Generalized pustular psoriasis—Dawn of a new era in targeted immunotherapy

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Abstract

Generalized pustular psoriasis (GPP) is a rare, inflammatory skin disease characterized by recurrent flares of pustulation accompanied by systemic symptoms. Due to its acuteness, sufficient diagnosis and treatment are essential, but often face challenges. We recently overviewed various treatment options of GPP utilizing established therapies in psoriasis vulgaris (PsO). Although there is a pathogenic relation to PsO, more and more evidence suggests a predominant involvement of the innate immune system in GPP. Recent discoveries on the genetic background of GPP with underlying mutations in IL36RN, CARD14, AP1S3 and SERPINA3 contributed to a better understanding of the pathogenesis and provide major opportunities in the development of innovative, targeted therapies. The proposed umbrella term "auto-inflammatory keratinization diseases" (AIKD) helps to categorize this heterogeneous disease. Finally, we address the problem of insufficient standardized assessment tools and propose a reproducible scoring system also capturing the systemic features of GPP. In summary, GPP is a prototype disease to demonstrate both obstacles and progress in dermatology—currently insufficient definition and diagnostic tools on the one hand side, yet major advances in dissecting disease heterogeneity, opportunities for novel diagnostic techniques and therapeutic decision-making based on molecular events on the other side.

KEYWORDS

biologics, generalized pustular psoriasis, inflammatory skin diseases, targeted immunotherapy

1 | INTRODUCTION

Generalized pustular psoriasis (GPP) is a chronic, non-communicable inflammatory skin disease which can involve multiple organs and potentially lead to a fatal outcome. GPP is characterized by acute, recurrent flares of sterile pustular lesions on erythematous skin with signs of systemic inflammation also affecting extracutaneous organs. It can be associated with a pre-existing plaque psoriasis or develop independently. Due to its low prevalence, it is defined as an orphan disease.[1-3]

In our review article of 2018 "Generalized pustular psoriasis—a model disease for specific targeted immunotherapy," we presented the concept that GPP is an ideal disease to illustrate current problems in the field of inflammatory skin diseases—starting from a precise definition of this heterogeneous disease overlapping with other types of pustular diseases,[4] advances in understanding the

pathogenesis of GPP, over standardized diagnostic approaches and ultimately targeted therapies. We concluded that there was no consensus whether GPP is to be regarded a variant of psoriasis vulgaris (PsO) or a distinct clinical entity with overlapping pathological findings to PsO. Moreover, we discussed how the lack of standardized clinical criteria for diagnosis challenged the classification of GPP. We summarized that in accordance with the pathogenetic overlap to PsO, several targeted immunotherapies including anti-TNF α, anti-IL23/12 or anti-IL17 were investigated with good success in GPP.

In this viewpoint essay, we discuss how this approach has continued in the last 2 years—with novel insights into genetics and the pathogenesis of GPP, a proposed classification system, a new diagnostic assessment tool and new as well as ongoing clinical trials. Today, GPP stands exemplary for an autoinflammatory disease with high unmet medical need for disease stratification and identification of biomarkers on the way to personalized medicine.

2 | NEW LABEL FOR GPP—AN AUTOINFLAMMATORY KERATINIZATION DISEASE

In our review of 2018, we discussed the problematic definition of GPP, regarded as a subtype of psoriasis by some authors versus as a distinct clinical entity by others. We summarized that the pathogenesis of GPP partly overlaps with typical pathways of PsO, but exhibits a pronounced activation of the innate immune system. Therefore, cytokines such as IL17A, IL22, IL23, TNF and interferons are found to be elevated in both PsO and GPP. However, GPP lesions showed higher IL-1 and IL-36 expressions compared to PsO lesions.[5,6]

