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Review Article

Spesolimab: A Novel Interleukin-36 Receptor Monoclonal Antibody for the Treatment of Generalized Pustular Psoriasis

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A B S T R A C T

Psoriasis is an autoimmune condition affecting multiple organs in the body (joints, cardiovascular, and central nervous system), especially the skin. Psoriasis is characterized by inflammation, epidermal hyperproliferation, and aberrant epidermal differentiation. One of the uncommon types of psoriasis is generalized pustular psoriasis (GPP) which is uncommon and associated with increased severity and systemic complications. Early diagnosis is the crucial step in treating GPP to manage its life-threatening complications. Pathogenesis of GPP is still under research. The treatment of GPP aims for symptomatic relief, to remove skin lesions, and to provide supportive care. However, there are no specific guidelines or therapeutic options and it mostly depends on the clinician's opinion that often follows for plaque psoriasis. Accumulating data revealed that the interleukin-36 (IL-36) pathway plays a major role and signaling to favor the pro-inflammatory activity, which is critical in the pathogenesis of GPP, thus starting the maneuver of development of targeted biological therapies for the disease. This article reviews the role of IL-36 in the pathogenesis of GPP and appraisals the evidence of safety, tolerability, potential,and superior efficacy of spesolimab, a novel IL-36 monoclonal antibody developed by Boehringer Ingelheim. It is recently approved for the treatment of GPP fares in adults in the US, the European Union, and Japan. Spesolimab is a first-in-class medication that changed a paradigm shift in the management of GPP based on evidence-based targeted biologic therapy and clinical success for this distinctive type of psoriasis disease.

KEY WORDS: Generalized pustular psoriasis, GPP, Interleukin-36, IL-36, Psoriasis, Spevigo, Spesolimab

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INTRODUCTION

Psoriasis is a hereditary, autoimmune chronic inflammatory condition that affects different body parts like skin, joints, cardiovascular and central nervous system. Skin psoriasis is characterized by inflammation, epidermal hyperproliferation, and aberrant epidermal differentiation. Skin psoriasis is of two types viz., pustular and non-pustular. Non-pustular psoriasis is subdivided into psoriasis vulgaris, guttate psoriasis, erythrodermic psoriasis, palmoplantar psoriasis, psoriatic arthritis, and inverse psoriasis whereas pustular psoriasis includes generalized pustular psoriasis, impetigo herpetiformis, and localized pustular psoriasis[1-4]. Localized pustular psoriasis is sub-classified as acrodermatitis continuous of hallopeau or palmoplantar psoriasis [1].Across the globe, around 60 million people are affected by psoriasis, an autoimmune condition that affects multiple organs requiring an extensive and integrative approach to care [2]. Generalized pustular psoriasis (GPP) which belongs to the pustular type of psoriasis is an uncommon form of psoriasis that is associated with a significant increase in severity with an increase in systemic complications. It is characterized by a breakout of sterile, superficial, and macroscopic pustules with or without systemic inflammation. Mostly the cause is unknown but it may develop due to the consequence of psoriasis vulgaris, sudden discontinuation of systemic steroidal medication or other intermittent driving incidents, hypocalcemia, etc.,[1]. Furthermore, intermittent flareups of GPP may sometimes have a partial remission in some cases complete remission which depends on disease severity, type, and extent of treatment provided due to its rare occurrence, lack of

knowledge on disease pathogenesis, misdiagnosis as other diseases, and often results in difficult to estimate the number of GPP cases [3,4]. There is no standard approach of care to treat GPP, all the available therapies are based on the data from case series, case reports, and non-randomized research, a small number of GPP-affected patients, and thus, it is challenging to conduct large-scale clinical trials [5,6]. Due to the availability of few therapeuticsand therapeutic paradigms that focus on symptomatic relief, frequently GPP is difficult to treat and attain complete remission. In some cases, GPP resembles plaque psoriasis and it becomes challenging for doctors to diagnose when GPP appears at the location of the prior plaques of plaque psoriasis[7]. Therefore, there is a need to understand the pathogenesis,to early and precise diagnoses of GPP flare-ups due to its life-threatening multi-organ consequences, to develop targeted therapeutics to manage flares, and to provide better patient care.

