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Current treatments for generalized pustular psoriasis: A systematic literature review

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The current treatment landscape for generalized pustular psoriasis (GPP) presents a paucity of high-quality evidence for treatments that can rapidly and completely resolve symptoms with an acceptable safety profile

PURPOSE

To identify, review and summarise current published literature on the efficacy, safety, quality of life (QoL) and economic burden associated with current interventions for the treatment of GPP, and to understand how these interventions are used in clinical practice.

INTRODUCTION

- GPP is a rare, debilitating and potentially life-threatening autoinflammatory skin disease characterised by recurrent flares of widespread pustules, which can occur with systemic inflammation and may be accompanied by plaque psoriasis[1–3]
- There are currently no approved GPP-specific therapies in the USA and Europe[1]
- A systematic literature review (SLR) was conducted, with a timeframe of the past 40 years, to identify and summarise the evidence for the treatment options for GPP and evaluate the robustness of this evidence
- The review was followed by summarisation of the treatment landscape of GPP and collation of data on efficacy, safety and QoL for the available treatments

CONCLUSIONS

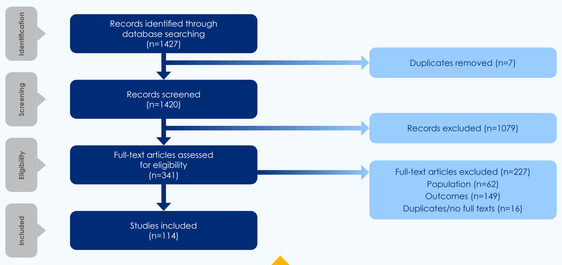
- This review is the first SLR conducted for GPP to include publications in all languages over a 40-year timeframe (1980-2021)
- Despite the wide search criteria, application of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group criteria determined that the included studies were of low or very low quality; therefore, the results of these should be interpreted with caution
- Approval of biologics in some countries, such as Japan, was based on small, open-label, uncontrolled studies that did not evaluate clinically robust endpoints for sustained long-term control of symptoms
- Evidence for other interventions is from small, open-label studies and case studies, and shows limited efficacy and unsuitability for life-long treatment due to an unacceptable safety profile and existing contraindications
- The small sample size owing to the rarity of GPP and lack of uniformity in the endpoints limited the robustness of the data
- There is a need for well-designed studies to investigate optimal treatment for patients with GPP

METHODS

- The search protocol containing detailed search strategy and eligibility criteria for inclusion of studies was logged in the PROSPERO database (CRD42021215437). The search strategy was comprehensive and no limits were applied with respect to population, intervention/comparator, study design and language
- Searches were conducted using EMBASE and PubMed databases to capture all relevant studies from 1980–2021. After deduplication, studies were screened by two independent reviewers. Any discrepancies were reconciled by an independent reviewer
- Details pertaining to publication, population, intervention, efficacy, safety and QoL were captured by reviewers and independently quality checked. Overall strength of evidence with respect to each treatment was determined based on precepts outlined in the GRADE working group criteria

RESULTS

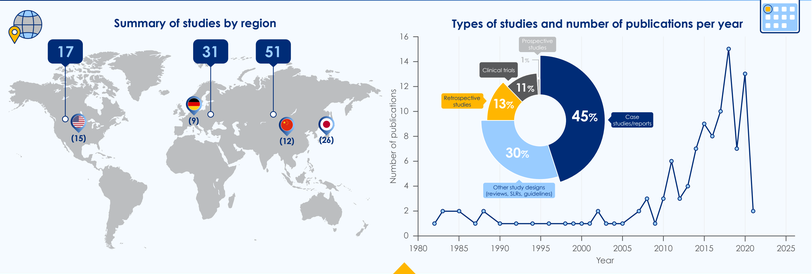
Study flow diagram



Of the total 1427 publications, 114 eligible publications passed both rounds of screening and were included in the review

RESULTS (CONT.)

Study characteristics



- **Most of the included studies were case studies/reports (45%), followed by observational studies, clinical trials and reviews**
- **Most studies were reported from Japan and China, followed by Europe and the USA**

Oral systemic treatments

Treatment	No. of patients	Population type	Efficacy	Safety	Grade of evidence
Corticosteroids	115		✓	✓	D C B A
Methotrexate	81		✓	✓	D C B A
Mycophenolate mofetil	1		✓	✗	D C B A
Hydroxyurea	10		✓	✓	D C B A
Leflunomide	7		✓	✗	D C B A
Cyclosporine	109		✓	✓	D C B A
Tacrolimus	4		✓	✗	D C B A
Apremilast	2		✓	✓	D C B A
Ro-10-9359	2		✓	✓	D C B A
Isotretinoin	2		✓	✓	D C B A
Etretinate	30		✓	✓	D C B A
Acitretin	155		✓	✓	D C B A
Fumaric acid esters	19		✓	✗	D C B A

