Original Article

Biological Treatments For Pustular Psoriasis: A Systematic Review

Zeiad Abdulaziz Alobead*[1], Asem AlMesfer[1], Ahmad Assiri[2]

[1]Department of Dermatology, King Fahad Medical City, Riyadh, Saudi Arabia
[2]Department of Dermatology, Jazan University Hospital, Jazan, Saudi Arabia
*Corresponding author: Zeiad Abdulaziz Alobead, E-mail: sts_611@hotmail.com
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Abstract

Objectives: To gather and analyze recent research on biologic treatments for pustular psoriasis, focusing on their effectiveness and safety. **Methods:** A thorough search across four databases identified 400 relevant publications. After removing duplicates using Rayyan QCRI and screening for relevance, the search yielded 614 publications, of which 92 full-text articles were reviewed, and 6 met the eligibility criteria for evidence synthesis. **Results:** We included six studies with a total of 208 GPP patients and less than half of them were females 58 (27.9%). In this review, biological treatments for pustular psoriasis, including secukinumab, ixekizumab, adalimumab, brodalumab, and guselkumab, were evaluated for efficacy and safety. Secukinumab showed consistent clinical improvement with manageable side effects like nasopharyngitis and pruritus. Ixekizumab demonstrated substantial efficacy, with mild adverse events, primarily injection site reactions. Adalimumab was effective even in resistant cases, though 30% of patients experienced significant adverse events, including hypocalcemia. Brodalumab rapidly alleviated symptoms, with nasopharyngitis being the most common side effect. Guselkumab showed therapeutic value with manageable side effects such as diarrhea and arthralgia. Overall, all treatments were effective, with tolerable safety profiles, though larger, more diverse studies are needed. **Conclusion:** Biologic treatments like secukinumab, ixekizumab, adalimumab, brodalumab, and guselkumab are emerging as reliable and effective options for treating Generalized Pustular Psoriasis. They offer better outcomes and longer-lasting effects compared to non-biologic therapies, making them a valuable addition to the treatment toolkit for GPP. However, more research is needed to fully understand the long-term safety of these treatments. Going forward, studies should aim to address the current gaps and further explore the potential of biologics to provide lasting relief for patients living with this challenging skin condition.

Keywords: Pustular psoriasis; Generalized Pustular psoriasis; Treatment; Biological therapy; Systematic review.

Introduction:

GPP is a rare and aggressive auto-inflammatory skin condition distinguished by the sudden onset and widespread appearance of superficial erythematous sterile pustules. It has a life-threatening possibility due to its multisystemic nature, and a history of plaque psoriasis may increase the chance of developing GPP [1, 2]. GPP affects both men and women and is more prevalent in adults than in youngsters. Its frequency varies by ethnicity, with Asians having a higher incidence than Caucasians [1, 3]. The greater prevalence of GPP among Asians is most likely due to hereditary factors. However, statistics are restricted because to differences in methodology, diagnostic mistakes, and inconsistent definitions. Because of these challenges, making direct comparisons is difficult, hence provided estimates should be viewed as indicating trends rather than accurate data [4].

Clinically, GPP varies greatly, as it might show as a relapsing disorder with recurring flares but no pustulation in between, or as a chronic disease with persistent pustular eruptions and exacerbations. It is characterized by the development of sterile pustules throughout painful, erythematous skin, which spreads and recruits previously unaffected tissue. In some circumstances, it results in erythroderma. Patients are clearly unwell, with high temperature, malaise, and arthralgia. Acute infections, menstruation, and abrupt withdrawal of systemic corticosteroids have all been shown to cause acute flares [5, 6].

With the introduction of new biologic medicines, notably those licensed to combat the symptoms of psoriasis, new therapeutic agents began to be examined for the treatment of GPP, bringing new and more effective choices. These novel medications targeted cytokines involved in psoriatic immune pathways (such as TNF, IL-17, or IL-23), which overlap at some places with the GPP pathway, and have shown good efficacy in persons with GPP. However, they should be taken with caution because, paradoxically, they have been shown to cause pustular illness in patients receiving therapy for other disorders [7, 8].

