【改訂のための原案】

病理学的事項					
水疱部	水疱初発位置	1. 表皮内	2. 接合部	3. 真皮内	
	基底細胞・有棘細胞の空胞変性	1. あり	2. なし	3. 不明	
非水疱部	係留線維の減少	1. あり	2. なし	3. 不明	
	半デスモソームの減少	1. あり	2. なし	3. 不明	
蛍光抗体法	ラミニン 332	1. 消失	2. 減弱	3. 普遍	4. 不明
	XVII 型コラーゲン	1. 消失	2. 減弱	3. 普遍	4. 不明
	α6β4インテグリン	1. 消失	2. 減弱	3. 普遍	4. 不明
	VII 型コラーゲン	1. 消失	2. 減弱	3. 普遍	4. 不明

遺伝子検査（実施している場合は記載してください。）

1. あり（患者：　　両親：　　）　2. なし

鑑別診断　下の疾患が鑑別できること

① 水疱性先天性魚鱗癬様紅皮症	1. 鑑別できる	2. 鑑別できない
② ポルフィリン症	1. 鑑別できる	2. 鑑別できない
③ 尋常性天疱瘡	1. 鑑別できる	2. 鑑別できない
④ 水疱性類天疱瘡	1. 鑑別できる	2. 鑑別できない
⑤ 線状 IgA 水疱性皮膚症	1. 鑑別できる	2. 鑑別できない
⑥ 疱疹状皮膚炎	1. 鑑別できる	2. 鑑別できない
⑦ 伝染性膿痂疹	1. 鑑別できる	2. 鑑別できない
⑧ 中毒性表皮壊死剥離症	1. 鑑別できる	2. 鑑別できない
⑨ 亜鉛欠乏による腸性肢端皮膚炎	1. 鑑別できる	2. 鑑別できない
⑩ 薬剤による水疱症	1. 鑑別できる	2. 鑑別できない
⑪ その他（　　）	1. 鑑別できる	2. 鑑別できない

医療上の問題点

【WISH入力不要】

医療機関名

医療機関所在地

医師の氏名　　電話番号　（　　）

印

記載年月日：平成　　年　　月　　日

（軽快者の症状が悪化した場合のみ記載）

症状が悪化したことを医師が確認した年月日　　平成　　年　　月　　日

特定疾患登録者証交付年月日　　平成　　年　　月　　日

20XX-XX-XX

【現　行】28　表皮水疱症（接合部型及び栄養障害型）　臨床調査個人票（2.更新）

ふりがな 氏　名		性別	1.男 2.女	生　年 月　日	1.明治 2.大正 3.昭和 4.平成	年　月　日生 （満　歳）	
住　所	郵便番号 電話　（　）			出　生 都道府県		発病時在住 都道府県	
発病年月	1.昭和 2.平成　年　月（満　歳）	初診年月日	1.昭和 2.平成　年　月　日	保険種別	1.政　2.組　3.船 4.共　5.国　6.老		
身体障害者手帳	1.あり（等級＿＿級）　2.なし	介護認定	1.要介護（要介護度＿＿）　2.要支援　3.なし				
生活状況	社会活動（1.就労　2.就学　3.家事労働　4.在宅療養　5.入院　6.入所　7.その他（＿＿）） 日常生活（1.正常　2.やや不自由であるが独力で可能　3.制限があり部分介助　4.全面介助）					初回認定年月 1.昭和 2.平成　年　月	
受診状況（最近1年）	1.主に入院　2.入院と通院半々　3.主に通院（＿＿/月）　4.往診あり　5.入通院なし　6.その他（　）						

治療と経過（前回申請からの変化を中心に具体的に記述）

【WISH入力不要】

疾患分類	1.接合部型　2.栄養障害型　3.その他（　）
経　過	1.ほぼ治癒　2.軽快しつつある　3.不変　4.悪化しつつある　5.その他（　）

臨床所見（経過観察中に発現したものを含む）

皮膚の水疱・びらん	1.あり	2.なし	3.不明	爪変形・爪脱落	1.あり	2.なし	3.不明
粘膜の水疱・びらん	1.あり	2.なし	3.不明	歯牙形成不全	1.あり	2.なし	3.不明
水疱・びらん治癒後の瘢痕	1.あり	2.なし	3.不明	筋ジストロフィー	1.あり	2.なし	3.不明
稗粒腫	1.あり	2.なし	3.不明	食道狭窄	1.あり	2.なし	3.不明
指（趾）間癒着	1.あり	2.なし	3.不明	肥厚性幽門狭窄	1.あり	2.なし	3.不明
掌蹠角化	1.あり	2.なし	3.不明	皮膚悪性腫瘍	1.あり	2.なし	3.不明
脱毛	1.あり	2.なし	3.不明	（扁平上皮癌）			