CURRENT TREATMENT OF GENERALIZED PUSTULAR PSORIASISAND THEIR LIMITATIONS

Treatment goals for GPP are mostly based on resolving the systemic symptoms as well as getting rid of acute skin lesions, such as pustules and inflammatory erythema, and maintaining a safety profile owing to the lack of specific clinical practice guidelines. Current treatment options have not shown proven efficacy in maintaining the health-related quality of life wherein long-term care to prevent flare-ups becomes challenging which enormously increases the risk of frequent hospitalization, economic burden, and consumption of time [8-10]. Although GPP is associated with a high risk of mortality, most of the management is through supportive care, correcting imbalances, and treating secondary infections which are mostly likely to cause fatal complications [11]. Notably, acitretin, cyclosporine, methotrexate, and infliximab are considered to be the first-line therapy whereas retinoids can be the best alternatives for infliximab and cyclosporine which can be helpful in severe illness. Moreover, methotrexate is useful in cases where the patients are unresponsive to retinoids or intolerant to retinoids [12-14]. The second-line therapy includes adalimumab, etanercept, psoralen plus ultraviolet-A radiation (PUVA) phototherapy, topical therapy, and combination therapy for the recalcitrant disease. These treatment options are not suitable for all patients and different age groups, in addition, they are associated with severe unwanted drug reactions [15,16].

IL-17 inhibitors, such as brodalumab, ixekizumab, and secukinumab are new treatment options for GPP whereas IL-23 antagonists, such as guselkumab and risankizumab, TNF alpha inhibitors, such as infliximab and adalimumab, and IL-1beta receptor antagonist anakinra have been reported to reduce the symptoms of GPP and IL-36RN mutations [11,13,15,16]. There is limited data available on the treatment of GPP which relies on the evidence from case reports and single-arm research, due to the lack of international consensus on treatment objectives, success standards, and diagnostic guidelines GPP became the most challenging to treat. Specific drugs approved for GPP are limited, and even though some potential treatment options exist physicians are hesitant to use them on the patients. However, due to its rarity, enrolling the patients made it difficult to assess the effectiveness and safety of the available medication [14,17,18]. Accumulating data indicates that GPP involves a complex pathogenic mechanism triggered by the interleukin-36 (IL-36) pathway which leads to inflammatory conditions, and blocking this pathway is one of the targeted paradigms and beneficial approaches to resolve the disease.

IL-36 FAMILY OF PRO-INFLAMMATORY CYTOKINES

IL-36 plays a major role in the pathogenesis of GPP which was first classified under the IL-1 superfamily due to its homology with the IL-1 family [8,16,19,20]. IL-36 cytokine family consists of IL-36 alpha, IL-36 beta, and IL-36 gamma, which have an agonistic effect and endogenous IL-36 receptor antagonist (IL-36 Ra) and IL-38 shows an antagonistic effect that acts as a first line of defense against skin diseases [12-15]. IL-36 is responsible for regulating innate immunity and specifically overexpression of IL-36 cytokines triggers inflammatory pathways in the pathogenesis of GPPwhereas plaque psoriasis is due to the activation of IL-17 and IL-23 pathways [8,16,19]. A wide range of cells produce IL-36 isoforms, their expression in the cells varies by the stimulus and type of tissue, mostly epidermal, bronchial, gingival, and intestinal epithelial layers show the highest levels of expression compared to cardiac, neural, synovial, and lymphatic tissues (Table 1). Owing to the widespread of IL-36 cytokines in the different cell types it is involved not only in the pathogenesis of GPP but also in several autoimmune and inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel diseases, Crohn's disease and ulcerative colitis [19,25].

