Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Use of Biological Therapies for the Management of Pustular Psoriasis: A New Era?

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Abstract: Generalized pustular psoriasis (GPP) is a severe and rare form of psoriasis, being a potentially life-threatening condition, characterized by recurring episodes or flares of widespread cutaneous erythema with macroscopic sterile pustules. An irregular innate immune response is linked to GPP, which is considered an auto-inflammatory disorder, while innate and adaptive immunopathogenic responses are involved in psoriasis pathogenesis. In consequence, different cytokine cascades have been suggested to be mainly involved in the pathogenesis of each different psoriasis form, with the interleukin (IL)23/IL17 axis implied in plaque psoriasis, and the IL36 pathway in the GPP. As regards GPP treatment, conventional systemic drugs available for plaque psoriasis are usually used as the first-line treatment option. However, contraindications and adverse events often limit the use of these therapies. In this scenario, biologic drugs may represent a promising treatment option. To date, even if 12 different biologics have been approved for plaque psoriasis, none of these is approved for GPP where they are employed off-label. Recently, spesolimab, an anti-IL36 receptor monoclonal antibody, has been recently approved for GPP. The purpose of this article is to assess the current literature about the use of biological therapies for the treatment of GPP to establish the basis for a shared GPP management algorithm.

Keywords: pustular psoriasis, treatment, biologic drugs

Introduction

Psoriasis is a chronic-inflammatory cutaneous disease, with a worldwide prevalence ranging from 2% to 3%.[1] Even if plaque psoriasis is the commonest clinical presentation, several phenotypes can be distinguished.[2] Among these, generalized pustular psoriasis (GPP) is a severe and rare form, as well as a potentially life-threatening condition.[3] It is characterized by recurring episodes or flares of widespread cutaneous erythema with macroscopic sterile pustules.[4,5] Its prevalence ranges from 0.18 to 18 cases per 100 000 habitants.[4,5] Acute episodes of GPP are often associated with systemic symptoms such as fatigue, high-grade fever, and leukocytosis.[4,5] Moreover, the GPP clinical course may be heterogenous, from relapsing disease with recurrent flares developing years after the initial diagnosis to a persistent disease continuously flaring over time. As regards risk factors, GPP is often idiopathic.[4,5] However, internal and external factors, such as pregnancy, corticosteroid withdrawal and infections, may trigger GPP flares.[4,5]

Plaque psoriasis is often present in patients with GPP, suggesting a shared pathogenesis.[4,5] However, an irregular innate immune response is linked to GPP, considered an auto-inflammatory disease, while innate and adaptive immunopathogenic responses are involved in psoriasis pathogenesis.[4,5] In consequence, different cytokine cascades have been suggested to be prevalent in the pathogenesis of each different psoriasis form, with the interleukin (IL)23/IL17 axis implied in plaque psoriasis, and the IL36 pathway in GPP.[6] Indeed, recent knowledge on GPP pathogenesis showed that IL36 plays a key pathogenetic role and the mutation of the IL36 receptor (IL36RN) is associated with more severe forms of disease.[6]

As regards GPP treatment, conventional systemic drugs used for psoriasis (methotrexate, oral retinoids and cyclosporin) are usually used as first-line treatment options.[7] However, there is limited GPP-specific evidence, clinical trials are

Received: 13 May 2023
Accepted: 21 June 2023
Published: 28 June 2023

absent, and contra-indications often limit the use of these therapies.[7] In this scenario, biologic drugs may represent a promising treatment option. Indeed, the excellent results in terms of safety and efficacy demonstrated for plaque psoriasis[8–10] suggest that these drugs are a valuable option for GPP management too. Currently, 12 biologics have been approved for psoriasis, acting on Tumor necrosis factor (TNF) α, IL 12/23, IL17, and IL23.[11] None of these is approved for GPP where they are employed off-label. However, to date only spesolimab, an anti-IL36 receptor monoclonal antibody, has recently been approved specifically for GPP disease.[12]

Globally, the lack of clinical evidence and guidelines led to the need for more studies investigating the effectiveness and safety of new drugs that can be used for GPP management. The aim of this article is to review current literature on the use of biologic drugs for the management of GPP in order to point out their potential therapeutic role in GPP and to offer a wide current clinical perspective.