医療上の問題点

【WISH入力不要】

医療機関名

医療機関所在地

電話番号　（　）

医師の氏名

印　記載年月日：平成　年　月　日

2007-01-01

【改訂のための原案】

28　表皮水疱症（接合部型及び栄養障害型）　臨床調査個人票（2.更新）

ふりがな 氏　名		性別	1.男 2.女	生　年 月　日	1.明治 2.大正 3.昭和 4.平成	年　月　日生 （満　歳）	
住　所	郵便番号 電話　（　）			出　生 都道府県		発病時在住 都道府県	
発病年月	1.昭和 2.平成　年　月（満　歳）	初診年月日	1.昭和 2.平成　年　月　日	保険種別	1.政　2.組　3.船 4.共　5.国　6.老		
身体障害者手帳	1.あり（等級＿＿級）　2.なし	介護認定	1.要介護（要介護度＿＿）　2.要支援　3.なし				
生活状況	社会活動（1.就労　2.就学　3.家事労働　4.在宅療養　5.入院　6.入所　7.その他（＿＿）） 日常生活（1.正常　2.やや不自由であるが独力で可能　3.制限があり部分介助　4.全面介助）			初回認定年月 1.昭和 2.平成　年　月			
受診状況 （最近1年）	1.主に入院　2.入院と通院半々　3.主に通院（＿＿/月）　4.往診あり　5.入通院なし　6.その他（　　）						

治療と経過（前回申請からの変化を中心に具体的に記述）

【WISH入力不要】

疾患分類	1.接合部型　（1.ヘルリッツ型　2.非ヘルリッツ型　3.幽門閉鎖合併型　4.その他） 2.栄養障害型（1.優性型　2.劣性重症汎発型　3.その他） 3.その他　（　　）
経　過	1.ほぼ治癒　2.軽快しつつある　3.不変　4.悪化しつつある　5.その他（　　）

臨床所見（経過観察中に発現したものを含む）

皮膚粘膜症状

1.水疱新生の数	1.毎日　2.週に4日以上　3.週に3日以下　4.なし　5.不明
2.水疱・びらんの面積	1. 15%以上　2. 5%以上-15%未満　3. 5%未満　4.なし　5.不明
3.口腔内など粘膜の水疱・びらん	1.毎日　2.月に3、4日以上　3.月に2日　4.なし　5.不明
4.水疱・びらん治癒後の瘢痕	1.あり　2.なし　3.不明
5.稗粒腫	1.あり　2.なし　3.不明
6.掌蹠角化	1.あり　2.なし　3.不明
7.脱　毛	1.あり　2.なし　3.不明
8.爪変形・爪脱落	1.あり　2.なし　3.不明

合併症

1.貧血	1.あり（ヘモグロビン値：　　g/dl）　2.なし　3.不明
2.低栄養	1.あり（血清アルブミン値：　　g/dl）　2.なし　3.不明
3.高ガンマグロブリン血症	1.あり（血清IgG値：　mg/dl，IgA値：　mg/dl，IgM値：　mg/dl） 2.なし　3.不明
4.慢性炎症反応	1.あり（CRP値：　　mg/dl）　2.なし　3.不明
5.全身性アミロイドーシス	1.あり（多臓器不全を伴う）2.あり（軽度臓器不全を伴う）3.なし　4.不明
6.歯牙形成不全	1.あり　2.なし　3.不明
7.筋ジストロフィー	1.あり　2.なし　3.不明
8.肥厚性幽門狭窄	1.あり　2.なし　3.不明
9.指（趾）間癒着	1.棍棒状癒着　2.可動制限を伴う癒着　3.可動制限の無い癒着 4.なし　5.不明
10.食道狭窄	1.嚥下困難を伴う重度なもの　2.軽度　3.なし　4.不明 食道狭窄拡張術の施行（　回）
11.扁平上皮癌の既往	1.あり（手術回数＿＿回）　2.なし　3.不明

【改訂のための原案】

12. 腎機能障害	1. あり（血清クレアチニン3mg/dl以上） 2. あり（血清クレアチニン3mg/dl未満）　3. なし　4. 不明
13. 視力障害（矯正不能）	1. あり（両眼）　2. あり（片眼）　3. なし　4. 不明
医療上の問題点 【WISH入力不要】	
医療機関名 医療機関所在地 電話番号　（　　） 医師の氏名 印　記載年月日：平成　年　月　日	

20XX-XX-XX

［V］

診療ガイドライン（英語版）

Guidelines for the Management of Generalized Pustular Psoriasis 2010: Treatment Guidelines with Reference to TNF α Inhibitors (Abridged Version)

Keiji IWATSUKI[1)], Tadashi TERUI[2)], Akira OZAWA[3)], Mayumi KOMINE[4)] Yoshinori UMEZAWA[3,7)], Hidetsugu TORII[5)] Gen NAKANISHI[1,8)], Hiroyuki HARA[2)] Tomotaka MABUCHI[3)], Yumi AOYAMA[1)], Yasuo KITAJIMA[6)], COMMITTEE FOR GUDELINES FOR THE MANAGEMENT OF GENERALIZED PUSTULAR PSORIASIS, AND THE MHLW RESEARCH PROJECT ON MEASURES FOR INTRACTABLE DISEASES COMMITTEE ON "RESEARCH FOR RARE INTRACTABLE SKIN DISEASES"

Departments of Dermatology, 1) Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2) Nihon University School of Medicine, 3) Tokai University School of Medicine, 4) Jichi Medical University, 5) Social Insurance Chuo General Hospital, 6) Kizawa Memorial Hospital, 7) King's College London School of Medicine, UK, 8) Shiga University of Medical Science

Abstract

Generalized pustular psoriasis normally occurs with fever and edematous erythema, accompanied by the formation of large numbers of sterile subcorneal pustules. The condition is histopathologically characterized by Kogoj's spongiform pustules. In some but not all cases, pustular psoriasis is preceded by psoriasis vulgaris-like eruptions. Repeated recurrence is characteristic of this condition. Throughout the clinical course, the patient will show laboratory anomalies associated with systemic inflammation. This form of psoriasis is often complicated by mucosal symptoms and arthritis, and very occasionally by respiratory failure, ocular symptoms, and/or secondary amyloidosis.