Table 1: IL-36 family of cytokines – Their location and function in autoimmune diseases [7,8,16,19,20]

Cytokine	Location	Function
IL-36 alpha	Keratinocytes, endothelial cells, CD68+ cells, macrophages, dendritic cells, Langerhans cells, to a lesser extent CD55+ dermal fibroblasts, and rarely in CD 79+ B cells	Induces IL-1 alpha expression IL-23/17A signaling pathway activation
Il-36 beta	Keratinocytes, endothelial cells, lower levels in macrophages, dendritic cells, and Langerhans cells	IL-23/17A signaling pathway activation Upregulates the complement C3, beta-defensin-defensin 2, S100A9, and Tumor necrosis factor (TNF)-alpha
IL-36 gamma	Keratinocytes, dendritic cells, macrophages, and much lower endothelial cells	1L-23/17A signaling pathway activation Amplifies IL-17 and TNF-alphapathways

IL-36 SIGNALING IN GENERALIZED PUSTULAR PSORIASIS

Pathogenesis of GPP is still under research and not thoroughly understood [26]. A cross-sectional descriptive study was conducted on 64 hospitalized patients due to GPP in the south and north Vietnam hospitals, all the patients were recruited based on diagnostic criteria of the Japanese dermatological associations in which results are interpreted as 43.8% CARD14 mutation, 15.6% IL 36RN mutation, both CARD14 and IL-36 RN mutations 34% and no mutations in 6.3% of patients [27].

IL-36RN is a gene that codes for a negative regulator of the IL-36 pathway which contributes to various types of inflammatory conditions of the skin, mutations in this gene result in the structural and functional abnormalities of IL-36Ra leading to the increased interaction of IL-36 agonists with their receptors and unchecked activation of nuclear factor NF-κB ultimately causing inflammation [3,28].There are several genetic risk factors associated with the pathogenesis of GPP, particularly mutations in genes, such as LCE3B, LCE3C, and CSTA which play an important role in skin barrier function. Other genes, such as IL12B, IL23A, IL23R, TYK2, IFIH1, ERAP1, and ZAP70 which have an important function to produce immunological responses are also linked with the pathogenesis of GPP. Whole exome single nucleotide polymorphism array technology revealed that C1orf141, ZNF683, TMC6, AIM2, IL1RL1, CASR, SON, ZFYVE16, and MTHFR genes are linked with psoriasis in Chinese people [25]. Current studies have found that mutations in genes, such as CARD14(maintains skin homeostasis) ASP13, and SERPINA3 have also an involvement in the pathogenesis of GPP and such mutations are most profoundly seen in individuals of GPP with pre-existing plaque psoriasis. People sharing European ancestry have a significant association for the loss of function mutation in AP1S3 which is involved in the production of a protein called autophagosomes. Mutations in SERPINA3, a gene that codes for alpha1 anti-chymotrypsin, have been found to produce excessive amounts of IL-36 agonists [6,16,19, 29,30].

The primary source of IL-36 in the skin is keratinocytes owing to their ability to synthesize and release most of IL-36 by autocrine and auto-inflammation routes. Indeed, IL-36 is originally produced as a precursor which has to be cleaved by neutrophil-derived proteases present in neutrophil extracellular traps (NETs) which results in N-terminal deletion and boosting its biologicalactivity by 1000 to 10,000 folds [8,22]. Upon stimulus, keratinocytes are stressed to release self-nucleotides and antimicrobial peptides which promote the activation of plasmacytoid dendritic cells (pDC) whereas interferon (IFN)-alpha, IFN-gamma, TNF-alpha, and IL-1beta are produced by activated and matured dendritic cells (mDC)[8,29,30].The cytokine intracellular signaling pathway is triggered when the truncated fraction of IL-36 binds to the extracellular portion of receptor IL-36R with high affinity and favors the recruitment of the interleukin-1 receptor accessory protein (IL-1RAcP) leading to the dimerization of IL-36R promoting phosphorylation of Toll/IL-1 receptor (TIR) domains whereas IL-36Ra inhibits the signaling through the IL-36R [8,24,29]. A central molecular route of inflammatory cascade mechanism in the pathogenesis of GPP has been identified as the IL-1/IL-36 chemokine neutrophil axis. When the IL-36 binds to the IL-36 receptor, the signaling pathway gets activated to induce nuclear factor NF-κB and mitogen-activated protein kinases (MAPKs) pathways resulting in the release of chemokines, such as CXCL20, CXCL8, CXCL1, CXCL2, IL-36, and the pro-inflammatory cytokines, such as IL-1beta and IL-8 from the keratinocytes and activates the neutrophils, T cells, and dendritic cells as well. In particular, keratinocytes generate IL-36 as a result of the synthesis of TNF-alpha, IL-17A, and IL-22 by Th17 and Th22 cells. Further, the release of the cytokines encourages to generation of neutrophil-rich cytokines which amplify the skin's pro-inflammatory responses through the inflammatory-related proteins six transmembrane epithelial antigen of the prostate (STEAP)1 and STEAP4. Indeed, IL-1beta, IL-6, and IL-23 help in the differentiation of Th17 cells when the myeloid cells are stimulated by IL-36[8,29-31]. This vicious cycle of pathogenic signaling pathways is responsible for producing skin inflammation (Fig.1).

