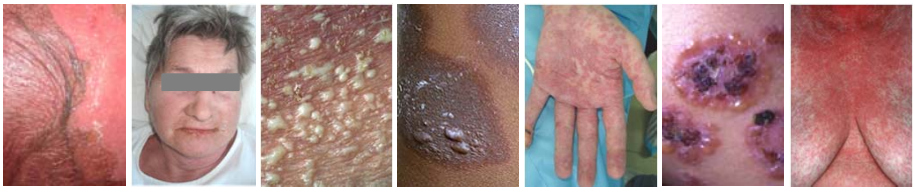


Syndrome de Lyell/SJS
Mise au point

Dr Benoit BENSAID
Centre de Reference sur les Dermatoses Bulleuses toxiques
CHU LYON CENTRE
Dermatologie/PAM medecine

Toxidermies Sévères Présentation

1. Nécrolyse épidermique (syndrome de Stevens-Johnson- SJS, syndrome de Lyell-TEN et formes de transition)
2. DRESS et Syndromes d'hypersensibilité
3. Pustuloses exanthématiques
4. Érythème pigmenté fixe bulleux
5. Érythème polymorphe majeur
6. Dermatoses bulleuses à IgA linéaire médicamenteuse
7. Autres manifestations cutanées graves aux médicaments (Toxidermie érythémateuse)

2

SJS/TEN
DEFINITION

- Toxidermie grave
- Erosions muqueuses et atteinte cutanée.
  - < 10% = SJS
  - >30% = TEN
  - 10-30% = transitional SJS/TEN
- 1 à 3 cas / million / an

Roujeau JC et al. Arch dermatol, 1990

3

SJS/TEN
GENETIQUE

Table 1 Genetic associations of Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) in various populations

Drug classification	Culprit drug	SJS and/or TEN	*HLA* allele and CYP	Ethnicity and references
Antibiotics	Sulfonamide	TEN	*A**29, *B**12, *DR**7	European [4]
	Sulfamethoxazole	SJS/TEN	*B**38	European [21]
Anticonvulsants	Carbamazepine	SJS/TEN	*B**15:02	Han Chinese [5, 150], Thai [19], Indian [22], Malaysian [23]
		SJS/TEN	*B**15:11	Japanese [6], Korean [7], Han Chinese [8, 9]
		SJS/TEN	*B**59:01	Japanese [14]
		SJS/TEN	*A**31:01	Japanese, northern European [15, 16]
	Lamotrigine	SJS/TEN	*B**15:02	Han Chinese [17]
	Oxcarbazepine	SJS/TEN	*B**15:02	Han Chinese [18]
	Phenytoin	SJS/TEN	*B**15:02	Han Chinese [17, 18], Thai [19]
		SJS/TEN	*CYP2C9**3	Han Chinese, Japanese, Malaysian [30]
Antiglaucoma drugs	Methazolamide	SJS/TEN	*B**59:01, *CW**01:02	Korean and Japanese [20]
Antiretrovirals	Nevirapine	SJS/TEN	*CYP2B6*	African in Mozambique [33]
			*C**04:01	African in Malawi [151]
NSAIDs	Oxicam	SJS/TEN	*A**2, *B**12	European [4, 21]
		TEN	*B**73	
Xanthine oxidase inhibitors	Allopurinol	SJS/TEN	*B**58:01	Han Chinese [13], Thai [12], Japanese [10], Korean [11], European [21]

Dodiuk Gad et al, AJD,2015

4

*HLA-B*59:01*: a marker for Stevens–Johnson syndrome/toxic epidermal necrolysis caused by methazolamide in Han Chinese

F Yang[1,6], J Xuan[2,6,7], J Chen[3,6], H Zhong[2], H Luo[4], P Zhou[5], X Sun[3], L He[2], S Chen[1], Z Cao[1], X Luo[1] and Q Xing[2]

Table 1. Clinical characteristics and HLA genotypes of patients with methazolamide-induced SJS/TEN

