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GUIDELINE

Japanese guidelines for the management and treatment of generalized pustular psoriasis: The new pathogenesis and treatment of GPP

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ABSTRACT

Generalized pustular psoriasis (GPP) is a rare disease characterized by recurrent fever and systemic flushing accompanied by extensive sterile pustules. The committee of the guidelines was founded as a collaborative project between the Japanese Dermatological Association and the Study Group for Rare Intractable Skin Diseases under the Ministry of Health, Labour, and Welfare Research Project on Overcoming Intractable Diseases. The aim of the guidelines was to provide current information to aid in the treatment of patients with GPP in Japan. Its contents include the diagnostic and severity classification criteria for GPP, its pathogenesis, and recommendations for the treatment of GPP. Since there are few clinical trial data with high levels of evidence for this rare disease, recommendations by the committee are described in the present guidelines.

Key words: **diagnostic criteria, generalized pustular psoriasis, severity criteria, treatment.**

CHAPTER I: INTRODUCTION TO 2014 CLINICAL PRACTISE GUIDELINES

Background and objectives

The manifestations of generalized pustular psoriasis (GPP) are fever and systemic flushing accompanied by many sterile pustules at onset, and histopathologically there is formation of subcorneal pustules and spongiform pustules of Kogoj. GPP is characterized by recurrences and may or may not be preceded by psoriasis vulgaris. Clinical manifestations associated with systemic inflammation are observed during the course of the disease. In addition, GPP is often accompanied by mucosal symptoms and arthritis, and is occasionally associated with respiratory failure, ocular symptoms and secondary amyloidosis.

In many countries, the clinical practise guidelines for psoriasis, especially plaque psoriasis, are based on a systematic review of the improvement of skin symptoms as the endpoint.[1,2] However, GPP should be viewed as systemic inflammatory response syndrome (SIRS), for which primary care, systemic maintenance, treatment of skin lesions and complications such as arthritis need to be taken into consideration. Guidelines are currently being prepared in the light of novel

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findings about the pathology of psoriasis and because treatment with biologics has become a reality.[3,4] Based on the findings of epidemiological and actual clinical treatment surveys,[5] the Ministry of Health, Labor and Welfare (MHLW) Study Group for Rare Intractable Skin Diseases proposed diagnostic and severity criteria and guidelines for the management and treatment of GPP in 2003 and 2010.[6,7] However, the subsequent development of treatment drugs and incorporation of evidence-based medicine necessitated revision of the first edition of the clinical practise guidelines of GPP.[7]

In 1999, the MHLW research project Overcoming Intractable Diseases had been launched to elucidate the pathology of a selected group of intractable diseases (which are known as specified, designated or target intractable diseases). Under this MHLW research project, in the Study of Rare Intractable Skin Diseases that was led by the principal investigators Yasuo Kitajima and Keiji Iwatsuki for fiscal years 2002–2007 and 2008–2013, respectively, the medical questionnaire form that patients with specified skin diseases used to apply for national health insurance coverage was standardized across Japan. This standardization made it possible to examine individuals' medical data reported on the questionnaire form at a national level. Clinical cases examined by the Study Group and individuals' medical data were combined to develop a database to allow for analysis of the sensitivity and specificity of diagnostic criteria and establish severity criteria.[7] At the same time as these criteria were being applied to develop clinical practise guidelines guided by evidence-based medicine (EBM), the application of biologics and their positioning within the guidelines were being reviewed.[8,9] Studies investigating familial cases of GPP showed mutations in the gene *IL36RN* one after another. This gene encodes the interleukin (IL)-36 receptor antagonist that regulates the function of IL-36 involved in the production of pro-inflammatory cytokines such as IL-8, which is essential for the migration of neutrophils.[10–12] Later, a study investigating sporadic cases of GPP reported that the majority of GPP cases with no preceding psoriasis vulgaris had a mutation in the *IL36RN* gene.[13] This study revealed that patients with not only the homozygous or compound heterozygous mutations of *IL36RN* but also the heterozygous mutations of the gene develop GPP.[13] The analysis of *IL36RN* mutations is also important in terms of advising patients of GPP-precipitating factors such as penicillin and pregnancy.[14,15] Figure 1 shows the locations of *IL36RN* gene mutations reported in 2014. Most *IL36RN* gene mutations found in Japanese patients belong to two founder mutations: c.28C>T (p.Arg10*) and c.115+6T>C (p.Arg10Argfs*1).[16] We had difficulty in finding studies reporting treatments for GPP that were supported by high-level evidence, so we collected as many currently important articles as possible and evaluated them in committee meetings while referring to guidelines that had recently been published in the USA.[17,18] At present, we are awaiting the evaluation results of mid- to long-term effect of granulocyte/monocyte adsorption apheresis (GMA), which was approved in 2012 as a novel treatment method for GPP.

Scope

The definition of pustular psoriasis varies among textbooks, and sometimes includes palmoplantar pustulosis as a localized form based on pathological similarity. In addition, a pediatric circinate annular form and psoriasis vulgaris with transient pustule formation are occasionally discussed as pustular psoriasis. The committee of the guidelines was founded as a collaborative project between the Japanese Dermatological Association and the Study Group for Rare Intractable Skin Diseases under MHLW's research project Overcoming Intractable Diseases. Consequently, the condition of GPP in the present guidelines is defined as pustular psoriasis that is designated by the MHLW as a specified disease (the term "designated intractable disease" has been used instead of "specified disease" since January 2015), and the diagnostic and severity criteria for GPP conform to those proposed by the MHLW Study Group. The present guidelines recommend treatments that are currently considered standard in Japan. However, because of variability in the symptoms and complications of GPP, primary care physicians should select the treatment method together with their patients. We do not seek complete adherence of the treatment method to the recommendations in these guidelines.

Primary features

The primary features of the present guidelines are that (i) GPP is considered as systemic inflammation, and (ii) in addition to primary care at the primary medical institutions, (iii) systemic management at the secondary and tertiary medical institutions and (iv) skin care treatments, (v) treatments for complications such as arthritis are also covered. The present guidelines also include treatments for (vi) acute phase, (vii) indications for biologics, (viii) long-term treatment plans that take into account the side-effects, and (ix) a review of standard treatments from the perspective of improved quality of life (QOL).

Because GPP is a rare disease, it is difficult to collect clinical trial data with high levels of evidence. Because a mere statement of treatments that are not supported by sufficient evidence could potentially confuse primary care physicians, recommendations by the committee are described in the present guidelines. We took the safety of drugs most seriously, but we found that, in order to fight this life-threatening disease, it was sometimes necessary to include drugs without current established safety records as a committee's opinion (treatments for pregnant or lactating women and children; see clinical questions [CQ] 20–

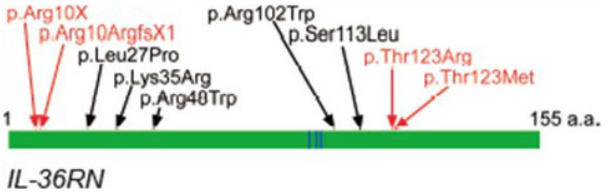

Figure 1. Mutation sites on the *IL36RN* gene (mutations in red are Japanese cases).

25). It is necessary to clearly inform patients and obtain informed consent before administrating any of these drugs.

Funding sources and conflicts of interest

The cost of establishing the guidelines was supported by research funding for the Rare Intractable Skin Diseases project, conducted as part of MHLW's research project Overcoming Intractable Diseases. In addition, those committee members who were involved in the development of particular drugs described in the guidelines were excluded from determinations of the degree of recommendations for these relevant drugs. The committee has no other conflicts of interest to declare in relation to the present guidelines.

Source of evidence

Databases used: PubMed, SCIRUS, SCOPUS, Ichushi, Cochrane Database of Systematic Reviews and US Food and Drug Administration (FDA).

Search period and references: Articles searched prior to August 2013 were used as references in these guidelines. However, if deemed important, articles published at a later date were also included.

Selection criteria: Systematic reviews of randomized controlled trials (RCT) and individual reports of RCT were prioritized. When these were unavailable, reports of cohort studies, case–control studies, guidelines published in Japan and overseas, and review of treatment methods were used. The present guidelines also include case series studies but not basic research studies.

Guidelines for the determination of levels of evidence and strength of recommendations

Levels of evidence and strength of recommendations in the guidelines conform to those in the Clinical Practise Guidelines for Skin Malignancy published by the Japanese Dermatological Association (Table 1).

Table 1. Levels of evidence and degree of recommendations

A. Classification of evidence level
- I. Systematic review/meta-analysis
- II: More than one randomized controlled studies
- III: Non-randomized controlled studies
- IV: Analytic epidemiological studies (cohort research and case-control studies)
- V: Descriptive studies (case reports and case series studies)
- VI: Committee or individual expert opinions[†]

B. Degree of recommendation classification[§]
- A: Strongly recommended for implementation (when efficacy is shown by at least one study with level I or high-quality level II evidence).
- B: Recommended for implementation (when efficacy is shown at least one study with low-quality level II, high-quality level III or extremely high-quality level IV evidence).
- C1: Implementation can be considered, but evidence is insufficient (when there is low-quality level III–IV, multiple high-quality level V evidence or level VI evidence supported by the Committee).[‡]
- C2: Not recommended because of lack of evidence[‡]
- D: Not recommended (based on high-quality evidence showing that it is ineffective or even harmful).

[†]Level equivalent to basic research data and theory based on the data.
[‡]Evidence here refers to findings from clinical or epidemiological studies.
[§]Degrees of the recommendation grades in the present guidelines does not necessarily correspond to those listed in the table above. This is because for some treatments, the degrees of the recommendation grades were determined based on consensus between the Committee members after taking into consideration the levels of evidence, the lack of evidence for the treatment of skin cancer nationally or globally, the fact that evidence obtained overseas cannot be applied directly to Japanese patients and practicality.

Prepublication review of the guidelines and method of publication

To gather comments and opinions, in March 2008 the old guidelines were published as a preliminary version on the homepage of the Japanese Dermatological Association, and data on biologics were collected and reported at the 23rd, 24th and 25th Annual Meetings of the Japanese Society for Psoriasis Research. After taking into consideration the comments and opinions received and modifying the content, a revised version was published in 2009. Then, after incorporating novel findings on causal factors, manifestations and treatments, the current revised version was reviewed and modified as necessary by the members of MHLW's Study Group for Rare Intractable Skin Diseases before publication.

Evaluation of the guidelines and plans for updates

After development, the present guidelines were approved by the Japanese Dermatological Association for publication in its official journal. The guidelines are to be evaluated based on outcomes, namely clinical efficacy and impact on patient QOL. For clinical evaluation, it will be necessary for the MHLW Study Group for Rare Intractable Skin Diseases to use the standardized individual medical questionnaire form, which enables a database to be developed.

Today, the discovery and continuous development of drugs one after another means the guidelines must be updated accordingly, as and when needed. We plan to revise the guidelines routinely every 3–5 years to incorporate the findings of certain treatment outcome evaluations.

Disclaimer

1. Physician discretion and medical malpractice litigation:

The role of these clinical practise guidelines is not to regulate the discretion of physicians but to objectively describe current medical standards from the perspective of clinicians.

2. Approved drugs and unapproved remedies:

The present guidelines are not a handbook of medical treatments covered by health insurance. Rather, the guidelines list drugs along with the strength of recommendations if they are supported by evidence obtained from Japan or overseas, independent of their health insurance coverage status. Drugs listed in the guidelines should also not be considered as freely accessible in actual clinical practise. When using unapproved remedies, the patients should be treated with adherence to the Ethical Principles for Medical Research Involving Human

Subjects after institutional approval for use to serve the interests of patients. It will be necessary to obtain informed consent from patients for the use of such drugs.

CHAPTER II: DIAGNOSTIC AND SEVERITY CRITERIA FOR GPP

Definition of GPP and the primary signs parameters required for diagnosis (2006)

Definition: GPP is a rare disease in which acute fever, generalized skin rashes and many sterile pustules develop. Histopathologically, GPP forms subcorneal pustules characterized by Kogoj's spongiform pustules. GPP may or may not be preceded by psoriasis vulgaris and is characterized by repeated disease recurrence. During the course of the disease, patients have abnormal clinical findings associated with systemic inflammation and often present with mucosal symptoms and arthritis as complications. Although rare, GPP may be accompanied by certain eye symptoms and secondary amyloidosis.

1. Primary parameters:

   a. Systemic symptoms such as fever and fatigue;
   b. Systemic or extensive flush accompanied by multiple sterile pustules that sometimes merge to form lakes of pus;
   c. Neutrophilic subcorneal pustules histopathologically characterized by Kogoj's spongiform pustules;
   d. The above clinical and histological features recur repeatedly. However, the diseases mentioned below can be excluded from initial-onset cases.

A definitive diagnosis of GPP can be made in patients with all four features above, and GPP would be suspected in those with features 2 and 3.

Comment: The point of making revisions to the previous version was to pay attention to serious complications by viewing GPP as not only a skin lesion but also systemic inflammation. Furthermore, GPP cases collected by the MHLW Study Group for Rare Intractable Skin Diseases and the medical data from patients with specified diseases (the term "specified disease" was replaced by "designated intractable disease" in January 2015) were analyzed to determine the primary signs based on sensitivity and specificity.

The types of GPP described in the present guidelines are acute GPP (von Zumbusch type), pediatric GPP, impetigo herpetiformis and acrodermatitis continua of Hallopeau, all of which are designated as intractable diseases. Pediatric circinate annular form and psoriasis vulgaris with transient pustules are not included (see "2. Reference signs for the diagnosis of GPP"). Therefore, the types of GPP described in the present guidelines differ from target illnesses analyzed in the clinico-epidemiological statistical study of pustular psoriasis by Ryan and Baker in 1971.[19]

Diagnostic criteria for GPP conform to those stated in the research report for the Study of Rare Intractable Skin Diseases published in 2006 by the MHLW.[20] In the latest diagnostic criteria, GPP is viewed as systemic inflammation, and in addition to skin symptoms, the definition incorporates complications that affect disease prognosis, such as joint symptoms and amyloidosis.[21] It is also essential to perform the clinical and histopathological evaluation of skin symptoms before making a diagnosis. Although recurrent symptoms are important diagnostic factors, examples of definitive and suspected cases are given in the present guidelines for patients with new-onset disease. Suspected cases will be updated when the renewal application for designated intractable disease begins for the next year.

The analysis of GPP in 41 patients gathered by the Study Group for Rare Intractable Skin Diseases showed that the sensitivity of the primary features 1, 2, 3 and 4 was 83%, 95%, 95% and 87%, respectively. In addition, the sensitivity was 78% for a definitive diagnosis based on all four features and 90% for a suspected diagnosis based on features 2 and 3.[22] To rule out acute generalized exanthematous pustulosis (AGEP), specificity was ensured by including "recurrent" under primary feature 4 and incorporating a diagnosis of exclusion.

*Specificity was calculated using AGEP (eight patients) as a target illness.

Parameters for reference in the diagnosis of GPP

1. Laboratory test findings necessary to assess the severity of the disease and complications*:

   a. Leukocytosis, left shift;
   b. Elevated erythrocyte sedimentation rate, positive for C-reactive protein (CRP);
   c. Elevated immunoglobulin (Ig)G or IgA levels;
   d. Hypoproteinemia, hypocalcemia;
   e. Tonsillitis, elevated anti-streptolysin O, other infections;
   f. Rheumatoid factor-negative polyarthritis including ankylosing spondylitis;
   g. Eye diseases (such as keratoconjunctivitis, uveitis and iritis);
   h. Hepatic, renal and urinary findings: treatment choice and evaluation of secondary amyloidosis.

2. Diseases included in GPP:

   a. Acute GPP (von Zumbusch type): classical examples of GPP;
   b. Impetigo herpetiformis: GPP associated with pregnancy or hormonal abnormalities;
   c. Acrodermatitis continua of Hallopeau: strictly speaking, this disease is rare and therefore requires careful diagnosis;
   d. Pediatric GPP: circinate annular form is excluded.

3. In principle, cases involving transient pustule formation are not included in this category, which however does not apply to the cases where recurrence is suppressed by ongoing treatment.

Explanation: Except for clinical and histopathological examinations, no other laboratory tests have high specificity for the diagnosis of GPP. The statistical analysis of various laboratory tests listed under the primary signs in the old diagnostic criteria revealed that they had insufficient sensitivity or specificity*. Therefore, these items were changed from clinical screening

items to reference items. However, screening for these signs is strongly recommended because they are essential factors for determining disease severity and complications.