Existing psoriasis guidelines[1,2] provide a systematic review that uses improvement in cutaneous symptoms as an endpoint and that focuses primarily on plaque-type psoriasis vulgaris. However, generalized pustular psoriasis should be considered as a form of systemic inflammatory response syndrome (SIRS), with consideration for primary care, systemic management, treatment for skin lesions, and complications such as arthritis. Work on these Guidelines was initiated because new findings in the pathophysiology of psoriasis have been reported and the use of biologics has become feasible in clinical practice[3]. The Ministry of Health, Labour, and Welfare (MHLW) Research Group for Rare Intractable Skin Diseases has provided diagnostic criteria for generalized pustular psoriasis, severity criteria, and treatment guidelines[4], but those criteria need to be revised to include the advent of new treatment modalities such as TNF α inhibitors and the introduction of methods that incorporate evidence-based medicine (EBM).

The MHLW Research Project on Measures for Intractable Diseases committee on "Research for rare intractable skin diseases" (principal investigator: Yasuo Kitajima 2002 through 2007, Keiji Iwatsuki from 2008), has been moving forward on the formulation of EBM guidelines for the treatment of generalized pustular psoriasis, and has reviewed the positioning of

biologics for treatment[5]. Generalized pustular psoriasis is a rare disease, so we encountered some difficulties in identifying journal articles that contained high-quality evidence regarding treatment. However, insofar as possible the committee has extensively reviewed the important literature that is currently available. The present report has summarized the essential tables and an algorithm of "Guidelines for the Management of Generalized Pustular Psoriasis 2010" proposed by Committee for Guidelines for the Management of Generalized Pustular Psoriasis. The original complete version of the guideline will be reviewed by Scientific Committee of Japanese Dermatological Association, then considered for publication.

1. Standards for the determination of evidence level and the degree of recommendation

Table 1. Evidence levels and the degree of recommendation

1. Classification of evidence level

I	Systematic review and/or meta-analysis
II	One or more randomized comparative studies
III	Non-randomized comparative studies
IV	Analytical epidemiology studies (cohort research and case-control studies)
V	Descriptive studies (case reports and case series studies)
VI	Opinions of expert committee and individual specialists@

2. Degree of recommendation classification#

A:	Strongly recommended for implementation (Efficacy shown by at least 1 report providing Level 1 or high-quality Level II evidence*)
B:	Recommended for implementation (Efficacy shown by 1 or more reports providing low-quality Level II, high-quality Level III, or very high-quality Level IV evidence*)
C1:	Implementation can be considered, but evidence* is insufficient. (low-quality III to IV, high-quality multiple V, or committee-approved VI evidence)
C2:	No evidence*; not recommended (No evidence of effectiveness, or evidence available of ineffectiveness)
D:	Recommended not to implement (High-quality evidence* of ineffectiveness or harmfulness)

@ Data from basic research and theories derived from such data are placed at this level.

Some of the "degree of recommendation" statements in this guideline are not in complete agreement with the above table. This is because these "degree of recommendation" grades were based on a consensus among the committee members, after due consideration of the shortage of evidence internationally and the fact that the evidence from overseas is not directly applicable in Japan.

* "Evidence" refers to knowledge from clinical trials and immunological research.

2. Diagnostic criteria and severity criteria for generalized pustular psoriasis (MHLW Rare and Intractable Skin Diseases, 2006)

Tbale 2. Generalized pustular psoriasis: Definition and primary parameters necessary for diagnosis (MHLW Rare and Intractable Skin Diseases, 2006)

Definitions

Generalized pustular psoriasis is a rare condition that manifests as a sudden fever with systemic skin flushing and the formation of large numbers of sterile pustules. These subcorneal pustules are histopathologically characterized as Kogoj's spongiform pustules. In some but not all cases, pustular psoriasis is preceded by psoriasis vulgaris-like eruptions. Repeated recurrence is characteristic of this condition. Throughout the clinical course, the patient will show clinical symptoms associated with systemic inflammation. This form of psoriasis is often complicated by mucosal symptoms and arthritis, and very occasionally by ocular symptoms and/or secondary amyloidosis.

Major criteria

1) The condition is accompanied by systemic symptoms such as fever or general malaise.
2) Flushing develops over the entire body or on broad areas of the skin surface, associated with large numbers of sterile pustules; in some cases the pustules coalesce into lakes of pus.
3) Histopathologically, the condition demonstrates neutrophilic subcorneal pustules characterized by Kogoj's spongiform pustules.
4) These clinical and histopathological findings occur repeatedly. At the initial occurrence, the diseases cited below (Table 4) can be excluded from diagnostic consideration based on the patient's clinical course.

If the condition fulfills the above 4 major criteria, a diagnosis of generalized pustular psoriasis (definite case) can be made. If the condition fulfills the major criteria described in 2) and 3) above, it should be diagnosed as a suspected case of generalized pustular psoriasis.