Case subject	Age (years)/ gender	SCAR	Exposure duration/ latency (days)	Dose (mg per day)	Mucosal involvement	Systemic manifestations	HLA-A genotype	HLA-B genotype	HLA-C genotype
1	51/F	TEN	17/14	50	Oral, eye, genitalia	LFI	*02:01/24:02*	*15:27/**59:01***	***01:02**/04:01*
2	59/F	TEN	32/32	50	Oral, eye, genitalia	RFI	*11:01/11:02*	*27:04/**59:01***	***01:02**/12:02*
3	58/F	TEN	10/23	50	Oral	Leukopenia, thrombocytopenia	*31:01/69:01*	*52:01/55:02*	*01:06/12:02*
4	38/M	TEN	16/12	50	Oral, genitalia	LFI	*03:01/11:01*	*44:02/**59:01***	***01:02**/05:01*
5	51/M	TEN	21/18	50	Oral, eye, genitalia	LFI, RFI	*02:06/24:02*	*48:03/**59:01***	***01:02**/08:01*
6	49/M	TEN	2/12	50	Oral, eye	RFI	*02:06/11:01*	*15:01/**59:01***	***01:02/01:02***
7	33/M	SJS	20/15	50	Oral, eye, genitalia	None	*33:03/11:01*	*58:01/**59:01***	***01:02**/03:02*
8	67/M	SJS	58/58	50	Oral, eye, genitalia	LFI	*11:01/11:01*	*45:01/**59:01***	***01:02**/06:02*

Abbreviations: F, female; LFI, liver function impairment; M, male; RFI, renal function impairment; SCAR, severe cutaneous adverse reaction; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis. The bold entries highlight that *HLA-B*59:01* or *HLA-C*01:02* is positive in these patients.

Table 3. Frequencies of *HLA-B*59:01, C*01:02* and the haplotype and association analyses with methazolamide-induced SJS/TEN

Genotype	Methazolamide–SJS/ TEN (n = 8)	Tolerant controls (n = 20)	OR (95% CI)	P-value	General population (n = 283)	OR (95% CI)	P-value
*B*59:01*	7 (87.5)	0 (0)	305.0 (11.3–8259.9)	6.3×10^{-7}	1 (0.35)	1974.0 (111.8–34868.4)	2.0×10^{-12}
*Cw*01:02*	7 (87.5)	11 (36.7)	12.1 (1.3–111.7)	0.016	88 (31.1)	15.5 (1.9–128.0)	2.0×10^{-3}
*B*59:01, Cw*01:02*	7 (87.5)	0 (0)	305.0 (11.3–8259.9)	6.3×10^{-7}	1 (0.35)	1974.0 (111.8–34868.4)	2.0×10^{-12}

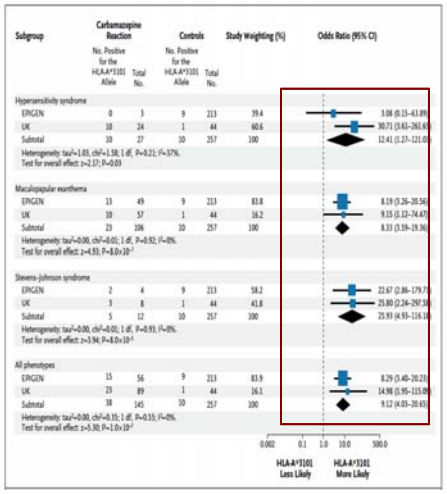
Abbreviations: CI, confidence interval; OR, odds ratio; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis. *P* values were calculated using Fisher's exact test.

