukin-23 monoclonal antibody in Japanese patients with generalized pustular psoriasis and
481 erythrodermic psoriasis: Efficacy and safety analyses of a 52-week, phase 3, multicenter, open-label
482 study. J Dermatol. 2018 May;45(5):529-39.
483 35. Esposito M, Mazzotta A, Casciello C, Chimenti S. Etanercept at different dosages in the
484 treatment of generalized pustular psoriasis: a case series. Dermatology. 2008;216(4):355-60.
485 36. Schottelius AJ, Moldawer LL, Dinarello CA, Asadullah K, Sterry W, Edwards CK, 3rd.
486 Biology of tumor necrosis factor-alpha- implications for psoriasis. Exp Dermatol. 2004 Apr;13(4):193-
487 222.
488 37. Boehner A, Navarini AA, Eyerich K. Generalized pustular psoriasis - a model disease for
489 specific targeted immunotherapy, systematic review. Exp Dermatol. 2018 Oct;27(10):1067-77.
490 38. Saikaly SK, Mattes M. Biologics and Pediatric Generalized Pustular Psoriasis: An
491 Emerging Therapeutic Trend. Cureus. 2016 Jun 22;8(6):e652.
492 39. Almutairi D, Sheasgreen C, Weizman A, Alavi A. Generalized Pustular Psoriasis Induced by
493 Infliximab in a Patient With Inflammatory Bowel Disease. J Cutan Med Surg. 2018
494 Sep/Oct;22(5):507-10.
495 40. Viguier M, Aubin F, Delaporte E, Pages C, Paul C, Beylot-Barry M, et al. Efficacy and safety

496 of tumor necrosis factor inhibitors in acute generalized pustular psoriasis. Arch Dermatol. 2012
497 Dec;148(12):1423-5.
498 41. Wilsmann-Theis D, Schnell LM, Ralser-Isselstein V, Bieber T, Schon MP, Huffmeier U, et al.
499 Successful treatment with interleukin-17A antagonists of generalized pustular psoriasis in patients
500 without IL36RN mutations. J Dermatol. 2018 Jul;45(7):850-4.
501 42. Lee E, Zarei M, LaSenna C, Villada G, Romanelli P. Psoriasis Targeted Therapy:
502 Characterization of Interleukin 17A Expression in Subtypes of Psoriasis. J Drugs Dermatol. 2015
503 Oct;14(10):1133-6.
504 43. Bachelez H, Choon SE, Marrakchi S, Burden AD, Tsai TF, Morita A, et al. Inhibition of the
505 Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis. N Engl J Med. 2019
506 Mar 7;380(10):981-3.
507 44. Papp K, Gordon K, Thaci D, Morita A, Gooderham M, Foley P, et al. Phase 2 Trial of
508 Selective Tyrosine Kinase 2 Inhibition in Psoriasis. N Engl J Med. 2018 Oct 4;379(14):1313-21.
509 45. Akiyama M, Takeichi T, McGrath JA, Sugiura K. Autoinflammatory keratinization
510 diseases. J Allergy Clin Immunol. 2017 Dec;140(6):1545-7.
511 46. Akiyama M, Takeichi T, McGrath JA, Sugiura K. Autoinflammatory keratinization
512 diseases: An emerging concept encompassing various inflammatory keratinization disorders of the
513 skin. J Dermatol Sci. 2018 May;90(2):105-11.
514 47. Takeichi T, Akiyama M. Familial or sporadic porokeratosis as an autoinflammatory
515 keratinization disease. J Dermatol. 2019 Apr;46(4):e125-e6.
516 48. Oi R, Takeichi T, Okuno Y, Kojima D, Sugawara K, Kono M, et al. An infant with
517 generalized pustular psoriasis and geographic tongue had a heterozygous IL36RN mutation and
518 IgG2 deficiency. J Dermatol Sci. 2018 May;90(2):216-8.
519 49. Akiyama M. Early-onset generalized pustular psoriasis is representative of
520 autoinflammatory keratinization diseases. J Allergy Clin Immunol. 2019 Feb;143(2):809-10.