Table 3. Parameters for reference in the diagnosis of generalized pustular psoriasis

1. Laboratory test findings necessary to assess severity and investigate complications
1) Leukocytosis, nuclear shift to the left
2) Elevated erythrocyte sedimentation rate, CRP positive
3) Elevated IgG or IgA
4) Hypoalbuminemia, hypocalcemia
5) Tests for tonsillitis, elevated ASLO titer, and other infectious foci
6) Rheumatoid factor-negative arthritis, including ankylosing spondylitis
7) Ocular lesions (including keratoconjunctivitis, uveitis, and iritis)
8) Liver, kidney, and urinary findings: Treatment selection and evaluation of secondary amyloidosis

2. Conditions that can be included in the category of generalized pustular psoriasis
1) Acute generalized pustular psoriasis (von Zumbusch type): Classical generalized pustular psoriasis
2) Impetigo herpetiformis: Generalized pustular psoriasis accompanying pregnancy and hormone imbalances.
3) Dissemination of acrodermatitis continua (Hallopeau): Strictly speaking, this condition is very rare, so careful and deliberate diagnosis is required.
4) Childhood generalized pustular psoriasis: Excluding the circinate annular form.

Table 4. Parameters for exclusion from the diagnosis of generalized pustular psoriasis

1. Cases of transient pustulation without recurrence are generally not included in the category of generalized pustular psoriasis defined as "intractable diseases". This exclusion criteria, however, may not apply if recurrence is being suppressed by the continuation of treatment.
2. In general, cases can be excluded from consideration if psoriasis vulgaris was clearly preexistent and pustules have developed temporarily due to treatment with agents such as corticosteroids. However, if a dermatologist has monitored a patient closely for a specified period, the results indicate that the patient is prone to recurrent pustule development, and it is judged that the case should be included within this category, then the category of generalized pustular psoriasis will apply.
3. Ordinarily, the systemic symptoms of the circinate annular form are mild, and the condition is excluded from this category. However, for those patients whose condition has transitioned to generalized pustular psoriasis, the category of generalized pustular psoriasis will apply.
4. Those cases that are diagnosed as 'subcorneal pustular dermatosis' or 'pustular drug eruption' (including acute generalized exanthematous pustulosis) are excluded from the diagnosis of generalized pustular psoriasis.

Table 5. Assessment of severity of generalized pustular psoriasis

A. Evaluation of cutaneous symptoms:

Erythema, pustules, edema (score A: 0 to 9)

B. Evaluation of systemic symptoms and laboratory test findings:

Fever, white blood cell count, serum CRP, serum albumin (score B: 0 to 8)

Severity classification:	Mild	Moderate	Severe
(Total score: A+B)	(0 to 6)	(7 to 10)	(11 to 17)

A. Evaluation of cutaneous symptoms (Score A: 0 to 9)

	Severe	Moderate	Mild	None
Area of erythema (overall)*	3	2	1	0
Area of erythema with pustules**	3	2	1	0
Area of edema**	3	2	1	0

* As percentage of body surface (severe: 75% or more; moderate: 25% to less than 75%; mild: less than 25%)

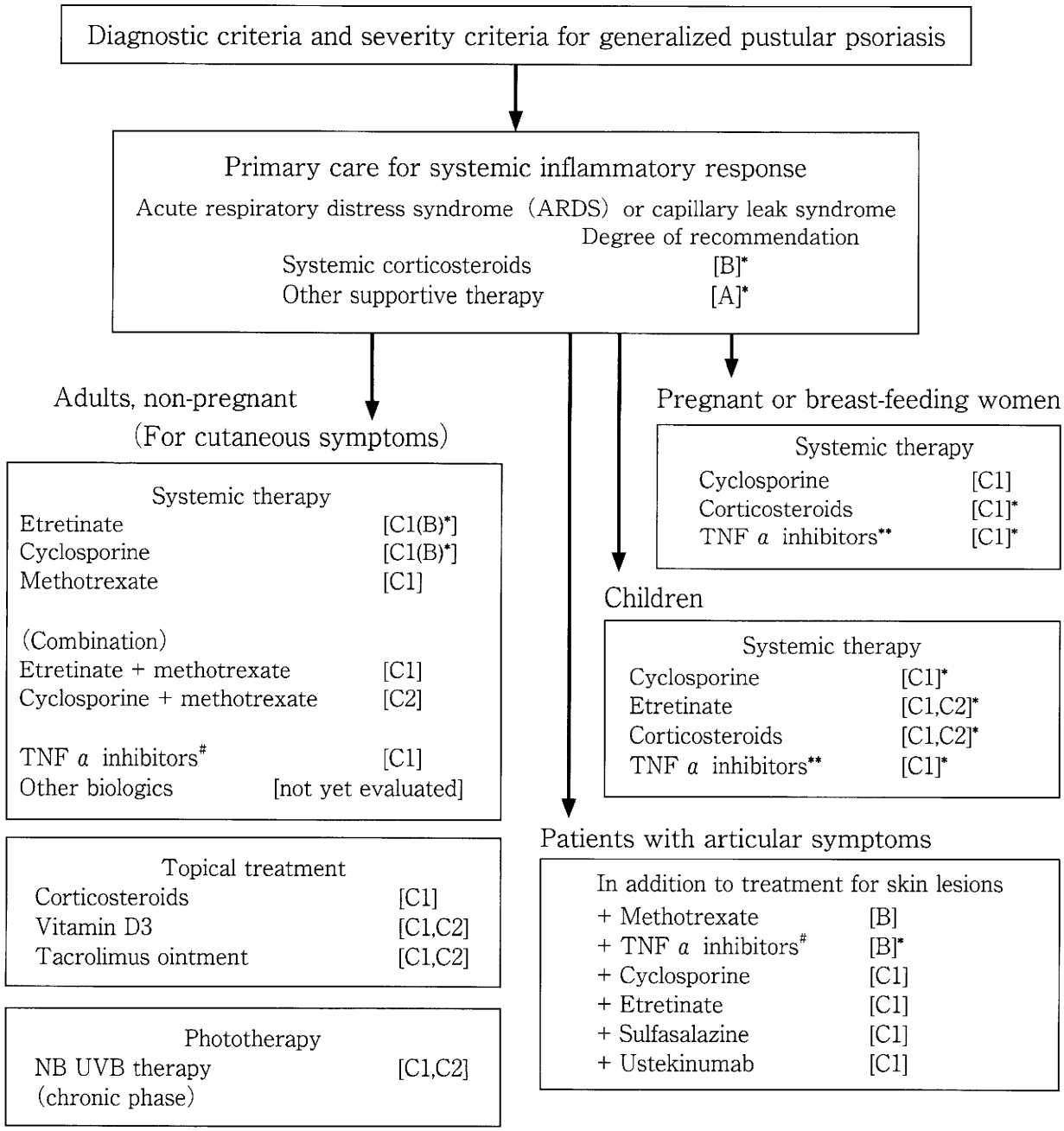
** As percentage of body surface (severe: 50% or more; moderate: 10% to less than 50%; mild: less than 10%)

