Protocol monitoring pulse therapy (Version 4)

Study: Multinational Open-trial of Steroid pulse therapy for SJS/TEN (MOSST Study)

Objective of the study

To evaluate the potential benefit and safety of steroid pulse therapy for the patients with SJS/TEN.

Patient and trial design

In an open prospective multinational pilot study, 20 consecutive intention-to-treat (ITT) patients with SJS/TEN will be treated with methylprednisolone pulse therapy (MPT).

Setting

- Multinational centres (Japan, Taiwan, European countries)
- Agreeing on
  - strict observance of the treatment protocol
  - inclusion of all patients who fit inclusion criteria during the whole duration of the study
  - keeping a chart of all potential patients included or not (reason for exclusion should be notified)
  - obtaining approval of the medical ethical committee
- The study will be notified to the Regi-SCAR

Inclusion criteria

1. Patients above 20-years old and below 90-years, with TEN or SJS with clinical score at least 14 (refer to Table 3. Scoring for clinical evaluation)
2. Onset of the disease (blistering) less than 3 days (including) before inclusion
3. Progression of the disease in the last 24 hrs, or no sign for improvement (judged by experts: treating physician/ dermatologist): new blisters or erythema on areas of previously uninvolved skin/ mucosae

4. After reading or being informed on the Informed Consent Agreement and signing it the subject or his deputy is willing and able to participate in the study.
5. Case ascertainment:
   - photos: overviews and details,
   - biopsy: histology (immunofluorescence to exclude autoimmune blistering diseases if needed),
   - evaluation of detachment in BSA, drug history, SCORTEN

Exclusion criteria

Contraindications

1. The subject has received any systemic immunosuppressants or immunomodulating agents (continuously) for at least 3 days within 7 days preceding inclusion. (Systemic immunosuppressants or immunomodulating agents include azathioprine, corticosteroids*, cyclophosphamide, cyclosporine, immunoglobulins, plasmapheresis, etc.) *predonisolone dose of more than 0.5 mg/kg
2. The subject is in the situation of pregnancy or breastfeeding.
3. The subject has previous allergy to glucocorticosteroid or preservatives (benzylalcohol or sodium metabisulfite)
4. The subject has active, untreated or uncontrolled severe infectious, or septicaemia
5. The subject has any severe, life threatening cardiac arrhythmia e.g. ventricular tachycardia, recent myocardial infarction within 6 weeks, uncontrolled severe hypertension, or any severe cardiac disease according to a consulted cardiologist.
6. The subject has active gastrointestinal bleeding, acute gastric ulcer, intestinal perforation
7. The subject has uncontrolled severe diabetes mellitus
8. The subject has past history of avascular necrosis
9. The subject having active viral hepatitis
10. The subject is HBV carrier (HBsAg+), or untreated latent tubercurosis
11. The subject under hemodialysis
12. The subject with SJS/TEN overlapping of DIHS/DRESS

13. The subject continuing culprit or cross-reacting drug
14. The subject has any concomitant illness, which, in the opinion of the investigator, will interfere with the evaluation of the study medication or presents a contraindication for steroid pulse therapy

Withdrawal of subjects:

□ Fully documented withdrawal is allowed at any time, either by patient or treating physician.

Systemic treatment:

1. infusion of methylprednisolone at 500~1000 mg/d (0.9% N/S in 3 hour) for 3 consecutive days.
   i. Oral predonisolone (0.5 mg/kg/d) was initiated on the day following the last dose of methylprednisolone, and prednisolone was subsequently tapered within 2 weeks.
   ii. Treatment failure: death, progressing/ Clinical deterioration -> withdrawal
2. Candida prophylaxis e.g. nystatine 3 dd 10 ml orally, if needed.
3. pneumocystis prophylaxis e.g. sulfamethoxasole-trimethoprim (Baktar®) 1-2 g/d orally, if needed.
4. Pain/stress: aggressive pain relief as required, e.g.morphium, oxazepam 3x5mg in combination with paracetamol (aminocetaphen) or opiates, e.g. tramadol 3x50mg. Dipidolor® (piritramide) 10 mg i.m., especially 30 minutes before wound treatment. NSAIDs: preferentially to be avoided!