521 50. Setta-Kaffetzi N, Navarini AA, Patel VM, Pullabhatla V, Pink AE, Choon SE, et al. Rare
522 pathogenic variants in IL36RN underlie a spectrum of psoriasis-associated pustular phenotypes. J
523 Invest Dermatol. 2013 May;133(5):1366-9.
524 51. Hoegler KM, John AM, Handler MZ, Schwartz RA. Generalized pustular psoriasis: a review
525 and update on treatment. J Eur Acad Dermatol Venereol. 2018 Oct;32(10):1645-51.
526 52. Hussain S, Berki DM, Choon SE, Burden AD, Allen MH, Arostegui JI, et al. IL36RN
527 mutations define a severe autoinflammatory phenotype of generalized pustular psoriasis. J Allergy
528 Clin Immunol. 2015 Apr;135(4):1067-70 e9.
529 53. Arakawa A, Ruzicka T, Prinz JC. Therapeutic Efficacy of Interleukin 12/Interleukin 23
530 Blockade in Generalized Pustular Psoriasis Regardless of IL36RN Mutation Status. JAMA
531 Dermatol. 2016 Jul 1;152(7):825-8.
532 54. Johnston A, Xing X, Wolterink L, Barnes DH, Yin Z, Reingold L, et al. IL-1 and IL-36 are

533 dominant cytokines in generalized pustular psoriasis. J Allergy Clin Immunol. 2017 Jul;140(1):109-
534 20.
535 55. Campbell JJ, Ebsworth K, Ertl LS, McMahon JP, Wang Y, Yau S, et al. Efficacy of
536 Chemokine Receptor Inhibition in Treating IL-36alpha-Induced Psoriasiform Inflammation. J
537 Immunol. 2019 Mar 15;202(6):1687-92.
538 56. Jordan CT, Cao L, Roberson ED, Pierson KC, Yang CF, Joyce CE, et al. PSORS2 is due to
539 mutations in CARD14. Am J Hum Genet. 2012 May 4;90(5):784-95.
540 57. Fuchs-Telem D, Sarig O, van Steensel MA, Isakov O, Israeli S, Nousbeck J, et al. Familial
541 pityriasis rubra pilaris is caused by mutations in CARD14. Am J Hum Genet. 2012 Jul 13;91(1):163-
542 70.
543 58. Takeichi T, Sugiura K, Nomura T, Sakamoto T, Ogawa Y, Oiso N, et al. Pityriasis Rubra
544 Pilaris Type V as an Autoinflammatory Disease by CARD14 Mutations. JAMA Dermatol. 2017 Jan
545 1;153(1):66-70.
546 59. Shao S, Fang H, Zhang J, Jiang M, Xue K, Ma J, et al. Neutrophil exosomes enhance the
547 skin autoinflammation in generalized pustular psoriasis via activating keratinocytes. FASEB J. 2019
548 Jun;33(6):6813-28.
549 60. Mahil SK, Twelves S, Farkas K, Setta-Kaffetzi N, Burden AD, Gach JE, et al. AP1S3