B. Evaluation of systemic symptoms and laboratory test findings (Score B: 0 to 8)

Score	2	1	0
Fever (°C)	38.5 or above	37 to less than 38.5	Less than 37
WBC count (/ μ L)	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

3. Treatment algorithm for generalized pustular psoriasis

Fig 1. Treatment algorithm for generalized pustular psoriasis (acute-phase treatment)



* Proposed by the committee

For appropriate use, see the "Guidelines and safety manual for use of anti-TNF- α agents in psoriasis" from the Japanese Dermatological Association Biologics Review Commission [Ref. 5].

** There is insufficient evidence available for the safety of TNF α inhibitor use in pregnant women and children. Such use should be considered only in cases that are resistant to other drug treatment.

(Committee's comments)
Generalized pustular psoriasis is a potentially life-threatening systemic inflammatory disease, so in some cases treatment will require the use of drugs for which safety has not been established in pregnant and breast-feeding women, and in children. According to Japanese guidelines for the treatment of psoriasis, the use of cyclosporine is contraindicated in pregnant and breast-feeding women. However, those guidelines include the use of cyclosporine in pregnant women with impetigo herpetiformis, which is a form of generalized pustular psoriasis. As of yet, an insufficient number of cases have been collected of the use of TNF α inhibitors (infliximab, adalimumab) in pregnant and breast-feeding women and in children with generalized pustular psoriasis. However, this form of therapy has been proposed as a potential treatment arm based on findings from the use of TNF α inhibitors in patients with conditions such as psoriasis vulgaris and rheumatoid arthritis. TNF α inhibitors should be considered for use in pregnant and breast-feeding women, and in children, only in those cases where the condition is life-threatening and other drugs have proved ineffective. For such use it is important to obtain fully informed consent.

4. Summary of recommended treatments for generalized pustular psoriasis

4-1. Primary care for systemic symptoms during the acute phase of generalized pustular psoriasis

The most common direct cause of death from generalized pustular psoriasis is cardio-circulatory failure, so systemic management and drug therapy are essential. There are rare instances of pulmonary complications, and of drug-induced pulmonary complications due to the use of drugs such as methotrexate and retinoic acid for the treatment of psoriasis. These complications can be successfully treated by respiratory management, the administration of antibiotics, discontinuation of the causative agent, and systemic corticosteroid administration (equivalent to prednisolone 1 mg/kg/day). The TNF α inhibitor, infliximab is effective in some cases. However, the potential for infusion reaction, which places considerable burden on the cardio-circulatory system, should be anticipated, so the use of TNF α inhibitors should be undertaken carefully and deliberately.

Table 6. Approaches to the treatment of ARDS/capillary leak syndrome and cardio-circulatory failure associated with generalized pustular psoriasis

1-1) General management for cardio-circulatory failure Degree of recommendation: [A]*
· Monitoring of vital signs
· Monitoring of weight gain (edema) and urine volume, and appropriate drug therapy
· Monitoring for cardiac and circulatory failure, and appropriate drug therapy
1-2) Treatment for respiratory failure (ARDS/capillary leak syndrome)
· Monitoring by means of image scans, blood tests, and blood gas tests
· Exclusion of infection
· Removal of causative drugs (such as methotrexate and retinoic acid)
· In cases of ARDS/capillary leak syndrome, introduction of systemic steroid therapy
1-3) Control of skin lesions
* No clinical research is available regarding this treatment, but there are high-quality clinical epidemiology studies regarding analysis of cause of death [Ref. 6]

4-2. Systemic therapy recommended for acute-phase pustular psoriasis

Table 7. Systemic therapy recommended for acute-phase generalized pustular psoriasis

(Adults, non-pregnant)