SPESOLIMAB, A NOVEL INTERLEUKIN-36 RECEPTOR MONOCLONAL ANTIBODY

Spesolimab, a 146 kDa monoclonal antibody, is an IL-36 receptor antagonist developed by Boehringer Ingelheim for immune-related diseases [32,33]. A proof of concept that the IL-36 pathway is responsible for the pathogenesis of GPP came from the Phase I (NCT02978690) study which recruited seven patients from 5 different countries. The activity was measured using the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score in which 5 of 7 patients responded rapidly by achieving clear or almost clear skin within one week of spesolimab infusion [32]. Effisayil 1 is a phase II, multicenter, double-blind, placebo-controlled study with a primary goal of comparing the resolution of GPP flare-ups, effectiveness, safety, and tolerability of spesolimab to placebo. A GPPGA score of 0 or 1 implies a positive clinical outcome and therapeutic benefit and is considered the study's early endpoint [10]. Particularly, 15 (65.2%) out of 23 subjects who received a single dose and 6 (50%) out of 12 subjects who received a second dose at week 1 achieved a subscore of 0 [34, 35]. Another Effisayil1 study assessed the safety and efficacy of spesolimab in 29 Asian patients in which a GPP pustulation subscore 0 was achieved by 10 of the patients at week 1 and the secondary goal to achieve GPPGA 0 or 1 attained by 8 (50%) or 2 (15.4%) patients, respectively [12,36]. An Asian patient with GPP and acrodermatitis continua of Hallopeau (ACH), when treated with spesolimab and secukinumab together, produced total resolution of nail lesions and skin clearance which produced evidence to treat ACH with secukinumab and spesolimab [37]. Effisayil 2 is a multinational, randomized, double-blind, placebo-controlled, phase II study, which assessed the effectiveness of maintenance therapy with spesolimab. The high-dose spesolimab therapy showed superiority over medium dose, low dose, and placebo. High-dose spesolimab group reported reduced recurrence of flare-ups when compared with other dose groups and placebo [5].

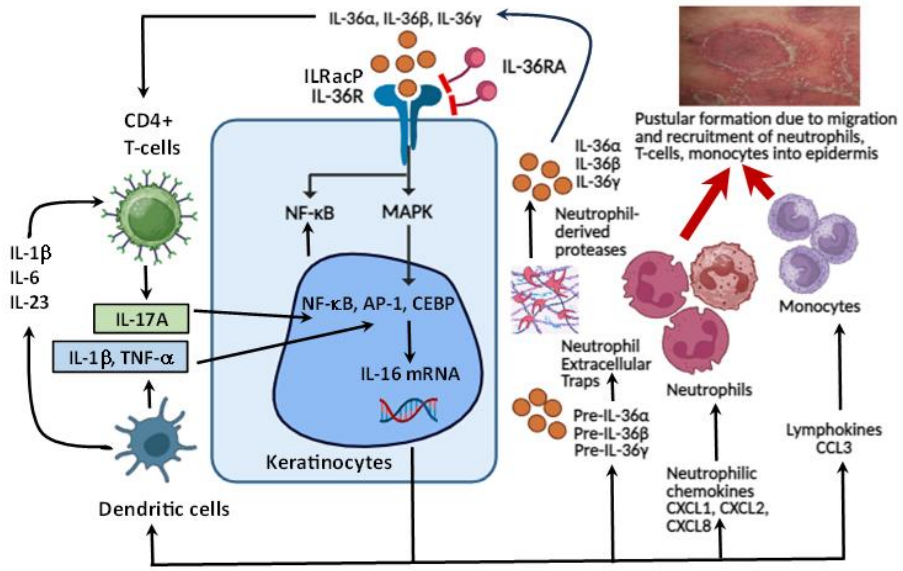

Figure 1: Autoimmune-mediated activation of IL-36 pathway in the pathogenesis of generalized pustular psoriasisin the skin[5,8,21,32,42].

