[IV]

研究成果の刊行に関する一覧表

※○印のあるものに関しては巻末に別刷りあり。

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[V]

班会議プログラム

厚生労働省科学研究費補助金
「難治性疾患克服研究事業：重症多形滲出性紅斑に関する調査研究
（**H22**‐難治‐一般‐**003**）」

平成 22 年度班会議プログラム

研究代表者：杏林大学医学部皮膚科、塩原哲夫

日時： 平成 22 年 7 月 30 日（金）９：３０から１７：００まで
場所： 東京駅前：マルビルコンファレンススクエア ルーム 1
住所：〒100-6307 東京都千代田区丸の内 2-4-1 丸ビル 8 階
TEL 03-3217-7111 （平日 10：00～19：00） FAX 03-3217-7501）
●JR ご利用の場合／東京駅丸の内南口より徒歩 1 分
●地下鉄をご利用の場合／丸ノ内線東京駅より直結
千代田線二重橋前駅 7 番出口より徒歩 2 分

9:30
開会の挨拶 研究代表者 塩原哲夫

厚生労働省健康局 疾病対策課 中川義章様 挨拶

講演 (1) DIHS を含む薬疹の全ゲノム関連解析および HLA 解析
理化学研究所 ゲノム医科学研究センター 遺伝子情報解析チーム
莚田泰誠 先生

講演 (2) 劇症 1 型糖尿病と DIHS
大阪大学大学院医学系研究科 内分泌･代謝内科学
今川彰久 先生

講演関連研究報告 DIHS と劇症 1 型糖尿病のアンケート結果-中間報告
藤山幹子 先生

分担研究者より関連演題

12:00 昼食 （お弁当） 事務局連絡、次回班会議日程など

Asian SCAR Meeting

13:00

1. Oral presentation

Drs. Chung et al.

13:20

2. Oral presentation

SJS/TEN の全国アンケートの調査報告

北見 周 先生

SJS/TEN の全国アンケートの調査報告（眼合併症）

外園 千恵 先生

3. Oral presentation

分担研究者報告

15:00 Coffee break

4. Oral presentation

分担研究者報告

厚生労働省科学研究費補助金
「難治性疾患克服研究事業：重症多形滲出性紅斑に関する調査研究
（**H22**‐難治‐一般‐**003**）」

平成 22 年度班会議プログラム

研究代表者：杏林大学医学部皮膚科、塩原哲夫

日時： 平成 22 年 12 月 25 日（土）９：３０から１７：００まで
場所： 東京駅前：マルビルコンファレンススクエア ルーム 5
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千代田線二重橋前駅 7 番出口より徒歩 2 分

Asian SCAR Meeting

9:30
開会の挨拶 研究代表者 塩原哲夫

○遺伝子多型解析の今後について
班長：塩原哲夫先生
9:35
1. 2005-2007 年の SJS/TEN の全国調査について
昭和大 北見周 先生
2008-2010 年の SJS/TEN 全国調査について

10:00
2. 杏林大における SJS/TEN のステロイド治療
杏林大 成田陽子 先生

10:20
3. SJS/TEN 眼科サイドからの報告
1) 2005-2007 年の SJS/TEN 疫学調査から：眼合併症調査

2) 症例呈示「SJS かどうか、眼障害の軽い症例」
京都府立大　外園千恵 先生

3) GVHD の眼病変 (15 min)
慶應大学　小川葉子　先生

11:10

4. Investigative report
1) Critical factors differentiating erythema multiforme major from SJS/TEN
昭和大学　渡辺秀晃　先生

2) SJS/TEN における血清中 HMGB1 値の推移
京都大学　椛島健治　先生

12:00　昼食 （お弁当）

12:50-13:00　事務局連絡、次回班会議日程など

13:00

5. Regi-SCAR study から提唱予定の DIHS/DRESS のスコアシステム解説 (30min)
班長：塩原哲夫 先生
杏林大症例における評価
杏林大　牛込悠紀子　先生

13:30

6. Steroids treatments and results between non-survivors and survivors of DRESS in Taiwan
Dr. Wen-Hung (Taiwan)
→Correspondence　杏林大

7. DIHS におけるヘルペスウイルスの再活性化
愛媛大学　藤山幹子　先生

14:30　Coffee Break

15:00

8. 重症薬疹難治例の症例検討(SJS/DIHS オーバーラップ、遷延する DIHS など)

