Psoriasis: Targets and Therapy

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REVIEW

Therapeutic Potential of Spesolimab-Sbzo in the Management of Generalized Pustular Psoriasis Flares in Adults: Evidence to Date

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Abstract: Generalized pustular psoriasis (GPP) is a rare, chronic, and severe skin disorder characterized by the eruption of non-infectious pustules on an erythematous background often associated with systemic symptoms. It may appear in association with plaque psoriasis or occur in previously healthy individuals. It differs from psoriasis vulgaris in clinical presentation, immunopathogenesis, histology, and therapeutic strategies. Overexpression of interleukin 36 (IL-36) or a loss-of-function mutation of IL-36 receptor antagonist (IL-36RA) are thought to play a pivotal role in the pathogenesis of this disease. There are currently no globally approved guidelines for the treatment of GPP, and the therapies used so far, with variable results, have given unsatisfactory results. Spesolimab, a selective humanized antibody against the IL-36 receptor that blocks its activation, is the first biologic drug approved in Europe in December 2022 for the treatment of GPP flares. It represents a promising therapy, demonstrating efficacy in reducing disease severity and improving patient outcomes. In our review, we have analyzed the latest advancements and findings regarding the efficacy and safety of spesolimab in the context of GPP management.

Keywords: spesolimab, anti-IL36R, GPP, pustular psoriasis

Introduction

Generalized pustular psoriasis (GPP) is a severe multisystem disease characterized by the eruption of sterile pustules over a background of diffuse erythematous skin. Systemic inflammatory symptoms, such as fever, general malaise, fatigue, edema, conjunctivitis, arthritis, uveitis, and neutrophilic cholangitis, are frequent findings. The disease has a chronic relapsing course characterized by exacerbations (flare-ups) and clinical remissions. Common laboratory abnormalities include neutrophilia, elevated C-reactive protein levels, hypocalcemia, hypoalbuminemia, and abnormal liver function tests.[1] The pathological mechanisms underlying GPP are unclear, but 24% of affected patients show mutations of IL36RA gene, which encodes the interleukin-36 receptor antagonist.[2] Genotype–phenotype studies have shown that GPP variants with mutations in the IL36RA gene are associated with an earlier age of onset and more widespread systemic inflammation. Interleukin 36 plays a major role in the inflammatory cascade, being responsible for the clinical manifestations of the disease. Currently, there are still few studies focused on the clinical course of GPP, because of the rarity and heterogeneity of the disease, as well as the lack of international consensus on the diagnosis, patient management and the definition of flares.[3] According to a recent systematic review, most GPP flares last 2–5 weeks and about 50% of these episodes require hospitalization.[4] GPP flares are often associated with infections, hypocalcemia, stress, drugs (lithium, antimalarials, interferon, beta-blockers, NSAIDs, penicillin, tetracycline) or abrupt discontinuation of steroid therapy. Management of GPP flares often includes hydration and systemic steroids,[5] but their role in management of GPP flares is controversial. Although steroids significantly reduce inflammation and prevent multiple organ failure (MOF), they can also lead to an increase in neutrophils in the blood, triggering or exacerbating pustulosis. Therapies used for vulgar psoriasis have been tried in managing GPP, such as acitretin, cyclosporine, methotrexate,

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infliximab, adalimumab, ixekizumab, ustekinumab, secukinumab,[6–11] with controversial results. Exploring new specific therapeutic targets for GPP becomes mandatory for the management of GPP and GPP flares, as they are burdened with high morbidity and disability. Spesolimab, a humanized antibody against the IL-36 receptor, has been approved by EMA (European Medicines Agency) in December 2022, for managing GPP flares.[12,13] The use of spesolimab has several notable advantages over already known therapies. It demonstrated significant efficacy in reducing the symptoms of pustular psoriasis and showed a rapid response, with improvements often observed within a week of starting treatment. In terms of safety, spesolimab has shown to be well tolerated by most patients, with mild side effects and good tolerability.[14] The aim of our review is to highlight the latest advancements and findings regarding the efficacy and safety of spesolimab in the context of GPP management.

Materials and Methods

A literature search was conducted using MEDLINE (PubMed) up to November 20, 2023. Manuscripts were identified, screened, and analyzed for relevant data according to the Preferred Reporting Items for Systematic Reviews. The following search terms were included: "generalized pustular psoriasis AND spesolimab", "spesolimab AND clinical trials", and "spesolimab AND efficacy". The scope of research included clinical trials and review of literature, removing duplicate entries and excluding manuscripts about spesolimab for other dermatological conditions. Abstract and body text of the selected articles were then reviewed to refine the search. Additionally, references were examined to include any potentially missed manuscript.