In 2011, Marrakchi et al laid the foundation on a new autoinflammatory perspective of GPP by discovering an underlying genetic mutation of the IL36 receptor antagonist (IL 36RN) in several cases of familiar GPP which led to the term DITRA (deficiency of IL36 receptor antagonist).[7] This missense mutation of the IL36RN results in a deficiency of IL36 receptor antagonist, an anti-inflammatory cytokine of the IL1-family, which normally antagonizes the binding of IL-36 cytokines (IL-36α, IL-36β and IL-36γ), mainly derived from keratinocytes, to the receptor and therefore inhibits downstream inflammatory pathways via NF-κB. The dis-inhibition leads to an uncontrolled binding of IL-36 to the IL36 receptor resulting in enhanced signal transduction of pro-inflammatory cytokines, for example IL-8, which is essential for the migration of neutrophils (Figure 1). [5,7,8] Data on the prevalence of DITRA in GPP patients vary significantly ranging from 23.7% to 82%, showing an association to GPP without concomitant PsO and therefore proposing a different genetic background of GPP without PsO than GPP with PsO.[9-11] In their review of 2018, Furue et al highlighted the role of IL-36 signalling in plaque psoriasis and pustular
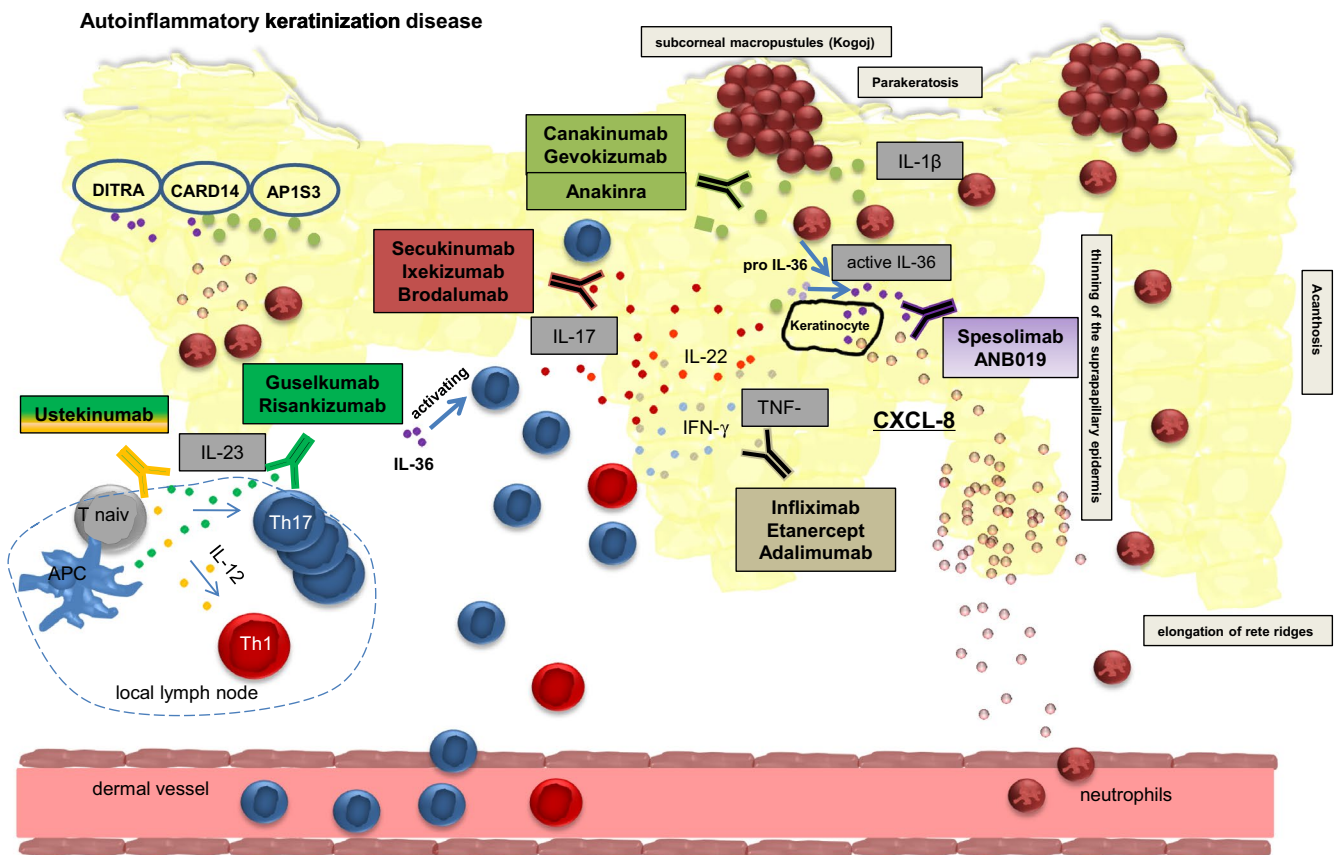

FIGURE 1 Pathogenesis and genetics of GPP (main mediators) including targets for immunotherapy. For a detailed explanation of GPP pathogenesis, we refer to our previous review of 2018.[43]

psoriasis and concluded that IL-36 is predominantly involved in the pathogenesis of pustular psoriasis, while the TNF-α/IL-23/IL-17/IL-22 axis mainly drives plaques psoriasis. However, both pathways are highly related and influence each other via a positive inflammatory loop.[12]

These findings consecutively led to a proposed classification of GPP as an autoinflammatory disease. Autoinflammation per se is characterized by sterile inflammation without pathogenic autoantibodies or auto-reactive T lymphocytes and by dysregulation of the inflammasome, a cytosolic multi-protein complex in innate immune cells. This leads to an excessive maturation and secretion of IL-1β and IL-18.[8] Patients typically present with recurrent or persistent systemic inflammation (eg fever), abdominal and chest pain and skin symptoms.[8] Classical autoinflammatory diseases present with skin symptoms such as urticarial eruptions, erythema nodosum-like lesions, pustules, pyoderma gangrenosum or erysipelas-like erythema. Typical representatives include familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), TNF receptor-associated periodic fever syndrome (TRAPS) and syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA). However, hyperkeratotic skin lesions are uncommon in autoinflammatory diseases.[13]

More recently, a subtype of pityriasis rubra pilaris (PRP), a papulosquamous skin disease, was included to the category of autoinflammatory diseases due to the identification of three different homozygous mutations in CARD14, a known activator of the pro-inflammatory nuclear factor kappa B (NF-κB).[9,14] Previously, similar mutations were identified in a subset of familial psoriasis.[14,15] The first description of a CARD14 mutation in a child with sporadic, early-onset generalized pustular psoriasis was followed by identifying a significant association between CARD14 and GPP with concomitant PsO in a small Japanese cohort in 2014.[15,16]