1) Two SJS/DRESS overlapping cases from Taiwan
Dr. Wen-Hung (Taiwan)

2) 強皮症腎で透析中に発症した抗結核薬による TEN -血漿交換の併用が有効であった 1 例-
横浜市大 松山阿美子

3) 経過の長い DIHS の 2 例
慶應大学 永尾圭介 先生

4) 分担研究者報告など

16:30 終了予定

[VI]

研究成果の刊行物・印刷

THE JOURNAL OF DERMATOLOGY

doi: 10.1111/j.1346-8138.2010.01154.x

Journal of Dermatology 2011; **38**: 236–245

INVITED ARTICLE

Efficacy of plasmapheresis for the treatment of severe toxic epidermal necrolysis: Is cytokine expression analysis useful in predicting its therapeutic efficacy?

Yoko M. NARITA, Kazuhisa HIRAHARA, Yoshiko MIZUKAWA, Yoko KANO, Tetsuo SHIOHARA

Department of Dermatology, Kyorin University, Tokyo, Japan

ABSTRACT

Toxic epidermal necrolysis (TEN) is a life-threatening, drug-induced disorder characterized by severe epidermal injury. Although there is no standard therapeutic intervention in TEN, plasmapheresis (PP) is being used increasingly to treat extremely ill TEN patients. In addition to conventional PP, double-filtration PP (DFPP) has been recently used for severe and refractory TEN. In this review, we focus on the clinical usefulness of PP by both demonstrating three cases of TEN refractory to conventional therapies, who were successfully treated with conventional PP or DFPP, and evaluating its therapeutic efficiency. We also provide evidence to suggest the mechanisms of action of PP by investigating the correlation between disease intensity and serum cytokine levels before and after treatment with PP or DFPP in these patients with TEN. At present, PP is a much more effective option for treatment of severe and/or recalcitrant TEN than any other treatment, such as pulsed corticosteroids and i.v. immunoglobulin.

Key words: corticosteroid, cytokine, double-filtration plasmapheresis, plasmapheresis, toxic epidermal necrolysis.

INTRODUCTION

Toxic epidermal necrolysis (TEN) is a rare life-threatening, drug-induced disorder characterized by extensive, full-thickness, epidermal necrosis and mucous membrane involvement. The mortality rate is approximately 30%, most deaths being due to systemic infection.[1,2] The most important prognostic factors are age and the extent of skin detachment related to body surface area: a severity-of-illness score for TEN (SCORTEN) has been recently validated to verify the predictive mortality in patients with TEN.[3]

Because drug-specific T cells are generally thought to play an important role in initiating the death of epidermal cells at the early stage of TEN, high doses of systemic corticosteroids, i.v. immunoglobulins (IVIG) and immunosuppressive drugs such as cyclophosphamide or cyclosporine have been used in the treatment of TEN with variable success.[4–6] The potential benefit of any specific treatment, however, has not been established, because none of these treatments have been evaluated in a prospective randomized trial. Thus, their use remains highly controversial and there is no standard intervention. Owing to concern of increased risk of infections and gastrointestinal bleeding, and masking of early signs of sepsis, many physicians consider that protracted use of high-dose corticosteroids should be avoided in TEN. Therefore, there is a continuing search for another safe and effective option for treatment of TEN refractory to conventional treatment modalities. In this regard, dramatic and rapid improvement of clinical symptoms has been reported to occur in severe and refractory TEN patients treated with plasmapheresis (PP).[7,8] In addition to conventional PP, double-filtration PP (DFPP), in which high molecular proteins

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including inflammatory cytokines can be selectively removed, has been recently used for severe and refractory TEN in limited studies.[9] However, only anecdotal experience is available to guide the choice of which methods should be used for TEN. In this review, we focus on the clinical usefulness of PP, by both demonstrating three cases with TEN refractory to conventional therapies, who were successfully treated with conventional PP or DFPP, and comparing the therapeutic efficacy. We also provide evidence to indicate that depletion of pro-inflammatory cytokines is one of the mechanisms whereby PP is efficacious in TEN, by demonstrating our results of serum cytokine levels in these patients before and after treatment. Based on these findings, we discuss novel intervention strategies for TEN.