Results

We considered a total of 2 completed trials[15,16] in our review. Among the completed trials with available results, two Phase II studies were identified. The Effisayil™ 1 phase II study assessed the efficacy of intravenous (IV) spesolimab for the treatment of GPP flares. In the trial described by Bachelez et al[17] 53 adults aged 18–73 years who had a diagnosis and flare-up of GPP before enrollment were selected. They were randomized (2:1) to receive a single dose of IV spesolimab 900 mg or placebo at baseline and were followed for 12 weeks. Both groups could receive an additional dose of spesolimab on day 8 or/and after day 8, as a rescue medication: they were followed for 12 weeks. Efficacy of the treatment was assessed by the primary end point Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulosis subscore of 0 (0 as for no clinically assessed pustules to 4 for severe pustulosis) at the end of week 1. The secondary key end point was a total GPPGA score of 0 or 1 at the end of week 1. At baseline, 35 subjects were assigned to receive spesolimab 900 mg ev and 18 to placebo. 46% (16 of 35) of patients who received spesolimab and 39% (7 of 18) who received placebo presented with a GPPGA pustulation subscore = 3; 37% (17) and 33% (6), respectively, had a GPPGA pustulation subscore = 4. At the end of first week, 54% (19) of the subject in the spesolimab group had a GPPGA pustulation subscore = 0, compared with 6% (1) of the placebo group (difference of 49% points; 95% CI – Confidence Interval, $p<0.001$). Regarding the key secondary endpoint, 43% of subjects who received spesolimab had a total GPPGA score of 0 or 1, compared with 11% of the subjects who received placebo (difference of 32% points; 95% CI, $p=0.02$). Drug reactions were observed in 2 patients who received spesolimab, in one case it occurred concomitantly with DILI (Drug-Induced Liver Injury).[18] Patients who received spesolimab at baseline reported infections 17% at week 1 (6 of 35); patients who received spesolimab at any time during the study, reported infections (47%) at week 12 (24 of 51). Anti-spesolimab antibodies were detected in 46% of patients (23 of 50) who received ≥ 1 dose of spesolimab.[15] Burden et al subsequently analyzed the efficacy of spesolimab in pre-specified patient subgroups, investigating the strengths and the weaknesses of the Effasayil 1 study.[15] Starting from clinical characteristics, they found that the two study arms were generally balanced, but in the placebo group there were more female and Asian patients than in the spesolimab arm (83% and 60% and 72% and 46%, respectively). At Week 1, the difference for spesolimab versus placebo for the primary endpoint (GPPGA pustulation subscore = 0) was 0.487 (95% CI 0.215–0.672), and for the secondary endpoint (GPPGA total score = 0 or 1) it was 0.317 (95% CI 0.022–0.527). The subgroups lying on or above the upper 95% CI limit had very few patients, that might have limited the strength of statistical analyses, and patients aged 75 years were excluded from the study. They also found limiting the achievement of study endpoints at Week 1, without long-term follow-up of subgroups regarding the treatment response.[15] Morita et al showed the results of Effisayil™ 2 phase II study, on efficacy and safety of subcutaneous (SC) spesolimab for the prevention of generalised pustular psoriasis flares.[5,16] A total of 123 patients aged 18–73 years, with a history of at least two GPP flares, and a GPP Physician Global Assessment (GPPGA) score = 0 or 1 at baseline, were enrolled

for the study. Patients were randomized 1:1:1:1 to three groups receiving a spesolimab SC 600 mg (loading dose) followed by spesolimab SC 300 mg (maintenance dose) every 4 weeks or every 12 weeks, or spesolimab SC 300 mg (loading dose) followed by spesolimab 150 mg (maintenance dose) every 12 weeks, and one group receiving placebo, for 48 weeks. Ninety-two were assigned to receive spesolimab: 30 subjects received spesolimab SC 600 mg + spesolimab SC 300 mg every 4 weeks, 31 subjects received spesolimab SC 600 mg + spesolimab SC 300 mg every 12 weeks, and 31 subjects received spesolimab SC 300 mg + spesolimab SC 150 mg every 12 weeks. Thirty-one subjects received placebo. Patients received their last dose at week 44 and were followed until week 48. Every enrolled subject experiencing a GPP flare within study period could receive spesolimab IV 900 mg and an optional second IV 900 mg dose. The primary endpoint was time to first GPP flare; the key secondary endpoint was the presence of at least one GPP flare during the study. Other secondary endpoints included time to worsening (defined as an increase of four points from baseline for the Psoriasis Symptom Scale – PSS and Dermatology Life Quality Index – DLQI) and the occurrence of adverse events by the end of the study period. Thirty-five patients experienced GPP flares; 23% patients (7 of 31) in the 300+150 mg spesolimab group, 29% patients (9 of 31) in the 600 +300 mg every 12 weeks spesolimab group, 10% patients (3 of 30) in the 600+ 300 mg every 4 weeks spesolimab group, and 52% (16 of 31 patients) in the placebo group. High-dose spesolimab was superior to placebo in preventing flares, with 84% reduction in the risk of flare development over 48 weeks and no flares after 4 weeks. It was found that high-dose of spesolimab was significantly superior versus placebo on the primary outcome of time to GPP flare (hazard ratio [HR] = 0.16, 95% CI 0.05–0.54; p = 0.0005) endpoint. Infection rates were similar between treatment arms, and there were no deaths.[5]