Materials and Methods

A search of the current literature on the Embase, Google Scholar, Cochrane Skin, PubMed, and clinicaltrials.gov databases (until March 31, 2023) was performed using the following terms: "psoriasis", "general pustular psoriasis", "biologic drugs", "efficacy", "safety", "infliximab", "certolizumab", "adalimumab", "etanercept", "ustekinumab", "ixekizumab", "secukinumab", "brodalumab", "bimekizumab", "tildrakizumab", "risankizumab", "guselkumab", and "spesolimab". The Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines were followed to point out relevant data from the screened and analyzed articles. Metanalyses, reviews, clinical trials, case reports and series, and real-life experiences were investigated in our review, selecting the most relevant articles. Only English-language articles were collected. The texts and abstracts of designated manuscripts were reviewed to refine the search. Bibliographies were also examined in order to avoid missing some relevant articles. This article is based on previously performed studies and does not contain any studies involving animals or human participants carried out by any of the authors.

Results

A total of 112 articles were collected in the present review. As regards GPP severity, the Japanese Dermatological Association (JDA) severity index was the most used.[13] This score is calculated from the sum of skin score (0–9), which includes 3 factors (erythema area with pustules, overall erythema area, and edema area), plus the systemic/laboratory score (0–8) (pyrexia, white blood cell count, C-reactive protein concentration and serum albumin concentration).[13] The total GPP score is categorized by the JDA severity index as follows: mild (0–6), moderate (7–10), and severe (11–17).[13]

The main results of the review are summarized in Table 1.

Adalimumab

Adalimumab is an anti-TNFα authorized for the treatment of psoriasis and psoriatic arthritis.[14,15] A 52-week, Phase III, multicenter study investigated the efficacy and safety of adalimumab 80 mg at week 0 followed by 40 mg every other week in 10 Japanese subjects affected by GPP.[16] The primary endpoint was clinical response, defined as reaching remission (total skin score: 0) or improvement from baseline (reduction of ≥1 point from a baseline total skin score of 3 or ≥2 points from a baseline total skin score of ≥4) at week 16.[16] A total of 7 (70.0%) patients achieved a clinical response at week 16, and 5 (50.0%) subjects reached the same score at week 52.[16] Of note, 5 (50.0%) subjects increased adalimumab dosage to 80 mg on or after week 8.[16] As regards safety, 9 patients experienced at least 1 adverse event (AE), with 3 serious AEs reported (moderate bacterial enterocolitis, renal failure, and chronic sinusitis).[16] The commonest AE reported was nasopharyngitis and pruritus (3, 30.0% each).[16] Globally, 5 (50.0%) patients completed the study; 3 (30.0%) subjects discontinued prematurely due to lack of efficacy and 2 (20.0%) due to AEs (moderate bacterial enterocolitis and renal failure).[16]

The efficacy and safety of adalimumab in GPP treatment was also shown by several case reports,[17–21] including pediatric patients,[22–24] as well as in combination with methotrexate[25] and acitretin.[26] Finally, two paradoxical GPP were reported during adalimumab treatment.[27,28]

Table 1 Detailed Data on Trials and Case Reports on GPP or Paradoxical GPP for Biologic Drugs

Drug	Clinical Trials	Total Case Report	Pediatric Cases	Cases During Pregnancy	GPP Paradoxical Cases
Adalimumab	1	16	9	0	2
Etanercept	0	11	2	0	0
Infliximab	2	24	5	2	9
Certolizumab	1	1	0	1	1
Ustekinumab	0	2	0	0	5
Ixekizumab	2	21	0	0	0
Secukinumab	3	17	8	2	2
Brodalumab	1	0	0	0	0
Bimekizumab	0	1	0	0	0
Guselkumab	1	0	0	0	0
Tildrakizumab	0	0	0	0	0
Risankizumab	1	2	0	0	1
Spesolimab	2	6	0	0	0
Total	14	101	24	5	20

Etanercept

Etanercept is an anti-TNFα drug. It is a soluble version of the TNF receptor that neutralizes the proinflammatory activity of TNF- α.[29]