The definition of pustular psoriasis varies among textbooks. In the present guidelines, the definition of GPP as a designated intractable disease is used in the present guidelines (Chapter I: 2. Significance of the Guidelines). Histologically speaking, the circinate annular form that is prevalent in children is often accompanied by small neutrophilic abscesses, but the cases of circinate annular form are excluded because they are mostly mild cases.

*The 3rd National Survey shows that specificity is 65% for leukocytosis, 67% for elevated erythrocyte sedimentation rate, 81% for a high level of CRP and 12% for hypocalcemia. Due to insufficient data, anti-streptolysin O and Ig were not analyzed.

Exclusion criteria for GPP

Three diagnoses of exclusion:

1. In principle, clear cases of psoriasis vulgaris with transient pustule formation after the application of corticosteroids are not included in this category. However, this does not apply to cases when pustules recur easily, and the dermatologist should decide whether to include the case in this category after careful observation for a certain period.
2. In general, the circinate annular form is excluded because of mild systemic symptoms, but the cases exhibiting a clear transition into GPP are included.
3. Cases where the diagnosis of subcorneal pustular dermatosis or pustular drug eruptions (including AGEP) is made after careful observation for a certain period are excluded.

Comments: In principle, the cases of transient pustule formation of psoriasis vulgaris are not included in this category. However, this does not apply to the cases where the recurrence of pustules appears to be suppressed by treatment. Subcorneal pustular dermatosis and pustular drug eruptions including AGEP, both of which present with clinical and histopathological findings similar to those of GPP, should be excluded.

Clinical statistics on GPP and reference items

Comments: Based on the database registered with the Japanese Society for Psoriasis Research (2003–2006), pustular psoriasis (including the generalized and other forms) accounts for approximately 1% of all psoriatic cases, and its incidence peaks during childhood and in the 30–39-year-old age group. GPP affects girls more than boys during childhood. While the incidence of psoriasis vulgaris in men is twice that in women, GPP affects women slightly more (male : female ratio = 1:1.2). The types of GPP included in the MHLW research project Overcoming Intractable Diseases are limited to those fulfilling the diagnostic criteria stated above (see Chapter I: 2. Scope).

In fiscal years 2004–2010, 1426–1679 patients/year with GPP were registered to receive public financial aid from the MHLW. In 2003, the MHLW started an online registration system of intractable diseases including GPP. The input rate of GPP in the national clinical database was 50.1–80.4%. New patient application rates were 9.2–13.0%. The national clinical database of 767 newly registered patients with GPP for the 7-year period (2004–2010) showed sex ratio which included slightly more men than women (male : female ratio = 1:0.88), revealing a ratio different from that calculated using the Japanese Society for Psoriasis Research Database. Age of onset distributions show that men have two peaks in age groups 30–39 and 50–69 years, while women have also two peaks in the age groups 25–34 and 50–64 years, but their overall distribution is equal.

In addition, GPP occasionally develops as a complication of Turner syndrome.[23,24]

Severity criteria for GPP (Table 2) and patient distribution

Comments: The severity of GPP is classified as mild, moderate or severe based on a total score after rating skin symptoms (erythema, pustules and edema) and systemic inflammation accompanied by certain laboratory findings (fever, white blood cell count, and serum CRP and albumin levels). Edema is considered a skin symptom in the new severity criteria (Table 2) because the analysis of deceased cases identified cardiovascular impairment as a leading cause of death in patients with GPP. Edema is also an important sign for acute respiratory distress syndrome (ARDS) and capillary leak syndrome (see CQ1, 2).

To establish the severity criteria, abnormal clinical and hematological findings were classified based on severity stratification of data from 40 patients collected by the Study Group for Rare Intractable Skin Diseases and statistical data from the national survey of individuals' medical data for 2003–2005 (Figs 2–4).

Generalized pustular psoriatic patients are considered in remission when: (i) no recurring skin symptoms are observed or the disease has changed into psoriasis vulgaris in the absence of disease-specific treatment; (ii) no complications such as arthritic or eye symptoms are observed during the acute or chronic phase; and (iii) no impairments in activities of daily living are observed.

Treatments of GPP and outcomes (according to the 2010 national clinical database) (Table 3)

Explanation: Table 3 shows the epidemiological information of 1350 patients with GPP (input rate of 80.4%), including 176 newly registered patients and 1174 continuously registered patients, in a Japanese national clinical database. The treatment and the efficacy in the application written by physicians included information about the past 6 months for newly registered patients and information about the past year for continuously registered patients. The analysis data show that etretinate accounted for 35.6% of all oral medications, with an efficacy rate of 87.1%, while the corresponding rates were 37.8% and 87.6% for cyclosporin, 6.4% and 84.9% for methotrexate, and 16.6%

Table 2. Severity criteria for generalized pustular psoriasis

A	Evaluation of skin symptoms	Erythema, pustule, edema (0–9)	
B	Evaluation of systemic symptoms and laboratory findings: Fever, white blood cell count, serum CRP, serum albumin (0–8)		
O Severity classification (Total score)	Mild (0–6)	Moderate (7–10)	Severe (11–17)

A. Evaluation of skin symptoms (0–9)

	Severe	Moderate	Mild	None
Area of erythema (whole body)†	3	2	1	0
Area of erythema with pustules‡	3	2	1	0
Area of edema‡	3	2	1	0

B. Evaluation of systemic symptoms and laboratory findings (0–8)

Score	2	1	0
Fever (°C)	38.5 or above	37 to less than 38.5	Less than 37
White blood cell count (/mL)	15 000 or above	10 000 to less than 15 000	Less than 10 000
CRP (mg/dL)	7.0 or above	0.3 to less than 7.0	Less than 0.3
Serum albumin (g/dL)	Less than 3.0	3.0 to less than 3.8	3.8 or above

†Percentage (%) of body surface area (severe, ≥75%; moderate, <75% but ≥25%; and mild, <25%). ‡Percentage (%) of body surface area (severe, ≥50%; moderate, <50% but ≥10%; and mild, <10%). CRP, C-reactive protein.

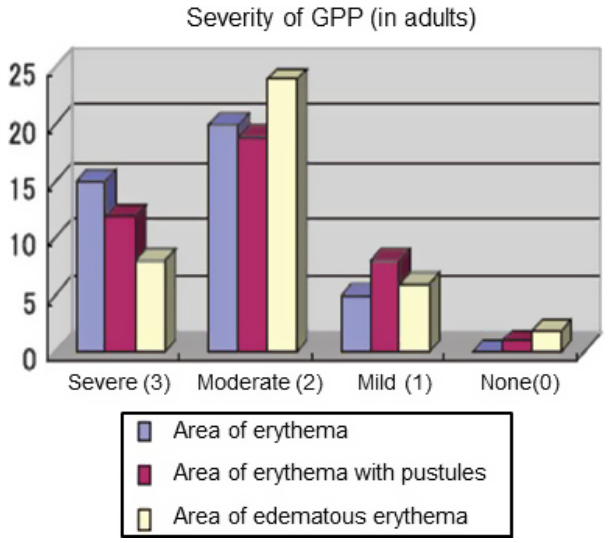

Figure 2. Distribution of skin symptoms based on the severity criteria (41 patients treated at the Study Group facilities). GPP, generalized pustular psoriasis.

and 83.5% for corticosteroids. As for topical medications, the usage and efficacy rates were 84.2% and 87.8% for corticosteroids, 65.7% and 86.6% for activated vitamin D_3, 11.0% and 74.5% for phototherapy, and 2.1% and 78.6% for ultraviolet light (UV) therapy called psoralen plus UV-A (PUVA) therapy. The nationwide GPP surveys on changes in treatment modalities over the last 25 years[5,25,26] show that cyclosporin has been selected increasingly more often while the usage rate of other drugs has been decreasing.

CHAPTER III: SUMMARY OF TREATMENT GUIDELINES FOR GPP

Treatment algorithm for GPP

See Figure 5.

Summary of clinical practise guidelines recommended for GPP

1. Primary care for systemic symptoms in acute phase GPP.

Systemic management and drug therapy are an essential part of GPP treatment because cardiorespiratory failure is often the direct cause of death. Although rare, respiratory complications may be observed, including those induced by psoriatic medications such as methotrexate and retinoids. Respiratory management, antibiotics and the discontinuation of the offending drug with concurrent systemic administration of corticosteroids (1 mg/kg per day of prednisolone equivalent) are effective. The tumor necrosis factor (TNF)-α inhibitor infliximab is also effective in some cases. However, TNF-α inhibitors should be used with caution as they may stress the cardiovascular system because of infusion-related reactions.

Key points: Measures against ARDS, capillary leak syndrome and cardiovascular impairment.

Degree of recommendations: A*.

*Although no studies have investigated the treatment, other studies reported high-quality clinico-epidemiological data on the cause of death (see CQ1, 2).

(1-1) Systemic management in patients with cardiorespiratory failure:

- Monitoring for vital signs

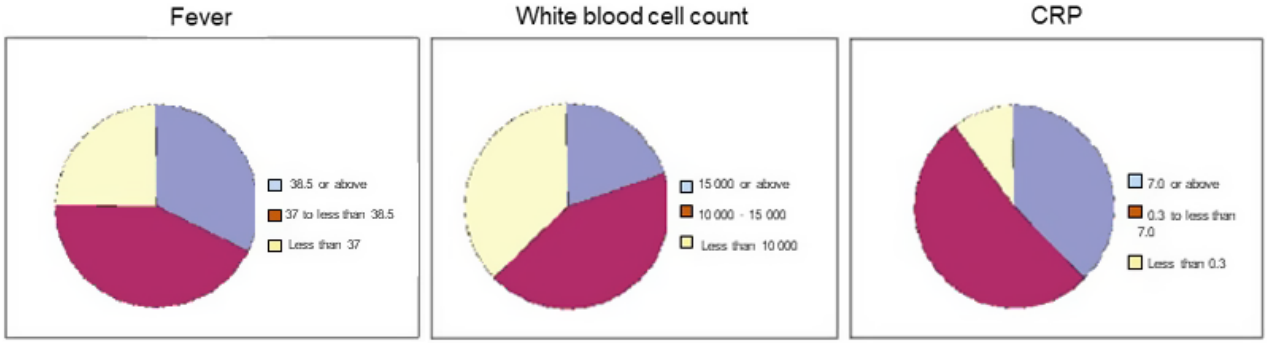

Figure 3. Distribution of abnormal clinical findings based on the severity criteria (analysis of 40 cases of adult generalized pustular psoriasis provided by the Study Group). CRP, C-reactive protein.

- Monitoring for weight gain (edema) and urine output and corresponding drug therapy
- Monitoring and drug therapy for cardiovascular impairment.

(1-2) Treatment for respiratory failure (ARDS/capillary leak syndrome):

- Monitoring using imaging modalities, hematological testing and the measurement of arterial blood gas
- Exclusion of infections
- Exclusion of causes involving drugs such as methotrexate and retinoic acid
- Application of systemic corticosteroids in ARDS/capillary leak syndrome.

(1-3) Control of the skin disease:

- Planning and providing treatment at specialized facilities.

(2) Systemic therapy recommended for acute phase pustular psoriasis (Table 4):

Table 4 shows systemic therapies, their dosage and administration, degree of recommendations for different patient populations and relevant clinical questions (CQ).

(3) For the safety of standard psoriatic treatments (Table 5):

Table 5 shows safety precautions for psoriatic treatments used in Japan.

(4) Treatment for psoriatic arthritis‡ accompanying pustular psoriasis (Table 6):

Table 6 summarizes treatment modalities recommended for pustular psoriasis.

(5) Phototherapy for pustular psoriasis (only in the chronic phase):

Phototherapy is not indicated for acute phase pustular psoriasis (CQ13), but may be indicated for chronic phase pustular psoriasis when the patients fail to respond to standard psoriatic treatments or as combination therapy to reduce the dose and thus alleviate the side-effects. Table 7 shows phototherapies used in chronic phase GPP (see CQ13 and 14 for use in pregnant women and children).

(6) GMA:

Granulocyte/monocyte adsorption apheresis is an extracorporeal therapy used to remove and suppress the functions of neutrophils, macrophages and monocytes that accumulate in the inflamed tissue and are involved in the manifestations. The effect and safety of GMA have been reported mostly in case reports. Although the effect and safety of GMA were demonstrated in a multicenter study,[32] an RCT has not been performed. GMA's utility is expected based on the mechanism of action (see CQ18, 24, 25 and 27). The administration manual in draft form of GMA is shown in Appendix I at the end of the Guidelines.

CHAPTER IV: SUMMARY OF CLINICAL QUESTIONS

Table 8 shows 28 CQ and their level of evidence and degree of the recommendations.

CHAPTER V: STRENGTH OF RECOMMENDATIONS AND COMMENTS FOR EACH TREATMENT

Primary care

Outline: Pathophysiology of SIRS, severe skin lesions and complications such as arthritis should be considered for the treatment of acute phase GPP. Because severity of these symptoms varies among each case, a professional treatment plan is required as well as primary care.

CQ1. Do systemic management and drug therapy during the acute phase effectively improve disease prognosis?

Degree of recommendation: A*.

*Opinion of the Committee.

General recommendations: Systemic management and drug therapy are essential parts of treatment because cardiovascular impairment is often the direct cause of death in patients with GPP. Attention must be paid to serious side-effects caused by treatment drugs for psoriasis; methotrexate-induced pulmonary fibrosis and respiratory failure called retinoic acid syndrome.

Comments:

1. In the 20-year period between 1965–1985, seven (0.7%) of 992 in patients with severe psoriasis died at a single

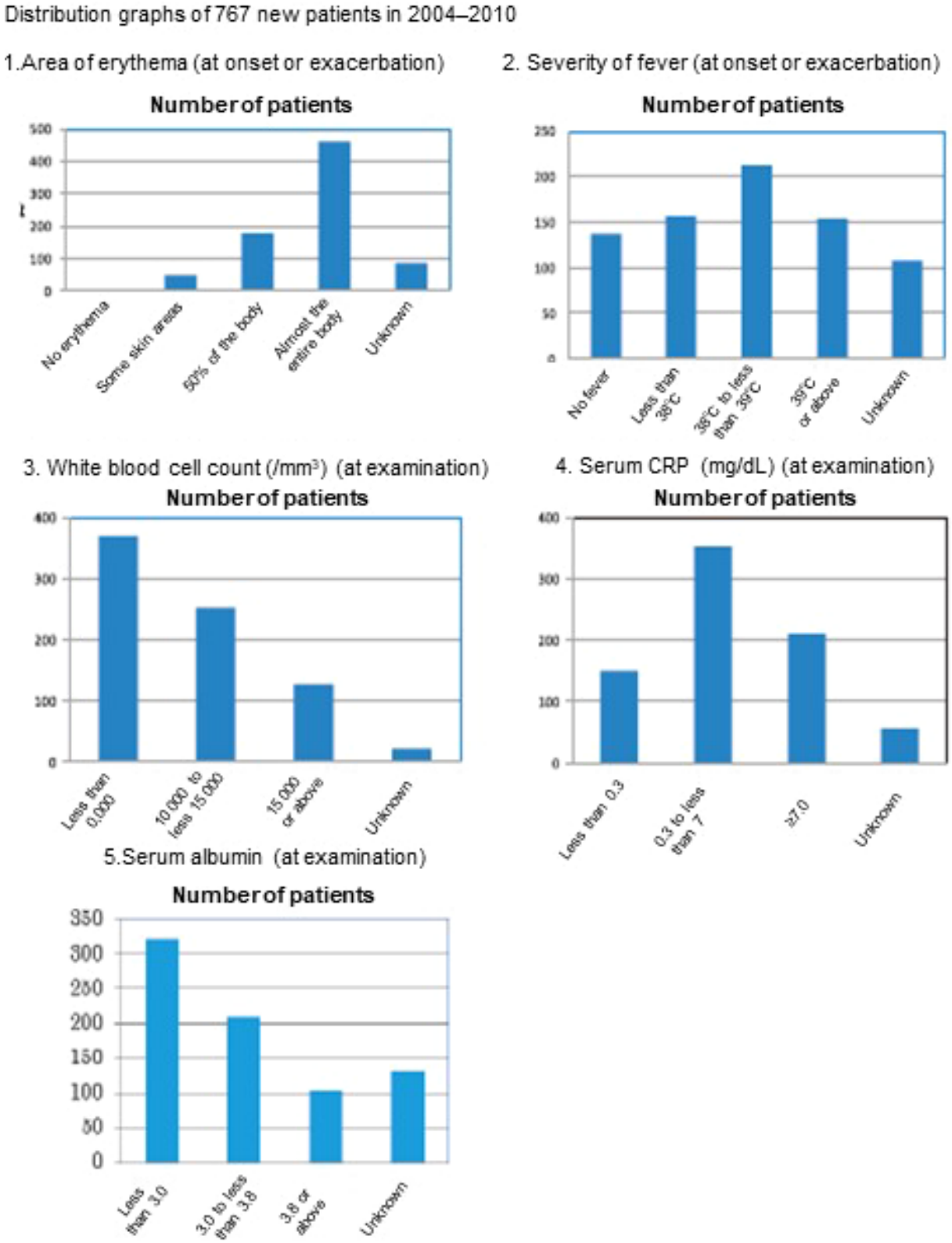

Figure 4. Patients with abnormal clinical and hematological findings were divided into groups according to the severity criteria (data collected from the national clinical database).