Recommended Treatment	Degree of recommendation	Notes
Etretinate	C1(B*)	Response seen in pustular psoriasis even at a dose of 0.5 to 0.75 mg/kg/day, with effectiveness appearing more rapidly than in psoriasis vulgaris. Somewhat effective against arthritis. In long-term use, patients should be monitored carefully for damage to bones and joints. Contraception must be used during and after the administration of this drug in men(6 months) and women(2 years).
Cyclosporine	C1(B*)	Based on 2004 guidelines for treating psoriasis with cyclosporine [Ref. 7-9].
Methotrexate	C1	Drug-induced deaths have been reported Contraception must be used during and after administration in men and women (3 months). Administration is contraindicated in hemodialysis patients.
Etretinate + Methotrexate	C1	Concomitant administration used for the treatment of psoriasis in order to achieve maximum effectiveness from the minimum dose.
Cyclosporine + Methotrexate	C2	Same as above. May increase the incidence of skin malignancy.
Infliximab(Remicade®)	C1@	Based on guidelines for the use of biologics [Ref. 3,5,10]. 5mg/kg, administered by slow drip infusion(2 hours or more) after initial administration, at 2 and 6 weeks after initial administration, and subsequently continued at 8-week intervals. Satisfactory levels of effectiveness are sometimes obtained after only 1 to 3 administrations.
Adalimumab(Humira®)	C1@	In adults, the initial dose is a subcutaneous injection of 80 mg. At the 2-week point and subsequently, 40 mg is administered subcutaneously every 2 weeks. If this provides insufficient effectiveness, a one-time increase to 80 mg can be used.(National Health Insurance coverage for psoriasis vulgaris and psoriatic arthritis)
Ustekinumab (Stelara®)	Not yet evaluated C1@	So far, only one case report with successful use [Ref. 11] 'C1' for psoriatic arthritis

(Pregnant and breast-feeding women)

Cyclosporine	C1@	Under psoriasis guidelines [Ref. 9], the use of cyclosporine is contraindicated in pregnant and breast-feeding women, but there have been reports of successful treatment in patients with generalized pustular psoriasis [Ref 12-14]. To be used in cases of great potential benefit to the patient, after obtaining informed consent.
Corticosteroids	C1	If the condition is accompanied by pronounced edema and systemic symptoms, systemic steroids can be used, but a type of steroid that is inactivated by the placenta, such as prednisolone, should be selected to minimize the effects on the fetus.
TNF α inhibitors	C1	Such use should be considered only if other drugs are ineffective and the patient's life is at risk. For such use it is important to obtain fully informed consent. [Ref.15-17]

(Children)		
Cyclosporine	C1[@]	Instances of successful treatment have been reported in children. According to data from the Japanese Society for Psoriasis Research, the use of cyclosporine therapy in children is increasing.
Etretinate	C1, C2[@]	This treatment arm should be selected only after considering the potential for adverse drug reactions such as early closure of the epiphyseal line. A careful and deliberate decision should be reached regarding whether to select cyclosporine or this drug as the treatment of first choice.
Corticosteroids	C1, C2[@]	If the condition is accompanied by pronounced edema and systemic symptoms, systemic steroids can be used
TNF α inhibitors	C1	Such use should be considered only if other drugs are ineffective and the patient's life is at risk [Ref.18].

* Opinion of the committee: On the basis of verified documentation, the degree of recommendation is C1. However, there are more obvious therapeutic results for this agent than for other forms of therapy that have a C1 recommendation. The committee gives this treatment a B recommendation. @ Committee opinion based on overall determination

Table 8. Safe use of standard psoriasis treatment methods

Etretinate	· Absolutely contraindicated in pregnant and breast-feeding women and in subjects with pregnant or breast-feeding partners because of teratogenicity. · Contraception required for 2 years in women and 6 months in men following discontinuation of administration. · Monitoring for ectopic calcification and hyperostosis
Cyclosporine	· Nephrotoxicity, hypertension, immunosuppression, carcinogenesis, etc. [Ref.7-9]. · For antihypertensives, angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, which suppress the renin-angiotensin system and also provide kidney-protective effects, are recommended. Conventional calcium antagonists also provide kidney-protective effects, but nifedipine can cause gingival hypertrophy [Ref.9]. · Administration is contraindicated* in pregnant and potentially pregnant women, and in breast-feeding women. (*: Globally, cyclosporine is categorized as a class C drug, and is not always considered to be contraindicated in these patient populations.) · Contraindicated for concomitant use with tacrolimus (Prograf®) and pitavastatin (Livalo®). · Generally not to be used concomitantly with PUVA or retinoids .
Methotrexate	· Monitoring for liver damage, myelosuppression, teratogenicity, immunosuppression, carcinogenesis, interstitial pneumonia, etc. · Absolutely contraindicated in pregnant or breast-feeding women and in subjects with pregnant or breast-feeding partners. · Contraindicated in patients under dialysis. · Contraception for 3 months after discontinuation of administration.
TNF α inhibitors	· In cases where no beneficial results are seen from standard psoriasis treatments, the use of TNF α inhibitors may be considered. Insufficient data has been collected on teratogenicity, but pregnant patients should be closely monitored for the development of VACTERL association (syndrome) (vertebral, anal atresia, cardiac defect, tracheoesophageal, renal and limb abnormalities).
Ustekinumab	· In cases where no beneficial results are seen from standard psoriasis treatments or TNF α inhibitors, the use of ustekinumab may be considered [Ref.11]

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試験実施計画書

試験実施計画書

ステロイド治療抵抗性の天疱瘡患者および類天疱瘡患者、後天性表皮水疱症患者を対象とした Rituximab の効果・安全性の探索的研究

Rtx-BD Trial

(Rituximab of Intractable Autoimmune Bullous Disease Trial)