550 Mutations Cause Skin Autoinflammation by Disrupting Keratinocyte Autophagy and Up-Regulating
551 IL-36 Production. J Invest Dermatol. 2016 Nov;136(11):2251-9.

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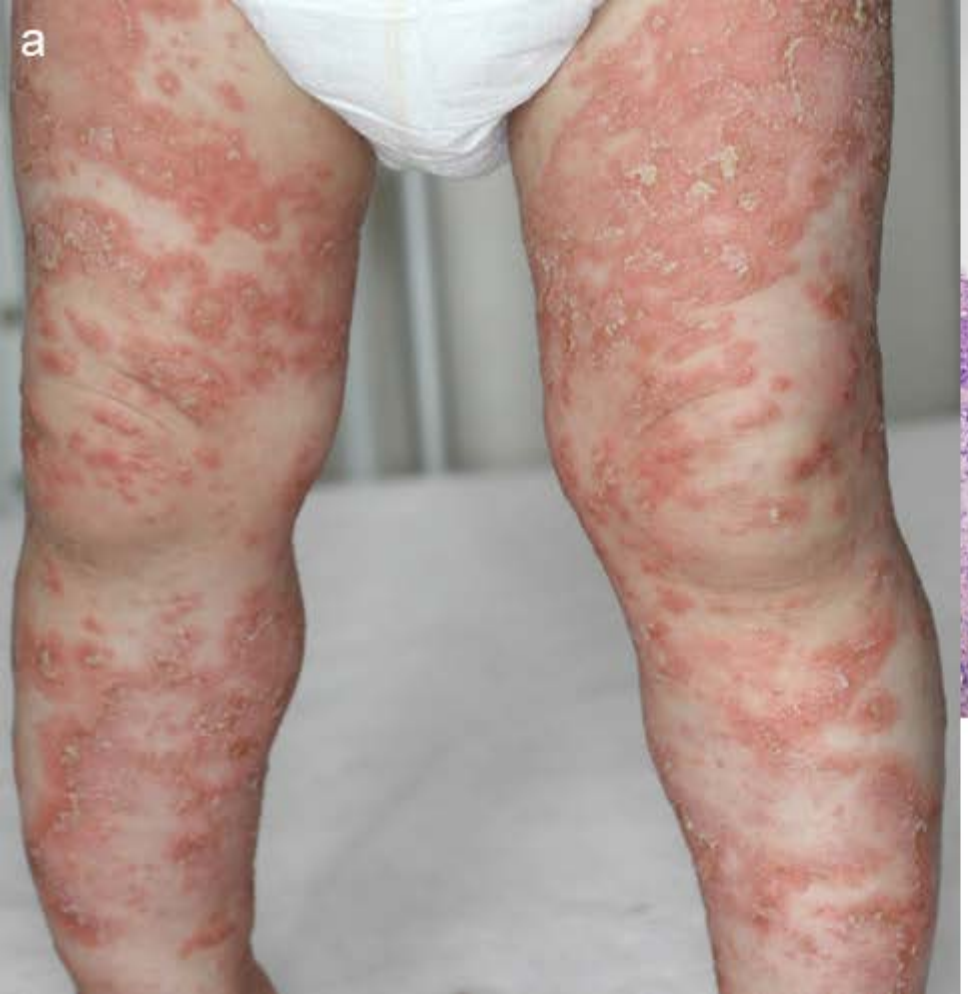
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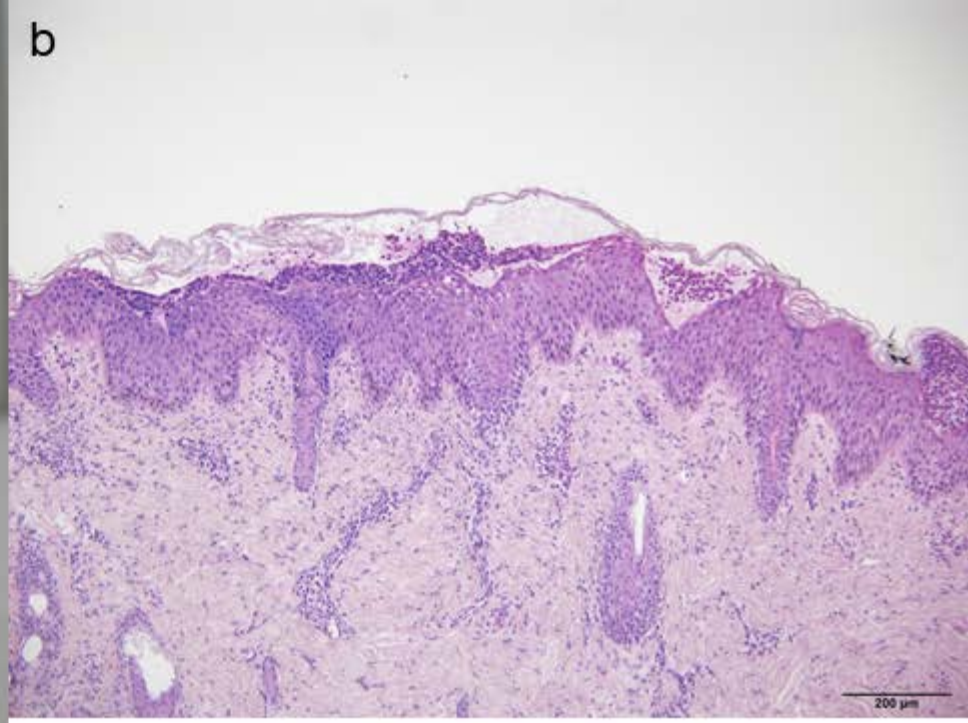
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