PP AS AN INTERVENTION STRATEGY FOR TEN

In PP, whole blood is withdrawn, plasma separated from the cellular constituents is discarded and the cellular constituents are reinfused back into the patient, together with albumin or pooled plasma.[2] PP has been thought to be a safe intervention in the more severe form of TEN and can be used as an adjunct treatment modality in selected patients, because pathogenic, non-dialyzable factors such as pro-inflammatory cytokines, autoantibodies, immune complexes and other unknown toxic substances can theoretically be removed from the circulation. PP consists of conventional PP (plasma exchange), DFPP, cryofiltration and immunoadsorption. Since Gerard *et al.*[10] reported the successful use of PP in the treatment of TEN, 100 patients with TEN have been reportedly treated with PP: 85 patients with conventional PP and the remaining 15 patients with DFPP.[11–18] In view of the reported observation that patients receiving PP had more extensive skin detachment (mean, 58.8%) than those receiving other treatment, the mortality rate (17%) is thought to be reduced by PP. Seventeen patients died of sepsis, disseminated intravascular coagulation and anamnestic malignancy and heart failure;[8] however, they were not necessarily elderly patients who have been shown to be associated with a poor prognosis.

In DFPP, two membrane filters with different pore sizes are used to selectively remove high molecular weight proteins including pro-inflammatory cytokines and pathogenic immune complexes. The pore size of the filter employed for DFPP is theoretically sufficient to remove high molecular weight proteins larger than albumin (69 kDa) while those smaller than albumin are retained in the circulation. Therefore, because tumor necrosis factor (TNF)-α has a molecular weight of 51 kDa, the DFPP procedure cannot theoretically remove TNF-α and other unwanted inflammatory substances including interferon (IFN)-γ (50 kDa), interleukin (IL)-1β (17 kDa), IL-6 (19–26 kDa) and soluble Fas ligand (sFasL) (26 kDa). Indeed, our studies showed that serum levels of pro-inflammatory cytokines were dramatically increased after treatment with DFPP or the next day, as described later. Nevertheless, because these cytokines could exist in a larger size due to binding to proteins and multimer forms in the circulation, some forms of these substances would be depleted even by the DFPP procedure. In terms of clearance efficiency, the DFPP procedure is unlikely to fulfill the purpose of selective depletion of unwanted inflammatory substances which had accumulated in patients (Fig. 1). In addition, even though selective depletion of these substances were sufficiently efficacious by choosing appropriate filters with the pore size that allow selective depletion of these substances, the rebound of cytokine synthesis typically observed in case 1, as described later, would be an obstacle to progress and the strategy to overcome the rebound synthesis would be needed.

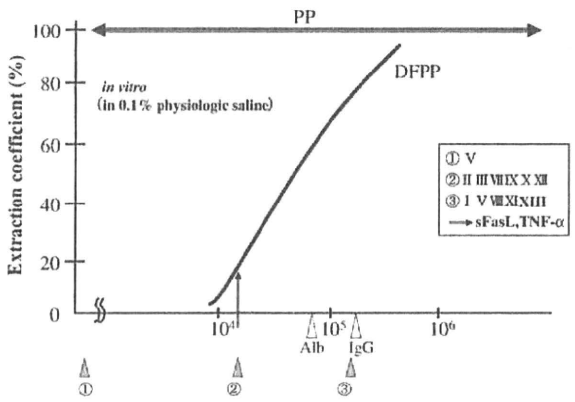

Figure 1. Selective depletion of high molecular weight proteins larger than albumin (69 kDa) including coagulation factors, which depends on the pore size of the filter employed for double-filtration plasmapheresis (DFPP).

METHODS FOR PP

Conventional PP is performed by the use of a plasma separator filter (Plasmaflo OP-05W; Asahikasei-Kuraray-Medical, Tokyo, Japan). On each exchange, 2 L of plasma is usually removed; the total volume of plasma removed is 4.0–6.0 L corresponding to 40 mL/kg of bodyweight. The replacement fluid consists of 2 L of fresh frozen plasma (FFP) to supply lost plasma including coagulation factors. The replacement fluid and original blood cell component are reconstituted and returned to the patient. Vascular access is obtained through the antecubital or femoral vein with a double-lumen Quinton catheter (Teflex Medical Japan, Tokyo, Japan).