Today, we know that a gain-of-function mutation in caspase recruitment domain family 14 (CARD14) is an underlying mutation occurring in up to 21.1% of GPP patients with concomitant PsO.[16,17] CARD14 is mainly expressed in the epidermal layers of the skin and consequently leads to an activation of the NF-κB and mitogen-activated protein kinase (MAPK) signalling pathways which subsequently induces neutrophilic inflammation in the skin via IL-8.[9,15]

Another mutation associated with autoinflammation found in GPP patients involves the adaptor-related protein complex 1 encoding the complex subunit sigma-3 (AP1S3). This mutation results in a reduction of toll-like receptor 3 (TLR3) trafficking, therefore leading to a decreased expression of IFN-β, which normally downregulates the production of IL-1. Genetic studies indicate a prevalence of around 6% in GPP patients.[18]

More recently, a rare loss-of-function mutation in SERPINA3 has been detected in a minority of GPP patients, which also leads to an activation of neutrophils (Figure 1).[19]

However, a recent study demonstrated that known susceptibility genes can only be identified in 36% of GPP patients.[11] In general, due to the low prevalence of GPP, genetic data are based on only small numbers of patients and often include an inhomogeneous distribution

of investigated ethnicities. Therefore, currently identified mutations in GPP cannot explain the full range of GPP endotypes.[10]

The improved understanding of the genetic background of GPP and other autoinflammatory skin diseases like PRP, triggering both autoinflammation and keratinization, led to the proposal of the umbrella term "autoinflammatory keratinization diseases" (AIKD) in 2017. According to Akiyama et al, AIKD are characterized by four criteria: (a) the primary and main inflammation affects epidermis and upper dermis; (b) inflammation leads to hyperkeratosis—the main and characteristic phenotype of AIKD; (c) AIKD are caused by primary genetic factors associated with exaggerated innate immunity (autoinflammation), mainly in the epidermis and upper dermis; and (d) the spectrum of AIKD encompasses diseases with mixed pathomechanisms of autoinflammation and autoimmunity.[20] The group of AIKD currently consists of pustular psoriasis with underlying mutations in IL-36RN, CARD14 or AP1S3, Pityriasis rubra pilaris type V (CARD 14) and familial keratosis lichenoides chronica (NLRP1).[6,20] Currently, most AIKD entities are difficult to treat and severely affect quality of life. Through a better understanding of the pathophysiology of AIKD in the future, new and innovative targeted therapies might be discovered.[13]

3 | ASSESSING THE SEVERITY OF GPP IS STILL CHALLENGING

The diagnosis and management of GPP are still challenging, especially due to its episodic nature and systemic component. For the development of sufficient therapeutic strategies and the assessment of treatment response, standardized scoring systems are essential. So far, there are no validated scoring systems available. Assessment tools for GPP in clinical trials vary and are frequently adapted from those for adult PsO adding pustular criteria to established scoring systems. The generalized pustular psoriasis area and severity index (GPPASI), for instance, is an adaption of PASI for PsO, in which the induration component is exchanged with a pustular component and therefore consists of erythema, scaling and pustules combined with the percentage of body surface area affected. It provides a numeric scoring ranging from 0 to 72 (maximum).[21]

Another commonly used assessment tool for GPP is the generalized pustular psoriasis physician global assessment (GPPGA), adapted from the PGA used in psoriasis.[22] For GPPGA, all lesions are scored from 0-4 (clear-severe) regarding erythema, pustules and scaling. The final score is calculated by taking the average of the separately graded criteria.[21]

To address the problem of solely skin-based scoring systems in GPP that neglect the assessment of systemic symptoms in a systemic disease, a new PsO independent scoring tool was developed in 2014. The Japanese Dermatological Association (JDA) severity index of GPP was introduced in the GPP Medical Practice Guideline aiming for the stratification of systemic symptoms through laboratory changes. Herein, the skin is evaluated via three criteria: (a) erythema area (overall), (b) erythema area with pustules and (c) oedema

TABLE 1 Overview of assessment tools of GPP

System	Skin assessment		Systemic features		Calculation	Total maximum score
	Components	Score per item (none-severe)	Components	Score per item (min.-max.)		
GPPASI	Erythema / Scaling / Pustules	0-4	NA	NA	Σ individual score per region x body region factor x area	72
GPPGA	Erythema / Scaling / Pustules	0-4	NA	NA	Average of separately graded components	4
JDA-SI	Erythema (overall) / Erythema w. pustules / Oedema	0-3	Pyrexia / White blood cell count / CRP / Serum albumin	0-2	Sum of each component	17

Abbreviations: CRP, c-reactive protein; GPP, generalized pustular psoriasis; GPPASI, generalized pustular psoriasis area and severity index; GPPGA, generalized pustular psoriasis physician global assessment; JDA-SI, Japanese Dermatological Association severity index; max., maximum; min., minimum; NA, not available; w., with.

area. The scoring ranges from 3 to 0 (severe, moderate, mild, none) with a maximum of 9 points. Secondly, the systemic involvement is assessed via pyrexia, white blood cell count, CRP and serum albumin with scores ranging from 2 to 0 (maximum 8 points). The sum of those two categories represents the total JDA severity index score of GPP varying from severe (17-11 points), moderate (10-7 points) to mild (0-6 points).[23] (Table 1).