Table 3. Findings of a 2010 clinical survey of treatment choices for new and renewed patients with pustular psoriasis

		New (n = 176)		Renewed (n = 1174)		New + renewed (n = 1350)	
Treatment		Treated (%)	Effective (%)	Treated (%)	Effective (%)	Treated (%)	Effective (%)
Oral therapies	Etretinate	77 (43.8)	44 (74.6)	404 (34.4)	375 (92.8)	481 (35.6)	419 (87.1)
	Cyclosporin	76 (43.2)	49 (64.5)	434 (37.0)	398 (91.7)	510 (37.8)	447 (87.6)
	Methotrexate	10 (5.7)	5 (50.0)	76 (6.5)	68 (89.5)	86 (6.4)	73 (84.9)
	Corticosteroid	49 (27.8)	35 (71.4)	175 (14.9)	152 (86.9)	224 (16.6)	187 (83.5)
	Other oral medication	37 (21.0)	12 (32.4)	259 (22.1)	211 (81.5)	296 (21.9)	223 (75.3)
Topical therapies	Topical corticosteroids	163 (92.6)	120 (73.6)	974 (83.0)	878 (90.1)	1137 (84.2)	993 (87.8)
	Topical activated vitamin D_3	114 (64.8)	79 (69.3)	773 (65.8)	689 (89.1)	887 (65.7)	768 (86.6)
	Phototherapy	44 (25.0)	21 (47.7)	105 (8.9)	90 (85.7)	149 (11.0)	111 (74.5)
	PUVA therapy	9 (5.1)	5 (55.6)	19 (1.6)	17 (89.5)	28 (2.1)	22 (78.6)

PUVA, psoralen plus ultraviolet A therapy.

institution in France.[21] A multi-institutional study conducted at the same period in this area revealed 46 fatal psoriatic patients including nine with psoriasis vulgaris, two with psoriasis associated with palmoplantar pustular psoriasis, two with generalized psoriasis, 15 with psoriatic erythroderma and 18 with GPP. Arthropathy was observed in 12 male and six female patients. GPP accounted for 39% of all death cases. It is indicated that patients with adolescent- and young adult-onset GPP and with the complication of arthritis have poor disease prognosis.

2. Factors causing death were metabolic/circulatory impairment in 19 patients (cardiovascular impairment in 11, cachexia in six, hypothermia in one and uncompensated diabetes in one); non-specific disorders in 15 (infection in 10, amyloidosis in three, neuropathy due to rheumatoid arthritis in one and glomerulonephritis in one); and treatment side-effects in 12 (related to methotrexate in eight, etretinate in two, systemic corticosteroids in one and mechlorethamine in one [epithelial cancer metastasis]).

The clinical study on 155 pustular psoriatic patients by Ryan and Baker[19] was not included in this statistics because their study involved steroid-induced pustular psoriasis and palmoplantar pustular psoriasis.

3. Recent studies reported many cases of respiratory and circulatory failure due to ARDS and capillary leak syndrome (see CQ2).
4. It should be noted that there are relatively large numbers of deaths or pulmonary complications due to psoriatic treatment drugs such as methotrexate and retinoic acid (see CQ2).

CQ2. Is the administration of corticosteroids effective for respiratory failure associated with GPP?

Degree of recommendation: B*.

*Opinion of the Committee.

General recommendations: Although rare, pulmonary complications of the disease or those induced by drugs such as methotrexate and acitretin develop in patients with GPP or erythrodermic psoriasis, necessitating respiratory management, antimicrobial therapy, discontinuation of drug administration and/or the systemic administration of corticosteroids (equivalent to 1 mg/kg per day of prednisolone).

Comments:

1. After exclusion of clear cases of infection, ARDS and capillary leak syndrome are the leading causes of respiratory failure in many patients with GPP or erythrodermic psoriasis, making them life-threatening complications.[33–36] Patients undergoing drug therapy for psoriasis with acitretin[35] or etretinate may develop capillary leak syndrome, which is considered retinoic acid syndrome.[33] Although methotrexate is a therapeutic agent, caution is advised because the drug sometimes causes serious side-effects such as pulmonary fibrosis and hepatic impairment (see CQ1).
2. Patients with ARDS and capillary leak syndrome respond well to the administration of corticosteroids (1 mg/kg per day of prednisolone equivalent) in addition to respiratory management and antimicrobial therapy.[34]
3. Other drugs: The TNF-α inhibitor infliximab is reported to be effective in patients with pustular psoriasis or erythrodermic psoriasis who developed multiple complications of SIRS, such as congestive heart failure and ARDS.[36] However, the drug should be administrated with care because the cardiovascular system may be stressed by the infusion reaction.

Oral therapies

Outline: Guidelines have been established for the duration of medication and combination therapies for psoriasis. In GPP as well, its treatment is principally based on that of psoriasis. However, to overcome life-threatening situations, it is sometimes necessary to use contraindicated drugs.

CQ3. Etretinate and retinoids

CQ3-1: Are etretinate or retinoids effective for GPP?. Degree of recommendation: C1.

General recommendations: For the treatment of pustular psoriasis, etretinate or a retinoid is recommended as a drug of first choice. However, when using etretinate over the long term, attention must be paid to various side-effects (e.g. hepatic

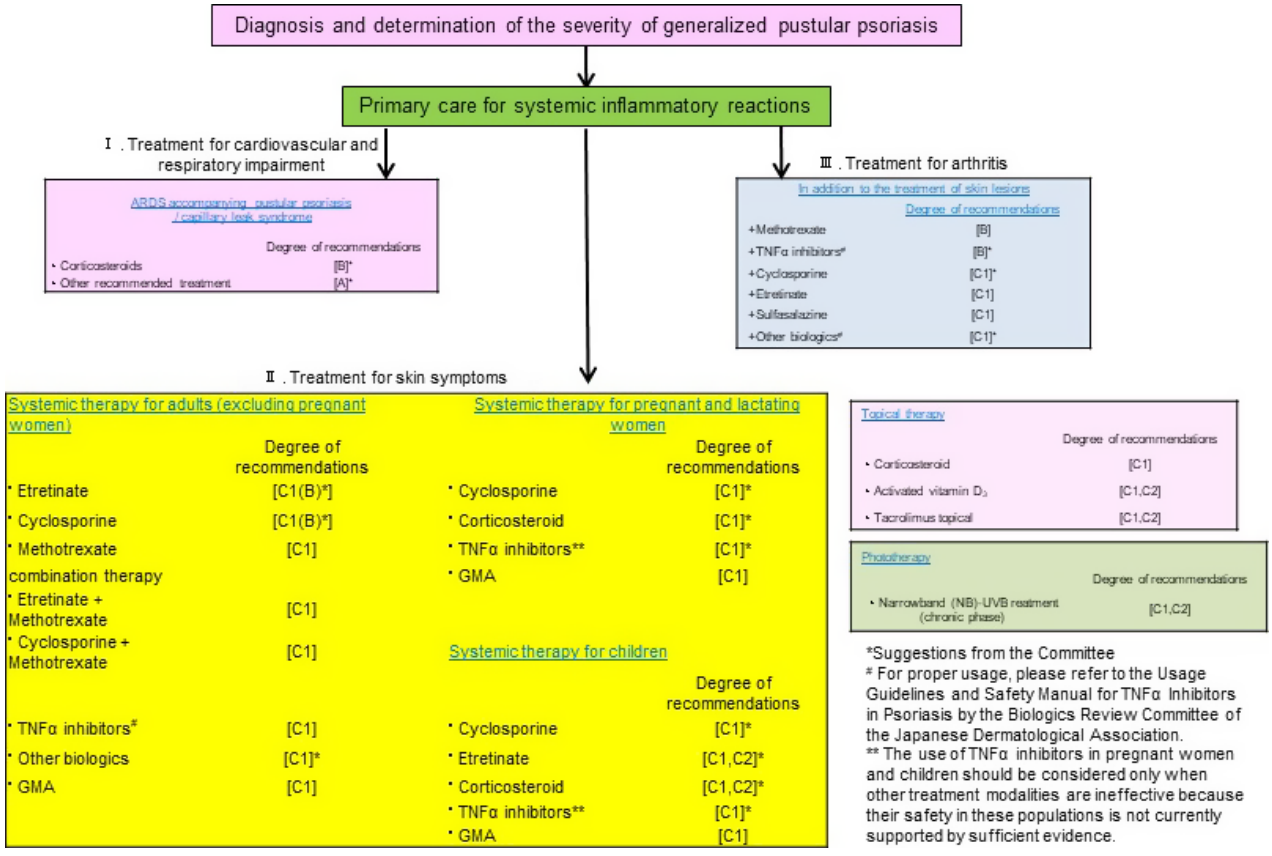

Figure 5. Treatment algorithm for generalized pustular psoriasis (GPP). Note: Because GPP is a life-threatening systemic inflammatory disease, it is sometimes necessary to use drugs that do not have well-established safety profiles with pregnant or lactating women or children. According to the national guidelines, the use of cyclosporin is contraindicated in pregnant or lactating women. However, the use of cyclosporin for impetigo herpetiformis, a type of GPP observed in pregnant women, is described in the present guidelines. In addition, the tumor necrosis factor (TNF)-α inhibitors infliximab and adalimumab are presented as a treatment choice based on their efficacy on psoriasis vulgaris and rheumatoid arthritis, even though the inhibitors have not been used in a sufficient number of pregnant or lactating women to date. TNF-α inhibitors are contraindicated in guidelines published recently in Germany (see Chapter V: 5. Biologics and 7. Selecting a treatment drug for pregnant or lactating women or children). However, the use of TNF-α inhibitors should be considered for patients in life-threatening situations when other drugs are ineffective. In such cases, proper informed consent must be obtained before administration. Granulocyte/monocyte adsorption apheresis (GMA) is included as a treatment choice because of its mild side-effects even though it does not have sufficient evidence of efficacy.

impairment, hyperostosis, early closure of the epiphysis and teratogenesis), and treatment should be performed with care after obtaining fully informed consent.

Comments: In general, the dose of etretinate for the treatment of GPP starts with 0.5–1.0 mg/kg per day and should be adjusted according to symptoms. Many case reports and case series reports showed the efficacy of etretinate in GPP.[5,37,38] However, RCT have not been performed to compare the efficacy of etretinate with that of other drugs or placebo.

Because GPP is relatively rare and very severe, it has been difficult to perform large-scale comparative studies with high levels of evidence. In Japan, therapeutic efficacy has been verified by investigating individuals' medical data (Table 3) and etretinate is considered the drug of first choice for GPP.

Attention must be paid to hypercalcemia when using topical vitamin D_3 concurrently.

Currently, most countries use acitretin because of its short half-life.[39]

CQ3-2: Are etretinate or retinoids effective for GPP in children?. Degree of recommendation: C1.

General recommendations: Compared with adult cases, pediatric GPP is often intractable, requiring a long treatment duration. Etretinate has been reported to be effective in pediatric cases as in adult cases, and therefore etretinate is recommended as a drug of first choice for GPP in Japan. However, it is necessary to pay attention to growth disturbance such as the early closure of the epiphysis and side-effects such as teratogenesis.

Table 4. Therapy recommended for the acute phase pustular psoriasis rash

Recommended therapy	Dose/ Administration	Degree of recommendations	Relevant CQ	Remarks
Adults (not pregnant)				
Etretinate	0.5–1.0 mg/kg/ day	C1 (B†)	3	Pustular psoriasis is responsive even at 0.5–0.75 mg/kg per day. Onset of action is earlier than that in psoriasis vulgaris. Mild efficacy in arthritis. Long-term use may cause bone and joint damage. Men and women taking this drug should use contraception for 6 months and 2 years, respectively
Cyclosporin	2.5–5 mg/kg per day	C1 (B†)	4, 18, 19	The use of the microemulsion preconcentrate (MEPC) form of cyclosporin complies with the 2004 Guidelines for Psoriasis Therapy with Cyclosporin MEPC.[2,27–29] See the section 4) below and relevant CQ for precautions
Methotrexate	5–7.5 (15) mg/ week	C1	5, 22	Methotrexate has been reported to cause fetal death (see CQ1). Individuals (both men and women) taking this drug should use contraception for 3 months. It is contraindicated in hemodialysis patients
Etretinate + methotrexate		C1	3, 5	These drugs are used concurrently to maximize the effect at a minimum dose in psoriasis
Cyclosporin + methotrexate		C2	4, 5	The same as above. The incidence of skin cancer may increase
Biologics				Comply with the guidelines for use of biologics.[8,30,31] However, see CQ15–17 and 20 for their use in pregnant and lactating women and children with pustular psoriasis
Infliximab		C1‡	15, 17	The initial dose of 5 mg/kg is given as a slow i.v. infusion over 2 h. The second and third administrations are given 2 and 6 weeks later, respectively, and subsequent administrations are given every 8 weeks. Dose may be increased up to 10 mg/kg, or the interval may be shortened up to every 4 weeks. A clear effect of the drug may be seen after 1–3 administrations
Adalimumab		C1‡	15, 17	The initial dose of 80 mg is given s.c. in adults, and after the second week, a dose of 40 mg is given s.c. every 2 weeks. If the efficacy is insufficient, the dose may be increased to 80 mg/administration
Ustekinumab		C1‡	16	s.c. injections of 45 mg at weeks 0 and 4 and every 12 weeks thereafter. If the efficacy is insufficient, the dose may be increased to 90 mg/administration
Secukinumab		C1‡	16	Weekly s.c. injections of 300 mg on weeks 0, 1, 2, 3, 4 and then every 4 weeks thereafter (may be decreased to 150 mg)
Ixekizumab		C1‡	16	s.c. injections of 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10 and 12, then 80 mg every 4 weeks thereafter
Brodalumab		C1‡	16	s.c. injections of 210 mg at weeks 0, 1, 2 and then every 2 weeks thereafter

Table 4. (continued)

Recommended therapy	Dose/ Administration	Degree of recommendations	Relevant CQ	Remarks
GMA		C1‡	18, 19	Used in patients with moderate to severe pustular psoriasis who are unresponsive to existing systemic therapies or in whom existing systemic therapies are contraindicated
Pregnant women				
Cyclosporin	2.5–5 mg/kg per day	C1‡	4, 20	In the 2004 Guidelines for Psoriasis Therapy with Cyclosporin MEPC,[29] cyclosporin is contraindicated in pregnant and lactating women, but the drug has been administrated successfully for the treatment of GPP in this patient population. The drug may be used only when the benefits outweigh the risks and after obtaining informed consent (see CQ20)
Corticosteroids		C1‡	7, 20	
TNF-α inhibitors		C1	15, 22	TNF-α inhibitors should be used only when the patients have failed to respond to other drugs and are in a life-threatening condition (see CQ15–17, 22)
GMA		C1	24	GMA is performed in pregnant women only when the benefits outweigh the risks
Children				
Cyclosporin	2.5–5 mg/kg per day	C1‡	4, 21	Guidelines are available. The drug has been used successfully in children. The frequency of use of cyclosporin in children has been increasing according to the data published by the Japanese Society for Psoriasis Research (see CQ21)
Etretinate	0.5–1.0 mg/kg per day	C1, C2‡	3, 21	Attention must be paid to the side-effects of etretinate, such as an early closure of the epiphyseal plate. It is important to carefully decide which drug should be the first choice, etretinate or cyclosporin
Corticosteroids		C1, C2‡	7, 21	
TNF-α inhibitors		C1	15, 23	TNF-α inhibitors should be used only when the patients have failed to respond to other drugs and the disease is life-threatening (see CQ15–17, 23)
GMA		C1	25	GMA can be used in children weighing ≥25 kg

†Opinion of the Committee: A grade C1 recommendation has been given to GMA after the careful evaluation of the reference articles. However, because these treatments have clearly outperformed other drugs with a grade C1 recommendation, the committee recommends these agents as B grade drugs. ‡Opinion of the Committee based on comprehensive judgment. CQ, clinical questions; GMA, granulocyte and monocyte apheresis; TNF, tumor necrosis factor.