In contrast, DFPP is performed with the use of Plasmaflo (OP-08W; Asahikasei-Kuraray-Medical) as the primary separation filter and Evaflax (2A20; Asahikasei-Kuraray-Medical) as the secondary separation filter; the second filter is used to selectively remove high molecular weight proteins including inflammatory cytokines. On each exchange, 1.8 L of plasma is processed; the total volume of plasma is processed is 3.6 L. The blood and plasma flow are approximately 100 mL/min. The processed plasma, replacement solution and original blood cell components are reconstituted and returned to the patient through the antecubital or femoral vein; usually 250–500 mL of a 5–20% human albumin solution are used as the replacement solution to supply the loss of albumin (Fig. 2). The treatment lasts for 3–4 h and approximately 2.5 L of plasma are removed from each patient. A second treatment session is usually initiated 7 days after the first treatment if necessary.

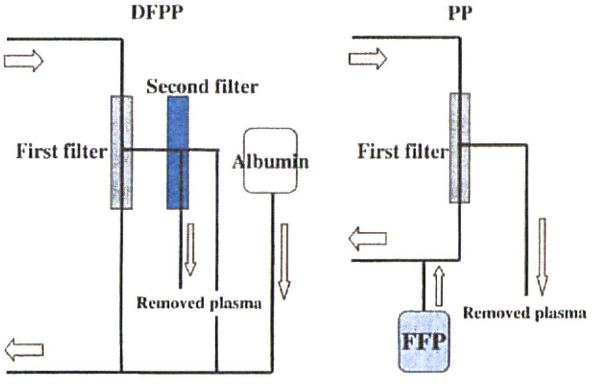

Figure 2. Diagrammatic representation of the arrangement of conventional plasmapheresis (PP) and double-filtration PP (DFPP). FFP, fresh frozen plasma.

OUR TREATMENT PROTOCOL

Patients usually receive one session consisting of two plasma exchanges, on 2 consecutive days. In our cases, medications taken before, during and after PP consisted of oral prednisolone, 50 mg/day. If a patient developed new lesions or skin and mucous membrane lesions did not resolve, the patient received the second session of two plasma exchanges at intervals of 1 week. Concomitant prednisolone was not tapered until the lesions had resolved and no new lesions had appeared for 3 days.

CASE PRESENTATION

To demonstrate a promising effect of PP as a safe and effective therapeutic option in the severe form of TEN refractory to conventional treatment modalities, three cases are shown together with one control case treated with pulsed corticosteroids.

Case 1

A 69-year-old woman with asthma was treated with montelukast sodium, codeine phosphate and prednisolone, 40 mg/day on an as-needed basis. Her medical and family history was unremarkable and she had not taken any other medication. A generalized skin eruption occurred 2 weeks after starting these therapies. She was admitted to our hospital with the generalized eruptions accompanied by high fever, conjunctivitis and painful hemorrhagic oral erosions. On admission, the trunk and limbs displayed widespread dull red macules and atypical target lesions. The eruption evolved into large areas of blistering with extensive epidermal necrosis. On hospital day 2, more than 70% loss of epidermis over the skin surface was noted, with severe conjunctival and oral involvement. Despite treatment with oral prednisolone (50 mg/day), the lesions rapidly extended over the entire body. In view of her age and acutely deteriorated condition (Fig. 3a), she was treated with DFPP for 2 days. Although the progression of blistering had stopped (Fig. 3b), re-epithelization was delayed as compared with that in cases 2 and 3. Nevertheless, the patient's condition began to improve 7 days after