Stephenson et al allude to this topic on reporting on a 4-year-old Caucasian boy with an underlying mutation in IL36RN, who developed pustular lesions with systemic symptoms at the age of 2. They suggest to assess the severe extracutaneous manifestations of this autoinflammatory DITRA disease via the autoinflammatory disease activity index (AIDAI) due to its symptom overlap to other autoinflammatory diseases.[24]

AIDAI was originally developed for other inherited autoinflammatory diseases such as familial Mediterranean fever (FMF) and consists of 12 items (fever, overall symptoms, abdominal pain, nausea/vomiting, diarrhoea, headaches, chest pain, painful nodes, arthralgia or myalgia, swelling of the joints, eye manifestations and skin rash) which are scored every day with 0 (no symptoms present) or 1 (symptoms present). A monthly score ≥9 out of 372 maximum points is described as an "active disease." For the scoring of skin focussed autoinflammatory diseases, the authors propose the 15-item DITRA/Autoinflammatory Keratinization Diseases Activity Index (DITRA/AIKD-AI), which consists of AIDAI and additionally particularizes "skin rash" into pustular, plaque-type with keratinization or unspecified and adds geographic tongue as a single criterion.[24] With further future validation, this specified assessment tool could be used not only to monitor disease activity but also provide a way to measure treatment response in multiple organs.

In our opinion, DITRA/AIKD-AI presents a detailed and comprehensive assessment of symptoms in GPP which might be used within clinical trials, but lacks feasibility in daily practice due to its time-consuming documentation. Adapted scores from PsO lack the evaluation of systemic symptoms in GPP. Therefore, we favour the practicable JDA severity index to be used as a standardized assessment tool in GPP in both clinical routine and clinical trials.

4 | NOVEL THERAPEUTIC OPTIONS IN GPP

We previously summarized the various treatment options for GPP, emphasizing the role of specific targeted immunotherapies in GPP. Due to its pathological overlap, we presented well-established biologics from PsO as promising treatment options in GPP. There are published data of successful management of GPP with therapeutic antibodies directed against TNF-α (infliximab, etanercept, adalimumab), IL-12/-23 (ustekinumab) and IL-17 (secukinumab, ixekizumab, brodalumab).[23,25-36] Unlike PsO, there is no GPP-specific medication approved in Europe and the United States until today, although there is an urgent need for treatment in this potentially life-threatening disease.[37]

TABLE 2 Updated overview of targeted immunotherapy in generalized pustular psoriasis—listing each publication included in this essay and the review of 2018 with its specific drug including dose, efficacy parameters, number of patients, concomitant immunosuppressant medication and the DITRA/CARD14 status

Target	Drug	Dose	Efficacy Pustule, clearance, d	Clinical improvement
TNF-α (n = 55)	Infliximab (n = 29)	NA	2	8/10
		Like PV	NA	3/3
		Like PV	NA	4/4
		Like PV	NA	3/3
		Like PV	2	1/1
		Like PV	1	1/1
		Like PV	2	1/1
		Like PV	2	1/1
		Like PV	NA	1/1
		4-5 mg/kg bw	3	2/2
		3 mg/ kg bw	2	2/2
	Adalimumab (n = 15)	NA	17,5	2/3
		80 mg eow	NA	4/4
		Like PV	NA	1/1
		Like PV	NA	1/1
		80 mg eow	NA	2/2
		Like PV	NA	1/1
		80 mg eow	5	1/1
		40 mg ew	NA	1/1
		Like PV	5	1/1
	Etaner-cept (n = 11)	NA	18	2/4
		25-50 mg BIW	NA	6/6
		50 mg BIW	NA	0/1
IL-12/IL-23 (p40) (n = 7)	Ustekinu-mab (n = 7)	Like PV	NA	4/4
		Like PV	NA	0/1
		Like PV	NA	1/1
		Like PV	NA	1/1
IL-23 (p19) (n = 8)	Guselku-mab (n = 8)	50 mg week 0,4, e8w, dose escalation 100 mg week 20	NA	7/8
IL-1 (n = 7)	Anakinra (n = 4)	100 mg/d	NA	1/1
		100 mg/d	NA	1/1
		NA	NA	2/2
	Canaki-numab (n = 1)	150 mg e4w	NA	1/1
	Gevoki-zumab (n = 2)	60 mg e4w	NA	2/2
IL-17 (n = 32)	Broda-lumab (n = 12)	140-210 mg eow	NA	9/12
	Ixeki-zumab (n = 5)	Like PV	NA	5/5
	Sekukinumab (n = 15)	Like PA-PV	NA	10/12
		Like PV	2	1/1
		Like PV	NA	1/1
		Like PV	NA	1/1
IL-36 (n = 7)	Spesolimab (n = 7)	10 mg/kg bw iv single dose	NA	7/7

Abbreviations: BIW, biweekly; bw, body weight; CaR, case report; CaS; case series; CR, complete response; CT, clinical trial; CTP3, clinical trial phase 3; CyA, cyclosporin A; d, day; DITRA, deficiency of the IL-36 receptor [IL-36R] antagonist; eow, every other week; e4w; every four weeks; IL, interleukin; MTX, methotrexate; NA, not available; NR, no or weak response; OL, open label; PA, psoriasis arthritis; PR, partial response; PV, psoriasis vulgaris; TNF, tumor necrosis factor.

[a]Analysis at week 16, one patient discontinued the study.

[b]Analysis at week 16, one patient discontinued study due to AEBIW.