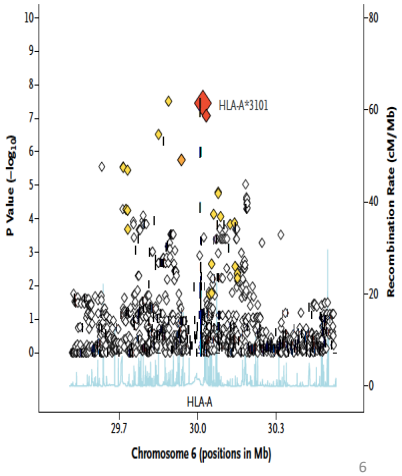
The Pharmacogenomics Journal (2015), 1–5

5

HLA A 31.01 associé au risque detoxidermies à la carbamazépine chez l'Européen

Mc Cormack. NEJM 2011





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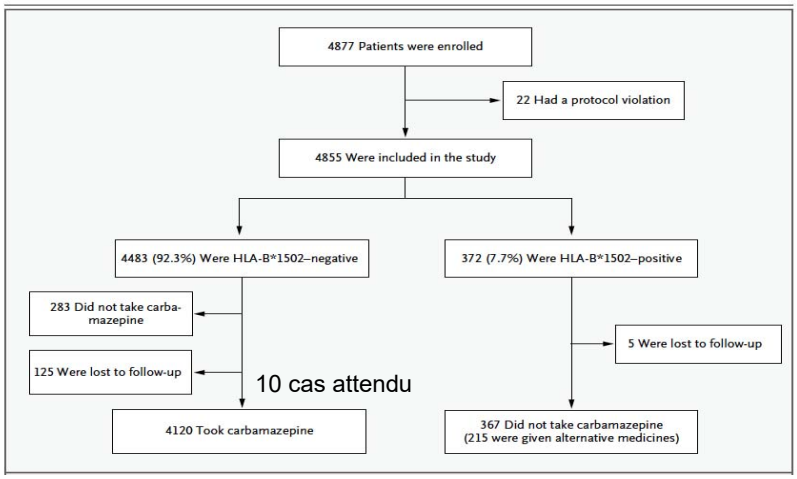
Intérêt du dépistage HLA B1502 avant de prescrire de la carbamazépine

Chen et al. NEJM 2011



7

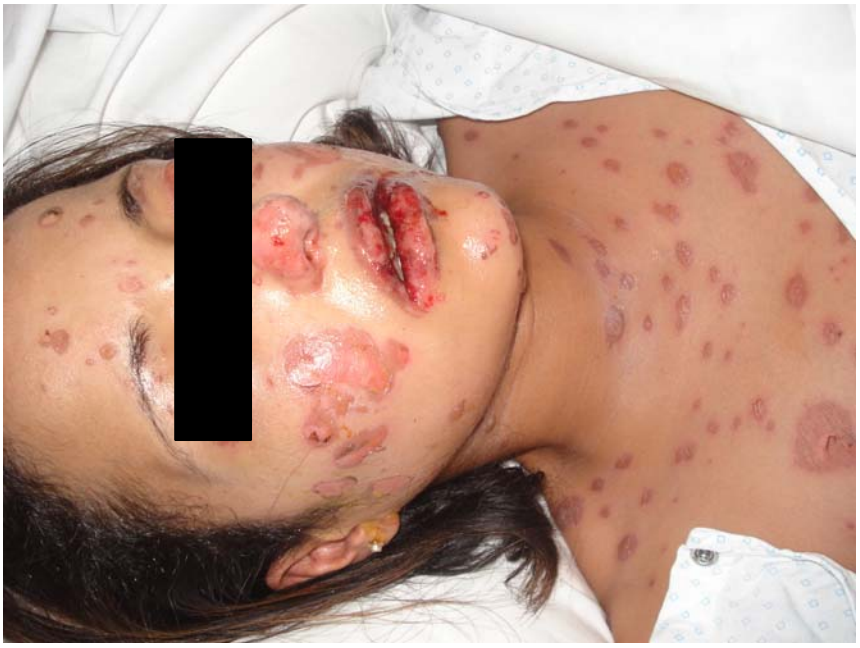
SJS/TEN

CLINIQUE

centre de référence maladies rares

- Début symptômes peu spécifiques +++ mais aigus
  = fièvre, AEG importante, picotements oculaires
- Lésions muqueuses parfois précessives (1/3 cas)
  - Au moins 2 sites muqueux dans >80% des cas
  - 90-100% buccaux
  - Ophtalmologiques 80%
  - Genitaux
- Eruption maculo-papuleuse douloureuse du visage, et haut du tronc.
- Puis extension et décollements cutanés avec Nikolsky pendant quelques jous