Comments: As in adults, case reports and case series on the effectiveness of etretinate in childhood GPP have been reported.[40–43] However, no RCT have been performed to compare the efficacy of etretinate with that of other drugs or placebo.

Because pediatric GPP is relatively rare and very severe, it has been difficult to perform large-scale comparative studies with high levels of evidence. In Japan, cyclosporin and etretinate are the only oral therapies for psoriasis that are covered by health insurance. Consequently, one of them would be selected as the first-line drug depending on patient age and dosing duration. However, growth disturbance such as the early closure of the epiphyseal plate may develop if the drug is continued at a high dose for a long time to maintain, for example, remission. In such cases, it is important to switch to another drug if possible.

CQ3-3: Are etretinate or retinoids effective for GPP in pregnant women?. Degree of recommendation: D.

General recommendations: Impetigo herpetiformis, GPP occurring in pregnancy, is rare and difficult to investigate. Only one case report exists that showed the efficacy of short-term retinoid therapy in a pregnant woman. Therefore, the efficacy of retinoids in GPP is currently not supported by sufficient evidence. The use of retinoids is contraindicated because of potential teratogenesis in the fetus.

Table 5. Summary of safety precautions for standard psoriasis treatments

Therapy	Treatment limitations/considerations	Safety considerations
Etretinate	Ectopic calcification, monitoring for hyperostosis (long-term administration and/or administration of ≥30 g)	• Teratogenesis, hyperlipidemia and so forth (absolute contraindication for pregnant and lactating women and their partners); women and men need to use contraception for 2 years and 6 months, respectively, after the discontinuation of drug administration (see CQ3)
Cyclosporin	Long-term aimless administration should be avoided: • Up to 2 years (UK, Germany) • Up to 1 year (USA)[28–30]	• Renal toxicity, high blood pressure,* immunosuppression, carcinogenesis,[29] and so forth (see CQ4) • Antihypertensive drugs such as angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors are recommended, because they suppress the renin–angiotensin pathway and have renal protective effects • Conventional calcium antagonists also have renal protective effects. However, nifedipine may cause gingival hypertrophy[8] • Contraindicated in pregnant/potentially pregnant women and lactating mothers* (*overseas, cyclosporin is not necessarily contraindicated, but recommended as a class C drug) • The concurrent administration of tacrolimus and pitavastatin is contraindicated • In principle, PUVA and retinoid therapies are not administrated concurrently[8]
Methotrexate	• Check for risk factors • Monitor liver function • Monitor for interstitial pneumonia • Alleviate side-effects by administrating folic acid	• Hepatic impairment, myelosuppression, teratogenesis, immunosuppression, carcinogenesis, interstitial pneumonia and so forth (absolute contraindication in pregnant/lactating women and their partners and hemodialysis patients) • Women and men should use contraception for 1 and 3 months, respectively, after the discontinuation of drug administration (see CQ5–3)
PUVA therapy	• Should not exceed 200 treatments or 1000 J/cm^2	• Immunosuppression, carcinogenesis (contraindicated in pregnant and lactating women because of the risk of carcinogenesis) • No evidence to support its efficacy in pustular psoriasis (CQ13)
NB-UVB		• No special limitations • No evidence to support its efficacy in pustular psoriasis (CQ14)
TNF-α inhibitors	Institutions need to be approved for the use of biologics	See the Usage Guidelines and Safety Manual for Biologics in Psoriasis issued by the Biologics Review Committee of the Japanese Dermatological Association. In the present guidelines, the degree of recommendations has been introduced after a thorough search for previous studies reporting the use in pregnant or lactating women or children with GPP
GMA	GMA is not indicated for patients with ≤2000/mm^3 granulocytes, infection or suspected infection	In addition, GMA should be administrated carefully in patients with liver or kidney disorders, allergies, severe cardiovascular diseases and a fever of ≥38°C, and patients who are sensitive to anticoagulants or have highly activated coagulation system (≥700 mg/dL fibrinogen)

CQ, clinical questions; GMA, granulocyte and monocyte apheresis; GPP, generalized pustular psoriasis; NB-UVB, narrowband ultraviolet B; PUVA, psoralen plus ultraviolet A therapy; TNF, tumor necrosis factor.

Comments: The efficacy of short-term retinoid (isotretinoin) in impetigo herpetiformis, GPP of pregnancy, was shown in only one case report.[44] The use of etretinate or other retinoids in pregnant women is not recommended because of the lack of evidence of efficacy and its contraindication in pregnant women.

CQ3-4: Is the safety of retinoids for long-term use established?. Degree of recommendation: C1.

General recommendations: Long-term retinoid therapy may be performed in patients with GPP. The appearance of side-effects is influenced by the amount and duration of drug administration. The side-effects of long-term retinoid use in

Table 6. Treatment for psoriatic arthritis associated with pustular psoriasis

Recommended therapy (in addition to the treatment of rash)	Dose and administration	Degree of recommendations	Reference CQ	Remarks
+Methotrexate	5–7.5 (15) mg/week	C1	22	Use is the same as that in antirheumatic therapy. Pay attention to pulmonary fibrosis, liver fibrosis and cirrhosis in patients with psoriasis. Contraindicated in patients undergoing hemodialysis
+TNF-α inhibitors			15, 17, 20	
Infliximab	5 mg/kg div (2–3 h) (at 0, 2nd and 6th week, and then every 8 weeks). Dose may be increased up to 10 mg/kg, or the interval may be shortened up to every 4 weeks	B†	15, 17	Chimeric human anti-TNF-α monoclonal antibody
Adalimumab	The initial dose of 80 mg is given s.c. and 40 mg is given every 2 weeks thereafter (may be increased to 80 mg)	B†	15, 17	Fully human anti-TNF-α monoclonal antibody
+Secukinumab	Weekly s.c. injection of 300 mg on weeks 0, 1, 2, 3, 4 and then every 4 weeks thereafter (may be decreased to 150 mg)	C1	26	Fully human anti-IL-17A monoclonal antibody
+Ixekizumab	s.c. injection of 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10 and 12, then 80 mg every 4 weeks thereafter	C1	26	Humanized anti-IL-17A monoclonal antibody
+Brodalumab	s.c. injection of 210 mg at weeks 0, 1, 2 and then every 2 weeks thereafter	C1	26	Fully human anti-IL-17RA monoclonal antibody
+Ustekinumab	Initial dose of 45 mg by s.c. injection (at 0 and 4th week, and then every 12 weeks; may be increased to 90 mg)	C1	26	Fully human anti-IL-12/23 p40 monoclonal antibody
+Cyclosporin	2.5–5 mg/kg per day	C1	20	Limitations in long-term use. In particular, pay attention to kidney failure
+Etretinate	0.5–1.0 mg/kg per day	C1	20	Caution is advised when using concurrently with cyclosporin. Pay attention to bone and joint lesions
+Sulfasalazine	2 g/day	C1	20	
+Azathioprine	3 mg/kg per day	C1	20	
+GMA		C1	27	

†Opinion of the Committee.
‡Because various forms of psoriasis such as generalized psoriasis, pustular psoriasis, and psoriatic arthropathy accompany each other, diagnosis made based on the major symptoms (disease name used for health insurance purposes) may change during the course of the disease. Severe psoriatic arthropathy (psoriatic arthritis) is observed in 30% of patients with GPP. CQ, clinical questions; GMA, granulocyte and monocyte apheresis; GPP, generalized pustular psoriasis; IL, interleukin; TNF, tumor necrosis factor.

children include growth disturbance such as early closure of the epiphysis, hyperostosis, ectopic calcification of ligaments, and hepatic and visual impairment. Therefore, despite the recognized efficacy, long-term retinoid therapy should be performed with care after informing the patients fully of the side-effects mentioned above.

Comments: The most common side-effects of retinoids include desquamation, cheilitis, dry mouth, hepatic impairment,

Table 7. Phototherapy for chronic phase generalized pustular psoriasis

Recommended therapy	Degree of recommendations	Level of evidence
Oral PUVA therapy	C2	V
Oral PUVA therapy + immunosuppressive drug	C2	V
NB-UVB therapy + acitretin	C1	V
NB-UVB therapy + dapsone	C1	V
NB-UVB therapy	C1	V

NB-UVB, narrowband ultraviolet B; PUVA, psoralen plus ultraviolet A therapy.

hyperlipidemia, itchy skin, bone abnormalities (e.g. hyperostosis and early closure of the epiphysis), ectopic calcification of ligaments, renal dysfunction and visual impairment. Therefore, radiographic and visual examinations are necessary every 3 months during retinoid therapy.[45]

In a previous study, 5-year administration of retinoids in patients with psoriasis did not significantly increase the occurrence of side-effects,[46] and the treatment duration was not associated with the occurrence of hyperostosis or ectopic calcification.[46] On the other hand, another study recommended 30 g as the maximum total dose.[47] It should be noted here that acitretin, which has a shorter half-life, is used instead in most overseas countries at present.[39]

CQ4. Cyclosporin

CQ4-1: Is cyclosporin effective for GPP?. Degree of recommendation: C1.

General recommendations: In Japan, cyclosporin is recommended as a first-line drug for the treatment of GPP. However, it is necessary to pay attention to various side-effects such as elevation of blood pressure and kidney failure. While the duration of continuous cyclosporin administration is not regulated in Japan, the guidelines used in other countries recommend discontinuing its administration after 1–2 years to avoid side-effects.

Comments: For the treatment of GPP, the dose of cyclosporin starts with 2.5–5.0 mg/kg per day (twice daily), and the maintenance dose needs to be adjusted based on the change in symptoms. Many case reports and case series reports (level V evidence)[5,37,38] have shown the efficacy of cyclosporin in GPP. However, no RCT or other comparative studies have been conducted to compare cyclosporin with other treatment methods or placebo.

Due to the small number of cases and the severity of disease, it is difficult to conduct large-scale comparative studies with a high level of evidence in GPP. In studies that enrolled patients in Japan, high efficacy has also been confirmed, and cyclosporin may be considered as a first-line drug for GPP.

The side-effects of cyclosporin depend on the dose and duration of administration. Blood pressure and renal function should be examined regularly for abnormalities, and when any abnormality is noted or when the level of serum creatinine is elevated, the dose should be adjusted in accordance with the guidelines.[29] Because kidney failure may progress as the duration of treatment increases, it is necessary to administrate the drug at the lowest effective dose. The recommended duration of cyclosporin administration is up to 2 years in the UK and Germany and up to 1 year in the USA.[48–50]

CQ4-2: Is cyclosporin effective for GPP in children?. Degree of recommendation: C1.

General recommendations: Compared with the adult cases, pediatric GPP is often refractory to treatment, requiring long-term therapy. As in adult patients, cyclosporin has been effective in pediatric patients with GPP, leading to the recommendation of cyclosporin as a first-line drug for pediatric GPP in Japan. However, it is necessary to pay attention to the side-effects, such as elevated blood pressure and kidney failure. While the duration of continuous cyclosporin administration is not regulated in Japan, the guidelines used in other countries recommend discontinuing administration after 1–2 years to prevent the development of side-effects.

Comments: Case reports and case series reports have shown the efficacy of cyclosporin in pediatric GPP.[42,43,51,52] However, no RCT or other comparative studies have been conducted to compare with other treatment methods or placebo.

Due to the small number of cases and severity of disease, it is difficult to conduct large-scale comparative studies with high evidence levels in pediatric GPP. In Japan, cyclosporin and etretinate are the only oral therapies for psoriasis covered by health insurance, and therefore one of them is selected as a first-line drug depending on the age of patient and duration of treatment. However, because kidney failure may progress in long-term treatment, it is recommended to administrate the drug at the lowest effective dose. The recommended duration of cyclosporin administration is principally up to 2 years in the UK and Germany and up to 1 year in the USA.[48–50]

CQ4-3: Is cyclosporin effective for GPP in pregnant women?. Degree of recommendation: C1*.

*Opinion of the Committee.

General recommendations: Cyclosporin should not be used for the treatment of GPP in pregnancy (i.e. impetigo herpetiformis) because of the small number of cases and the potential adverse effect on the fetus. However, because cyclosporin has been used in many renal transplant patients who were pregnant, the drug may be used as a first-line drug for the treatment of GPP in pregnant women if no other treatment is available (see CQ18).

Comments: Case reports have shown the efficacy of cyclosporin in impetigo herpetiformis.[53,54] As for the safety of

Table 8. Clinical questions and their levels of evidence and degree of the recommendations

Clinical questions	Levels of evidence	Degree of the recommendations
1. Primary care		
CQ1. Do systemic management and drug therapy in the acute phase improve disease prognosis?	Not evaluated	A[†]
CQ2. Is the administration of corticosteroids effective for ARDS associated with GPP?	V	B[†]
2. Oral therapies		
CQ3. Are oral retinoids effective for pustular psoriasis?	II	C1 (B[‡]), D[§]
CQ4. Is oral cyclosporin effective for GPP?	II	C1 (B[‡])
CQ5. Is oral methotrexate effective for pustular psoriasis?	II	C1, D[§]
CQ6. Is oral dapsone effective for pustular psoriasis?	V	C2 (C1, in cases other drugs ineffective)
CQ7. Are oral steroids effective for pustular psoriasis?	V	C2, B[¶] C1[††]
CQ8. Is oral colchicine effective for pustular psoriasis?	V	C2
CQ9. Is antimicrobial therapy effective for pustular psoriasis?	V	C2
3. Topical therapies		
CQ10. Are topical steroids effective for pustular psoriasis?	V	C1, C2
CQ11. Is topical active form vitamin D_3 effective for pustular psoriasis?	V	C1, C2
CQ12. Is topical tacrolimus effective for pustular psoriasis?	V	C1, C2
4. Phototherapy		
CQ13. Is PUVA therapy effective for pustular psoriasis?	V	C2, D[‡‡]
CQ14. Is UV-B therapy effective for pustular psoriasis?	V	C1, C2
5. Biologics		
CQ15. Are TNF-α inhibitors effective for pustular psoriasis?	II	C1
CQ16. Are biologics other than TNF-α inhibitors effective for pustular psoriasis?	II	C1
CQ17. Do TNF-α inhibitors improve QOL in patients with pustular psoriasis?	II	C1
6. Granulocyte and monocyte adsorption apheresis (GMA)		
CQ18. Is GMA effective for GPP?	III	C1
CQ19. Does GMA improve QOL in patients with GPP?	III	C1
7. Treatment selection in pregnant and lactating women and children		
CQ20. Is cyclosporin effective for pustular psoriasis in pregnant and lactating women?	V	C1 (D)[§§]
CQ21. Is cyclosporin effective for pustular psoriasis in children?	V	C1
CQ22. Are TNF-α inhibitors effective for GPP in pregnant women?	V	C1
CQ23. Are TNF-α inhibitors effective for GPP in children?	V	C1
CQ24. Is GMA effective for GPP in pregnant and lactating women?	V	C1
CQ25. Is GMA effective for GPP in children?	IV	C1
8. Treatment for complications and the outcome		
CQ26. Is antirheumatic therapy effective for joint symptoms in patients with pustular psoriasis?	II	A–C2
CQ27. Is GMA effective for joint symptoms in patients with pustular psoriasis?	V	C1
CQ28. Do treatments that are in line with the guidelines improve QOL?	Not evaluated	n/a

[†]No clinical studies have been performed, but the importance of primary care in emergency situations is clear based on the epidemiological studies of the cause of death in patients with pustular psoriasis.
[‡]Opinion of the Committee on the urgent treatment of men and non-pregnant women.
[§]Administration in pregnant/lactating women and their partners. [¶]Administration in acute ARDS/capillary leak syndrome.
[††]Administration for the treatment of joint symptoms, especially when systemic amyloidosis secondary to chronic inflammation is suspected.
[‡‡]Systemic PUVA therapy in pregnant and lactating women.
[§§]Although cyclosporin is contraindicated in the Guidelines for Psoriasis Therapy with Cyclosporin MEPC, its use is absolutely necessary in some cases.
ARDS, acute respiratory distress syndrome; CQ, clinical questions; GMA, granulocyte and monocyte apheresis; GPP, generalized pustular psoriasis; MEPC, microemulsion preconcentrate; PUVA, psoralen plus ultraviolet A therapy; TNF, tumor necrosis factor; QOL, quality of life, UV, ultraviolet.

cyclosporin in pregnant women, an overseas study of 405 pregnant women who were renal transplant recipients showed that 304 (75%) women gave birth to a healthy child with no abnormalities, but the rates of low-birthweight and premature babies were high.[55] Because cyclosporin is secreted in breast milk, breast-feeding should be avoided while on cyclosporin.

CQ4-4: Is the safety of cyclosporin for long-term use established?. Degree of recommendation: C2.