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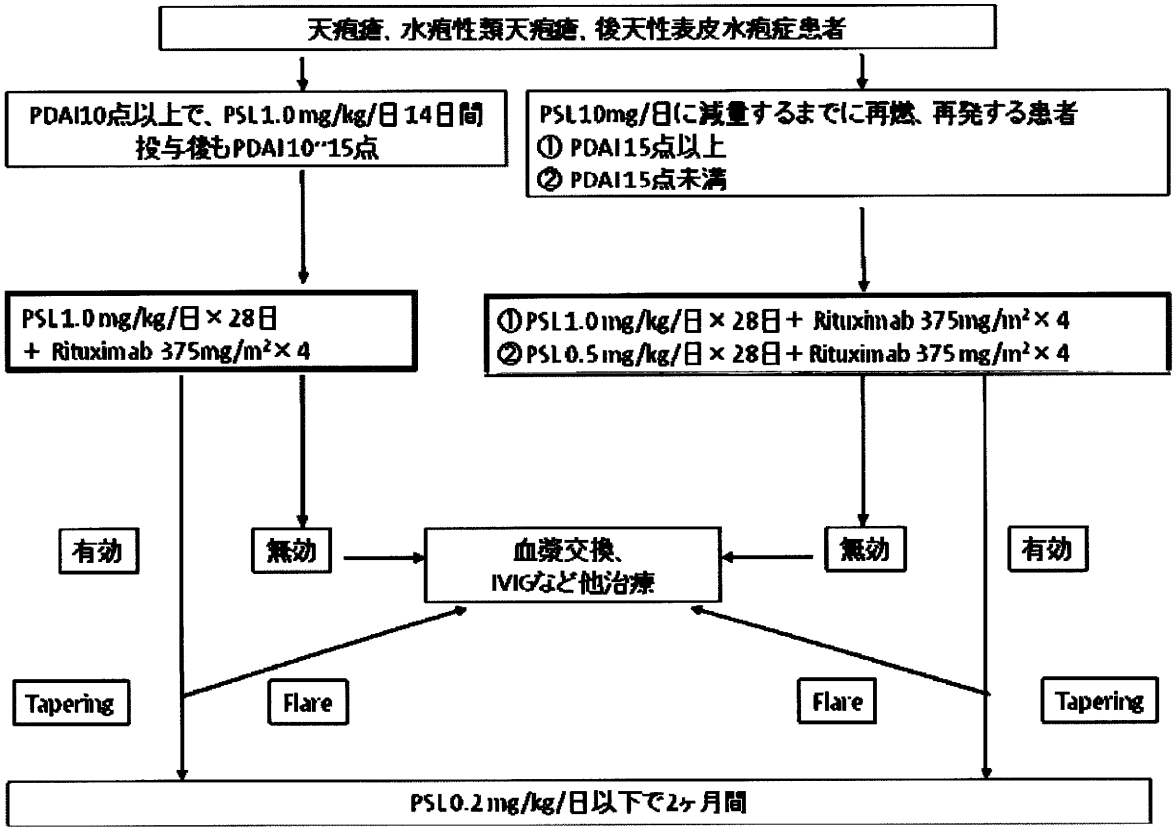
0.概要

0.1 スキーム



0.2 目的

ステロイド療法に抵抗性の重症天疱瘡、類天疱瘡、後天性表皮水疱症患者におけるリツキシマブ（リツキサン注®10mg/mL）の有効性・安全性を評価する。

0.3 対象

尋常性天疱瘡、落葉状天疱瘡、類天疱瘡、後天性表皮水疱症患者で、PDAI (Pemphigus Disease Area Index) 10 点以上であり、PSL 1.0 mg/kg/day を 2 週間以上投与しても PDAI10~15 点である患者、または PSL 使用中の患者で PSL 10mg/day に減量するまでの間に、再燃、再発する患者。

0.4 治療

リツキシマブ 375 mg/m² を、週 1 回、合計 4 回の点滴を入院下で行う。

＜PSL 漸減方法＞

30mg/日＜　　5mg/週ずつ減量

20mg/日～30mg/日	5mg/2 週ずつ減量
10mg/日~20mg/日	2.5mg/4 週ずつ減量
＜10mg/日	1mg/4 週ずつ減量

各体重別 PSL 漸減方法　　「付録 6」参照

0.5 予定登録数、登録期間、介入・追跡期間、総研究期間及び参加施設

予定登録	20 例
登録期間	3 年
介入・追跡期間	96 週間（約 2 年間）
総研究期間	5 年
参加施設	慶應義塾大学病院　皮膚科
	岡山大学病院　　皮膚科
	久留米大学病院　　皮膚科
	北海道大学病院　　皮膚科

0.6　問合せ先

登録手順、試験変更基準等、臨床的判断を要するもの：研究事務局（表紙、17.2）

記録用紙記入等：データセンター（17.6）

有害事象報告：効果・安全性評価委員会事務局（17.4）

1. 目的

ステロイド療法に抵抗性の重症天疱瘡、類天疱瘡、後天性表皮水疱症患者におけるリツキシマブ（リツキサン注®10mg/mlL）の有効性・安全性を評価する。

2. 背景と試験計画の根拠

2.1 対象

2.1.1 対象疾患

本研究の対象患者はステロイド療法に抵抗性の重症天疱瘡、類天疱瘡、後天性表皮水疱症患者とする。

天疱瘡は、皮膚・粘膜に病変が認められる自己免疫性水疱性疾患であり、病理組織学的に表皮細胞間の接着が障害される結果生じる棘融解（acantholysis）による表皮内水疱形成を認め、免疫病理学的に表皮細胞膜表面に対する自己抗体が皮膚組織に沈着するあるいは循環血中に認められることを特徴とする疾患である。天疱瘡抗原蛋白は、表皮細胞間接着に重要な役割をしているカドヘリン型細胞間接着因子、デスモグレインである。天疱瘡は、尋常性天疱瘡、落葉状天疱瘡、腫瘍随伴性天疱瘡、その他に大別される。