Standardized symptomatic treatment and nursing:

According to the standard of the treating hospital

1. Peptic (stress) ulcer prophylaxis only if considered necessary (active ulcer, raised serum urea).
2. Antibiotics: no prophylactic use, and only when needed and then ASAP.
3. Nutrition: high protein/caloric, preferentially enteral, if necessary with (soft) nasogastric feeding tubes.
4. Controlled fluid intake/balance.

5. Wound care according to the standard of the treating hospital (e.g. sterile dressings, paraffin gauzes, Mepilex Transfer® or Mepitel®). Debridement or mechanical scrubbing of the skin is not recommended.
6. If possible: protective isolation.
7. If possible: no arterial lines.
8. If possible: daily bathing e.g. povidone-iodine scrub/solution /chlorhexidine.

Investigations: (refer to Table 1. Time table)

1. Baseline ECG and chest X-Ray
2. SCORTEN at admission/before starting day
3. Scoring for clinical evaluation (refer to Table 3), percentage of detachment (% of BSA), percentage of erythema (% of BSA) and re-epithelization day
4. Photographs (overviews front/back and details) every 2 days until day 10/20/discharge (±1 day allowed), and at 8 +/-2 wks follow-up
5. Vital sign (body temperature, pulse, respiratory rate) at day 0/4/7/10/20/discharge (±1 day allowed), and at 8 +/-2 wks follow-up
6. Monitoring using laboratory investigations (day 0/4/7/10/20/discharge) (±1 day allowed)
7. Regular check for HSV, bacterial infections, mycoplasma, Cytomegalovirus (at least 8 +/-2 wks follow-up).
8. Specimens
   i. skin: histology (and immunofluorescence to exclude autoimmune blistering disorders)
   ii. serum: for biomarker evaluation (interferon [IFN]-gamma, tumor necrosis factor [TNF]-alfa, interleukin [IL]-6 and IL-10, granulysin)

Assessment for efficacy and safety

1. Outcome measures
   i. Primary end point: Effectiveness in Scoring for clinical evaluation on day7 (Effective: more than 6 point decrease)
   ii. Secondary end points: Observed death compared with expected death (% alive at 8+/-2 weeks compared with expected from SCORTEN at day1)
   iii. Percentage of skin detachment (% of BSA)

iv. Percent of erythema (% of BSA)

v. Criteria of SIRS

vi. Duration of total hospitalization

vii. Eye sequelae

viii. Biomarkers: Blood sample cytokine change

2. Safety measures

i. Infections (sepsis, severe infections, lung involvement, etc.)

Adverse events (see CRF)

Duration of study

1. Individual patient: 8 +/- 2 wks
   i. Systemic treatment 3 days
   ii. Hospitalisation up to recovery
   iii. Follow-up visit at 8 +/- 2 wks
2. Study: 36 months

Attachment

Table 1. Time table

Table 2. SCORTEN

Table 3. Scoring for clinical evaluation (Each symptom (1)~(11) are individually counted: maximal total score 39)

Table 1
Time table for steroid pulse therapy for SJS/TEN

Name ID Doctor

check	Informed consent	Steroid pulse Day1	Day2	Day3	servation after pulse thera Day4	Day5	Day6	Day7	Day8	Day9	Day10	Day20	8Weeks
Year Mon day													
Informed consent	○												
Background	○	○											
Complication	○	○											
SCORTEN		○*											
Blood test	○	○*			○			○			○	○	
Clinical evaluation	○	○*			○			○			○	○	○
Corneal evaluation	○	○**											
Photograph		○*		○		○		○			○	○	○
Bital sign	○	○*	○	○	○	○	○	○	○	○	○	○	○
Additional Drugs	○												
Additional Therapy	○												
Chest X-Ray	○												
ECG	○												
Pulse		○	○	○									
Anti-fungal		○***											
ST		○***											
pain relief		○***											
Anti-gastric ulcer		○***											
Skin biopsy		○											
Serum reserve		○***			○***			○***			○***	○***	
Complications		○**											