Type of clinical response	Concomitant immunosuppressant medication	[1]DITRA; [2]CARD14	Type	Author
CR (NA), PR(NA), NR (2)		[1]2/10 (2); [2]NA	CaS	Viguier M.
CR (2), PR (1)		NA	CaS	Poulalhon N.
PR(2), CR (2)		NA	CaS	Matsumoto, A
CR (3)		[1]2/3 (2); [2]NA	CaS	Sugiura K.
PR		NA	CaR	Chandran N.
PR		NA	CaR	Smith N.
PR		NA	CaR	Newland M.
CR		NA	CaR	Schmick K.
CR	Acitretin 35 mg/d	NA	CaR	Tang M.
CR (2)	Prednisolon 30 mg/d (1)	NA	CaR	Weishaupt C
PR(1), CR(1)	Acitretin 20 mg/d (1)	NA	CaR	Kim H.
CR (NA), PR(NA), NR (1)		[1]1/3 (1); [2]NA	CaS	Viguier M.
PR(2), CR (2)		NA	CaS	Matsumoto A.
CR	CyA 400 mg/d and MTX 20 mg/w	NA	CaR	Callen J.
CR	Acitretin 50 mg/d	NA	CaR	Gallo E.
PR(2)	MTX 5 mg/d	NA	CaR	Kawakami H.
PR		[1]1/1 (1); [2]NA	CaR	Huffmeier U.
CR		NA	CaR	Kimura U.
CR		NA	CaR	Zangrilli A.
CR	MTX 10 mg/d	NA	CaR	Gkalpakiotis S.
CR (NA), PR(NA), NR (2)		[1]2/4 (1); [2]NA	CaS	Viguier M.
CR (6)		NA	CaS	Esposito M.
NR		[1]1/1; [2]NA	CaR	Huffmeier U.
CR (4)	Acitretin 10-20 mg/d (3)	[1]1/4; [2]NA	CaS	Arakawa A.
NR		NA	CaR	Matsumoto A.
CR	CyA	NA	CaR	Storan E.
CR		NA	CaR	Dauden E.
CR (4), PR (3), NR (1)		NA	CTP3 (OL)	Shigetoshi S.
PR	Prednisolon	[1]1/1 (1); [2]NA	CaR	Huffmeier U.
PR	Prednisolon 10 mg/d	[1]0/1; [2]NA	CaR	Skendros P.
CR (NA), PR(NA),	NA	[1]1/2 (1); [2]NA	CaR	Viguier M.
CR	Hydroxyurea, Prednisolon	[1]0/1; [2]NA	CaR	Skendros P.
PR (2)		NA	CT (OL)	Mansouri B.
CR(6), PR(3), NR(2)[b]	Retinoid (1)	NA	CTP3 (OL)	Yamasaki K.
CR (2), PR (3)	Prednisolon < 10 mg/d (NA)	NA	CTP3 (OL)	Saeki H.
CR(9), PR(1), NR(1)[a]	CyA (4), Etretinate (3), MTX (1), Prednisolon (1);	NA	CTP3 (OL)	Imafuku S.
CR	MTX	NA	CaR	Böhner A.
CR		NA	CaR	Mugheddu C.
CR		NA	CaR	Polesie S.
CR (7)	MTX (1)	[1]3/7 (3); [2]1/7 (1)	CTP1 (OL)	Bachelez H.

In 2017, guselkumab, an IL23-p19 antibody, was approved for the treatment of PsO.[38] One multicentre, open-label, phase-3 study reports on 10 Japanese GPP patients treated with this monoclonal IL-23 antibody at week 0, 4 and then every 8 weeks. Five out of 10 patients showed successful treatment, defined as improvement of the Global Impression Score within the first week, consecutively leading to a 100% success rate in the patients who completed the study (8/10) at week 52, demonstrating efficacy without safety concerns.[39] Currently, there is an ongoing phase-3 trial investigating the efficacy of risankizumab, another anti-IL23-p19 antibody, in GPP patients. Safety was already proven, but publication of efficacy data is still pending.[40,41]

Since the discovery of the IL36RN mutation in GPP, therapies targeting autoinflammation via inhibition of the inflammasome were followed. Initial studies investigated antibodies targeting IL-1β or the IL-1 receptor (canakinumab, gevokizumab, anakinra) in the treatment of GPP.[33,34,36] More recently, a better understanding of the pathogenesis and the genetics of GPP paved the way for the development of specific therapies targeting IL-36.

Published results from a phase-I proof-of-concept study with BI655130 (spesolimab), a monoclonal antibody against the IL-36 receptor, demonstrated a response in all 7 patients after a single intravenous dose. The clinical endpoint (Physician global assessment, PGA 0 or 1 at a five point scale) was achieved in 5 patients during the first week and in all patients by week 4 and maintained over a 20-week period. Interestingly, similar to previous reports on anti-IL-1 treatment in GPP, efficacy was shown regardless of the genetic mutation status, since only 4 patients had an identified homozygous IL36-RN-mutation and 1 patient had a mutation in CARD14[21] (Table 2). Spesolimab is currently investigated in phase-III clinical trials, without published data so far.