General recommendations: The side-effects of cyclosporin depend on the dose and duration of administration. Because kidney failure may progress in long-term treatment, it is recommended that the drug should be administrated at the lowest effective dose. While the duration of continuous cyclosporin

administration is not regulated in Japan, the guidelines used in other countries recommend discontinuing administration after up to 1–2 years to prevent the development of side-effects.

Comments: The incidence of renal dysfunction increases significantly when cyclosporin therapy continues for 2 years or more,[39] and if continued longer, irreversible chronic kidney failure may develop. Although the duration of continuous cyclosporin administration is not regulated in Japan, the recommended duration of cyclosporin administration is up to 2 years in the UK and Germany and up to 1 year in the USA.[28,48–50]

The incidence of cancer increases significantly for malignant skin tumors, especially squamous cell carcinoma,[28,56] but not for visceral malignancies.[28]

CQ5. Methotrexate

CQ5-1: Is methotrexate effective for GPP?. Degree of recommendation: C1.

General recommendations: Methotrexate is recommended for patients who do not respond well to etretinate or cyclosporin and patients with severe arthritis. The Japanese Dermatological Association has been applying its approval, but at present methotrexate is not covered by health insurance for the treatment of psoriasis. Methotrexate should be administrated with care after obtaining fully informed consent, and attention should be paid to the side-effects, including hepatic impairment, bone marrow suppression, interstitial pneumonia and teratogenesis.

Comments: In general, 7.5 mg methotrexate is administrated in three divided doses every 12 h once weekly for the treatment of GPP. The efficacy of methotrexate in GPP has been shown in many case reports and case series reports.[5,37,57] However, no RCT or other comparative studies have been performed to compare this drug with other treatment methods or placebo.

Because of the small number of cases and severity of disease, it is difficult to conduct large-scale comparative studies with a high level of evidence to investigate GPP. Because its efficacy on GPP has been verified, methotrexate should be selected when patients do not respond to treatment with etretinate or cyclosporin. In addition, because of its efficacy in alleviating joint symptoms, methotrexate should be considered for patients with severe joint symptoms (see CQ22–1).

Methotrexate is contraindicated for use in pregnant or lactating women, habitual alcohol drinkers, individuals sensitive to methotrexate, and patients with alcohol liver disease, chronic hepatitis, immunodeficiency syndrome or bone marrow suppression. In addition, methotrexate is relatively contraindicated for use in patients with renal or hepatic dysfunction, active infection, obesity or diabetes.[39] Furthermore, risk factors for methotrexate-induced liver toxicity are habitual alcohol drinking, persistent hepatic dysfunction, liver disease including hepatitis B and C, a family history of hereditary liver disease, a history of taking hepatotoxic medications, diabetes, obesity (body mass index of >30) and dyslipidemia, and patients with many risk factors should take other medications.[39,58,59] Low-risk patients do not need to undergo liver biopsy prior to methotrexate therapy, but they are recommended to undergo hepatological examination regularly to monitor hepatic function.[39,58,59] Oral administration of 1–5 mg/week of folic acid (at 24–48 h after the last oral administration of methotrexate) can be performed as a measure to prevent side-effects such as stomatitis, nausea, vomiting and cytopenia, but this may reduce the efficacy of methotrexate.[39]

CQ5-2: Is methotrexate effective for GPP in children?. Degree of recommendation: C1.

General recommendations: Methotrexate is reported to be effective in pediatric GPP, but this finding was based on case reports and thus lacks sufficient evidence. The Japanese Dermatological Association has been applying its approval, but at present methotrexate is not covered by health insurance for the treatment of psoriasis. Methotrexate should be administrated with care after obtaining fully informed consent and attention should be paid to the side-effects.

Comments: Case reports of efficacy of methotrexate in children with GPP have been published,[42,60,61] but its efficacy is still not supported by sufficient evidence. In the USA, the application of methotrexate in juvenile-onset rheumatoid arthritis has been approved and low-dose methotrexate is considered to be safe.[39,58] The side-effects of methotrexate, such as hepatic dysfunction, stomatitis, nausea and vomiting, were shown to improve after discontinuation of the drug.[39,58]

CQ5-3: Is methotrexate effective for pustular psoriasis in pregnant women?. Degree of recommendation: D.

General recommendations: Methotrexate should not be used because its use in impetigo herpetiformis has not been reported previously and the drug is contraindicated for use in pregnant women in principle.

Comments: Methotrexate should not be used in pregnant women because its application in impetigo herpetiformis has not been reported and the drug is teratogenic to fetuses (methotrexate embryopathy), so it is contraindicated for use in pregnant women.[39,58] Women and men need to use contraception for 1 and 3 months, respectively, because of potential teratogenesis. In addition, methotrexate is contraindicated for use in lactating women because the drug is secreted in breast milk.[62]

CQ5-4: Is the safety of methotrexate for long-term use established?. Degree of recommendation: C1.

General recommendations: It is necessary to pay attention to the side-effects of long-term methotrexate administration, such as liver fibrosis, cirrhosis and bone suppression. If necessary, long-term treatment is possible by combining with regular hematological examination and oral folic acid as a preventive medication. It should be noted here that the Japanese Dermatological Association has been applying its approval, but at present methotrexate is not covered by health insurance for the treatment of psoriasis. Methotrexate should be administrated with care after obtaining fully informed consent and attention should be paid to the side-effects.

Comments: The side-effects of liver fibrosis, cirrhosis and bone suppression are related to the dose and duration of methotrexate. If necessary, long-term treatment is possible if

regular hematological examination is conducted and oral folic acid is given as a preventive medication.[39] The systematic review of the long-term safety of methotrexate monotherapy was reported in a study of rheumatoid arthritis, but not psoriasis.[63] In this meta-analysis of 3808 patients with rheumatoid arthritis (mean dose of 10.5 mg/week and mean duration of 55.8 months), liver enzymes were elevated in 20.2% of the patients, of which 12.9% had levels more than twice the upper limit of normal and 3.7% had to discontinue the treatment because of liver toxicity. Two other studies examining sequential liver biopsies conducted before and after the long-term administration of methotrexate (≥4 years) showed no evidence for liver fibrosis or cirrhosis. In addition, a meta-analysis of 3463 patients with rheumatoid arthritis (mean dose of 8.8 mg/week and mean duration of 36.5 months) showed that pancytopenia was rare, developing in only 0.96–1.4% of the patients.

CQ6. Is dapsone effective for GPP?

Degree of recommendation: C2 (as a first-line drug), C1 (when the initial treatment is ineffective).

General recommendations: Dapsone is not recommended for use as a first-line drug. However, it may be considered as an alternative treatment when the first-line drugs like cyclosporin, etretinate and methotrexate are ineffective. At present, dapsone is not covered by health insurance for the treatment of psoriasis.

Comments: Dapsone is thought to exhibit anti-inflammatory effects by inhibiting the adherence and migration of neutrophils. In general, 50–100 mg/day of dapsone is taken orally in 2–3 divided doses. In Japan, the national health insurance system covers the use of dapsone for bullous disease, vasculitis and discoid lupus erythematosus, but not for pustular psoriasis. In addition, the efficacy of dapsone in GPP has been shown only in case reports,[64,65] and therefore dapsone may be considered as an alternative medication only when the first-line drugs cyclosporin and etretinate fail to improve GPP. In principle, dapsone is contraindicated in pregnant women and children because its safety has not been established. Patients taking dapsone should be regularly monitored for adverse side-effects such as anemia and liver and kidney failure.

CQ7. Are oral steroids effective for GPP?

Degree of recommendation: C2 (B when used urgently for acute respiratory symptoms; C1 for joint symptoms unresponsive to other drugs; C1 for impetigo herpetiformis [pustular psoriasis of pregnancy]).

General recommendations: Despite the reported efficacy, oral steroid monotherapy is not recommended as a first-line drug because it may induce pustules. However, oral steroid monotherapy was shown to be an effective adjuvant therapy for acute and systemic symptoms (see CQ2). Based on these, oral steroid monotherapy should not be used as a first-line treatment for GPP rash, but it may be useful as concurrent therapy in impetigo herpetiformis (pustular psoriasis of pregnancy) which is normally accompanied by systemic symptoms and marked edema. It is considered appropriate to use oral steroid therapy in accordance with the guidelines for the treatment of rheumatoid arthritis when severe joint complications are present.

Comments: Because of the potential induction of pustules, oral steroids should not be used as a first-line drug for pustular psoriasis.[66] However, oral steroids may be used as an effective adjuvant therapy when patients have acute and systemic symptoms[34] or joint symptoms unresponsive to other therapies.[67] As adjuvant therapy in pregnant women, prednisolone should be used because of the low rate of placental transmission. In addition, long-term steroid therapy in children should be avoided because growth impairment is one of the side-effects. During oral steroid therapy, regular monitoring is necessary for common side-effects such as increased susceptibility to infection, peptic ulcer, psychiatric symptoms, diabetes, hypertension and osteoporosis.

CQ8. Is colchicine effective for GPP?

Degree of recommendation: C2.

General recommendations: The use of colchicine in GPP is not currently supported by high-level evidence.

Comments: To date, the efficacy of colchicine for GPP has been shown in only a few case reports,[68] suggesting that its efficacy is not supported by sufficient evidence. Colchicine is not covered by health insurance for the treatment of psoriasis.

CQ9. Is antimicrobial therapy effective for GPP?

Degree of recommendation: C2.

General recommendations: The use of antibiotics as the standard treatment for GPP is not recommended. However, antibiotics may be used as an adjuvant therapy to treat upper respiratory tract infection, as this is an aggravating factor for GPP.

Comments: Effectiveness of antibiotics monotherapy in GPP has been reported.[69,70] However, in principle, antibiotics should be used as adjuvant therapy. In particular, the concurrent use of antibiotics is appropriate when patients present with the prodromal symptom of upper respiratory tract infection, an aggravating factor for GPP.

Topical therapies

Outline: The topical treatments are not recommended strongly in the acute phase treatment of GPP. They should be considered as maintenance or adjuvant therapy for psoriasis-like skin symptoms in the post-acute phase.

CQ10. Are topical steroids effective for GPP?

Degree of recommendation: C1, C2.

General recommendations: Topical steroids may be used as adjuvant therapy for GPP. However, the duration and dose of topical steroids should be monitored carefully because of the potential induction of pustules.

Explanation: No clinical studies have investigated whether topical steroid monotherapy or the combination therapy with systemic therapy is effective for GPP. Topical steroids have been shown to be effective only in case reports,[71,72] and therefore the efficacy is not supported by high-level evidence. However, topical steroids have been used frequently in

combination with systemic therapy for GPP in Japan and overseas,[73] supporting the use of topical steroids as local therapy. However, there are case reports showing the induction of pustular psoriasis after discontinuation of topical steroids.[74–76] Thus, long-term administration of potent and large amount of steroids should be avoided.

CQ11. Is topical active form vitamin D_3 effective for GPP?

Degree of recommendation: C1, C2.

General recommendations: Topical active form vitamin D_3 can be used as concurrent therapy for GPP, but its use should be monitored carefully, especially in the beginning, because topical active form vitamin D_3 has been reported to induce GPP. Topical active form vitamin D_3 is not covered by health insurance for the treatment of pustular psoriasis.

Comments: As in topical steroids, no clinical studies have investigated whether topical vitamin D_3 monotherapy or combination therapy with topical steroid or systemic therapy are effective for GPP. Its efficacy was shown only in case reports,[77–79] and therefore it is not currently supported by a high level of evidence. However, as in topical steroids, topical active form vitamin D_3 has been used frequently in combination with systemic therapy (Table 3), providing a reasonable basis for its use. However, careful attention must be paid when using topical active form vitamin D_3 because of some case reports showing the induction of GPP.[80,81]

CQ12. Is topical tacrolimus effective for GPP?

Degree of recommendation: C1, C2.

General recommendations: Topical tacrolimus can be used carefully as combination therapy for GPP when topical steroids and topical vitamin D_3 cannot be used for some reasons. Topical tacrolimus is not covered by health insurance for the treatment of psoriasis.

Comments: The efficacy of topical tacrolimus in pustular psoriasis has been shown only in two case reports[82,83] and not in clinical studies. In addition, unlike topical steroids or topical active form vitamin D_3, topical tacrolimus has been used less frequently, and therefore accumulation of further studies is required to discuss the efficacy.

Phototherapy

Outline: Only a few studies investigated the efficacy of phototherapy alone in GPP. Many of the studies are case reports of phototherapy use compared with other treatment modalities, and no RCT have been conducted to date. Under these circumstances, any references concerning the usefulness of phototherapy for GPP have to be categorized as an expert opinion.

CQ13-1: Is PUVA therapy effective for GPP?

Degree of recommendation: C2 in acute phase GPP, C1 in chronic phase GPP.

General recommendations: Long wavelength UV therapy can be considered in the treatment of GPP, but it is not supported by sufficient evidence.

Comments: Many case reports of localized pustular psoriasis are available, but only a few reported the efficacy of phototherapy in GPP: acute phase GPP[84–91] and chronic phase GPP with recurring pustules.[5,92,93] No RCT have investigated the efficacy of phototherapy in GPP, and although some experts are against phototherapy for the treatment of acute phase GPP,[94] others promote the concurrent use of UV therapy in the post-acute phase to stabilize symptoms.[17] Other experts express their concerns that UV therapy will turn psoriasis into pustular psoriasis.[95]

The side-effects of long-term PUVA therapy depend roughly on the total amount of irradiation and total number of treatments. The known side-effects are pigmented macules, skin aging, keratotic lesions, tumors (e.g. solar keratosis, Bowen disease, basal cell carcinoma, squamous cell carcinoma and malignant melanoma), conjunctivitis and keratitis (cataract is rare), excessive hair growth, subungual bleeding, acne-like skin rash and contact/photo-contact dermatitis. Because oral PUVA therapy using oral psoralen could induce connective tissue disease, bullous disease, leukemia and various other conditions, its application should comply with the treatment guidelines for PUVA therapy.[96]

CQ13-2: Is PUVA therapy effective for GPP in children?

Degree of recommendation: C2, D in patients aged 10 years or under.

General recommendations: Long wavelength UV therapy can be considered in the treatment of GPP, but it is not supported by sufficient evidence.

Comments: Pustular psoriasis often develops suddenly in children who have no previous history of psoriasis vulgaris. From this point of view, although the evidence is poor, PUVA therapy for pediatric GPP may largely correspond to the acute phase treatment described in CQ13-1. Oral PUVA therapy was reported to be effective in pediatric GPP unresponsive to oral steroids, cyclosporin or retinoids.[97] However, according to the guidelines for the treatment of psoriasis with PUVA therapy,[96] phototherapy in children aged 10 years or under is contraindicated because of concern about carcinogenesis and photo-aging with long-term treatment. Therefore, fully informed consent should be obtained before commencing the therapy.

CQ13-3: Is PUVA therapy effective for GPP in pregnant women?

Degree of recommendation: D for oral PUVA therapy.

General recommendations: PUVA therapy is not recommended for the treatment of GPP in pregnant women because of lack of evidence.

Comments: Previous studies reported the efficacy of topical PUVA therapy in GPP of pregnancy and retinoid PUVA therapy after childbirth.[86,91] According to the review of psoriasis vulgaris in pregnant women, oral PUVA therapy should be contraindicated for pregnant women due to the toxicity of 8-methoxypsoralen (8-MOP).[98] Although some reports are

available, topical PUVA therapy should not be used because its safety has not been established.

CQ14. UV-B therapy

CQ14-1: Is UV-B therapy effective for GPP?. Degree of recommendation: C2, C1 (when used concurrently with a first-line drug or as an after treatment).

General recommendations: Medium wavelength UV therapy can be considered in the treatment of GPP, but the therapy lacks sufficient evidence.

Comments: Although RCT has not been performed, there are some case reports in which narrowband UV-B (NB-UVB) is effective in a chronic phase of GPP.[72,99–101]

While photo-aging is known to be a long-term side-effect of medium wavelength UV therapy, data on NB-UVB therapy are not available. Although the side-effect of greatest concern is carcinogenesis, no clear data on carcinogenesis are currently available due to the short history of use of NB-UVB therapy. Animal studies have shown that the rates of carcinogenesis are comparable between broadband UV-B (BB-UVB) and NB-UVB therapies.[102] In one study, BB-UVB therapy had a higher rate of carcinogenesis,[103] while in another, NB-UVB therapy had a higher rate of carcinogenesis,[104] revealing inconsistent results. One study suggested that the combined use of biologics and BB-UVB therapy promotes photocarcinogenesis.[105]

CQ14-2: Is UV-B therapy effective for GPP in children?. Degree of recommendation: C1.