Data on the use of etanercept for the management of GPP are limited to a few case reports. Among these, Esposito et al reported the use of etanercept at different dosages on 6 patients with GPP.[30] Mean Psoriasis Area Severity Index (PASI) was 18.6.[30] Among these, 2 patients received 25 mg every 2 weeks while the remaining patients received 50 mg every 2 weeks.[30] The authors showed that the dosage of 50 mg biweekly was effective, with good efficacy and rapidity of effect. Subjects continuously treated at this dose for 24 weeks presented stable conditions and long-term maintenance until week 48, even after a dosage reduction to 25 mg.[30] Indeed, 2 patients received 25 mg every 2 weeks and showed an unsatisfactory response at week 12 (patient 1: PASI 13.5 vs 17.8 at baseline; patient 2: PASI 12.2 vs 19.8 at baseline) and 2 subjects who reduced the dosage from 50 mg to 25 mg at week 12 showed disease worsening.[30]

A few other case reports showed the efficacy of etanercept in GPP management,[31–33] also in pediatric patients.[34,35]

Infliximab

Infliximab is a chimeric human–murine monoclonal antibody targeting TNFα.[36]

The efficacy and safety of infliximab in GPP has been reported in a multicenter study involving 7 patients receiving infliximab at the dose of 5 mg/kg at weeks 0, 2 and 6 and then every 8 weeks up to week 46.[37] The primary endpoint was the response rate of global improvement, defined as the proportion of subjects assessed as "resolved" or "improved".[37] All of the patients reached a response defined as "improved" at weeks 2 and 6.[37] Moreover, the response rate at week 50 was 100.0%, with 3 patients rated as "resolved" and 1 patient as "improved".[37] As regards safety, 7 (100%) patients reported at least 1 AE, with infection as the most common (5, 71.4%).[37] Moreover, 5 (71.4%) serious AEs were collected in 2 (28.6%) patients ("pustular psoriasis", "herpes zoster", "retroperitoneal abscess", "intervertebral discitis", and "spondylitis").[37]

Similarly, a large-scale prospective post-marketing surveillance study enrolled 164 patients receiving infliximab 5 mg/kg at weeks 0, 2 and 6, and every 8 weeks thereafter up to 6 months. JDA severity score was used to assess clinical disease. Only 56 subjects (34.1%) had completed data. At baseline, patients with mild, moderate, and severe GPP were 38 (67.9%), 14 (25.0%) and 4 (7.1%) while, at final assessment, there were 53 (94.6%), 1 (1.8%) and 2 (3.6%), respectively. The safety issue specifically in relation to patients with GPP has not been discussed.[38] These results were confirmed by several case reports.[39–53]

Infliximab has been reported to be safe and effective for the management of GPP during pregnancy[54–57] and for pediatric patients.[58–61]

Finally, 9 cases of paradoxical GPP developed during treatment with infliximab have been reported.[62–68]

Certolizumab

Certolizumab is an anti-TNFα agent which has demonstrated long-term safety and efficacy in treating moderate-to-severe plaque psoriasis.[69] Its role in GPP management has been reported in an exploratory analysis of a 52-week, Phase II/III, double-blind, placebo-controlled, multicenter, randomized trial.[70] A total of 7 Japanese patients were enrolled and randomized to receive certolizumab 400 mg every 2 weeks (n = 3) or certolizumab 200 mg every 2 weeks after a loading dose of certolizumab 400 mg at weeks 0, 2, and 4 (n = 4).[70] At baseline, mean JDA score was 6.3 ± 4.0 and 5.5 ± 2.4 in the certolizumab 400 mg and 200 mg cohorts, respectively. JDA total score improvement was reported at week 16 (2.0–2.5) and continued to improve up to week 52 (1.7–2.0). Moreover, Global Improvement Score (GIS) responders, defined as patients "very much improved", "much improved", or "minimally improved", were 7 (100%) at week 16 and 6 (85.7%) at week 52, respectively.[70] All the patients reported at least 1 AE.[70] Of note, 2 serious AEs were reported (neutropenia and pustular psoriasis), all without requiring treatment discontinuation.[70]