Pustular psoriasis is a rare and serious form of psoriasis that causes painful pustules to form on the skin, often leading to significant discomfort and a diminished quality of life. Traditional treatments, such as topical creams and systemic medications, frequently prove ineffective in managing this condition. In recent years, biologic therapies have emerged as a new approach, offering more targeted treatment options aimed at the specific immune pathways involved in the disease. With ongoing advancements in these therapies, it is essential to review the latest evidence on their effectiveness and safety. This will help healthcare professionals make better treatment choices and guide future research to improve care for patients with pustular psoriasis. This systematic review aims to gather and analyze recent research on biologic treatments for pustular psoriasis, focusing on their effectiveness and safety. By reviewing clinical trials, observational studies, and case reports, the goal is to provide a clear overview of how these treatments are working in practice and their impact on patient outcomes.

Methods:

Search strategy

The systematic review adhered to the PRISMA and GATHER criteria. A thorough search was undertaken to locate relevant studies on the biological management of pustular psoriasis. The reviewers looked at four electronic databases: PubMed, Cochrane, Web of Science, and SCOPUS. Studies published between 2014-2019 were included. We uploaded all of the titles and abstracts identified through electronic searches into Rayyan, removing any duplicates. All texts from papers that met the inclusion criteria based on title or abstract were collected and thoroughly inspected. Two reviewers independently evaluated the appropriateness of the extracted publications and resolved any contradictions through discussion.

Study population—selection

The PICO (Population, Intervention, Comparison, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Patients diagnosed with pustular psoriasis, (ii) Intervention: Biological treatment, (iii) Comparator: Other treatments than the biological, (iv) Outcome: effectiveness and safety of biological treatment. Only primary investigations studying the administration of biological treatment to pustular psoriasis were included.

Data extraction

Two unbiased reviewers retrieved data from studies that met the inclusion criteria in a consistent and established format. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Participants' number, (v) Age, (vi) Gender, (vii) Follow-up duration (in weeks) (viii) disease duration (in years), (ix) Type of treatment, (x) Psoriasis type, (xi) Main outcomes (Efficacy, safety, and complications).

Quality review

The Cochrane Risk of Bias Instrument [9] was used to conduct a critical appraisal of the identified RCTs. This tool evaluates the risk of bias in seven fields: arbitrary sequence generation, allocation secrecy, blinding of participants and employees, blinding of outcome evaluation, inadequate outcome data, selective reporting, and additional bias sources. The risk of bias in each of these domains was classified as low, unclear, or high.

Results:

The specified search strategy yielded 614 publications **(Figure 1).** After removing duplicates (n =301), 313 articles were evaluated based on title and abstract. Of these, 221 failed to satisfy eligibility criteria, leaving just 92 full-text articles for comprehensive review. A total of 6 satisfied the requirements for eligibility with evidence synthesis for analysis.

Sociodemographic and clinical outcomes

We included six studies with a total of 208 GPP patients and less than half of them were females 58 (27.9%). All of the included studies RCTs [11-16]. Five studies were implemented in Japan [11, 12, 13, 15, 16], and one was multi-centered [14]. The follow-up duration was 52 weeks in the six studies.

Secukinumab

Secukinumab showed a generally favorable safety profile. Across the studies, no unexpected warning signs or fatalities were observed during the 52-week follow-up. However, common side effects included nasopharyngitis, pruritus, arthralgia, and headaches. These adverse events were manageable, suggesting the drug's safety for long-

term use. Patients treated with secukinumab showed significant improvements in the severity of pustular psoriasis, with notable improvements in skin symptoms and quality of life. It was effective in reducing disease activity, as reflected in clinical response scores, indicating sustained efficacy over a 52-week period [11, 14].