General recommendations: Medium wavelength UV therapy can be considered in the treatment of pediatric GPP, but insufficient evidence is available to consider the therapy as effective monotherapy.

Comments: Some studies reported the efficacy of NB-UVB therapy in pediatric GPP.[99–101] Although it has been suggested that UV-B therapy is effective for inverse psoriasis including pustular psoriasis, which is more common among children and the elderly,[106] it is necessary to obtain fully informed consent before commencing the therapy.

CQ14-3: Is UV-B therapy effective for GPP in pregnant women?. Degree of recommendation: C1 (when the first-line drugs are contraindicated or when disease is resistant to these therapies)

General recommendations: Medium wavelength UV therapy can be considered in the treatment of GPP in pregnant women, but such use is not supported by sufficient evidence.

Comments: NB-UVB therapy is reported to be effective in GPP of pregnancy.[72] According to the review of the treatment of psoriasis vulgaris in pregnant women,[98] for those unresponsive to oral therapies and thus in need of phototherapy, UV-B therapy is recommended instead of PUVA therapy, which raises a concern of potential 8-MOP toxicity. Etretinate and retinoids are contraindicated for use in pregnant women.

1. Phototherapy for acute phase GPP: Oral PUVA therapy is contraindicated for pregnant women because of potential 8-MOP toxicity. Despite the application in previous cases, topical PUVA therapy should not be performed because its safety has not been established.
2. Phototherapy for chronic phase GPP: UV-B therapy may be used as combination therapy for chronic phase pustular psoriasis when patients do not respond to regular therapies for psoriasis or when the amount of treatment drugs need to be reduced to alleviate side-effects.

Biologics

Outline: Biologics are a group of drugs that have been developed relatively recently owing to marked advances in immunological and molecular biological technologies. In particular, the clinical application of TNF-α inhibitors, such as infliximab, adalimumab and etanercept, started approximately 15 years ago, and these biologics have been used in patients with Crohn's disease, ulcerative colitis, ankylosing spondylitis, juvenile idiopathic arthritis and rheumatoid arthritis, leading to the accumulation of evidence for psoriasis and psoriatic arthritis treatment.[107] In 2010, infliximab and adalimumab were included in a group of drugs covered by the national health insurance system in Japan. Several double-blind RCT have shown the efficacy of TNF-α inhibitors in psoriasis vulgaris and psoriatic arthritis,[49,108,109] leading to the establishment of clinical practise guidelines for these diseases. Furthermore, a monoclonal antibody that targets the p40 subunit shared by IL-12 and -23 (the anti-p40 antibody ustekinumab) has been developed and shown to be effective for psoriasis vulgaris[49] and psoriatic arthritis.[110] Subsequently, ustekinumab was included in a group of drugs covered by health insurance in 2011. Compared with TNF-α inhibitors, ustekinumab has not been used widely in other areas and so there is relatively little evidence for its long-term safety or efficacy in relieving joint symptoms.[49,107,109] In 2015, secukinumab, an anti-IL-17A antibody, became one of the drugs covered by health insurance for use in psoriasis vulgaris and psoriatic arthritis, and also for GPP. In 2016, ixekizumab (anti-IL-17A antibody) and brodalumab (anti-IL-17 receptor A antibody) have been approved for coverage by health insurance in Japan for psoriasis vulgaris, psoriatic arthritis, psoriatic erythroderma and GPP. Any of the drugs mentioned above is expected to work for GPP based on their mechanism of action,[17] and in patients unresponsive to or contraindicated for infliximab, other biologics have been used. However, to reveal the role of biologics in the treatment of GPP from the perspective of EBM, RCT are needed to compare the efficacies of biologics and other treatment methods. However, at present, it is necessary to rely on the open-label studies[111–114] or on the accumulation of case reports because of the limited number of clinical cases and severity of disease in many cases.

In addition to the conventional oral therapies, infliximab is considered the first-line drug in the consensus on treatment of pustular psoriasis issued by the Medical Board of the National Psoriasis Foundation in the USA.[17] In Japan, the use of adalimumab in the treatment of psoriasis vulgaris and psoriatic arthritis and the use of infliximab in psoriasis vulgaris, psoriatic

arthritis, pustular psoriasis and erythrodermic psoriasis have been covered by health insurance since 2010. In 2011, ustekinumab was also included in a group of drugs covered by health insurance for use in psoriasis vulgaris and psoriatic arthritis, but not for GPP. The use of the anti-IL-17A antibody secukinumab for GPP was approved for health insurance coverage in 2015 in addition to psoriasis and psoriatic arthritis. In 2016, another anti-IL-17A antibody, ixekizumab, and an antibody to IL-17 receptor A, brodalumab, were approved for health insurance coverage for psoriasis vulgaris, psoriatic arthritis, erythrodermic psoriasis and GPP. To clinically use these drugs, it is necessary to fulfill requirements such as approval for the physicians and institutions, indications, health insurance coverage, reactions anticipated to occur on administration and regular monitoring, as well as to comply with the Guideline/Safety Manual for the Use of Biologic Agents in Psoriasis.[9] Although ustekinumab or adalimumab are not covered by health insurance for the treatment of GPP, their efficacy is expected based on the mechanism of action, and their efficacy in some patients has been reported.[115] Despite the approval of alefacept and efalizumab, both of which inhibit the interaction between T cells and dendritic cells, for use in psoriasis vulgaris by the FDA, the marketing of efalizumab was discontinued because of fatal infections. In Japan, alefacept or efalizumab are not covered by health insurance for the treatment of psoriasis.[9]

CQ15. Are TNF-α inhibitors effective for GPP?

Degree of recommendation: C1 (for skin lesions*), B (when complicated with severe arthritis*).

*Opinion of the Committee.

General recommendations: TNF-α inhibitors are effective for GPP.

Comments:

(1) The findings of RCT studies conducted in many countries clearly show the efficacy of TNF-α inhibitors such as infliximab, adalimumab and etanercept in psoriasis vulgaris, leading to the establishment of treatment guidelines in several countries, such as the USA and Germany.[49,108] The degree of recommendation for psoriasis vulgaris is A (strongly recommended).[49,108] Similarly, several RCT of the agent in the treatment of psoriatic arthritis have been performed, and according to the clinical practise guidelines for psoriatic arthritis, the degree of recommendation is A.[108] In Japan, TNF-α inhibitors used in the treatment of psoriasis are infliximab and adalimumab (Table 9); etanercept is not covered by insurance for the treatment of psoriasis vulgaris or psoriatic arthritis. The efficacies of infliximab and adalimumab for both conditions have been shown in clinical studies conducted in Japan.[116,117] However, many adverse side-effects are reported. In particular, preventive therapies and measures against anaphylaxis-like infusion reactions toward infliximab are necessary. In addition, the development of autoantibodies such as antinuclear antibodies, lupus-like syndrome, antibodies against TNF-α inhibitors, demyelinating disorder and cytopenia have been reported.[118] The safety profiles of long-term use of TNF-α inhibitors have been reported, and the findings suggest an increase in the risk of infection. However, the safety of TNF-α inhibitors is relatively high compared with conventional therapies.[107]

On the other hand, although no RCT have been conducted, the application of infliximab in GPP has been analyzed in case reports,[119–124] including a retrospective clinical study of infliximab in GPP conducted in Japan[125,126] and a retrospective case series study of TNF-α inhibitors in acute phase GPP.[18] Because of the cardiovascular complications in some GPP cases, it is important to establish measures against infusion reaction caused by TNF-α inhibitors. As the FDA clearly warns,[127] as paradoxical side-effects of TNF-α inhibitors, the onset of new psoriasis and the exacerbation and pustule formation of existing psoriasis have occasionally been reported. In Japan, adalimumab is covered by health insurance for the treatment of psoriasis vulgaris and psoriatic arthritis and infliximab is covered by health insurance for the treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis and erythrodermic psoriasis. In the consensus on treatment of pustular psoriasis from the medical board of the National Psoriasis Foundation in the USA, infliximab is listed as a first-line drug along with retinoids, cyclosporin and methotrexate.[17] On the other hand, together with PUVA therapy, adalimumab and etanercept are considered second-line therapies for GPP.

The effect of infliximab is seen within 24–48 h in many cases. However, long-term administration of infliximab leads to the production of neutralizing antibodies in 20–30% of the patients. Although etanercept is not as fast-acting as infliximab, its long-term use induces neutralizing antibodies less frequently, and the drug has been used as an effective maintenance drug after discontinuing infliximab in two cases of GPP.[128] However, because of the short history of use of etanercept, its potential side-effects after long-term use are currently unclear. As for adalimumab, some case reports have been published periodically,[129–134] but the drug has not been used extensively.

Table 9. TNF-α inhibitors used for the treatment of psoriasis in Japan

Drug name	Type	Administration
Infliximab	Chimeric human anti-TNF-α monoclonal antibody	Drip infusion of 5 mg/kg for 2–3 h at 0, 2nd and 6th week, and then every 8 weeks (dose may be increased up to 10 mg/kg, or the interval may be shortened up to every 4 weeks)
Adalimumab	Fully human anti-TNF-α monoclonal antibody	Initial dose of 80 mg by s.c. injection, 40 mg on alternating weeks (may be increased to 80 mg)

TNF, tumor necrosis factor.

(2) The use of TNF-α inhibitors in expectant mothers (see CQ22) is generally safe based on their previous use in rheumatoid arthritis and Crohn's disease[135] and in psoriasis vulgaris and psoriatic arthritis.[136] A systematic review of 50 articles published until 2011 on TNF-α inhibitors reported that no significant difference was observed in the rates of spontaneous abortion, congenital abnormality and birth compared with the general population.[136] The FDA classifies infliximab, adalimumab and etanercept as category B drugs in pregnancy. However, because of a lack of adequate studies, the use of TNF-α inhibitors in pregnancy is absolutely contraindicated in Germany's clinical practise guidelines for psoriasis vulgaris.[49] For use in pregnancy, fully informed consent is required after taking into consideration the risks and benefits of using TNF-α inhibitors.[137–140] Diphenhydramine used as a premedication to prevent infusion reactions is contraindicated in pregnant women because of its teratogenic effect.

(3) TNF-α inhibitors were reported to be effective and safe in two pediatric patients (<16 years old) (see CQ23).[130,141] On the other hand, the FDA warned in 2009 that pediatric and adolescent patients who had been treated with TNF-α inhibitors had a high incidence of lymphoma and malignant tumor.[127] However, it is unclear whether such incidence was due to TNF-α inhibitors alone because immunosuppressive drugs were used concurrently in most cases. The same warning revealed 69 cases with the development of psoriasis, which included 17 of pustular psoriasis and 15 of palmoplantar pustulosis, in a group of patients who had been treated with TNF-α inhibitors for autoimmune disease or rheumatoid arthritis. The consensus on treatment of pustular psoriasis from the medical board of the National Psoriasis Foundation in the USA recommends acitretin, prednisolone, methotrexate and cyclosporin as first-line drugs, but a small number of experts include etanercept as a first-line drug. Along with UV-B therapy, adalimumab and infliximab are second-line drugs in the consensus.[17]

CQ16. Are biologics other than TNF-α inhibitors effective for GPP?

Degree of recommendation: C1 for secukinumab, ixekizumab, brodalumab and ustekinumab.

General recommendations: Secukinumab, ixekizumab and brodalumab are effective for treating GPP. Ustekinumab is expected to be effective, but lacks sufficient evidence. Consequently, it should be used only in patients resistant to other treatment modalities.

Comments: In 2014, the anti-IL-17A antibody secukinumab was approved for health insurance coverage in Japan for patients with psoriasis vulgaris and psoriatic arthritis. In December 2015, it was approved for coverage by health insurance for treatment of GPP in Japan. It is the first biologic to be approved as a first-line systemic treatment in the European Union for treatment of moderate to severe plaque psoriasis vulgaris. Its efficacy and safety for GPP patients have been reported in a recent open-label trial.[142] Several case studies of GPP successfully treated with secukinumab have also been reported.[143–145] In 2016, another anti-IL-17 antibody, ixekizumab, and an anti-IL-17 receptor antibody, brodalumab, were approved for health insurance coverage in Japan for patients with psoriasis vulgaris, psoriatic arthritis, pustular psoriasis and psoriatic erythroderma. The efficacy and safety of ixekizumab and brodalumab including GPP patients in an open-label trial have been reported.[111–113] Some characteristic side-effects of IL-17 blockage have been reported including *Candida albicans* infection, exacerbation of Crohn's disease and neutropenia.[146] One report presents a case treated with brodalumab, demonstrated rebound flare up after discontinuation of brodalumab,[114] suggesting the necessity for caution when discontinuing brodalumab treatment. Although we have less experience of IL-17 antagonists in other areas, it is considered relatively safer for severe infections compared with TNF inhibitors,[147] and the Biologics Review Committee of the Japanese Dermatological Association recommends secukinumab equally as other biologics.[148]

In 2011, Japan approved health insurance coverage for the use of the anti-IL-12/23 p40 antibody ustekinumab in patients with psoriasis vulgaris and psoriatic arthritis. There have been several RCT of ustekinumab in psoriasis vulgaris[149] and a meta-analysis on the efficacy and side-effects of biologics including ustekinumab has been published.[150] In the guidelines established in the USA[108] and Europe,[3,49] the degree of recommendation for the use of ustekinumab in psoriasis vulgaris is rated A (strongly recommended). In addition, ustekinumab is considered equivalent to other biologics in those guidelines.[3,49,108] Recent RCT of patients with psoriatic arthritis suggest that ustekinumab is effective for joint symptoms caused by psoriatic arthritis.[110,151] As for its efficacy in GPP, only a limited number of case reports, but no RCT, are available.[115,152,153] On the other hand, three previous studies have independently shown the exacerbation or new occurrence of pustular psoriasis in association with the administration of ustekinumab.[154–156] Due to insufficient evidence, it is proper to use ustekinumab in patients with GPP only when they are resistant to other treatment modalities.

While the anti-IL-17A antibody secukinumab is covered by health insurance for the treatment of psoriasis vulgaris, its use in pustular psoriasis should be performed with care after considering the risks and benefits and only when other drugs are ineffective because of the lack of evidence. As for alefacept, several double-blind RCT have reported its efficacy in psoriasis vulgaris and psoriatic arthritis. In the guidelines used in the USA, a grade A recommendation (strongly recommended) is given to the use of alefacept in psoriasis vulgaris.[108] A prospective cohort study of 16 patients with psoriasis, including four with pustular psoriasis, is the only reference currently available for GPP.[157] No systemic clinical studies or RCT have been performed. The application of efalizumab in psoriasis vulgaris is rated A in the guidelines used in the USA,[108] and based on the mechanism of action, the drug is expected to suppress the symptoms of GPP effectively. However, a report of the induction of GPP following the application of efalizumab in psoriasis vulgaris[158] makes its use difficult because of concerns over rebound effects following discontinuation. Due to cases of fatal infection, the

marketing of efalizumab was discontinued in the USA and Europe. Alefacept is not covered by health insurance for the treatment of psoriasis in Japan.

CQ17. Do TNF-α inhibitors improve QOL in patients with GPP?

Degree of recommendation: C1 (for skin lesions*), B (for severe joint complications*).

*Opinion of the Committee.

General recommendations: TNF-α inhibitors are expected to improve QOL in patients with GPP. In particular, they are recommended for patients with joint symptoms.

Comments: There are RCT reports on the improvement of QOL in psoriasis vulgaris[159] and psoriatic arthritis,[160] but no RCT study has been published on QOL in GPP. A recent cross-sectional study suggests that the pathological condition affects QOL more adversely in patients with pustular psoriasis than those with psoriasis vulgaris.[161] However, because of the clinical efficacy in pustular psoriasis (case reports, see CQ15), TNF-α inhibitors are expected to improve QOL in patients. Psoriasis contains several different clinical types including pustular psoriasis, psoriatic arthritis and psoriasis vulgaris, and shifts between different clinical types are sometimes observed. Therefore, when GPP is accompanied by joint symptoms, it is desirable to comply with indications for psoriatic arthritis, including the use of TNF-α inhibitors.

GMA

Outline: GMA is an extracorporeal circulation therapy for the inhibition and removal of neutrophils, macrophages and monocytes, all of which accumulate in inflamed tissues and contribute to the formation of lesions. The efficacy and safety of GMA in GPP, shown mostly in case reports, have been verified in a multicenter study,[32] but no RCT have been performed to date. Because of the limited number of cases and severity of GPP and the extracorporeal aspect of GMA, it is difficult to conduct double-blind, placebo-controlled studies, making it necessary to rely on the accumulation of case reports. There is a report demonstrating that GMA selectively removes activated pathogenic granulocytes and monocytes.[162] According to this mechanism, effectiveness can be expected. The instruction manual of GMA in draft form, possible side-effects and the prevention of infection at the needle insertion site are described at the end of the present guidelines.