Adults · Children · Pregnant women · ✓ Reported per treatment · ✗ Not reported

Systemic immunosuppressants · Calcineurin inhibitor · Non-immunosuppressants · Retinoids · Fumarates

- **The most commonly used treatment options included cyclosporine, methotrexate and acitretin**
- **The overall grade of evidence was low**

Biologics

Treatment	No. of patients	Population type	Efficacy	Safety	Grade of evidence
Infliximab	51		✓	✓	D C A
Adalimumab	34		✓	✓	D C A
Etanercept	5		✓	✗	D C A
Secukinumab	36		✓	✓	D C A
Ixekizumab	20		✓	✓	D C A
Brodalumab	12		✓	✓	D C A
Ustekinumab	21		✓	✓	D C A
Guselkumab	15		✓	✓	D C A
Anakinra	5		✓	✓	D C A
Gevokizumab	2		✓	✗	D C A
Canakinumab	1		✓	✗	D C A
Spesolimab	7		✓	✓	D C A

Adults · Children · Pregnant women · ✓ Reported per treatment · ✗ Not reported

IL, interleukin; R, receptor; TNF, tumour necrosis factor.

TNF-α inhibitor · IL-17A inhibitor · IL-17 inhibitor · IL-12-23 inhibitor · IL-23 inhibitor · IL-1Ra · IL-1β inhibitor · IL-36R inhibitor

- **The evidence for biologics mostly comes from uncontrolled clinical studies and case studies/reports**
- **The evidence for biologics showed favourable efficacy, faster time to clearance of GPP pustules and a good safety profile**

Other therapies

Treatment	No. of patients	Population type	Efficacy	Safety	Grade of evidence
Phototherapy	167		✓	✗	D A
Oral psoralen and UV-A (PUVA)	77		✓	✓	D C B A
GMA	43		✓	✓	D C A
GCAP	6		✓	✓	D C A
Colchicine	5		✓	✓	D C A
Glycyrrhizin	9		✓	✗	D C A
Topical steroid	4		✓	✓	D C A
Zinc acetate	1		✓	✗	D C A
Penicillin	1		✓	✗	D C A
Macrolide	44		✓	✗	D C A
Thiamphenicol	4		✓	✓	D C A

Adults · Children · Pregnant women · ✓ Reported per treatment · ✗ Not reported

GCAP, granulocyte and monocyte adsorption apheresis; GMA, granulocyte-monocyte apheresis; UV, ultraviolet.

Phototherapies · Apheresis · Other treatments · Antibiotics

- **The strength of evidence for other therapies varies from medium to very-low quality**
- **PUVA demonstrated the highest quality of evidence; many agents were used in combination with other existing modalities**

Patient-reported outcomes

Treatment	QoL/functional improvement: EQ-5D	SF-36 (HRQoL)	Pain/VAS	FACIT	Patient experience	Indirect burden	Caregiver experience	Other QoL measures	Dermatology-specific QoL parameters: DLQI	Psoriasis Disability Index	SKINDEX	PSS	Itch - NRS
Infliximab	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Adalimumab	✗	✓	✓	✗	✗	✗	✗	✓	✓	✓	✓	✗	✗
Brodalumab	✗	✓	✗	✗	✗	✗	✗	✓	✓	✗	✗	✓	✗
Gevokizumab	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗
Guselkumab	✗	✓	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗
Ixekizumab	✗	✗	✗	✗	✗	✗	✗	✓	✓	✗	✗	✓	✗
Secukinumab	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗
Ustekinumab	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Spesolimab	✗	✗	✓	✓	✗	✗	✗	✓	✗	✗	✗	✗	✓
GMA	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗

✓ Reported per treatment · ✗ Not reported

DLQI, Dermatology Life Quality Index; EQ-5D, EuroQoL five dimension scale; FACIT, Functional Assessment of Chronic Illness Therapy; GMA, granulocyte-monocyte apheresis; HRQoL, health-related quality of life; NRS, Numeric Rating Scale; PSS, Psoriasis Symptom Scale; SF-36, Short Form 36; VAS, visual analogue scale.

- **Impact of treatment on patient QoL has been most commonly evaluated in studies of biologics, which focussed on functional improvement, patient experience and patient perception of dermatological parameters**
- **Generic QoL tools like the EQ-5D and SF-36 were evaluated in limited studies of biologics; of the dermatology-specific QoL tools, the DLQI was the most widely evaluated across studies**

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