Ixekizumab

Ixekizumab was associated with some adverse events, including infections, allergic reactions, and injection site reactions. Despite these side effects, there were no reports of fatalities, and the drug was generally well-tolerated. The outcomes were positive, with substantial improvements observed in patients with generalized pustular psoriasis (GPP). The drug demonstrated strong efficacy, leading to symptom reduction and better clinical outcomes over the study period [12].

Adalimumab

Safety data for adalimumab showed that around 30% of participants experienced major adverse events. Common AEs included nasopharyngitis, itching, and hypocalcemia. While these side effects were present, they were manageable, and the treatment was generally well-tolerated. Adalimumab proved to be effective even in patients who did not respond to prior treatments. It was efficacious in reducing the symptoms of pustular psoriasis over a 52-week period, making it a viable option for long-term management of the condition [13].

Brodalumab

Brodalumab's safety profile indicated that 91.7% of patients experienced adverse events, with nasopharyngitis being the most common. Despite the high incidence of AEs, there were no new or severe warning signs, suggesting a favorable safety profile. The drug showed a strong therapeutic effect, rapidly alleviating symptoms of GPP. Brodalumab was effective in managing the disease, with positive clinical outcomes and sustained efficacy without producing any new safety concerns [14].

Guselkumab

Guselkumab's treatment-emergent side effects included alopecia, nasopharyngitis, diarrhea, nausea, and arthralgia. These adverse events were commonly reported, but no severe or life-threatening issues were identified, indicating the drug's safety. The study showed that guselkumab had a therapeutic benefit in managing GPP. Patients experienced improved clinical outcomes, which demonstrates the drug's efficacy in treating pustular psoriasis over the course of the study [15].