CQ18. Is GMA effective for GPP?

Degree of recommendation: C1.

General recommendations: GMA may be performed in patients with GPP as a safe treatment modality with a relatively small number of side-effects, but the therapy lacks sufficient evidence.

Comments: The efficacy and safety of GMA in GPP have been shown only in case reports, case series including a report on neutrophilic skin disorders and reviews.[162–167] No RCT have been performed, but one multicenter study[32] has shown improvement in the area of erythema, erythema with pustules, and edema, and in the severity score defined in the 2010 guidelines for the management and treatment of GPP. Among 15 cases, adverse events were reported in three patients, but none were serious, suggesting the safety of GMA.[32] In addition, no serious side-effects were reported in the case series.[162–167]

CQ19. Does GMA improve QOL in patients with GPP?

Degree of recommendation: C1.

Table 10. Selection of therapy for pregnant or lactating patients with psoriasis (Cited with modification from Reference 98)

	Pre-pregnancy drug-free period	
Methotrexate	3 months in both sexes	
Etretinate	2 years in women (6 months for men in Japan)‡	
Topical therapy	Safety of various therapies for psoriasis	Systemic therapy
	Safe therapy	
Emollient (such as Vaseline)		UVB therapy
Topical steroids (mild, moderate, and potent)		
Dithranol		
	Relatively safe therapy	
Coal-tar formulations		Cyclosporine†
Powerful topical steroids (trace amount)		GMA‡
	Therapy to be avoided	
Topical retinoids		Retinoids†
Active form vitamin D3		Methotrexate†
		PUVA therapy†
	Therapy with unknown side effects	
		Fumarate ester†
		Biologics†
		Hydroxyurea†

†Contraindicated in pregnant/lactating women.
‡Addition although not described in Reference 98.

General recommendations: GMA is expected to improve QOL in patients with GPP.

Comments: No RCT have assessed the effect of GMA on QOL in patients with GPP. However, a significant improvement in QOL has been reported by a multicenter study using the Dermatology Life Quality Index.[32]

Selection of medications in pregnant/lactating women and children (Table 10)

Outline: Although safe drug administration is the basic principle, because GPP is a life-threatening systemic inflammatory disease, it is sometimes necessary to administrate drugs with known risks and no established safety records in pregnant/lactating women and children because of the potential benefits. In such cases, it is necessary to obtain fully informed consent.

CQ20. Is cyclosporin effective for GPP in pregnant and lactating women?

Degree of recommendation: D (based on the package insert and the Guidelines for Psoriasis Therapy with Cyclosporine MEPC), C1 (according to the evaluation by the Committee).

General recommendations: According to the guidelines used in Japan[29] and the package insert, cyclosporin is contraindicated in pregnant and lactating women. However, it is sometimes necessary to administrate cyclosporin because GPP is a systemic inflammatory disease that is life-threatening to expectant mothers and fetuses and systemic steroid therapy does not always work adequately. Fully informed consent is required before administrating cyclosporin.

Comments: In Europe and North America, the application of etretinate and methotrexate in pregnant and lactating women is designated as pregnant category X, namely absolute contraindication, whereas cyclosporin is a pregnant category C medication, namely lacking safety information.[98] In Japan, cyclosporin is contraindicated in the Guidelines for Psoriasis Therapy with Cyclosporine MEPC[29] as well as in the package insert.

Overseas, cyclosporin has been used in several cases of impetigo herpetiformis to control the acute symptoms in combination with steroids and later as a post-therapy medication to manage the symptoms until the delivery of the child.[53,168–170] In cases of organ transplantation, where cyclosporin was administrated to pregnant women post-transplant, the odds ratio for teratogenicity was 3.83 (95% confidence interval [CI], 0.75–19.6), and the incidence of teratogenicity was 4.1% (95% CI, 2.6–7%), with no statistically significant difference, revealing no evidence for teratogenesis.[50,171,172]

When patients with GPP have marked generalized edema or complication of ARDS/capillary leak syndrome, it is desirable to use systemic steroids (20–40 mg/day of prednisolone equivalent) as the first-line drug. However, the use of systemic steroids for the management of skin lesions should be avoided. Although systemic steroids may be indicated for pustular psoriasis of pregnancy (impetigo herpetiformis) accompanied by marked edema or systemic symptoms, it is recommended to select steroids, such as prednisolone, that are inactivated in the placenta and thus have fewer effects on the fetus. There is no justification to recommend etretinate or methotrexate, both of which are already contraindicated for use in pregnancy (see CQ22 for more information on TNF-α inhibitors).

CQ21. Is cyclosporin effective for GPP in children?

Comments of recommendation: C1 (opinion of the Committee).

General recommendations: Cyclosporin is recommended as a first-line drug for pediatric pustular psoriasis, but the application of etretinate or systemic steroid therapy may be necessary when patients do not respond to cyclosporin.

Comments: Cyclosporin is selected increasingly more often as systemic therapy for pediatric pustular psoriasis. The case reports of pediatric pustular psoriasis suggest the utility of cyclosporin,[101,173–176] with a wide range in dose (0.5–5 mg/kg per day) and various application methods. In addition, etretinate and systemic steroids have been used according to the Japanese Society for Psoriasis Research and the medical records of patients with designated intractable diseases. Etretinate is not recommended as a first-line drug for use in children due to potential bone growth impairment. However, it is sometimes necessary to select etretinate or systemic steroid therapy when patients do not respond to cyclosporin or have difficulty in reducing the dose. For long-term etretinate use, the side-effects should be monitored carefully.

When using cyclosporin for the management of acute symptoms, it is appropriate to use short-term therapy for crisis intervention. The safety of long-term cyclosporin use in pediatric pustular psoriasis lacks evidence. However, a previous study of 329 patients with juvenile chronic arthritis who underwent long-term cyclosporin use (mean maintenance dose, 3.4 mg/kg per day; mean duration of administration, 1.8 years) revealed a 12% incidence of side-effects, including excessive hair growth, elevated creatinine levels, hypertension and gastrointestinal dysfunction.[177] Therefore, to avoid side-effects, short-term or intermittent administration of the lowest possible dose is desirable.

CQ22. Are TNF-α inhibitors effective for GPP in pregnant/lactating women?

Degree of recommendation: C1 (opinion of the Committee).

General recommendations: The use of TNF-α inhibitors may be considered when the monotherapy or combination therapy with cyclosporin or systemic steroids is ineffective and the lives of the patient and fetus are in danger.

Comments: Three pregnant patients with pustular psoriasis have been successfully treated with TNF-α inhibitors, and a low-birthweight newborn was delivered from one of them.[178–181] TNF-α inhibitors are generally safe in expectant mothers based on previous reports of patients with rheumatoid arthritis or Crohn's disease[135] and those with psoriasis vulgaris or psoriatic arthritis.[136] According to the former classification by the FDA, infliximab, adalimumab and etanercept are pregnancy category B medications (the effects on the fetus are unknown due to the lack of controlled studies of pregnant women, even though no abnormality was observed in animal studies).

In the guidelines established in the USA, along with cyclosporin, systemic corticosteroids and topical therapies, infliximab is recommended as a first-line drug for the treatment of

pustular psoriasis of pregnancy. In addition, infliximab is described as a beneficial treatment in the acute phase because it is a fast-acting pregnancy category B medication.[17] However, due to an accumulation of an insufficient number of cases, the use of TNF-α inhibitors in pregnancy is absolutely contraindicated in the German guidelines on the treatment of psoriasis vulgaris.[49] According to the systematic review of 50 articles published before November 2011,[137] TNF-α inhibitors were administrated to 472 pregnant patients (194 with infliximab, 261 with adalimumab and 17 with certolizumab), with the occurrence of non-specific congenital abnormality in 19 (4.1%; nine with infliximab, 10 with adalimumab and none with certolizumab) of the patients. The incidence rates of spontaneous abortion and congenital abnormality in these women were comparable with those in the general population. The live birth rate among these women was also comparable with that in the general population.

Infliximab is an IgG1-based monoclonal antibody drug with no evidence of teratogenesis in animal studies, which has yet to be verified in humans. In the first trimester, the placenta is impermeable to IgG1, preventing the fetus undergoing organogenesis from exposure to the drug. However, infliximab administrated during late pregnancy was detected in the blood for up to 6 months after birth due to an increase in the permeability of IgG through the placenta in the second and third trimester.[182] These infants had immune dysfunction and it was suggested that they avoid immunization with live vaccines for the first 6 months after birth. Indeed, an infant born to a mother treated with infliximab during pregnancy died of disseminated bacillus Calmette–Guérin (BCG) infection after undergoing immunization with a live BCG vaccine.[183] Avoidance of infliximab during late pregnancy was also suggested in some studies. Adalimumab is also an IgG1-based monoclonal antibody. Despite the lack of indication for pustular psoriasis, adalimumab may be used when infliximab is no longer potent. Little information on the permeability of adalimumab through the placenta is currently available, but similarly to infliximab, adalimumab was detected in the blood of infants up until 6 months of age in a study conducted by Mahadevan *et al.*[184] Again, adalimumab was not teratogenic in animals, but this needs to be verified in humans. A previous study recommended the discontinuation of adalimumab administration 8–10 weeks before the due date.[184]

According to a case report of a 32-year-old pregnant woman treated with 10 mg/kg of infliximab five times, with the last infusion 2 weeks before delivery, infliximab (39.5 μg/mL) was detected in her breast-fed infant at 6 weeks after birth, but not in her breast milk, suggesting that infliximab was transferred to the infant through the placenta.[185] Although the number of cases is still small, no fetal abnormality due to the administration of ustekinumab in pregnancy has been observed.[152] In addition, diphenhydramine used as a premedication against infusion reaction is contraindicated for use in pregnant women because of known teratogenicity. When using biologics in pregnancy, fully informed consent needs to be obtained after careful consideration of the risks and benefits.

CQ23. Are TNF-α inhibitors effective for GPP in children?

Degree of recommendation: C1.

General recommendations: TNF-α inhibitors may be used when cyclosporin alone or systemic steroid therapy is ineffective, patients have severe joint symptoms or rapid responses are needed.

Comments: The efficacy of TNF-α inhibitors in pediatric psoriasis has been reported,[186–189] whereas only a few studies investigated the administration of TNF-α inhibitors in pediatric GPP.[121,141,190–194] Ovarian cyst, gastroenteritis, pneumonia, bronchitis, pharyngitis, herpes simplex and herpes zoster are the side-effects of TNF-α inhibitors administrated for pediatric psoriasis, juvenile chronic arthritis and Crohn's disease.[186,195,196] In addition, adalimumab was reported to be effective and safe in children with Crohn's disease.[130,197] Although the FDA warned of a potential increase in the incidence of malignant tumors such as lymphoma in pediatric and adolescent patients treated with TNF-α inhibitors,[127] because of the combination therapy with 6-mercaptopurine or azathioprine in some of such cases, further studies are necessary to elucidate their carcinogenic properties.

In the consensus on treatment of pustular psoriasis published in the USA, along with the retinoid (acitretin), cyclosporin and methotrexate, some experts recommend etanercept as a first-line drug for the treatment of pediatric pustular psoriasis despite insufficient evidence. Furthermore, together with UV-B therapy, adalimumab and infliximab are considered second-line drugs.[17] In pediatric pustular psoriasis, with secondary malignancies due to long-term use in mind, it is recommended that TNF-α inhibitors be used for crisis intervention to manage acute symptoms. However, the incidence of infusion reactions and the development of antibodies against the drug may be increased with this type of "as needed" use.

CQ24. Is GMA effective for GPP in pregnant and lactating women?

Degree of recommendation: C1.

General recommendations: GMA may be used for the treatment of pregnant and lactating patients with pustular psoriasis as a safe treatment method with few side-effects, but it is not supported by sufficient evidence.

Comments: The effect of GMA on pregnant/lactating women has not been investigated in RCT. The post-marketing surveillance study of GMA on pustular psoriasis reported three cases of pregnant women; GMA was effective in two cases and none had side-effects or adverse effects on the fetus or delivery. The efficacy and safety of GMA in inflammatory bowel diseases in pregnant women were described.[198–200] However, fully informed consent is required because the safety of GMA in pregnant/lactating women has not been established yet.

CQ25. Is GMA effective for GPP in children?

Degree of recommendation: C1.

General recommendations: GMA may be considered as a safe treatment modality with few side-effects for children with

pustular psoriasis, but the treatment is not supported by sufficient evidence.

Comments: No RCT have investigated the efficacy of GMA in children. However, the efficacy and safety of GMA in inflammatory bowel diseases in children, such as ulcerative colitis and Crohn's disease, were described in a case series report.[201] The safety of GMA for pediatric cases was also verified in a prospective and retrospective study.[202,203] In addition, the efficacy and safety of GMA in 10 children aged 15 years or younger was reported in a post-marketing surveillance study of ulcerative colitis. Studies of circulatory dynamics suggest that GMA is safe in children weighing 25 kg or more. However, fully informed consent is required because the safety of GMA in children has not been established yet.

Treatment of complications and outcome

Outline: In GPP, it is often necessary to treat complications such as joint symptoms, iritis and other eye symptoms. The incidence of joint complications is particularly high and often leads to sequelae such as joint deformity. In addition, secondary amyloidosis may occur due to chronic inflammation. To avoid complications and improve QOL, drug therapies that are effective for skin symptoms caused by GPP and for the disease activity and severity of joint diseases should be given as early as possible, and the therapy for joint disease should be continued even when the rash is under control.

CQ26. Is antirheumatic therapy effective for joint symptoms accompanying pustular psoriasis?

Degree of recommendation: A–C1 (see the section for each drug).

General recommendations: Improvement in arthritis accompanying psoriasis has been noted from treatment based on therapy for rheumatoid arthritis.

Comments: It is important to evaluate not only skin lesions caused by GPP, but also the urgency and severity of arthritis complications to decide which manifestation should be the main focus for the establishment of a novel treatment strategy. Because of the various disease types, such as psoriasis vulgaris, pustular psoriasis and psoriatic arthritis, the diagnosis (for health insurance purposes) may vary depending on the main symptoms, and therefore the treatment strategy needs to be updated according to the latest symptoms.

While almost no sequelae are observed after the treatment of psoriasis rashes, arthritis is associated with permanent joint deformity and other sequelae. Patients with psoriatic arthritis have a mortality rate that is 1.62-times higher than that observed in the general population, and according to a cohort study, prognostic factors in these patients are: (i) a previous history of active or severe lesions; (ii) treatment level; (iii) erosive lesions; and (iv) elevated erythrocyte sedimentation rate.[204] In addition, if the level of serum amyloid A remains elevated due to chronic arthritis, some patients may develop kidney failure, cardiac failure and gastrointestinal symptoms due to secondary AA amyloidosis. Therefore, it is important to provide proactive intervention and careful monitoring of arthritis. Decline in QOL and in function are comparable between patients with psoriatic arthritis and those with rheumatoid arthritis.[204] It is important to select monotherapy or multiple drug therapy based on the severity of psoriasis rash and joint symptoms.

The efficacy of colchicine in psoriatic arthritis varies among the studies, even though those of other drugs stay consistent. Patients with psoriatic arthritis are more susceptible to placebo effects than patients with rheumatoid arthritis. Improvement in skin symptoms may influence the efficacy on arthritis. Gold drugs are not highly effective in psoriatic arthritis, and among the drugs examined, methotrexate was highly effective. Explanations provided below are based on the assessment of the efficacy of standard antirheumatic drugs before the era of cyclosporin and biologics and etretinate in psoriatic arthritis[205] and recent reviews on the treatment of arthritis.[206–208]

1. Methotrexate.

Degree of recommendation: B–C1.

General recommendations: Low-dose weekly methotrexate is expected to improve arthritis.