Another humanized monoclonal IL-36-receptor antibody, ANB019, is also currently scrutinized in a clinical trial for GPP.[42]

Table 2 presents an update on the detailed overview of our review from 2018 listing each publication including its specific biologic with dose, efficacy parameters, number of patients, concomitant immunosuppressant medication and the DITRA/CARD14 status.[43]

As discussed in our previous review, there is a potential source of selection bias, since due to the higher prevalence, most of the published cases include Asian patients, exhibiting a different genetic background and therefore results might not apply to other ethnicities. Additionally, in contrast to, for example, Japan, there are no approved biologics for GPP in Europe.

5 | THE FUTURE: DISEASE STRATIFICATION BY IDENTIFICATION OF BIOMARKERS?

Advances in our knowledge of genetic variants of GPP, the interaction of autoinflammation and clinical phenotypes, and numerous therapeutic options to treat GPP set the ground for a future of precision medicine in the field. Today, we have opportunities to treat GPP by targeting IL-23, IL-17, TNF-α, IL-1 α/β or IL-36 either blocking the cytokines directly or via their receptors. However, in contrast to PsO, all so far published studies in GPP are one-armed, uncontrolled, open-labelled trials with only a small number of patients and some targets are solely investigated in case reports and case series. Although applying those novel, cost-demanding biologics in GPP comes with good chance to relieve the patient almost completely from disease symptoms, selecting the right treatment for an individual patient remains challenging. Due to the lack of specific objective biomarkers, it is currently impossible to predict the therapeutic response of a given biologic in GPP.

In chronic inflammatory skin diseases, numerous efforts are currently undertaken to identify molecular biomarkers for improving diagnostics, assess disease severity and stratify patients according to chances of therapeutic response.[44-46] For instance, HLA-C*06:02 genotype has been identified as a biomarker of biologic treatment response in psoriasis predicting the response chances between ustekinumab and adalimumab.[47]

In the era of autoinflammatory keratinization diseases, the CARD14 mutation has recently been proposed as a biomarker predicting therapy response to ustekinumab in familial PRP.[48,49] Yet, so far biomarkers investigated in GPP like CRP are rather unspecific and solely monitor disease activity.[50] More recently, plasma retinol has been suggested as a predictive biomarker of disease activity and response to acitretin,[51] a conventional treatment option in GPP with rather moderate efficacy. In this study, Yang et al present a significant reduction of plasma retinol levels in GPP patients compared to patients with PsO, which correlated negatively with disease severity. Moreover, response to treatment with acitretin, defined as the reduction of PASI, correlated with an increase of plasma retinol levels.[51]

The oligogenic rather than monogenic inheritance in GPP suggests that even more genetic disorders may underlie the pathogenesis of GPP. This is highlighted by the fact that IL-36 antagonizing biologics succeed even in patients without an identified mutation in relevant genes. Since the genetic background of GPP already indicates differences between GPP with and without concomitant PsO, further studies are needed to explore their role as biomarkers in disease stratification and prediction of therapeutic response. The Pustular Psoriasis Elucidating Underlying Mechanisms (PLUM) study is currently investigating genetic features and associated biomarkers which may complete the understanding of the GPP pathomechanism and lead to an individual-based, personalized targeted medicine in the future.[37]

In summary, more and more genetic and expression biomarkers are proposed to define GPP, assess its severity, or predict therapeutic response. On the other hand, our understanding of the underlying pathogenesis of GPP improves and numerous therapeutic options are available. Once we succeed to implement biomarkers into our therapeutic strategy at an individual patient's level, GPP can become a driving disease on the way to precision medicine in (auto-)inflammatory skin diseases.

CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Dr(s) RN, KE and AB had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RN and AB conceived and designed the study. RN acquired, analysed and interpreted the data. R.N and AB drafted the manuscript. KE and AB critically revised the manuscript for important intellectual content. AB supervised the study. All authors have read and approved the final manuscript.