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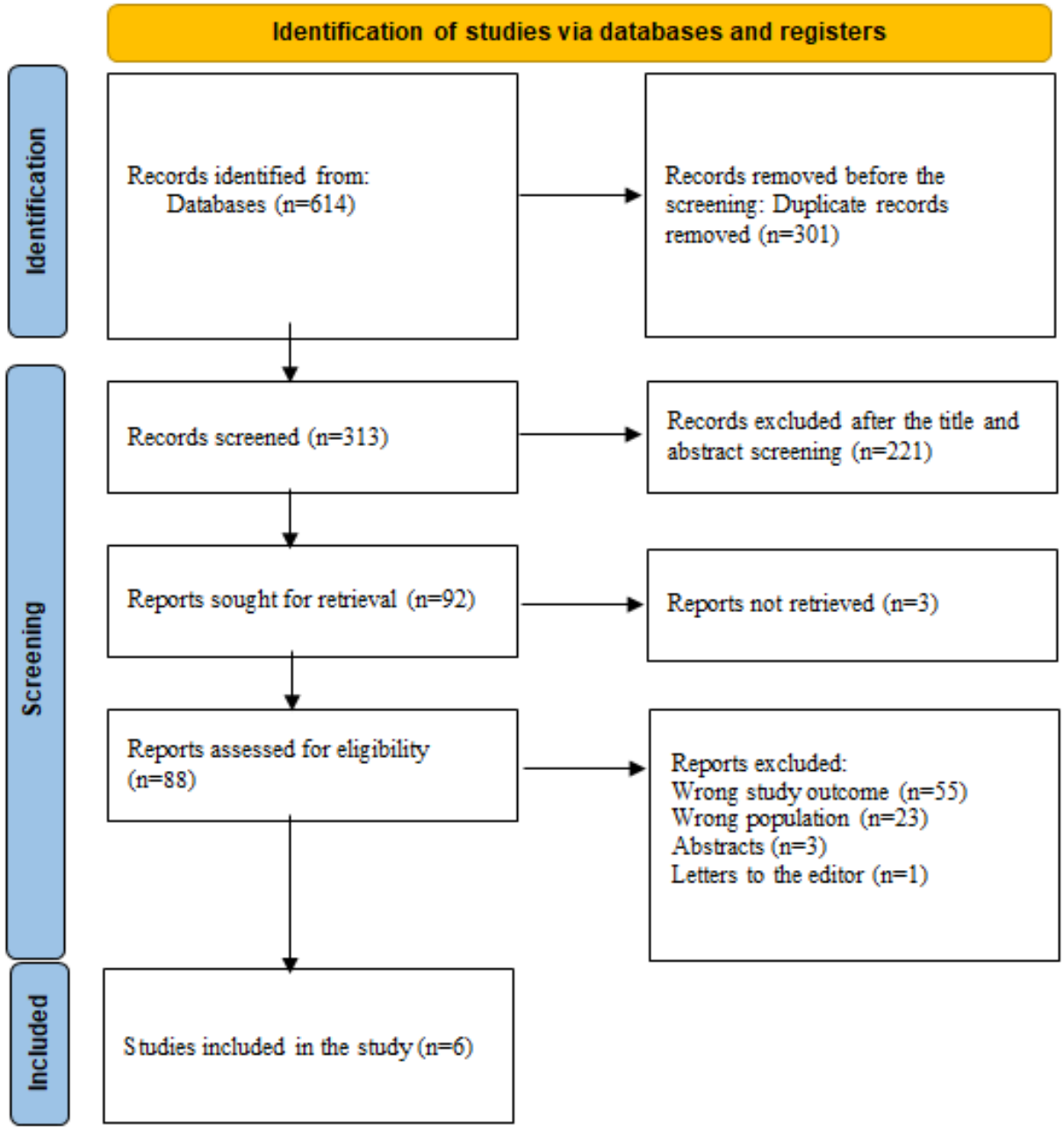
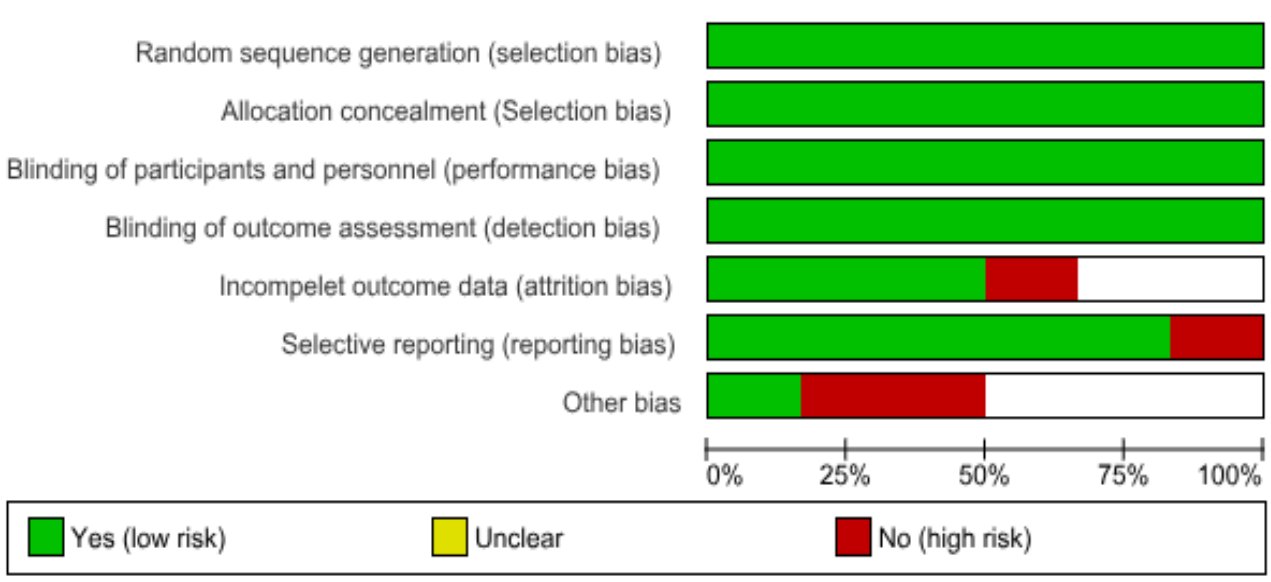


Figure (1): PRISMA flowchart [10].