Comments:

(1) Utility as monotherapy: Methotrexate is administrated once weekly as a single dose or divided into three doses for administration every 8 h. The dose starts at 2.5–5 mg and is increased gradually to 7.5–22.5 mg/week. The efficacy of methotrexate for arthritis has been reported by many studies.[67,209] A small, double-blind, placebo-controlled RCT was conducted,[210] but the end-point of the study was overall improvement as determined by primary physicians. Although observational clinical studies provide much data, their evidence level is not high. In a comparative study, the efficacy of methotrexate for arthritis was similar to that of cyclosporin.[211]

(2) Major side-effects and preventive measures: Due to teratogenesis, pregnancy should be avoided for 3 months after treatment discontinuation. The patient's partner should also use contraception. Because of the occasional bone marrow suppression and the enhancement of side-effects by concurrent drugs, it is necessary to undergo screening every 1–3 months. The incidence of pulmonary fibrosis due to the administration of methotrexate appears to be lower in patients with psoriasis (which is thought to be with plaque-type lesions, and its incidence is unclear in pustular psoriasis, as noted by the author) compared with those with rheumatoid arthritis.[211] In contrast, the incidence rates of liver fibrosis and cirrhosis are high in patients with psoriasis, and the drug is contraindicated for use in hemodialysis patients. In the consensus conference for methotrexate,[211] liver biopsy was recommended with every additional dose of 1.5 g methotrexate.[212] In recent years, however, patients are divided into groups based on risk factors such as a history of alcohol intake, hepatic dysfunction, hepatitis B or C, diabetes, obesity and hyperlipidemia. Patients with no risk factors need to undergo nine screenings during the 12-month period after the initiation of drug therapy, and they are subjected to liver biopsy when screening findings show elevated aspartate transaminase levels consecutively in five of the nine screenings or a reduction in serum albumin levels. In addition, patients with no risk factors need to undergo liver biopsy

or switch to other medication after a cumulative dose of 3.5–4 g of methotrexate.[58]

When taken 1 or 2 days after the final administration of methotrexate, 1–5 mg/day of folic acid can alleviate stomatitis, macrocytic anemia and gastrointestinal symptoms (nausea, vomiting), but it may also suppress the effect of methotrexate.[213]

(3) Combination therapy: In patients with rheumatoid arthritis, it is possible to administrate methotrexate concurrently with cyclosporin without the development of major side-effects, which can be an effective combination therapy for psoriasis accompanied by arthritis. The TNF-α inhibitor infliximab, originally developed for concurrent use with methotrexate, was reported to be effective also for psoriatic arthritis in a recent study.[214]

2. TNF-α inhibitors:

2-1. Infliximab.

2-2. Adalimumab.

2-3. Etanercept.

(In Japan, etanercept is not covered by health insurance for the treatment of psoriasis.)

Degree of recommendation: B.

General recommendations: Etanercept, infliximab and adalimumab are all effective for psoriatic arthritis. Among the three medications, infliximab and adalimumab are currently covered by health insurance for psoriatic arthritis in Japan For the use of TNF-α inhibitors, it is important to consider their risks and benefits, treatment cost and outcome, and the long-term treatment strategy.

Comments:

Systematic reviews of psoriatic arthritis[215,216] and high-quality double-blind, randomized, placebo-controlled studies showing the efficacy of infliximab, adalimumab and etanercept[217–221] are available. In particular, the Identification and Management of Psoriasis Associated Comorbidity (IMPACT) study of 104 patients and the IMPACT2 study of 200 patients are representative studies of infliximab. In the latter study using the American College of Rheumatology criteria-20 (ACR20), 58% of the patients on 5 mg/kg of infliximab achieved 20% improvement after 14 weeks, compared with 11% of the patients in the placebo group.[218] In the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) conducted in 2005, ACR20:50:70 improvement rates after 24 weeks were 57%:39%:23% in the adalimumab group compared with 15%:6%:1% in the placebo group, with the radiographic findings of cessation of joint destruction in the former group.[221] In the recent Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis (PRESTA), once-weekly and twice-weekly administrations of 50 mg etanercept produced similar results in patients with arthritis, but the higher dose was more effective for the rash.[221] Analysis using the York Model showed that etanercept had better cost-effectiveness than infliximab.[222] Evaluation using the Health Assessment Questionnaire Disability Index revealed that 40% of patients taking either etanercept or infliximab scored 0, showing an improvement in QOL. In Japan, etanercept is not currently covered by health insurance for use in psoriasis.

The multifaceted evaluation of clinical effects (short and long term), persistent effects, long-term treatment outcome, medical cost, QOL and comparison with existing therapies is necessary when deciding indication of TNF-α inhibitors for pustular psoriasis accompanied by arthritis.

3. Biologics other than TNF-α inhibitors (IL-17 inhibitors, ustekinumab).

Degree of recommendation: C1.

General recommendations:

(3-1) IL-17 inhibitors: secukinumab, ixekizumab, brodalumab.

Degree of recommendation: C1.

General recommendations: The efficacy and safety of secukinumab, ixekizumab and brodalumab have been demonstrated for psoriasis vulgaris,[223–225] psoriatic arthritis,[226–228] and their superior effects have been shown in several RCT over other biologics.[229–235] Their effects are also confirmed with Japanese populations.[113,236–238] Their efficacy for GPP have also been reported, especially in Japanese populations.[111–114,142] However, long-term safety data and data from daily clinical practise are needed. For the use of IL-17 inhibitors, it is important to consider their risks and benefits, treatment cost and outcome, and the long-term treatment strategy.

Comments:

Secukinumab was approved for coverage of health insurance in December 2014 for psoriasis vulgaris and psoriatic arthritis, and was approved in December 2015 for pustular psoriasis in Japan. In 2016, ixekizumab and brodalumab were approved for psoriasis vulgaris, psoriatic arthritis, erythrodermic psoriasis and pustular psoriasis in Japan. Although we have less experience of IL-17 inhibitors in other areas, it is considered relatively safer for severe infections compared with TNF inhibitors in European countries, and the Biologics Review Committee of the Japanese Dermatological Association recommends secukinumab equally as other biologics.[148] However, there are concerns on adverse effects of candidiasis,[239] exacerbation of Crohn's disease and neutropenia, and accumulation of cases and data of their longer term safety will be needed to evaluate their true value in the future.

(3-2) Ustekinumab:

Efficacy is expected but is not supported by sufficient evidence. Therefore, ustekinumab should be used only when patients are resistant to other therapies.

Comments: In Japan, the anti-IL-12/23p40 antibody ustekinumab was included in a group of drugs covered by health insurance for use in psoriasis vulgaris and psoriatic arthritis in 2011. The latest version of British guidelines published in 2017 position ustekinumab as a first-line biologic drug similar to adalimumab and secukinumab for psoriasis vulgaris.[3] However, ustekinumab is considered second to adalimumab or secukinumab for psoriatic arthritis.[3] The guidelines published in the USA[108] and Germany[49] consider ustekinumab and other biologics as equals. Recent RCT have shown that ustekinumab is effective for joint symptoms in patients with psoriatic arthritis.[110,151]

4. Salazosulfapyridine.

Degree of recommendation: C1.

General recommendations: The administration of 2–3 g/day of sulfasalazine is mildly effective for peripheral arthritis.

Comments: Sulfasalazine was mildly effective for rheumatoid factor-negative spondylitis including psoriatic arthritis and particularly peripheral arthritis.[240–243]

5. Azathioprine.

Degree of recommendation: C2.

General recommendations: Mild efficacy is expected.

Comments: Efficacy was shown in an RCT conducted by Levy *et al.* in 1972[244] and was also reported in the aforementioned review by Jones *et al.*[205] However, in subsequent clinical studies the efficacy was not confirmed, and it is considered that azathioprine could simply suppress the progression of arthritis.[245]

6. Etretinate.

Degree of recommendation: B–C1.

General recommendations: Because of its superior effect on pustular psoriasis rash, etretinate may be indicated primarily for the improvement of moderate to severe rash, as well as for the management of mild arthritic symptoms.

Comments: A double-blind study showed mild improvement of joint symptoms by etretinate compared with ibuprofen.[246] In addition, an open-label trial also reported its efficacy.[247] Etretinate is contraindicated for use in pregnant women. For use in children, it is necessary to evaluate the benefits and duration of etretinate therapy to establish an appropriate treatment plan.

7. Cyclosporin.

Degree of recommendation: B–C1.

General recommendations: Cyclosporin is believed to be an appropriate agent for primarily improving moderate to severe pustular psoriasis rash and for managing mild arthritic symptoms. Cyclosporin may be used in pregnant women and children, in whom etretinate is contraindicated, but the safety of cyclosporin has not been established yet.

Comments:

(1) Efficacy in arthritis: The efficacy of cyclosporin monotherapy has been reported.[248–252] Prospective open-label clinical studies of 3–5 mg/kg per day cyclosporin and methotrexate showed that joint symptoms were slightly improved by both drugs.[252–254] In a study evaluating the alleviation of arthritic pain as an end-point, 3 mg/kg per day of cyclosporin was more effective than sulfasalazine.[255] The administration of non-steroidal anti-inflammatory drugs (NSAIDs) is sometimes necessary to manage arthralgia, but the concurrent administration of NSAIDs and cyclosporin is a large burden on the kidneys, and high blood pressure and renal dysfunction should be monitored carefully.

(2) Guidelines for administration of cyclosporin: An international consensus on the appropriate use of cyclosporin was published in 2004.[27] Also in the same year, the Guidelines for Psoriasis Therapy with Cyclosporine MEPC were published in Japan.[29] However, the utility of cyclosporin for psoriatic arthropathy is not supported by sufficient data.

8. Alefacept.

Degree of recommendation: C1.

General recommendations: Alefacept monotherapy or combination therapy with methotrexate is expected to improve joint symptoms and skin lesions of psoriasis. In Japan, alefacept is not currently covered by health insurance.

Comments: The clinical application of alefacept improved joint symptoms and reduced the number of T cells and macrophages in synovial tissue.[256,257] In addition, in combination therapy with methotrexate, alefacept was effective compared with placebo.[258]

9. Other medications:

9-1. Corticosteroids.

Degree of recommendation: C2, C1 (when patients do not respond to other drugs).

General recommendations: When the number of diseased joints is small, the intra-articular administration of corticosteroids works well. The systemic administration of corticosteroids should be performed with care because pustular psoriasis may be induced when tapering the dose.

Comments: A small amount of prednisolone is administrated in combination with an antirheumatic drug in patients with rheumatoid arthritis. However, because prednisolone may induce pustular psoriasis during tapering the dose or after discontinuation, it should not be used for the treatment of arthritis without thorough consideration.[207,243] However, it is sometimes impossible to avoid the administration of corticosteroid concurrently with other drugs when patients have severe joint symptoms that are unresponsive to other antirheumatic drugs. The use of corticosteroids as a first-line drug should be avoided (C2) but may be necessary when patients do not respond to other drugs (C1).

(9-2). NSAIDs.

Degree of recommendation: C1 (for pain and swelling), C2 (for improvement in rash and erythrocyte sedimentation rate).

General recommendations: NSAIDs manage pain effectively. However, they may not improve rash or reduce a raised erythrocyte sedimentation rate.

Comments: Compared with placebo drugs, NSAIDs alleviate pain and swelling, but may not improve rash or an elevated erythrocyte sedimentation rate. Although NSAIDs were conventionally thought to exacerbate psoriasis rash through the production of leukotrienes in the arachidonic acid pathway, this did not result in a major problem in a recent study.[259]

CQ27. Is GMA effective for joint symptoms accompanying pustular psoriasis?

Degree of recommendation: C1.

General recommendations: GMA may be considered as a safe treatment modality with few side-effects for psoriatic arthritis, but it is not supported by sufficient evidence.

Comments: No RCT have investigated the efficacy of GMA in patients with psoriatic arthritis. The efficacy and safety of GMA have been shown only in a case series report on psoriatic arthritis[260] and case series studies that included patients with

neutrophilic dermatoses.[162,261,262] In one of the case series studies, GMA improved psoriatic arthritis in 17 of 21 patients, with no serious side-effects.[261]

CQ28. Does therapy conducted in line with the guidelines effectively improve QOL?

Degree of recommendation: Not evaluated.

General recommendations: The treatment of pustular psoriasis and its complications in line with the guidelines is expected to improve clinical symptoms and alleviate side-effects. However, further studies are needed to evaluate QOL improvement as the ultimate outcome.

Comments: The Study Group for Rare Intractable Skin Diseases conducted a national survey (the Medical Outcome Survey Short Form 36 version 2 [SF-36v2]) on QOL in patients with pustular psoriasis and is currently analyzing the data by dividing 98 patients with GPP into three groups in view of norm-based scoring score from eight kinds of subscales rated by SF-36v2: (i) no decline in QOL; (ii) a major decline in QOL; and (iii) a minor decline in QOL. As an interim result, patients' QOL showed no decline in 15 (15.3%), a major decline in 25 (25.5%) and a minor decline in 58 (59.2%) patients, demonstrating that QOL had declined in 84.7% of the patients.[263] In other words, most GPP patients have an overall decline in QOL, and as in the previous report,[161] patients with psoriatic arthritis and pustular psoriasis suffer a large decline in QOL, possibly resulting in the formation of a cluster different from that for psoriasis vulgaris and other forms.

The average life expectancy of male and female patients with severe psoriasis is 3.5 and 4.4 years shorter, respectively, than that in healthy individuals.[264] In addition, a study reported a correlation between psoriasis, various skin diseases and smoking.[265]

Prospective studies are needed to investigate the outcomes of standard treatments for pustular psoriasis. The registration and follow up of patients with pustular psoriasis is an important research topic for the next Study Group for Rare Intractable Skin Diseases.

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APPENDIX I: MANUAL OF GRANULOCYTE AND MONOCYTE ADSORPTION APHERESIS IN DRAFT FORM

Operation

Materials required

(1) Necessary components

- GMA column (Adacolumn®)
- Blood pump (Adamonitor® or pre-existing blood pump)
- Catheter for blood circulation (Adacircuit® or pre-existing blood circuit)
- Physiological saline solution
  - For cleaning the column, 1500 mL
  - For priming (addition of anticoagulant*), 500 mL
  - For retransfusion, 100–300 mL
- Pump for continuous infusion of anticoagulants
- Two indwelling needles**

(2) Additional components

- Tourniquet

- Alcohol pads for antiseptic wipe
- Hemostatic pads
- Isodine
- Forceps, as many as needed
- Blood pressure monitor, thermometer
- Two extension tubing
- Two three-way stopcocks
- Two 10-mL syringes

**Indwelling needles for GMA

- 18G Medicut Cannula with Clamping Tube
- 18G Medicut Cannula Easy Clamp
- 18G Medicut cannula
- 18G Happycath Clamping Type, among others.

Treatment flow

(1) Cleaning and priming (~30 min)

- Setting-up the blood circuit
- Cleaning, priming, removal of air bubbles
- Setting up the pump for continuous infusion of anticoagulants
- Leak test

(2) GMA therapy (~60 min)

- Observation of general conditions (blood pressure, heart rate, body temperature)
- Cut down (for removing and returning blood), connecting a blood circuit, and administering anticoagulants through a bolus injection of the amount specified in Table 11.
- After a bolus injection of anticoagulants, the pump is rotated at 30 mL/min for 60 min to circulate 1800 mL of blood.
- During the circulation, physiological saline solution containing anticoagulants is injected continuously.

(3) Re-transfusion (~15 min)

- After the completion of blood circulation, the blood inside the circuit and column is returned using physiological saline solution.
- Needle removal and hemostasis
- Observation of general conditions (blood pressure, heart rate, body temperature)

SIDE-EFFECTS TO BE MONITORED DURING GRANULOCYTE AND MONOCYTE ADSORPTION APHERESIS

Side-effects reported in a clinical study of 80 patients with inflammatory bowel disease

Four cases of headache and one case each of fever, lightheadedness, dizziness, nausea, facial redness, pain at the injection site, itchy legs, myodesopsia-like symptom, palpation, nasal congestion and bad mood.

Side-effects reported in a multicenter study of 15 patients with pustular psoriasis

Headache, dizziness, exacerbation of complication (bullous pemphigoid) and X-ray shadows in the lungs* (one case each).

(*A history of infliximab administration 2 months prior to the initiation of GMA therapy, the concurrent use of methotrexate starting 1 month before the initiation of the study and ending at the end of the study period.)

None of the side-effects stated above were serious.

PREVENTION OF INFECTION THROUGH THE INJECTION SITE OF AN INDWELLING NEEDLE

A healthy skin area is used for injection.

An alcohol pad for antiseptic wipe is enough to clean healthy skin, but isodine should be used if the injection site is near pustules or erosion.

Table 11. Recommended dose of anticoagulants used in granulocyte and monocyte adsorption apheresis

Anticoagulant	Dose at priming	Dose at the start of circulation	Maintenance dose during circulation
Heparin sodium	2000 units	1000–3000 units	500–1500 units
Heparin calcium	2000 units	1000–3000 units	500–1500 units
Low-molecular-weight heparin	1000 units	Bleeding tendency: Yes, 15–20 units/kg No, 10–15 units/kg	Bleeding tendency: Yes, 7.5–10 units/kg No, 7.5 units/kg
Nafamostat mesilate	20 mg	–	20–50 mg/h