Pharmacodynamics:

When the IL-36 pathway is sensitized it activates epidermal keratinocytes leading to the release of pro-inflammatory cytokines and ultimately causing IL-36-regulated chemotactic signaling which is responsible for the pathophysiology and clinical features of GPP [38]. Spesolimab (BI 655130) is a humanized monoclonal immunoglobulin (Ig) G1 antibody that selectively binds to the IL-36R and acts by preventing the IL-36 receptor activation, thus reducing the downstream pro-inflammatory signaling regardless of IL-36RN mutation status[3,14]. When spesolimab specifically binds to the IL-36 receptor leads to downstream signaling of the IL-36 pathway, which blocks the activity of IL-36 ligands like IL-36 alpha, IL-36 beta, IL-36 gamma, ultimately leading to anti-inflammatory and anti-fibrotic effect, this suggests that IL-36 plays a major role in GPP than plaque psoriasis, which results through the activation of IL-23/17 pathway (Fig. 1) [29,30,33]. Spesolimab reduces the inflammatory markers, TH1/TH7, innate inflammatory signaling, neutrophilic mediators, and keratinocyte-driven inflammation pathway in GPP patients. Indeed, it significantly reduced relevant serum biomarkers and cell types in GPP skin lesions, including CD3+ T, CD11c+, and IL-36+ cells as well as lipocalin-2-expressing cells [38,39]. Immunopathogenesis of palmoplantar psoriasis (PPP; psoriasis on hands and feet) is unclear due to a lack of research but some studies have shown that there is an increased expression of genes and proteins related to IL-1 and IL-36 in PPP lesions[40]. Inhibition of the IL-36 pathway may also benefit certain diseases, such as hidradenitis suppurativa, rheumatoid arthritis, systemic lupus erythematosus, pyoderma gangrenosum, and Netherton syndrome. However, a single clinical trial that provides strong evidence of therapeutic benefit has not been conducted to date. Therefore, clinical research is highly needed to explore the role of the IL-36 pathway in autoimmune diseases for the betterment of patient care.

Pharmacokinetics:

Spesolimab follows the linear pharmacokinetics with a typical volume of distribution of 6.4L with a dosing range of 0.3-20mg/kg when administered intravenously. Its metabolism involves catabolic breakdown into tiny peptides and amino acids which are similar to endogenous IgG. The drug clearance is 0.184 L/day in a typical adenosine deaminase (ADA)-negative patient weighing 70kg and the terminal half-life is reported to be 25.5 days. Hepatic and renal function impairmentsare not investigated, though it is unlikely to affect elimination. Plasma concentrations are found lower in patients with heavier weights and high ADAs. Indeed, it has not been officially investigated for drug interactions. Moreover, the pharmacokinetic profile of the drug seems to be unaffected by changes in gender, age, and race [32,33,39].Of particular importance, the subcutaneous bioavailability of spesolimab is increased with the increase in the dose and that was greater when applied to thigh. Positive anti-drug antibody responses were noted in 26.7-33.3% of participants who received intravenous spesolimab and 16.7-37.5% who received subcutaneous spesolimab. There were no major side effects recorded, and intravenous dosages of up to 1200mg are well-tolerated in healthy participants in a study [41].

Approval status:

It has been approved for the therapeutic management of GPP in more than 48 countries including the USA, Japan, and the European Union as of to date. In October 2018, the USFDA designated spesolimab as an orphan drug for the treatment of GPP flare-ups in adults.The FDA granted breakthrough therapy designation and subsequently granted priority review for spesolimab for the treatment of GPP flares in December 2021. Initial approval of spesolimab for medical use in the US was on 1stSeptember 2022, in Japan on 26th September 2022, and in the European Union in December 2022[12,15,42].