8



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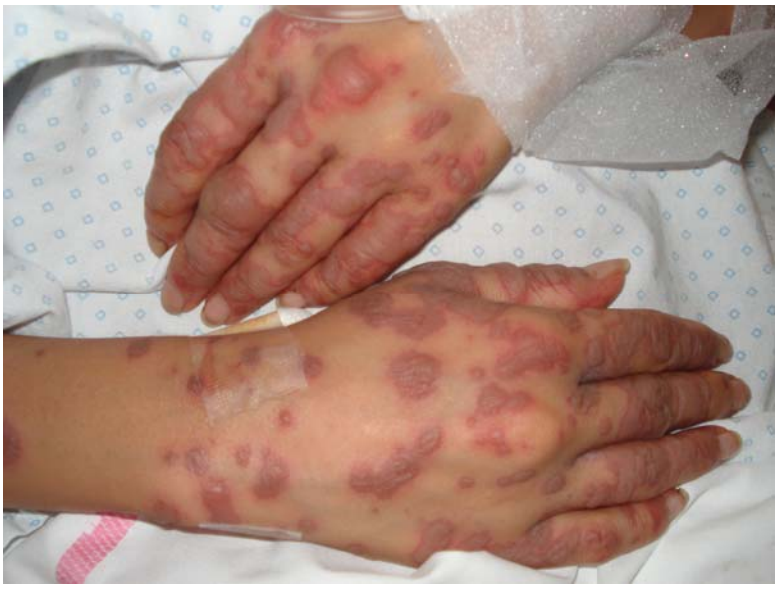

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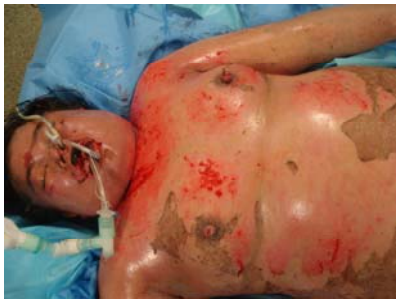
NECROLYSE EPIDERMIQUE TOXIQUE (NET)



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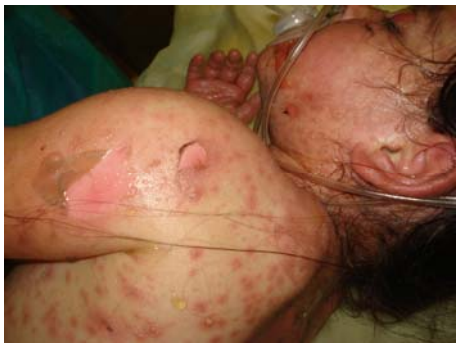

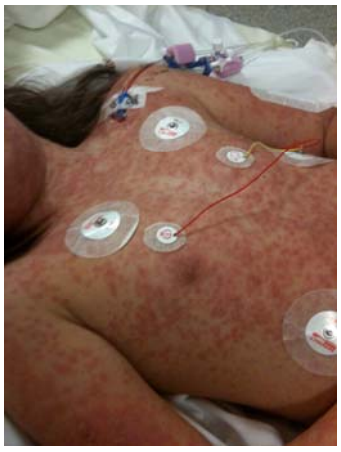

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SJS/TEN
ATTEINTES EXTRA CUTANÉES