*Perform before pulse therapy
**Perform as possible
***Perform as required

Table 2 SCORTEN

Prognosis factors	0	1
Age	40>	40≦
Malignancy	No	Yes
Body surface area detached	10>	10≦
Tachycardia	120>	120≦
serum BUN (mg/dl)	27>	27≦
serum glucose (mg/dl)	250>	250≦
Serum bicarbonate (mmol/L)	20≦	20>

Table 3. Scoring for clinical evaluation

score		score 0	score 1	score 2	score 3	score 4	score 5	score 6
eye involvement	(1) pseudomembranous	none	mild	eye open possible	eye open impossible			
	(2) conjunctivitis	none	mild	moderate	severe			
lip/oral mucosa involvement	(3) bleeding, crust, erosion	none	erosion	erosion with bleeding, crust on lip	erosion with bleeding, crust on oral			
skin involvement	(4) exudate on erosion/ulcer	none	faint	mild	high			
	(5) bleeding on erosion/ulcer	none	mild	moderate	high			
	(6) area of skin detachment (%)	0	<5	5≦ , <10	10≦ , <15	15≦ , <20	20≦ , <30	30≦
	(7) area of erythema	0	<10	10≦ , <20	20≦ , <30	30≦ , <40	40≦ , <50	50≦
	(8) pain of skin/mucosa	none	faint	moderate	severe			
general findings	(9) feeding	no problem	most	half	small			
	(10) fatigue	none	sometimes	often	severe			
	(11) fever	<37	37.0≦ , <37.5	37.5≦ , <38.5	38.5≦			

Each symptom from (1) to (11) are individually counted: maximal total score 39)

スティーブンスジョンソン症候群及び中毒性表皮壊死症患者を対象としたステロイドパルス療法のオープン試験日程表

患者氏名　　ID　　担当医師

チェック項目	同意取得時	ステロイドパルス期間 1日目	2日目	3日目	投与後観察期間 4日目	5日目	6日目	7日目
年月日								
同意取得	○							
背景調査	○	○						
合併症調査	○	○						
SCORTEN		○*						
臨床検査	○	○*			○			○
臨床症状評価	○	○*			○			○
角膜病変評価	○	○**						
写真撮影		○*		○		○		○
バイタルサイン	○	○*	○	○	○		○	○
併用薬調査	○							
併用療法調査	○							
胸部レントゲン	○							
心電図	○							
パルス処方		○	○	○				
抗真菌薬処方		○***						
ST合剤処方		○***						
鎮痛薬処方		○***						
抗潰瘍薬処方		○***						
皮膚組織検査		○						
血清保存		○***			○***			○***
有害事象調査		○**						

*パルス療法前に実施してください。
**可能な限り実施してください。
***必要に応じて適宜実施してください。

スティーブンスジョンソン症候群及び中毒性表皮壊死症患者を対象としたステロイドパルス療法のオープン試験日程表

8日目	9日目	10日目	20日目	終了時(8週)
		○	○	
		○	○	○
		○	○	○
○	○	○	○	○
		○***	○***	

*パルス療法前に実施してください。
**可能な限り実施してください。
***必要に応じて適宜実施してください。

v.　班会議招聘状及びプログラム

P.97～P.106

厚生労働省科学研究費補助金
「難治性疾患等政策研究事業（難治性疾患政策研究事業）：重症多形滲出性紅斑に関する調査研究（H26－難治等（難）－一般－081）」
平成 27 年度 第１回班会議プログラム

研究代表者：杏林大学医学部皮膚科　塩原哲夫

日時：　平成 27 年 7 月 18 日（土）
９：３０～１６：３０（予定）

場所：　TKP 東京駅前カンファレンスセンター　　カンファレンスルーム 4A
http://tkptokyoeki-cc.net/access.shtml
住所：〒103-0028 東京都中央区八重洲１丁目５－２０ 石塚八重洲ビル
03-6214-1633 （事務所直通）
・JR 線 『東京駅』八重洲北口 徒歩１分
・東京メトロ東西線『大手町駅』B9 出口 徒歩 3 分
（B10 出口は工事に入ったため現在は利用できません）
・東京メトロ銀座線 『日本橋駅』A3 出口 徒歩 3 分