Therapeutic indications:

In the USA, it is indicated for the treatment of GPP in adults and in 12 years of age and above pediatric patients weighing at least 40 kg[42,43]. Pyoderma gangrenosum (PG) is an inflammatory neutrophilic condition that has a rare prevalence in its occurrence which is characterized by painful skin ulcers. Its pathogenesis is due to its activation by keratinocytes resulted due to an abnormal IL-36 pathway. As there is no

standardized therapy for PG, however, some of the systemic therapies, such as prednisolone, cyclosporine, etc., are used for symptomatic therapy. A case report shows evidence of the improvement of PG upon administration of spesolimab after obtaining approval for emergency drug use from the FDA [44,45]. ACH is one of the rare forms of psoriasis associated with sterile pustules affecting fingers and toes. There are no clinical trials specifically conducted for ACH when co-existed with GPP. Nevertheless, a case report showed evidence and therapeutic potential of spesolimab in patients with GPP coexisting with ACH resulting in a resolution of nail lesions, which is a symptomatic feature of ACH [37].

Dosage and administration:

Spesolimab is sold under the brand name SPEVIGO in the USA and is administered as a single 900 mg intravenous infusion over 90 min. For persistent flare-ups after the initial dose, another dose should be given one week later. Before administering the spesolimab, it should be diluted with 0.9% normal saline. Each 7.5ml spesolimab vial contains 450mg of spesolimab. A preparation of spesolimab is made from a 100ml package container of 0.9% normal saline, 15 ml of 0.9% normal salineshould be discarded, then two vials of 7.5ml spesolimab are added. Before administration of spesolimab, the patient should be tested for severe illnesses such as tuberculosis because of its immunosuppressive action [42,43].

Adverse drug reaction:

Spesolimab is well tolerated in patients with GPP, PPP, and ulcerative colitis. The most commonly reported adverse effects when used for GPP were nausea and vomiting, asthenia and fatigue, headache, pruritus and prurigo, infusion site hematoma and bruising, and opportunistic and urinary tract infections [3,33]. Skin rashes, nasopharyngitis, headache, and acne were reported when the spesolimab was tested for ulcerative colitis [33].

Contraindications:

Spesolimab is contraindicated in patients who experienced severe or life-threatening hypersensitivity to spesolimab-sbzo or any of the excipients in its pharmaceutical formulation. Indeed, several hypersensitivity reactions have already been reported including drug reactions with eosinophilia and systemic symptoms (DRESS)[42,43].

Clinical trials of spesolimab other than GPP:

A randomized pilot study on spesolimab in palmoplantar pustulosis showed effectiveness in 32% of patients while achieving a 50% reduction in PPP which is indicative of the primary endpoint compared to placebo [33]. A multicenter, randomized, double-blind, placebo-controlled trial conducted to examine the effectiveness of spesolimab in atopic dermatitis was also shown in the reduction of EASI score [44].However,further development of spesolimab for atopic dermatitis was discontinued. A randomized trial conducted on ulcerative colitis patients showed positive results like mucosal healing, but there were no or lower rates of clinical remission [33]. In addition to this, an open-label, long-term extension, and interventional study of spesolimab treatment in adult patients with hidradenitis suppurativa is under investigation [46,47].

SUMMARY

It is well known that the IL-36 pathway is involved in the pathogenesis of several auto-immune diseases and is highly critical and strongly responsible for immune cell activation and damage to keratinocytes in the skin of GPP, a rare and distinctive type of psoriasis. Indeed, spesolimab is a novel IL-36 monoclonal antibody approved for the management of GPP in adults. Moreover, it has been undergoing clinical developmentfor the management of various other autoimmune diseases, though the results are not fully promising. Some of the disadvantages of these current clinical trials are low sample size and short duration of trial period. There is a need to evaluate spesolimab in specific immune diseases to prove its effectiveness which ultimately helps in treating the patient, improving the quality of life, decreasing the burden of disease, andoverall cost of treatment. Future research is needed for a deep understating of pathogenesis to evaluate the existing target-based biologics and to develop new targeted therapies that effectively reduce and/or prevent the progression of GPP.

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