Table (1): Outcome measures of the included studies

Study ID	Country	Study design	Sociodemographic	Follow-up (weeks)	Disease duration (years)	Treatment type	Psoriasis type	Safety	Main outcomes
Imafuku et al., 2016 [11]	Japan	RCT	N=12 Mean age: 56.3 Males: 8 (66.7%)	52	NM	Secukinumab	GPP	There were no unanticipated warning signs in the safety evaluation of secukinumab in this study, and no deaths were recorded until the 52-week mark. The most often reported AEs were arthralgia, urticaria, DM, and nasopharyngitis.	A significant number of patients showed improvement during treatment, with a clinical global impression (CGI) score of "much improved" or "very much improved" at week 16. There was a quick reaction seen in relation to the Japanese Dermatological Association severity index.
Saeki et al., 2017 [12]	Japan	RCT	N=5 Mean age: 48.2 Males: 2 (40%)	52	15.1±9.5	Ixekizumab	GPP	No mortalities were recorded. Side efffects included infection, allergic reactions, and injection site reaction.	Ixekizumab demonstrated a sbstantial efficacy in GPP
Morita et al., 2018 [13]	Japan	RCT	N=10 Mean age: 49.8 Males: 7 (70%)	52	10.6 ± 12.6	Adalimumab	GPP	Three patients (30%) had major AEs, and nine of them (90%) had one or more AEs. Nasopharyngitis, itching, and hypoalbuminemia were the most frequent adverse events.	Even in individuals who had not responded to prior infliximab treatment, adalimumab proved to be efficacious and well-tolerated for a maximum of 52 weeks when administered to Japanese patients with GPP. Additionally, no novel safety concerns were detected during this time.
Mrowietz et al., 2019 [14]	Multi-centered	RCT	N=159 Mean age: 50.7 Males: 32 (20.1%)	52	NM	Secukinumab	PPP	During a 52-week period, PPP patients treated with 300 mg of secukinumab demonstrated improvements in PPPASI75 responses and a higher quality of life. The most common adverse events were pruritus, headache, and nasopharyngitis.	During a 52-week period, PPP patients treated with 300 mg of secukinumab demonstrated improvements in palmoplantar Psoriasis Area and Severity Index (PPPASI75) responses and a higher quality of life.
Yamasaki et al., 2017 [15]	Japan	RCT	N=12 Mean age: 43.1 Males: 3 (25%)	52	6·56 ± 7·2	Brodalumab	GPP	11 out of 12 patients (91.7%) experienced AEs; nasopharyngitis was the most common AE.	Shortly after starting treatment, brodalumab can alleviate a patient's symptoms and has shown favorable safety profiles without producing any new warning signs.
Sano et al., 2018 [16]	Japan	RCT	N=10 Mean age: 42.6 Males: 6 (60%)	52	14.9 ± 31	Guselkumab	GPP	The most frequently reported treatment-emergent side effects included alopecia, nasopharyngitis, diarrhea, nausea, and arthralgia.	This study demonstrates guselkumab's therapeutic value in the management of GPP.