Discussion

Generalized pustular psoriasis (GPP) is a rare and chronic inflammatory disease characterized by the sudden eruption of neutrophilic pustules and the appearance of systemic symptoms. Although it can also occur in patients with plaque psoriasis, it differs in clinical presentation, immunopathogenesis, histology and therapeutic strategies. The absence of global specific guidelines has made GPP a therapeutic challenge for several years.[19] Current therapeutic options used for GPP can be classified into biological and non-biological systemic agents.[20] According to Japanese guidelines, the most used non-biologic drugs for patients with GPP are retinoids, cyclosporine and methotrexate.[4] However, there is limited evidence about the effectiveness of these treatments in GPP.[7,14,21] Among biologic therapies, some TNFα blocking agents (adalimumab, infliximab, and certolizumab pegol) are approved in Japan for the treatment of GPP but may be prescribed off-label in Europe for this indication.[20] Their use in GPP is based on case reports and small, uncontrolled, open-label, single-arm studies.[22–25] Brodalumab and secukinumab were found to be effective in the treatment of GPP in Phase III open-label multicenter studies, but the small sample size and open-label study design limit their use.[9,26] Hidehisa Saeki et al published the results of three Phase III, open-label, multicenter studies, including 5 Japanese patients with GPP, with Ixekizumab, an IL-17A antagonist, shown to be effective in the treatment of GPP. However, this study is limited by the small sample size of GPP patients, the open-label study design, and the lack of a control group.[11] Risankizumab, a humanized IgG monoclonal antibody targeting the p19 subunit of IL-23 was approved in March 2019 in Japan for the treatment of GPP, however, data about efficacy and safety are lacking.[27] In this field of therapeutic options, spesolimab, a humanized antibody selective against the IL-36 receptor, emerges as a promising alternative for GPP, demonstrating efficacy in reducing disease severity and improving patient outcomes. Overexpression of IL-36 or a loss-of-function mutation of IL-36RA are believed to play a central role in the onset of the disease, and the targeting of IL-36 pathway represents a novel approach for managing this challenging condition.[2] The phase II study Effisayil™ 1 represents the first randomized controlled trial in GPP. It shows the power of IV spesolimab in managing GPP flares. This was demonstrated by the reduction of GPPGA pustulation subscore to 0 (indicating no visible pustules) and a GPPGA total score of 0 or 1 (indicating clear or nearly clear skin) by Week 1. Interestingly, patients who received placebo at T0 also showed similar enhancements in clinician-reported outcomes after receiving spesolimab on Day 8. These positive changes were maintained in both treatment groups up to Week 12. The study also confirms the pivotal role of IL-36 as pathogenic driver in GPP. In total, 14–37% of patients with GPP have loss-of-function mutations in IL36RN, encoding the IL-36 receptor antagonist, which ameliorates IL-36-mediated proinflammatory signalling and neutrophil recruitment and activation. Other IL-36 pathway-associated genes are also implicated in GPP (CARD14 and AP1S3).[12] Higher infection rates (17% vs 6%) were noted, after IV spesolimab, but no information regarding the pathogen was added and the baseline systemic therapy was unspecified. In the spesolimab group, two subjects showed symptoms resembling Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), but a subsequent review revealed that one case did not meet

the diagnostic criteria, while the other was labeled as "possible DRESS". Interestingly, 46% of patients in the spesolimab group developed anti-drug antibodies, potentially impacting long-term outcomes.[5,12] Effisayil™ 2 phase II study evaluates the efficacy and safety of SC spesolimab for the prevention of GPP flares. Spesolimab consistently demonstrated efficacy of 84% in preventing GPP flares over a 48-week period compared to placebo. This effectiveness was observed regardless of IL36RN subtypes, the pre-existence of plaque psoriasis, or BMI status.[28,29] The research program regarding spesolimab is now advancing to its subsequent phase: Effisayil ON, an open-label extension study to assess safety and effectiveness of spesolimab among subjects with GPP who have successfully completed prior trials. Recently Dattola et al and Bellinato et al published two articles on the real-life experience of spesolimab in the treatment of GPP, which showed positive experience on the effectiveness of spesolimab in the flare of GPP which is not responsive to other conventional and biological systemic treatments.[30,31]

Conclusion and Future Directions

Spesolimab represents the first real therapeutic strategy targeting the IL-36 pathway, crucial in GPP. Intravenous spesolimab has been shown to be safe and effective in the management of GPP flares with an excellent clinical response as early as the first week after administration. Similar response rates were also observed in patients receiving placebo at T0 after spesolimab administration at day 8. In addition, spesolimab SC was also effective in preventing GPP flare-ups compared to placebo. In a monoclonal field, where the previous therapeutic strategies were lent by vulgar psoriasis, we strongly believe that spesolimab can represent a trailblazer for further investigations in GPP management and etiopathology.

Ethics Statement

The study was performed following the principles of the Declaration of Helsinki.

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All listed authors made a significant scientific contribution to the manuscript, approved its claims and agreed to be an author listed in this work.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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