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REFERENCES

[1] B. D. Zelickson, S. A. Muller, *Arch Dermatol* **1991**, *127*, 1339.
[2] F. Augey, P. Renaudier, J. F. Nicolas, *Eur J Dermatol* **2006**, *16*, 669.
[3] S. E. Choon, N. M. Lai, N. A. Mohammad, N. M. Nanu, K. E. Tey, S. F. Chew, *Int J Dermatol* **2014**, *53*, 676.
[4] A. A. Navarini, A. D. Burden, F. Capon, U. Mrowietz, L. Puig, S. Köks, K. Kingo, C. Smith, J. N. Barker, *J Eur Acad Dermatol Venereol* **2017**, *31*, 1792.
[5] A. Johnston, X. Xing, L. Wolterink, D. H. Barnes, Z. Q. Yin, L. Reingold, J. M. Kahlenberg, P. W. Harms, J. E. Gudjonsson, *J Allergy Clin Immunol* **2017**, *140*, 109.
[6] T. Takeichi, M. Akiyama, *Am J Clin Dermatol* **2020**, *21*, 227.
[7] S. Marrakchi, P. Guigue, B. R. Renshaw, A. Puel, X.-Y. Pei, S. Fraitag, J. Zribi, E. Bal, C. Cluzeau, M. Chrabieh, J. E. Towne, J. Douangpanya, C. Pons, S. Mansour, V. Serre, H. Makni, N. Mahfoudh, F. Fakhfakh, C. Bodemer, J. Feingold, S. Hadj-Rabia, M. Favre, E. Genin, M. Sahbatou, A. Munnich, J.-L. Casanova, J. E. Sims, H. Turki, H. Bachelez, A. Smahi, *New England J Med* **2011**, *365*, 620.
[8] R. Papa, P. Picco, M. Gattorno, *Adv Protein Chem Struct Biol* **2020**, *120*, 1.
[9] K. Sugiura, *J. Dermatol. Sci.* **2014**, *74*, 187.
[10] S. Twelves, A. Mostafa, N. Dand, E. Burri, K. Farkas, R. Wilson, H. L. Cooper, A. D. Irvine, H. H. Oon, K. Kingo, S. Köks, U. Mrowietz, L. Puig, N. Reynolds, E.-T. Tan, A. Tanew, K. Torz, H. Trattner, M. Valentine, S. Wahie, R. B. Warren, A. Wright, Z. Bata-Csörgő, M. Szell, CEM Griffiths, A. D. Burden, S.-E. Choon, C. H. Smith, J. N. Barker, A. A. Navarini, F. Capon, *J Allergy Clin Immunol* **2019**, *143*, 1021.
[11] R. Mössner, D. Wilsmann-Theis, V. Oji, P. Gkogkolou, S. Löhr, P. Schulz, A. Körber, J. C. Prinz, R. Renner, K. Schäkel, L. Vogelsang, K.-P. Peters, S. Philipp, K. Reich, H. Ständer, A. Jacobi, A. Weyergraf, K. Kingo, S. Köks, S. Gerdes, K. Steinz, T. Schill, K. G. Griewank, M. Müller, S. Frey, L. Ebertsch, S. Uebe, M. Sticherling, H. Sticht, U. Hüffmeier, *Br J Dermatol* **2018**, *178*, 740.
[12] K. Furue, K. Yamamura, G. Tsuji, C. Mitoma, H. Uchi, T. Nakahara, M. Kido-Nakahara, T. Kadono, M. Furue, *Acta Dermato Venereologica* **2018**, *98*, 5.
[13] M. Akiyama, T. Takeichi, J. A. McGrath, K. Sugiura, *J Dermatol Sci* **2018**, *90*, 105.
[14] D. Fuchs-Telem, O. Sarig, M. A. M. van Steensel, O. Isakov, S. Israeli, J. Nousbeck, K. Richard, V. Winnepenninckx, M. Vernooij, N. Shomron, J. Uitto, P. Fleckman, G. Richard, E. Sprecher, *Am J Hum Genet* **2012**, *91*, 163.
[15] C. T. Jordan, L. I. Cao, E. D. O. Roberson, K. C. Pierson, C.-F. Yang, C. E. Joyce, C. Ryan, S. Duan, C. A. Helms, Y. Liu, Y. Chen, A. A. McBride, W.-L. Hwu, J.-Y. Wu, Y.-T. Chen, A. Menter, R. Goldbach-Mansky, M. A. Lowes, A. M. Bowcock, *Am J Hum Genet* **2012**, *90*, 784.
[16] K. Sugiura, M. Muto, M. Akiyama, *J Invest Dermatol* **2014**, *134*, 1755.
[17] Z. Li, Q. Yang, S. Wang, *Medicine* **2018**, *97*, e11741.
[18] N. Setta-Kaffetzi, M. A. Simpson, A. A. Navarini, V. M. Patel, H.-C. Lu, M. H. Allen, M. Duckworth, H. Bachelez, A. D. Burden, S.-E. Choon, CEM Griffiths, B. Kirby, A. Kolios, MMB Seyger, C. Prins, A. Smahi, R. C. Trembath, F. Fraternali, C. H. Smith, J. N. Barker, F. Capon, *Am J Hum Genet* **2014**, *94*, 790.
[19] S. Frey, H. Sticht, D. Wilsmann-Theis, A. Gerschütz, K. Wolf, S. Löhr, S. Haskamp, B. Frey, M. Hahn, A. B. Ekici, S. Uebe, C. Thiel, A. Reis, H. Burkhardt, F. Behrens, M. Köhm, J. Rech, G. Schett, G. Assmann, K. Kingo, S. Köks, R. Mössner, J. C. Prinz, V. Oji, P. Schulz, L. E. Muñoz, A. E. Kremer, J. Wenzel, U. Hüffmeier, *J Invest Dermatol* **2020**, *140*, 1451.
[20] M. Akiyama, T. Takeichi, J. A. McGrath, K. Sugiura, *J Allergy Clin Immunol* **2017**, *140*, 1545.
[21] H. Bachelez, S. E. Choon, S. Marrakchi, *N Engl J Med* **2019**, *380*, 981.
[22] R. G. Langley, S. R. Feldman, J. Nyirady, P. van de Kerkhof, C. Papavassilis, *J Dermatolog Treat* **2015**, *26*, 23.
[23] A. Morita, F. Yamazaki, T. Matsuyama, *J Dermatol.* **2018**, *45*, 1371.
[24] C. Stephenson, V. H. Prajapati, C. Hunter, P. Miettunen, *Pediatr Dermatol* **2020**, *37*, 670.
[25] M. Viguier, F. Aubin, E. Delaporte, *Arch Dermatol* **2012**, *148*, 1423.
[26] N. S. Chandran, W. S. Chong, *Aust. J. Dermatol* **2010**, *51*, 29.
[27] A. Matsumoto, M. Komine, M. Karakawa, M. Kishimoto, M. Ohtsuki, *J Dermatol* **2017**, *44*, 202.
[28] S. Gkalpakiotis, P. Arenberger, P. Gkalpakioti, *J Eur Acad Dermatol Venereol* **2015**, *29*, 2063.
[29] C. E. Griffiths, B. E. Strober, P. van de Kerkhof, *New Engl J Med* **2010**, *362*, 118.
[30] A. Arakawa, T. Ruzicka, J. C. Prinz, *JAMA Dermatol* **2016**, *152*, 825.
[31] E. R. Storan, S. M. O'Gorman, T. Markham, *Clin Exp Dermatol* **2016**, *41*, 689.
[32] R. G. Langley, B. E. Elewski, M. Lebwohl, K. Reich, C. E. M. Griffiths, K. Papp, L. Puig, H. Nakagawa, L. Spelman, B. Sigurgeirsson, E. Rivas, T.-F. Tsai, N. Wasel, S. Tyring, T. Salko, I. Hampele, M. Notter, A. Karpov, S. Helou, C. Papavassilis, *N Engl J Med* **2014**, *371*, 326.
[33] U. Huffmeier, M. Watzold, J. Mohr, M. P. Schon, R. Mossner, *Br J Dermatol* **2014**, *170*, 202.
[34] P. Skendros, C. Papagoras, I. Lefaki, A. Giatromanolaki, I. Kotsianidis, M. Speletas, I. Bocly, I. Theodorou, V. Dalla, K. Ritis, *Br J Dermatol* **2017**, *176*, 212.
[35] M. Viguier, P. Guigue, C. Pages, A. Smahi, H. Bachelez, *Ann Intern Med* **2010**, *153*, 66.
[36] B. Mansouri, L. Richards, A. Menter, *Br J Dermatol* **2015**, *173*, 239.
[37] M. J. Gooderham, A. S. Van Voorhees, M. G. Lebwohl, *Expert Rev Clin Immunol* **2019**, *15*, 907.
[38] Z. Z. Yiu, R. B. Warren, *Immunotherapy* **2018**, *10*, 67.
[39] S. Sano, H. Kubo, H. Morishima, R. Goto, R. Zheng, H. Nakagawa, *J Dermatol* **2018**, *45*, 529.
[40] A. Khatri, D. Eckert, A. Oberoi, A. Suleiman, Y. Pang, L. Cheng, A. A. Othman, *J Clin Pharmacol* **2019**, *59*, 1656.
[41] A study to assess efficacy and safety of two different dose regimens of Risankizumab administered subcutaneously in Japanese subjects with generalized pustular psoriasis or erythrodermic psoriasis. ClinicalTrials.gov Identifier: NCT03022045.
[42] A study to evaluate the efficacy and safety of ANB019 in subjects with generalized pustular psoriasis (GPP). ClinicalTrials.gov Identifier NCT03619902.