NM=Not-mentioned



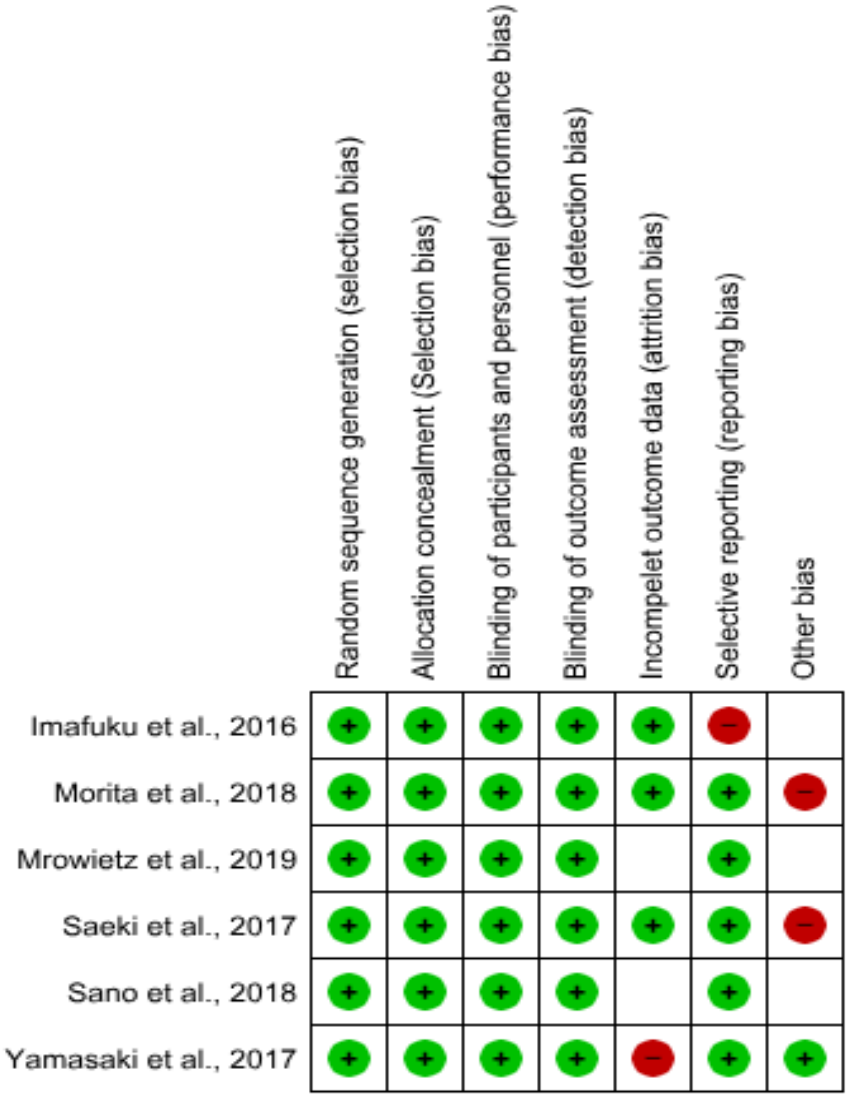


Figure (2): Cochrane risk of bias assessment.

Discussion:

This review sheds light on the growing role of biological treatments for GPP, with evidence suggesting that drugs like Ixekizumab, Secukinumab, and Guselkumab are effective and generally well-tolerated. Guselkumab, in particular, appears to have an edge when it comes to reducing recurrence. This suggests that Guselkumab may offer more robust benefits for GPP patients compared to the alternatives. We also found that Secukinumab, meanwhile, has shown superior results in clearing skin compared to Ustekinumab. Despite these encouraging findings, concerns about the long-term safety of these biological therapies remain and need further investigation. The overall positive outcomes point to biologics becoming an essential tool in the management of GPP, especially for patients with more chronic conditions. Sevrain **et al.** reported that IL-36 plays an important role in the pathophysiology of GPP by initiating the inflammatory cascade that leads to the illness. As a result, spesolimab and imsidolimab, IL-36 receptor inhibitors, were created specifically to treat GPP. Following clinical testing, these medications were demonstrated to be significant improvements, and they have already been licensed for the treatment of GPP flares. IL-36 receptor inhibitors have demonstrated promising outcomes and are shifting the therapy paradigm for GPP [17].