Asian SCAR Meeting

9:30
開会の挨拶
研究代表者 塩原哲夫

9:35
ご挨拶
国立保健医療科学院　研究事業推進官（厚生労働科学研究費補助金（健康安全・危機管理対策総合研究事業、難治性疾患政策研究事業））
健康危機管理研究部 上席主任研究官　厚生労働省大臣官房厚生科学課
武村真治　様

9:45
1. 分子標的薬治療指針案について
Therapeutic policy for cutaneous adverse reactions due to molecular-targeted agents
川島　眞 M. Kawashima　（女子医大）

10:25
2. SJS と TEN の診断基準案について
Diagnostic criteria for SJS/TEN
末木博彦 H. Sueki （昭和大）

11:15

3. SJS/TEN の治療指針案について
   Therapeutic policy for SJS/TEN
   相原道子 M. Aihara　(横浜市大)

12:00

Lunch

・事務局連絡 (Official announcement of the next meeting)
次回班会議 (Next Asian-SCAR Meeting)
候補日: 2015. 12.26 (Sat) or ??

・新しい Seeds について（HLA 検索, SCAR 長期再発例集積, Overlap 症例, Anti-IL-6, 動物モデルなど）

13:00

4. ステロイドパルス療法　進捗状況
   Clinical trial of steroid pulse therapy for SJS/TEN
   森田栄伸 E. Morita　（島根大）

13:30

5. SJS 及び TEN 診療ガイドライン作成
   Guidelines for SJS and TEN
   Q and A の検討、追加項目、SJS と TEN

14:00

6. 1) DIHS patient with long term treatment due to un-explained flares and visceral involvement
   2) Co-existence of histopathological features is characteristic in drug reaction with eosinophila and systemic symptoms (DRESS) and correlates with high grades of cutaneous and hematological abnormalities
   Chia-Yu Chu (National Taiwan University Hospital)

   In vitro cross-reactivity study of anticonvulsants-induced SCAR
   Wen-Hung Chung, Mu-Tzu Chu (Chang Gung Memorial Hospital)

14:50

Coffee break

15:05

7. DIHS の重症度スコア作成の試み
   Severity score for DIHS
   平原和久 K. Hirahara （杏林大）

15:30

8. 分担研究者報告・症例報告・SJS/TEN, DIHS の長期フォロー例
   1) 一過性の後天性掌蹠角化症を続発した非典型薬剤性過敏症症候群の 1 例
   A case of atypical drug-induced hypersensitivity syndrome followed by transient acquired palmoplantar keratosis
   野村尚史 T. Nomura、椛島健治（京都大）

   2) 紅斑の再燃を半年以上繰り返す DIHS 症例 2 例—パルス療法は DIHS 長期予後に影響するか？
   Two cases of drug-induced hypersensitivity syndrome with relapsing course initially treated with steroid pulse therapy
   青山裕美 Y. Aoyama （川崎医大附属川崎病院)

16:30

終了予定

ご案内

◎ 7th Drug Hypersensitivity Meeting 2016： 21-23, April 2016, Malaga, Spain

◎ next iSCAR：

招聘状

分担研究者，関係者各位殿

前略

下記のごとく厚生労働省科学研究費補助金「難治性疾患等政策研究事業（難治性疾患政策研究事業）：重症多形滲出性紅斑に関する調査研究（H26－難治等（難）－一般－081）」の平成27年度 臨時班会議を開催いたしますので、ご出席いただきますようお願い申し上げます。

草々

――――記――――

日時：平成27年11月21日(土曜日)　午前7時30分～9時00分（予定）
場所：島根県民会館内　3階　307会議室
〒693-8501 島根県出雲市塩冶町89-1
TEL 0853 20 2210