- Anomalies Hémato-biologiques
  - ✧ Anémie, **Neutropénie** (mauvais pronostic), lymphopénie, hypoalbuminéme, hypophosphorémie, cytolyse hépatique, pancréatite (amylasemie :salivaire)…
  - ✧ Insuffisance rénale aigue (NIA, NTIA, NTA..)
  - ✧ Auto-immunité: facteur de risque et conséquences
- Atteinte Digestive= PRONOSTIC
  - ✧ Nécrose épithélium digestif, débris épithéliaux
  - ✧ Diarrhées importantes de mauvais pronostic (svt glairo-sanglantes)
  - ✧ Jusqu'à perforation
- Atteinte Pulmonaire= PRONOSTIC 25-39% des cas
  - ✧ 41 patients/ 10 atteintes pulmonaires précoces.
  - ✧ 25% IOT
  - ✧ 100% dyspnée et hypoxie
  - ✧ Rx thorax = N (80%), infiltrat interstitiel (20%), SDRA
  - ✧ Fibroscopie : décollement épithélium bronchique des voies aériennes proximales (100%)

Lebargy et al. Intensive Care Med, 1997
De Prost et al , Vrit Care Med, 2014

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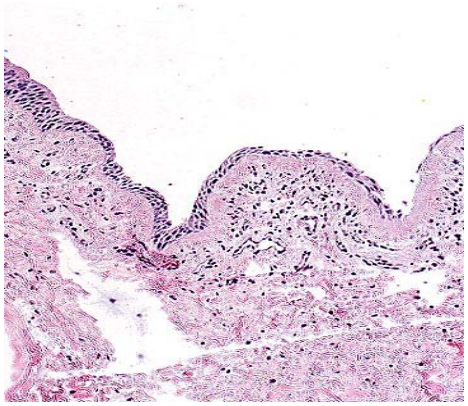
SJS/TEN
HISTOLOGIE

centre de référence maladies rares



NECROLYSE EPIDERMIQUE TOTALE

INFILTRATION LYMPHOCYTAIRE MODERE

Immun histochimie: utile pour différentier Érythème polymorphe et LYELL
= SJS richesse moindre en CD4 et Fox P3+(LT reg) Vs EMM

Rôle pronostic de l'infiltrat cellules mononuclées et de la nécrose complète de l'épiderme?

Cd4++, moins de CD56 etde GLY en faveur EPF

Iwai S et al. J dermatol, 2012
Quinn et al ,Arch Dermatol, 2005
Valeyrie-Allanore et al, JAAD, 2013
Chu et al ,JAAD,2014

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SJS/TEN
CAUSES

centre de référence maladies rares

- 4 à 28 jours après introduction
  - ½ vie longue +++
- Sulfamides antibactériens / Anticomitiaux / AINS (oxicams) / Allopurinol / Nevirapin.
- Rôle infection: mycoplasmes +++ /virus (enterovirus…)
- HIV (RR=10), LES, Radiothérapie, greffe de moelle, tumeurs cérébrales, typage HLA favorisant/ Auto-Immunite, Genetiques.

Kelemen JJ et al. Coll Surg, 1995
Chung et al, CID, 2014

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SJS/TEN
CAUSES

centre de référence maladies rares

Table 4 High-risk drugs for Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) [65, 152, 153]

Drugs	General population [65][a]	Children [152][b]	Africa [153][c]
Allopurinol	✔ Highest incidence in Europe and Israel		✔
Antibacterial sulfonamides	✔	✔	✔ Highest incidence in Africa
Antiepileptic agents	✔ Carbamazepine Lamotrigine Phenobarbital Phenytoin	✔ Carbamazepine Lamotrigine Phenobarbital	✔
NSAIDs	✔ Oxicam NSAIDs		✔
Nevirapine	✔		✔
Sulfasalazine	✔		
Antituberculosis agents			✔
Amino-penicillin			✔
Analgesics			✔

Kelemen JJ et al. Coll Surg, 1995
Chung et al, CID, 2014

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SJS/TEN
CAUSES

Table 5 Details of the algorithm of drug causality for epidermal necrolysis (ALDEN)