[43] A. Boehner, A. A. Navarini, K. Eyerich, *Exp Dermatol* **2018**, *27*, 1067.

[44] K. Eyerich, S. Eyerich, *J Eur Acad Dermatol Venereol.* **2018**, *32*, 692.

[45] N. Garzorz-Stark, L. Krause, F. Lauffer, A. Atenhan, J. Thomas, S. P. Stark, R. Franz, S. Weidinger, A. Balato, N. S. Mueller, F. J. Theis, J. Ring, C. B. Schmidt-Weber, T. Biedermann, S. Eyerich, K. Eyerich, *Exp Dermatol* **2016**, *25*, 767.

[46] F. Lauffer, M. Jargosch, L. Krause, N. Garzorz-Stark, R. Franz, S. Roenneberg, A. Böhner, N. S. Mueller, F. J. Theis, C. B. Schmidt-Weber, T. Biedermann, S. Eyerich, K. Eyerich, *J Invest Dermatol* **2018**, *138*, 1785.

[47] N. Dand, M. Duckworth, D. Baudry, A. Russell, C. J. Curtis, S. H. Lee, I. Evans, K. J. Mason, A. Alsharqi, G. Becher, A. D. Burden, R. G. Goodwin, K. McKenna, R. Murphy, G. K. Perera, R. Rotarescu, S. Wahie, A. Wright, N. J. Reynolds, R. B. Warren, CEM Griffiths, C. H. Smith, M. A. Simpson, J. N. Barker, M. Benham, S. Hussain, B. Kirby, L. Lawson, K. McElhone, A. Ormerod, C. Owen, M. R. Barnes, P. Di Meglio, R. Emsley, A. Evans, K. Payne, D. Stocken, *J Allergy Clin Immunol* **2019**, *143*, 2120.

[48] S. M. Lwin, C. K. Hsu, L. Liu, H. Y. Huang, N. J. Levell, J. A. McGrath, *Br J Dermatol* **2018**, *178*, 969.

[49] L. M. Nieto-Benito, O. Baniandrés-Rodríguez, A. Moreno-Torres, A. Hernández-Martín, A. Torrelo-Fernández, M. Campos-Domínguez, *J Eur Acad Dermatol Venereol.* https://doi.org/10.1111/jdv.16548. Online ahead of print.

[50] S. Wang, Z. Xie, Z. Shen, *An Bras Dermatol* **2019**, *94*, 542.

[51] H. Yang, Q. Tan, G. H. Chen, J. S. Chen, Z. Fu, F. L. Ren, X. Y. Luo, H. Wang, *J Eur Acad Dermatol Venereol.* **2020**, *34*, 16244.