Furthermore, case reports reported the effectiveness and safety of certolizumab in GPP management,[71] also during pregnancy.[72]

Finally, a de novo-onset of palmoplantar pustulosis followed by GPP in a patient with rheumatoid arthritis during treatment with certolizumab has been reported.[72]

Ustekinumab

Ustekinumab is an IL-12/23 inhibitor.[73] Daudén et al first described the effectiveness of ustekinumab in a 47-year-old man with GPP unresponsive to multiple topical agents, etretinate, acitretin, retinoids with psoralen plus ultraviolet A and methotrexate, infliximab and efalizumab.[74] Similarly, Storan et al reported the case of a 90-year-old woman affected by GPP successfully treated with ustekinumab.[75]

Finally, several cases of paradoxical GPP during treatment with ustekinumab have been reported.[76–80]

Ixekizumab

Ixekizumab is an IL-17A antagonist, licensed for use in moderate-to-severe plaque psoriasis.[81] The effectiveness and safety of ixekizumab (two 80 mg subcutaneous injections at baseline followed by 80 mg every 2 weeks through week 12 and 80 mg every 4 weeks thereafter) for up to 52 weeks has been reported in a Phase III trial (UNCOVER-J) involving 5 patients with GPP.[82,83] PASI reduction from baseline (12.8 ± 5.5) was observed as early as week 1 (6.9 ± 3.0).[82,83] Moreover, PASI75/90/100 were reached by 4 (80.0%), 3 (60.0%) and 1 (20.0%) patients at week 12, and by 4 (80.0%), 2 (40.0%) and 2 (40.0%) at week 24, respectively.[82,83] All patients experienced at least 1 AE, all without requiring treatment discontinuation.[82,83]

An extension of this study up to week 244 showed the long-term efficacy of ixekizumab, with an observed mean PASI of 1.8 and 1.6 at week 52 and week 244, respectively.[84,85] Similarly, all patients had a GIS of "resolved" or "improved" from week 12 onwards; none of the patients had a GIS of "unchanged" or "worsened" during the remaining study period.[84,85]

The efficacy and safety of ixekizumab for GPP have been reported also in real-life studies. Nagata et al reported a case series on 10 patients with GPP. Mean PASI at baseline was 25.5 ± 9.5).[86] PASI75 response was achieved by 6/9 (66.7%) patients at week 4, by 9/9 (100%) subjects at week 12 and by 7/8 (87.5%%) patients at week 24.[86] Similarly,

PASI90 and PASI100 were achieved by 4/9 (44.4%) and 2/9 (22.2%) subjects at week 4, 6/9 (66.7%) and 2/9 (22.2%) patients at week 12 and by 6/8 (75.0%) and 0 (0%) subjects at week 24.[86] Treatment interruption was registered in 3 patients: colon cancer, referral to another hospital because of other disease, or difficulty attending the hospital because of worsening of dementia.[86]

Other data on the use of ixekizumab in GPP have been reported by Morita et al in their cohort of 7 patients.[87] Of these, 1 (14.3%) discontinued treatment for lack of efficacy while 6 (85.7%) subjects reached week 12. Moreover, 2 patients (28.6%) continued the study up to week 20.[87] At baseline, mean PASI and GPP severity index scores were 10.2 and 3.1 ± 1.7. At week 12, 4 (57.1%) patients with GPP scored "resolved", 2 (28.6%) "improved", and 1 (14.3%) "worsened". Among the 2 patients continuing treatment until week 20, one scored "resolved" and one "improved". No drug-related AEs were reported.[87]

These data in terms of efficacy and safety were also confirmed by several case studies.[88–91] Finally, ixekizumab was found to improve inflammatory markers in patients with GPP with systemic inflammation.[92]

