

Review Article

Interleukin-36 and Generalized Pustular Psoriasis: A Narrative Review of the Role of IL-36 in Generalized Pustular Psoriasis and an Update on Treatments

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Abstract

Generalized Pustular Psoriasis (GPP) is one of the rare variants of Psoriasis vulgaris. It can be life-threatening, especially in pregnant women or in a setting of multiple co-morbidities. The pathophysiology of chronic plaque psoriasis is well known, however, that of GPP has been the subject of debate and research until recently with the identification of certain genetic mutations and inflammatory mediators. Traditionally, the same treatments for Chronic plaque psoriasis have been used to treat GPP, with variable success, which led to investigations into the pathobiology of GPP. The recent identification of the role of interleukin-36 and its receptor has led to an understanding of the pathophysiology of the disease. This knowledge has allowed the development of novel biologic treatments that target interleukin-36 inflammatory pathways and could revolutionize how dermatologists manage GPP. In this review, we discuss the role of interleukin-36 in GPP and its treatment.

Keywords: Interleukin-36; IL-36; Generalized Pustular Psoriasis; Imsidolimab; Spesolimab

Introduction

Generalized Pustular Psoriasis (GPP) is a rare variant of psoriasis. This can occur as a first presentation of psoriasis or as a change in the morphology of the lesions in patients with chronic plaque psoriasis [1]. GPP is more common in women than in men or children [2]. It is multi-systemic and can be life-threatening in a setting of pregnancy or multiple co-morbidities [3]. GPP has an annual prevalence of 1.76 per 1,000,000 persons in France in 2004 to 1.53 per 100,000 in Sweden in 2015 and a point prevalence from 7.46 per 1,000,000 persons in Japan (1983 - 1989) to 9.1 per 100,000 persons in Sweden (2004-2015) [4-6].

GPP presents clinically with either relapsing or persistent widespread sterile pustules with or without accompanying systemic symptoms and is associated with significant morbidity and mortality. This systemic involvement could include fever, acute kidney injury, acute respiratory distress syndrome, heart failure and sepsis [7]. Studies have also reported mortality rates associated with GPP in the range of 2-8% [8].

In conducting this narrative review of interleukin 36 and its role in GPP we performed an online literature search. The search was implemented by searching the terms, Generalized Psoriasis, GPP, generalized pustular psoriasis, pustular psoriasis,

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Interleukin 36, IL-36, IL-36 inhibitors, Interleukin 36 inhibitors, treatments for GPP and Pustular psoriasis in PubMed, Embase and Medline.

Clinical Features of Generalized Pustular Psoriasis

GPP is a rare, severe skin condition characterized by the appearance of widespread sterile pustules on non-acral skin which may or may not be associated with signs and symptoms of systemic inflammation. It has been reported that approximately 65% of patients with GPP have had a prior diagnosis of Chronic plaque psoriasis before they developed GPP [9]. The European Rare and Severe Psoriasis Expert Network has explained that the clinical course of GPP could be relapsing, at least once or persistent for more than 3 months [7]. Flares in GPP can occur autonomously but can be triggered by the use or sudden withdrawal of oral corticosteroids, hypocalcaemia, emotional stress, withdrawal of cyclosporin, antibiotics, infections and pregnancy amongst other triggers. Paradoxical GPP has also been reported following the initiation of psoriasis treatments such as methotrexate, ustekinumab and tumor necrosis factor- α (TNF- α) [7,10].

Leucocytosis, elevated liver enzymes, elevated ESR and C-Reactive Proteins (CRP) are also typical findings in the laboratory tests of patients with GPP. Other variants of pustular psoriasis include localized forms like Palmoplantar pustular psoriasis and acrodermatitis continua of Hallopeau [1,9,11]. Skin histology of GPP is characterized by the typical features of acanthosis, parakeratosis and accumulation of dermal neutrophilic inflammatory infiltrates with dense epidermal neutrophilic infiltrates forming pustules [1].

Interleukin-36 in the Pathophysiology of Pustular Psoriasis and Clinical Variants

The exact pathophysiologic mechanism of GPP had remained unknown until recently. Advances in our understanding of the biology and genetic mechanisms of autoinflammation and autoimmunity led to the characterization of critical genetic mutations associated with the incidence and pathogenesis of GPP. These include mutations in the genes for Interleukin 36 receptor (IL36RN), Caspase recruitment domain-containing protein 14 (CARD-14) and Myeloperoxidase (MPO) [1].