尋常性天疱瘡は、一般的に落葉状天疱瘡に比べ難治性で、予後は悪く、特に口腔粘膜病変は治療抵抗性であることが多い。ただし、紅皮症化した落葉状天疱瘡はこの限りではない。本疾患の第一選択薬はステロイド剤の全身投与であり、ステロイド療法導入により、その予後は著しく向上したが、ステロイドの副作用による合併症が問題となる他、ステロイド剤のみでの治療に抵抗性の難治例も認められる。早期にステロイド剤を減量させるために免疫抑制剤、血漿交換療法、IVIG 大量療法の導入などが推奨されているが、ステロイド剤、および血漿交換療法、IVIG 大量療法以外は保険適応外使用である。

類天疱瘡は抗表皮基底膜部自己抗体（IgG）により表皮下水疱を形成する自己免疫性疾患である。臨床的には全身の皮膚に掻痒を伴う浮腫性あるいは滲出性紅斑や多数の大型緊満性水疱を形成する。稀に粘膜疹を伴う。主要な自己抗原として180kDa水疱性類天疱瘡抗原（BP180）と230 kDa 水疱性類天疱瘡抗原（BP230）の 2 種類が知られており、いずれもヘミデスモゾームに存在する。本疾患の治療は、軽症例ではテトラサイクリン・ニコチン酸アミド併用療法、ステロイド外用、中等症以上ではステロイド剤の全身投与を行う。ステロイドで効果の得られない重症例ではステロイドパルス療法、血漿交換療法、免疫抑制剤内服、IVIG 大量療法などが行われるが、ステロイド剤および血漿交換療法以外は保険適応外使用である。

後天性表皮水疱症は表皮基底膜を形成するⅦ型コラーゲンに対する IgG 自己抗体による自己免疫性皮膚疾患である。臨床的には四肢を中心に外力が加わる部位に水疱を生じる。治療はステロイド内服、免疫抑制剤、DDS、コルヒチンが有効な場合があるが、難治であり、症状は長期にわたり持続する。

リツキシマブ（マウス・ヒト キメラ型抗 CD20 モノクローナル抗体）は、B リンパ球表面に特異的に発現している CD20 抗原に結合し、その細胞傷害作用（補体依存性、抗体依存性細胞介在性、細

胞死誘導）により、CD20陽性のB細胞を傷害する。CD20抗原はB細胞に特異的に発現しており、その抗体は他の細胞に作用しない。近年は自己免疫性疾患である天疱瘡・類天疱瘡に対しても有効であるとの報告が海外より多く出されている[1,2,3,4]が、本邦ではB細胞リンパ腫を伴う腫瘍随伴性天疱瘡での症例報告以外では報告例がない。

よって、ステロイド療法により臨床症状の改善が認められない天疱瘡患者、類天疱瘡患者、および後天性表皮水疱症に対する治療として、リツキシマブの投与の効果・安全性についての研究を行うことにした。

2.1.2 対象疾患に関連する合併症、増悪形式

病勢が激しく全身に水疱が出現すると、水疱後のびらんが広範を占めることになり、熱傷と同様、蛋白質や水分が体外に漏出することで体が消耗する。また、びらん面では皮膚のバリアが壊れているため、容易に感染が起こる。口腔内にびらんが生じる場合、疼痛のため食事摂取が困難になる。

2.1.3 対象疾患の予後因子

ステロイドの長期内服治療が必要になるため、糖尿病や高血圧などの基礎疾患の合併は交絡要因となる。また感染症が予後を悪化させるため、免疫抑制状態も交絡要因となる。このため、今回は重度の基礎疾患を持つ患者や免疫抑制状態である患者は除外する。

2.1.4 対象疾患に対する標準治療

天疱瘡、類天疱瘡、後天性表皮水疱症患者に対する標準治療はステロイド内服、免疫抑制剤の使用、ステロイドパルス療法、血漿交換、大量IVIG治療などがあげられる。

2.2 対象患者の選択基準

今回は、ステロイド療法や既存の治療に抵抗性の重症天疱瘡、類天疱瘡、後天性表皮水疱症患者を対象とする。治療抵抗性とは、PDAI 10点以上でありPSL 1.0 mg/kg/dayを2週間以上投与してもPDAI10~15点である患者、もしくはPSL使用中またはPSLと免疫抑制剤を併用中の患者で、PSL 10mg/dayに減量するまでの間に、再燃、再発する患者とした。また除外基準については、主要評価項目および副次的評価項目に影響を与える項目を設定した。

2.3 治療計画設定の根拠

2.3.1 薬剤

リツキシマブ（マウス・ヒト キメラ型抗 CD20 モノクローナル抗体）は、Bリンパ球表面に特異的に発現しているCD20抗原に結合し、その細胞傷害作用（補体依存性、抗体依存性細胞介在性、細胞死誘導）により、CD20陽性のB細胞を傷害する。CD20抗原はB細胞に特異的に発現しており、