議題：1. 診療ガイドライン2015（Ver 2）
2. 確認事項：分子標的薬関連情報収集項目

- 資料（診療ガイドライン2015（Ver 2）など）はメールで本会議前に送付しますので、各自ご持参くださいますようお願い申し上げます。

平成27年11月吉日
研究代表者：杏林大学医学部皮膚科
塩原哲夫

厚生労働省科学研究費補助金
「難治性疾患等政策研究事業（難治性疾患政策研究事業）：重症多形滲出性紅斑に関する調査研究（H26－難治等（難）－一般－081）」
平成 27 年度 第 2 回班会議プログラム

研究代表者：杏林大学医学部皮膚科　塩原哲夫

日時：　平成 27 年 12 月 26 日（土）
９：３０～１６：３０（予定）

場所：東京駅前　朝日生命大手町ビル フクラシア東京ステーション
会議室 6 階
住所：〒100-0004　東京都千代田区大手町 2-6-1　朝日生命大手町ビル 5F/6F
・JR [東京]駅・地下鉄[大手町]駅　地下直結　（メトロポリタンホテル向かい側）
・JR [東京]駅・日本橋口徒歩 1 分
・JR 地下鉄[大手町]駅　B6 出口直結
電話：03-3510-3051

Asian SCAR Meeting

9:30
開会の挨拶 Opening Remarks
研究代表者 塩原哲夫

9:40
1. SJS/TEN 診断基準・治療指針/ガイドライン最終版作成
Guideline version 3 for SJS/TEN: Diagnostic criteria and therapeutic policy
追記確認
今後の予定：H28 年 1 月の日皮会ガイドライン作成委員会へ提出

10:30
2. 分子標的薬関連皮膚病変演題
1)EGFR 阻害剤治療中の皮膚細菌感染症
Cutaneous bacterial infection during treatment with EGFR inhibitors
藤山幹子 M. Tohyama, 佐山浩二 K. Sayama （愛媛大）

10:45

2)当科で経験した Nivolumab 投与で生じた皮膚障害 7 例のまとめ
Cutaneous adverse effects of anti-PD-1 antibody in 7 cases.
渡邊友也 T. Watanabe, 山口由衣 Y. Yakaguchi, 相原道子 M. Aihara（横浜市大）

11:00

3)ニボルマブに続いてベムラフェニブを投与し, 全身に紅斑を生じた悪性黒色腫
Skin rashes associated with vemurafenib administration following nivolumab therapy
加藤峰幸 M. Kato, 水川良子 Y. Mizukawa, 大山学 M. Ohyama, 塩原哲夫
T. Shiohara（杏林大）

11:15

4)Helicobacter pylori 除菌後に生じた皮疹の機序解明
Mechanism of skin reactions related to *Helicobacter pylori* treatment
伊東孝政 T. Ito, 阿部理一郎 R. Abe（北大/新潟大）

11:35

3. 分子標的薬関連皮膚病変の集積：今後の方針を含めて
Cutaneous lesions induced by molecular targeted medicine
末木博彦 H. Sueki （昭和大）

12:05

・Lunch

12:50

・事務局連絡 (Official announcement of the next meeting)
確認事項
＊薬疹遺伝子多型の検索（倫理委員会書類変更、情報収集施設
島根大へ移行）
＊職位変更の連絡　H 28 年 3 月末まで両施設に連絡

・次回班会議 (Next Asian-SCAR Meeting)
候補日: 2016. 7. 23 (Sat) or 7. 30(Sat) など

13:00

4. ステロイドパルス療法臨床治験　進捗状況
1) Recent Report: Steroid pulse therapy project for SJS/TEN
森田栄伸 E. Morita（島根大）

2) Steroid pulse therapy project for SJS/TEN
Wen Hung Chung (Chang Gung Memorial Hosp.)