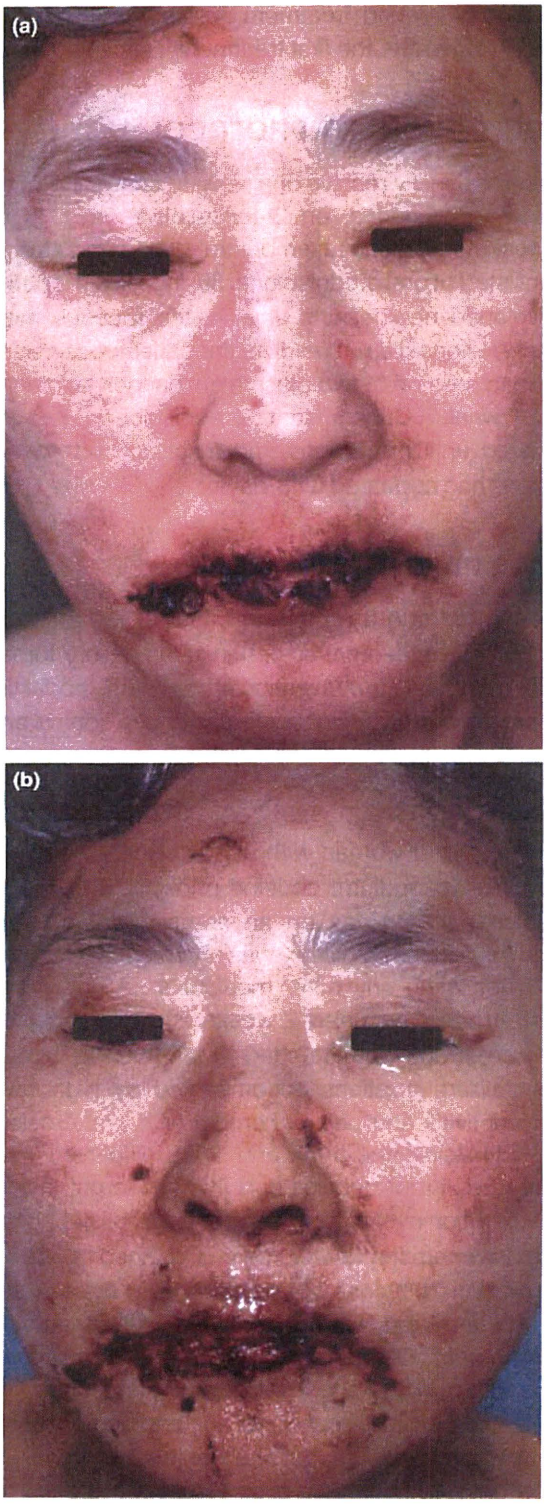

Figure 3. Clinical appearance 1 day before double-filtration plasmapheresis (a) and 1 day after double-filtration plasmapheresis (b) in case 1.

DFPP. The prednisolone dosage was gradually tapered over 4 week.

Case 2

A 39-year-old woman was referred from another hospital where she had been admitted with a presumptive diagnosis of TEN and treated with pulsed corticosteroids (i.v. methylprednisolone at a daily dose of 1 g for 3 days) and IVIG (15 g/day for 3 days) without benefit. Despite these treatments, she developed dusky red patches, bullae and sloughing of the skin which rapidly extended over the trunk and limbs to involve more than 40% of her skin surface. Ophthalmological examination showed acute conjunctivitis with corneal erosions. She was admitted to our hospital on day 9 of the illness. On admission she had tender oral ulcers and hemorrhagic crusts on her lips. Four days later, the eruption intensified and re-epithelization was delayed despite oral prednisolone at 50 mg/day. Conventional PP was started as a last attempt to arrest the progression of her lesions. After 2 days, the progression of blistering with extensive epidermal necrosis had stopped and rapid re-epithelization occurred. Despite a course complicated by sepsis due to Gram-negative bacillus, she rapidly recovered within 7 days and is alive and well.

Case 3

A 48-year-old woman was referred to the Department of Medicine in our hospital because of high fever, severe cough and difficulty in breathing. On the day of admission, the diagnosis of *Mycoplasma pneumoniae* respiratory infection was made and therapy was then started with pulsed corticosteroids (i.v. methylprednisolone at a daily dose of 1 g for 3 days), together with ciprofloxacin, ceftriaxone and azithromycin. Intermittent positive-pressure breathing was also immediately initiated. Treatment included maintenance i.v. fluid replacement and antipyretics. After starting pulsed corticosteroids, her respiratory status rapidly improved. During the period of 10 days after pulsed corticosteroids, there was a complete absence of any skin and mucosal lesion. Three days after tapering her methylprednisolone to 80 mg/day, she developed slightly edematous, symmetrical erythema on the trunk that spontaneously resolved within 2 days. The patient was placed on a gradually reducing dose of prednisolone: a 3–5 day-tapered