Secukinumab

Secukinumab is a biologic drug acting against IL-17A.[93] The efficacy and safety of secukinumab for the management of GPP were investigated in a 52-week Phase III study involving 12 Japanese patients. Secukinumab was administered at the dosage of 150 mg at baseline, weeks 1, 2, 3 and 4, and then every 4 weeks.[94] Of note, 2 non-responder subjects were up-titrated to 300 mg at weeks 8 and 24, respectively, and 1 patient discontinued the study for protocol deviation. The main endpoint was treatment success (defined as "minimally improved", "much improved" or "very much improved" in Clinical Global Impression [CGI] as per the JDA severity index) at week 16.[94] Secondary endpoints included the achievement of treatment success and PASI75/90/100 at week 52.[94] The mean JDA and PASI scores at baseline were 6 and 17.4, respectively. Globally, 10 (83.3%) reached treatment success at week 16 and at week 52.[94] As regards PASI, 8/11 (72.7%) subjects reached PASI75 at week 52 while PASI90 and PASI100 were reached by 7/11 (63.6%) and 3/11 (27.3%) patients at the same timepoint, respectively. No unexpected safety signals were collected, with nasopharyngitis (6, 50.0%) as the most common AE registered.[94]

Several case reports seem to confirm these results,[95–102] also during pregnancy.[103,104]

Secukinumab seems to be a valuable weapon for GPP also in pediatric patients, as reported in a 48-week retrospective real-world study involving 18 pediatric patients (mean age 7.9 ± 2.3 years) receiving secukinumab 75 mg at weeks 0, 1, 2, 3, and 4 and then every 4 weeks, with the purpose of assessing the change in the Generalized Pustular Psoriasis Area and Severity Index (GPPASI) and Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) scores from the baseline to weeks 2, 4, 12, 24, and 48.[105] GPPASI scored from 31.7 (baseline) to 5.1 at week 2, continuing to decrease to 1.3 (week 4), and maintaining clinical response up to week 48.[105] GPPASI scores of 90 and 100 at week 48 were reached by 2 (11.1%) and 16 (88.9%) patients, respectively. No serious AEs were reported.[105]

Of interest, a recent real-world study compared the effectiveness and safety of acitretin (16 patients) and secukinumab (20 patients) in a pediatric population.[106] JDA score at baseline was 9.0 ± 3.5 for the secukinumab cohort and 10.1 ± 2.3 for the acitretin group.[106] A significant response for patients receiving secukinumab was reported from week 1 (2.8 ± 1.74) up to week 12 (0).[106] In the acitretin group, JDA score reduced to 6.1 ± 2.3 at week 1 and to 0.7 ± 0.9 at week 12.[106] Globally, the authors reported that the effectiveness of secukinumab was better and more rapid than that of acitretin. Secukinumab was also well tolerated, with no severe AEs reported. The dosages of secukinumab and acitretin has not been reported.[106]

Another 9 case reports suggest the effectiveness and safety of secukinumab in GPP management.[107–111]

Finally, two cases of paradoxical GPP induced by secukinumab have been reported.[112,113]

Brodalumab

Brodalumab is a biologic agent that acts through the blockage of the IL-17 receptor.[114] A 52-week, open-label, multicenter, Phase III study involving 12 Japanese patients affected by GPP investigated the effectiveness and safety of brodalumab (140 mg at day 1 and weeks 1 and 2, and then every 2 weeks) for this form of psoriasis.[115] The main outcome was the assessment of the change from baseline of CGI. Secondary endpoints included the assessment of PASI

and Pustular Symptom Score (PSS: range 0–17) reduction. At baseline, mean PASI was 15.0 ± 12.1 and mean PSS was 4.4 ± 2.4. A CGI classification of "improved" or "remission" at weeks 2, 12 and 52 was reached by 9 (75.0%), 10 (83.3%) and 11 (91.7%) patients, respectively.[115] PASI reduced to 5.2 ± 8.6 at week 12 and to 1.8 ± 4.9 at week 52, respectively, with 4 (33.3%) and 10 (83.3%) patients achieving PASI90 at these timepoints.[115] As regards PSS, 4 (33.3%) patients had a score of 1 at week 2, whereas 5 (41.7%) had the same score at weeks 12 and 52. PSS 0 was reached by 3 (25.0%) and 6 (50.0%) patients at weeks 12 and 52, respectively.[115] As regards safety, AEs were reported in 11 (91.7%) patients and 3 of these were considered serious (serious AEs occurred in five patients: three of 12 patients with GPP (lumbar vertebral fracture, exacerbation of pustular psoriasis and hepatocellular carcinoma).[115] However, none were considered treatment related.[115]