Central to this pathogenetic basis of GPP is interleukin 36 (IL-36). The IL-36 cytokines IL-36 α , IL-36 β , IL-36 γ and IL-36 receptor antagonist (IL-36Ra) - which are part of the IL-1 family are expressed in a variety of cell types including keratinocytes. The activation of the interleukin 36 receptor (IL 36R) by these interleukins leads to the activation of inflammatory pathways, causing the release of chemokines which activate macrophages, neutrophils, T-cells and other inflammatory cells. IL36N gene encodes for IL-36Ra which suppresses the pro-inflammatory responses triggered by IL-36 α , IL-36 β and IL-36 γ . A mutation in the IL36N gene leads to an exaggeration of the downstream IL-36 signaling, this mutation is more commonly a loss of function mutation [12,13].

Most notably, IL36RN mutations have been identified in cases of sporadic and familial GPP from around the world [14]. These loss-of-function mutations in the IL-36 receptor antagonists result in the hyperactivation of IL-36 signaling due to the unopposed stimulation of the IL-36 receptor by its ligands, IL-36 α , IL36 β and IL-36 γ . The increased production of IL-36 induces the production of chemokines by keratinocytes, leading to neutrophil accumulation in the epidermis; which drives the pathogenesis of GPP and the formation of the characteristic pustules seen in GPP [15-17]. Research has also found a positive correlation between IL-36 γ expression and the disease activity of chronic plaque psoriasis which was suppressed by TNF- α inhibitors [17]. Studies have found that the IL36RN mutations are more common in patients with GPP especially those without a concomitant diagnosis of chronic plaque psoriasis [18,19]. In the GPP cohorts, IL36RN mutations have been found to occur between 23% and 37% of the cases. DITRA (deficiency of IL-36Ra) is the name given to the condition seen in patients with acute GPP and IL36RN mutations that resulted in decreased IL-36Ra activity; high fevers and malaise are common features of flares in this GPP cohorts. In a meta-analysis of 233 patients with GPP, it was discovered that the presence of recessive IL36RN alleles, which were found in 21% of cases, was linked to early disease onset in people without pathogenic IL36RN alleles, systemic inflammation and the absence of concurrent plaque psoriasis [18,20]. Although IL-36RN alleles are mostly inherited in an autosomal recessive pattern, there are cases of GPP occurring in patients with single heterozygous mutations [7].

Gene expression studies have also shown that the GPP transcriptomes share some characteristics with chronic plaque psoriasis but the inflammatory process in GPP is an innate immune response rather than an adaptive immune response which plays a

central role in chronic plaque psoriasis [21,22]. Pustular psoriasis is also thought to develop as a result of functional IL-36R activation and loss-of-function mutation of IL-36Ra, whereas plaque psoriasis develops as a result of the TNF-/IL-23/IL-17/IL-22 axis [1,21].

Traditional Treatments for Generalised Pustular Psoriasis

Neither the United Kingdom (UK) nor Europe has licensed any GPP-specific therapies as of now. With the exception of Japan, where several biologics, including the TNF α inhibitors adalimumab, infliximab and certolizumab pegol; the IL-17/IL-17R inhibitors secukinumab, brodalumab and ixekizumab; and the IL-23 inhibitors risankizumab and guselkumab, are currently approved for the treatment of GPP [10,24,25]. Taiwan and Thailand have also approved brodalumab for the treatment of GPP [24,25].

Standard systemic treatment for GPP in clinical practice includes acitretin, cyclosporin, methotrexate, or a biological agent with a rapid onset of action. Acitretin is an effective treatment for GPP, although it has a dose-dependent side effect profile; it is teratogenic and should be avoided in pregnant or childbearing women [26]. According to a recent systematic review of 101 cases of GPP in published literature who had received targeted immunotherapy, it was reported that the most common treatment they received prior to or in addition to their targeted therapy were cyclosporin and retinoids, followed by methotrexate and oral corticosteroids [27]. Other systemic agents for GPP reported in case reports include apremilast and dapsone [28,29]. If there are no other systemic options clinicians have resorted to systemic corticosteroids with a slow weaning regimen to avoid triggering a flare of pustular psoriasis on rapid withdrawal. Topical corticosteroids and topical calcineurin inhibitors are also effective treatments for localized disease or adjuncts to systemic therapy in patients with widespread disease.