14:00

3) 関連演題
ステロイドパルス療法を行った薬疹の 3 例
Three cases of drug reaction successfully treated with steroid-pulse therapy
新原寛之 H. Niihara, 森田栄伸 E. Morita（島根大）

14:20

5. Proton pump inhibitors related SCAR
Wen Hung Chung (Chang Gung Memorial Hosp.)

14:45

Coffee break

15:00

6. 分担研究者報告
1)ニコランジルによる口腔潰瘍
Nicolandil-induced oral ulcer
藤山幹子 M. Tohyama, 佐山浩二 K. Sayama （愛媛大）

15:15

2)薬剤性過敏症症候群全国疫学調査後の追跡(後遺症)調査
Follow-up study after nationwide epidemiological survey of DIHS
黒沢道子 M. Kurosawa （順天堂大)

15:35

3)DIHS の重症度スコアと実際の運用
Severity score for DIHS
平原和久 K. Hirahara （杏林大）

15:50

4)フェノバルビタールによって誘発された類天疱瘡
Bullous pemphigoid induced by phenobarbital
橋爪秀夫 H. Hashizume, 影山玲子 R. Kageyama, 植田寛子 H. Ueda（島田市民）

16:05

5) 口腔粘膜疹を有した全身薬疹の 1 例

A case of tegafur/gimeracil/oteracil (TS-1) induced systemic eruption accompanied with oral mucosal lesion

要石就斗 S. Kanameishi, 加来洋 H. Kaku, 野村尚史 T. Nomura, 椛島健治 K. Kabashima（京大）

16:20

主任研究者交代　平成 28 年 1 月から　(新主任研究者 : 森田栄伸先生　ご挨拶)

16:30

閉会　Closing Remarks

<<ご案内>>

◎ 7th Drug Hypersensitivity Meeting 2016 : 21-23, April 2016, Malaga, Spain

◎ next iSCAR :

Dear colleague,

The **7th Drug Hypersensitivity Meeting (DHM)**, the "world congress on drug hypersensitivity" held every second year, is planned **in April 2016 in Malaga, Spain**. The provisional meeting dates are 21 – 23 April 2016 and will be confirmed in the New Year. The meeting will start on Thursday afternoon and finish Saturday lunchtime. We have the honor to organise it, but in order to develop an outstanding programme need the help of others. We hope that you will find time to participate in this meeting and that **you will accept to work in the organising committee**.

The previous meetings with their interdisciplinary approach have been a huge scientific success, and the last meeting in April 2014 in Bern broke all records with more than *150* abstracts and *300* registered delegates. The need to work interdisciplinary between scientists and clinicians guarantees a wide audience. We strongly believe that the interest in this topic is still increasing and are convinced that the meeting in Malaga will also be successful and informative. As previously, the meeting will be organised by the European Academy of Allergy and Clinical Immunology.

In order to organise a high quality meeting and attract world leaders in the fields of allergy, genetics, immunology, pharmacology and toxicology we need the help of a dedicated committee with expertise in the field of drug hypersensitivity. Thus, we have set up an organising committee (see list below) and ask if you would like to participate. The main aim of this committee is to provide input into the scientific programme, to continue the tradition of an interdisciplinary approach to this topic.

Please confirm whether you are able to accept our invitation to be a member of the Organsising Committee at your earliest convenience to viviane.knerr@eaaci.org.

We thank you in advance for your contribution and look forward to hearing from you soon and to welcoming you to Malaga.

Maria Torres
DHM 2016 Chair

Knut Brockow
DHM 2016 Co-Chair

Ronald van Ree
EAACI Vice-President
Congresses

Scientific Organising Committee

Maria Torres, Malaga, Spain DHM 2016 Chair
Knut Brockow, Munich, Germany DHM 2016 Co-Chair

Core Committee

Miguel Blanca, Malaga, Spain
Patrizia Bonadonna, Padova, Italy
Elizabeth Phillips, Perth, Australia and Nashville, Tennessee, USA
Werner J. Pichler, Bern, Switzerland
Jean-Claude Roujeau, Paris, France

Annick Barbaud, Nancy,France
Mariana Castells, Boston USA
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Shuen-Iu Hung, Taipei, Taiwan
Simon Mallal, Perth Australia and Nashville, Tennessee, USA
Clare Mills, Manchester, United Kingdom
Maja Mockenhaupt, Freiburg, Germany
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Mario Sanchez-Borges, Caracas, Venezuela
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Nikos Papadopoulos, Greece

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Ronald Van Ree, The Netherlands

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