Finally, the possible rebound of GPP in patients having to discontinue brodalumab for reasons such as pregnancy or surgery has been reported.[116]

Bimekizumab

Bimekizumab is a humanized antibody that selectively acts on the biologic functions of IL-17A and IL-17F.[117–119]

Recently, a case of a 69-year-old Japanese woman with GPP successfully treated with bimekizumab in combination granulocyte monocyte adsorption apheresis was reported.[120]

Guselkumab

Guselkumab is a monoclonal antibody acting through the blockade of the IL-23 cytokine pathway.[121] Despite its efficacy and safety for psoriasis management having been widely described,[122,123] data on its use for GPP are scant. However, Sano et al reported the results of a 52-week, Phase III, multicenter study investigating the use of guselkumab on 10 Japanese patients with GPP. The main aim of the study was to assess the proportion of patients achieving treatment success, defined as a CGI score of "very much improved", "much improved" or "minimally improved" (range: 1 = "very much improved" to 7 = "very much worse") after 16 weeks of treatment.[124] Through week 52 the secondary outcomes were also evaluated, which included change of JDA severity index (from 0 [best] to 17 [worst]) and of PASI. Guselkumab was scheduled at the dosage of 50 mg at weeks 0, 4 and every 8 weeks thereafter. At week 20, dose escalation to 100 mg was allowed.[124]

At week 16, a CGI of "very much improved" or "much improved" or "minimally improved" was reached by 2 (22.2%), 2 (22.2%) and 3 (33.3%) patients, respectively. Two patients discontinued the study (1: squamous cell carcinoma of the skin, 1: lack of efficacy).[124] As regards secondary outcomes, a PASI reduction from baseline (29.3 ± 20.0) was observed at week 8 (−13.8 ± 12.68), continuing to decrease up to week 52 (4.8 ± 6.4).[124] Similarly, JDA reduction from 5.4 ± 1.8 was observed as early as week 1 (−0.2 ± 2.0) up to week 52 (−3.0 ± 2.4).[124] All patients experienced at least one AE, with only two of these considered serious: fall and loss of consciousness and squamous cell carcinoma of skin.[124] Of note, guselkumab was administered at a different dosage as compared to a labelled one (100 mg), with the same time of administration.[124]

Tildrakizumab

Tildrakizumab is a humanized IgG1 monoclonal antibody acting on IL-23 p19.[125] Even if several studies have shown its effectiveness and safety in psoriasis management,[126–128] data on its use on GPP are still absent.

Risankizumab

Risankizumab is a fully human monoclonal antibody that selectively targets IL-23A.[129,130] The effectiveness and safety of risankizumab for the management of GPP have been reported by a primary analysis and 180-week follow-up results of the Phase III, multicenter IMMspire study, involving 8 Japanese patients with GPP, randomized 1:1 to receive risankizumab 150 mg or 75 mg at week 0, week 4 and every 12 weeks up to week 160.[131] The main aim was the assessment of the percentage of subjects reaching clinical response at week 16, defined as "slightly improved" in the overall improvement rating from baseline according to the JDA score.[131] Secondary end points comprised the percentage of subjects reaching clinical response at week 52 as well as PASI90 response at weeks 16 and 52. Other efficacy end

points evaluated in weeks were the achievement of clinical responses, PASI 90, DLQI 0/1, and change from baseline in total JDA score. At baseline, mean PASI was 17.4 ± 9.4 and mean JDA 4.8.[131]

The primary endpoint at week 16 was reached by all patients, regardless of the dose of risankizumab.[131] Clinical response was maintained in all those subjects who continued the study.[131] JDA reduction was reported as early as week 4 (−3.5 SD ± 1.9]), continuing to decrease through week 52 and maintaining the response through week 160.[131] Globally, 87.5% of patients reached PASI90 at week 16, and most of maintained this result through week 160. Similarly, DLQI 0/1 was reached by 75.0% of subjects at week 16, remaining stable among patients who did not interrupt the study. Finally, no drug-related serious AEs were reported.[131] Recently, a case of acute GPP and a flare of GPP following BNT162b2 vaccine successfully treated with risankizumab have been reported.[132,133] Finally, a case of risankizumab-induced paradoxical GPP has been described.[134]