In pregnant women and lactating females, data on the treatment options for GPP are comparatively limited. Treatment options include cyclosporin (at a reduced dose), oral corticosteroids, topical agents and phototherapy with narrow-band UV-B [30].

Emerging Treatment Options for Generalized Pustular Psoriasis

The identification of IL-36 signaling as a key player in the pathobiology of GPP has led to the development of specific biologic therapies for GPP which target the IL-36 signalling pathway. Spesolimab, a humanized monoclonal antibody targeting the IL-36 receptor, was studied in a phase 2 clinical trial for its effectiveness in treating flares of GPP. This was following a successful proof-of-concept in 2019 in GPP patients with and without the homozygous IL36RN mutation [31,32]. In the Effisayil 1 trial, 53 patients with GPP flare were randomly assigned in a 2:1 ratio to receive either a single dose of Spesolimab (900 mg) intravenously or placebo on day 1. The patients in both treatment and control groups were also able to receive an open-label dose of Spesolimab on day 8, another open-label dose after day 8 as a rescue therapy, or both and are then followed up for 12 weeks. At the end of the first week of treatment, just above half of the patients (19 of 35) who received Spesolimab had complete clearance compared to just 6% of the patients in the control group (1 out of 18). Forty-three percent (43%) of the patients in Spesolimab group also had a reduction in their Generalized Pustular Psoriasis Physician Global Assessment score (GPPGA) score compared to 11% in the placebo group. This showed that the treatment was very effective for GPP. Spesolimab was associated with an increased risk of infection and pyrexia by 12 weeks the percentage of participants with an infection was 46% of patients who had at least one dose of spesolimab, although there was no particular pattern to the nature of the organism or site affected [32]. There have been two incidences of spesolimab-related Drug Response with Eosinophilia and Systemic Symptoms (DRESS) in patients. DRESS, or severe cutaneous adverse drug reaction, is most frequently brought on by a small number of medications, including allopurinol, anticonvulsants and antibiotics. It was eventually ruled out to be DRESS-related in both instances following external investigations; in one case a flare of GPP caused the observed rash, while in the other case, it was attributed to spiramycin, an antibiotic received by the patient prior to the onset of the symptoms [33].

Based on the results of the above trial and subsequent phase 3 clinical trials, Spesolimab was granted FDA approval in September 2022 for use in the USA. It also received approval in Japan following this in October 2022 for treating flares of GPP and gained positive opinion from the EU regulators in October 2022 [34].

Imsidolimab is another GPP treatment that has shown promise in recent phase 2 clinical trials. In the GALLOP Trial, the IL-36 receptor antibody was administered in the open-label, single-arm, multiple-dose trial to patients with GPP to study its efficacy,

tolerability and safety. In the study, eight patients received a single dose of Intravenous Imsidolimab (750 mg), followed by the administration of three doses of 100 mg of Imsidolimab on days 29, 57 and 87 respectively. Most patients showed rapid improvement in symptoms and GPPGA scores as early as day 3 through day 113 with minimal, mild adverse effects. The medication was well tolerated by all participants. Imsidolimab shows promise for GPP, but it would require more robust clinical trials to further demonstrate clinical efficacy and safety. Based on the above results, double-blinded, placebo-controlled, randomized, multicentre phase 3 trials are currently ongoing [35]. No mortality or early termination of treatment due to treatment-related adverse events were reported. However, three-quarters of the participants reported at least one treatment-related adverse event, including blood and lymphatic system disorders; gastrointestinal disorders; infections and infestations, respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders. One patient suffered a mild flare of plaque psoriasis, while the second patient experienced a mild sore throat. These two patients both reported treatment-related adverse reactions that were assessed to be moderate in severity and likely connected to the study drug treatment. Infusion site responses or injection site reactions were not reported by any patients [35].

Conclusion

GPP is a rare and potentially fatal form of psoriasis with limited effective therapies. The identification of the role of IL-36 receptor signaling in the pathobiology of GPP has presented dermatologists with a rare opportunity to develop targeted biologic therapies for GPP.

Conflict of Interest

The authors have no conflict of interest to declare.

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