International treatment guidelines for people with GPP are insufficient, and the majority of current therapies are utilized off-label due to efficacy in plaque psoriasis or minimal data collected from case reports and petite, uncontrolled, open-label, single-arm experiments in GPP [18]. Recent developments in our comprehension and management of GPP provide numerous potential for improving patient care.

Posso-De Los Rios et al. also reported that biologics have excellent clinical outcomes for persistent pustular psoriasis and long-term responsiveness. Despite the promising results of pustular psoriasis therapy as demonstrated in case reports on the safety and efficacy of biologics, additional trials and basic investigations are required to ensure long-term control of pustular psoriasis. Recruitment of a homogeneous group of patients is difficult due to the unanticipated and lifelong variation in clinical course of pustular psoriasis. Because pustular psoriasis is a lifelong condition, these individuals may have used a variety of medicines, both systemic and external; therefore, background therapy must be included in future research studies of biologics for pustular psoriasis [19]. A similar systematic review by **Hoegler et al.** also found that with the recent expansion of biologic therapies for plaque psoriasis, novel medicines have been shown to be successful in this condition. Infliximab, a TNF-α inhibitor, has the strongest evidence for efficacy, safety, and quick response [20].

The findings from this review highlight important takeaways for clinical practice. Biologic therapies, especially Guselkumab and Secukinumab, should be considered as primary options for patients with GPP, particularly for those who haven't responded well to traditional treatments. Patients with a longer history of the disease seem to benefit more from these treatments, suggesting that biologics may be a more suitable choice earlier in the disease course. That said, given the uncertainty around their long-term safety, doctors should continue to monitor patients closely and weigh the benefits against the risks.

Strengths and limitations:

First and foremost, we covered a wide range of therapies, including secukinumab, ixekizumab, adalimumab, brodalumab, and guselkumab. This variety is particularly valuable as it offers clinicians the opportunity to compare different treatment options, helping them make more informed decisions tailored to individual patients. It's also a strong point that the table does not just focus on efficacy but provides detailed safety data, giving a clearer picture of what healthcare providers can expect when administering these drugs. Understanding the common adverse events like nasopharyngitis, pruritus, and injection site reactions is crucial for ensuring patient safety and long-term treatment success.

Another advantage is that it reports on treatments over a relatively long follow-up period—typically 52 weeks. This allows us to see how patients fare in the longer term, both in terms of improvements in their symptoms and the development of any side effects. In a chronic disease like pustular psoriasis, having this extended data is especially important because it helps ensure that the benefits of treatment are not short-lived and that no serious safety concerns arise after prolonged use.

The limitations included the small sample sizes in some of the studies. For example, certain studies had only 5 or 10 participants, which makes it harder to confidently generalize the results to the broader population. Larger, more inclusive studies would help solidify the findings and offer stronger evidence for clinical decision-making. Additionally, all the studies were conducted in Japan, meaning the results may not fully apply to patients from other regions, who might have different genetic backgrounds or healthcare systems. This lack of geographic diversity limits our understanding of how these treatments might work in other populations.

Finally, while we provided good insight into the short- and mid-term safety of these treatments, it does not go far enough in addressing potential long-term risks. For chronic conditions like pustular psoriasis, patients may need to use these therapies for years, if not decades, and having more data on long-term safety would be invaluable.

Conclusion:

Overall, biologic treatments like secukinumab, ixekizumab, adalimumab, brodalumab, and guselkumab are emerging as reliable and effective options for treating Generalized Pustular Psoriasis. They offer better outcomes and longer-lasting effects compared to non-biologic therapies, making them a valuable addition to the treatment toolkit for GPP. However, more research is needed to fully understand the long-term safety of these treatments. Going forward, studies should aim to address the current gaps and further explore the potential of biologics to provide lasting relief for patients living with this challenging skin condition.

Conflict of interest: None.

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