Spesolimab

Recent knowledge on GPP pathogenesis, in particular the role of IL-36 which seems to induce neutrophil chemokine expression, infiltration, and pustule formation, suggests this cytokine as a potential therapeutic target.[135] Spesolimab is an IL-36 receptor antagonist recently approved by US FDA (1 September 2022) and by the EMA (9 December 2022) for the treatment of GPP flares in adults at the dosage of a single intravenous dose of 900 mg over 90 minutes followed by a second infusion one week after in the case of persistant symptoms.[136] Its efficacy and safety in GPP management have been evaluated in a Phase II randomized trial (Effisayl 1) involving 53 patients randomized to receive a single 900-mg intravenous dose of spesolimab (n = 35) or placebo (n = 18).[137] The primary end point was the achievement of a GPPGA pustulation sub-score of 0

(range: 0 [no visible pustules] to 4 [severe pustulation]) at the end of week 1.[137] Globally, 19 (54%) and 1 (6%) patient in the spesolimab and placebo group reached a pustulation sub-score of 0 ($p<0.001$) and 15 (43%) and 2 (11%) subjects reached a GPPGA total score of 0 or 1 in the same groups, respectively ($p=0.02$) at week 1.[137] As regards safety, a total of 23 (65.7%) patients receiving spesolimab experienced at least 1 AE, with infection as the most common (6, 17.1%). Of note, 2 (5.7%) AEs were classified as serious.[137]

Recently, a placebo-controlled study (Effasyl 2) involving subjects with GPP has been planned to investigate whether spesolimab maintenance treatment can prevent flares, providing sustained control of the disease.[138] Patients will be randomized 1:1:1:1 to receive a spesolimab 600-mg subcutaneous loading dose followed by a 300-mg maintenance dose managed every 4 or 12 weeks, or a spesolimab 300-mg induction dose followed by a 150-mg dose every 12 weeks, or placebo, for 48 weeks.[138] The main endpoint is time to first GPP flare.[138] Finally, 6 cases of GPP successfully treated with spesolimab have been reported.[139,140]

Discussion

The introduction of biologic drugs positively impacted on the treatment of moderate-to-severe forms of plaque psoriasis.[141–143] Their effectiveness and safety were also confirmed during the Covid-19 pandemic period,[144,145] which completely changed daily clinical practice.[146–148] However, there is still an unmet need for the treatment of rare forms of the disease. Among these, GPP is characterized as primary, sterile, macroscopically visible pustules on non-acral skin (excepting cases where pustulation is limited to psoriatic plaques) and may or may not be associated with systemic inflammation and/or plaque psoriasis.[149] As regards clinical presentation, GPP flares are acute events, which may be elicited by several factors, such as corticosteroid withdrawal, infections, drugs (including paradoxical reaction to biologic drugs), and stressful life events.[149,150] The management of GPP is challenging, particularly because of the different pathogeneses with respect to plaque psoriasis. Indeed, different cytokine cascades seem to be predominant in the pathogenesis of each different psoriasis form, with the IL23/IL17 axis implied in plaque psoriasis, and the IL36 pathway in GPP.[151] In particular, GPP derives from dysregulation of the innate immune system, mainly the IL36 pathway, which leads to an inflammatory keratinocyte response, with the recruitment of neutrophils.[151] This pathogenetic mechanism has been confirmed by studies reporting that mutations in IL36RN (the most common), CARD13, MPO, TNIP1, AP1S3, SERPINA1, and SERPINA3 are associated with GPP.[151] In particular, IL36RN, MPO, and SERPINA 1/3 mutations lead to the upregulation of the IL36 pathway, which further stimulates the downstream proinflammatory NF-κB and MAPK

cascade.[151] Similarly, the loss-of-function mutation of AP1S3 and TNIP1 as well as the gain-of-function mutations of CARD14 are involved in IL36 signaling by hyperactivating the NF-κB pathway.[151] Globally, upregulation of the IL36 cascade triggers the proliferation of IL-17-producing CD4+Th17 cells, which continue to spread these inflammatory responses by stimulating the expression of IL-36 and other inflammatory cytokines.[151] Finally, the interaction of the IL36 and the IL17/IL23 pathways indicates that both the innate and the adaptive immune responses intertwine in the GPP pathogenesis.[151]

Thus, the different pathogenesis of GPP, as compared with plaque psoriasis, may lead to the need for a personalized approach.[152] Indeed, conventional systemic drugs are often ineffective or contraindicated and use of biologics approved for plaque psoriasis is off-label.[153] Moreover, the reduced prevalence of GPP makes clinical trials challenging and current management recommendations are founded on insufficient evidence.[153] In this scenario, we performed a review of current literature with the aim of evaluating the effectiveness of biologic drugs for the management of GPP in order to offer a wide current clinical perspective.

The efficacy of biologics targeting IL23, IL17 and TNFα has been reported by a few clinical trials (adalimumab, infliximab, certolizumab, ixekizumab, secukinumab, brodalumab, guselkumab, risankizumab) and limited case reports. However, all of the clinical trials involved only Japanese patients and up to 10% of subjects did not respond to treatment. Moreover, drug dosage was often different and inferior compared to EMA- or FDA-approved dosage for psoriasis. Finally, clinical outcomes investigated in clinical trials are often different, making a standardized endpoint necessary to allow an indirect comparison among these drugs.

As regards real-life data, infliximab has the highest number of case reports collected (24/101, 23.8%) (Table 1). In our opinion, the most frequently reported use of infliximab may derive from its longer period of approval as compared with other biologics. Some biologics have been successfully used in pediatric GPP (adalimumab, etanercept, infliximab, secukinumab), with adalimumab as the most common (9/24, 37.5%) (Table 1). Furthermore, the use of biologic drugs in GPP management has also been reported in patients during pregnancy (infliximab, secukinumab, and certolizumab).

Finally, 20 cases of paradoxical GPP have been reported during biologic treatment (adalimumab, certolizumab, infliximab, secukinumab, ustekinumab, and risankizumab). However, the possible pathogenetic mechanism of these paradoxical reactions has not been identified.

Recently, spesolimab, an IL-36 receptor antagonist, has been approved for the management of GPP.[136] In particular, it is the first biologic drug licensed for this use and the unique on-label biologic available for GPP management. The use of spesolimab revealed excellent results in terms of efficacy and safety in the management of GPP. Indeed, Effisayl 1 showed that 54% of patients receiving spesolimab reached a pustulation sub-score of 0 as compared with 6% in the placebo group ($p<0.001$); 43% and 11% of participants reached a GPPGA total score of 0 or 1 in the same groups, respectively ($p= 0.02$) after 1 week of treatment.[137] The safety of spesolimab was suggested, with AEs reported in 65.7% of patients.[137]

Despite its recent approval, real-life data are limited to 6 cases of GPP successfully treated with spesolimab being reported.[139,140] Moreover, concerns regarding the effectiveness of maintenance treatment with spesolimab in the prevention of GPP flares were raised. The Effasyl 2 trial will try to address these concerns.[138]

To sum up, several gaps in GPP knowledge still remain. On the one hand, variations in response to spesolimab and other biologic therapies across different ethnic groups should be investigated; on the other hand, the recent approval of spesolimab led to the need for new guidelines/treatment algorithms. In this scenario, more data on the efficacy of other biologic drugs are required, especially in the long term for flare up prevention.

Conclusion

GPP is a severe and potentially life-threatening form of psoriasis which requires an effective and rapid approach. Our review highlights the current available data on biologics for GPP. Although several studies investigating the use of biologics in GPP have been conducted, an indirect comparison of biologics is not allowed, as clinical evaluation differ. Certainly, the rarity of the disease is the main challenge for the definition of targeted guidelines. This scenario may be completely changed by spesolimab, the first biologic approved for GPP, specifically acting on the IL-36 pathway. Promising data have been reported in clinical trials and long-term studies are ongoing. However, real-life data are still

scant and the efficacy of this drug in preventing GPP flares has yet to be elucidated. Thus, more studies are required in order to better define the most adequate GPP treatment algorithm.

Disclosure

The authors report no conflicts of interest in this work.

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