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	−3 to 3
	Compatible +2	From 29 to 56 days	
	Likely +1	From 1 to 4 days	
	Unlikely −1	>56 Days	
	Excluded −3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day	−3 to 0
	Doubtful −1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present	
	Excluded −3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a], without liver or kidney function alterations or suspected drug interactions[b]	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	−2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar[c] drug or other reaction with same drug	
	Positive unspecific: 1	Other reaction after use of similar[c] drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative −2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	−2 or 0
	Negative −2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case–control studies[d]	−1 to 3
	Associated 2	Drug with definite but lower risk according to previous case–control studies[d]	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected −1	No evidence of association from previous epidemiology study[d] with sufficient number of exposed controls[e]	
		Intermediate score = total of all previous criteria	−11 to 10
Other cause	Possible −1	Rank all drugs from highest to lowest intermediate score	−1
		If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	
Final score −12 to 10			

Sassolas et al, Clin Pharm Ther, 2010

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SJS/TEN
PHYSIOPATHOLOGIE

centre de référence maladies rares

- Role des LT CD8/NK
- Granulysine/Cytotoxicité
- Nécroptose
- T reg
- Th17
- Rôle du métabolite
- Rôle de la clairance du médicament
- Rôle Hla

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SJS/TEN
PHYSIOPATHOLOGIE

centre de référence maladies rares

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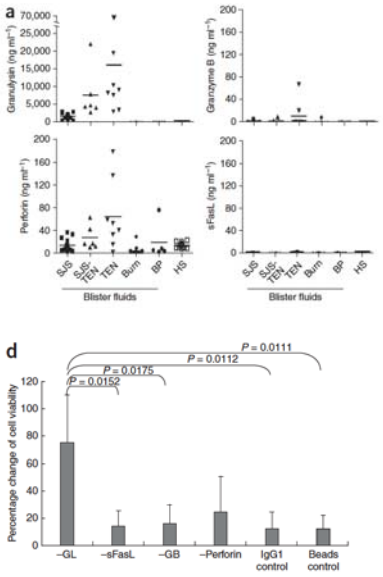
19

Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis



- Les bulles des NET sont riches en LT CD8 Cytotoxiques, en cellules NK (CD(CD56+) et NKT.
- Sécretion massive de GRANULYSINE dans les SJS NET à l'origine d'une apoptose massive des cellules et des signes cliniques de SJS NET
- GRANULYSINE>>>GRANZYME B avec action cytotoxique marquée
- NIVEAU DE GRANULYSINE correlé à la sévérite de la maladie
- Prometteur pour monitorer la maladie?

Chung et al. Nature Medecine 2008

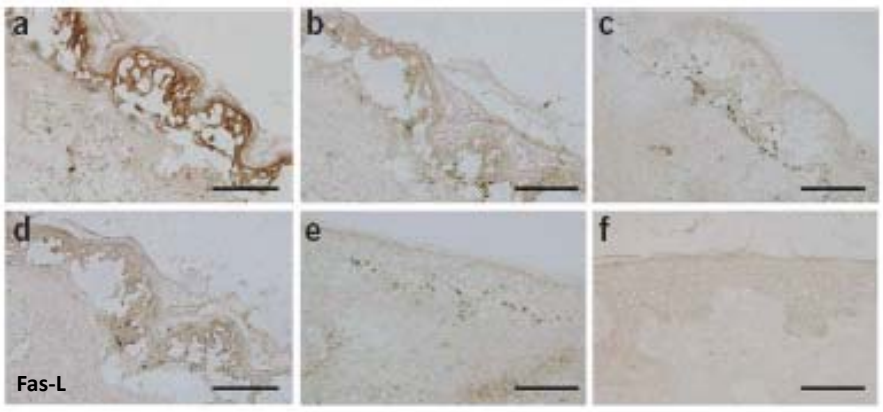


Figure 3 Immunohistochemistry staining of cytotoxic proteins in skin biopsies. (a–d) Serial sections of a skin biopsy from a subject with TEN were stained with antibodies against granulysin (a), granzyme B (b), perforin (c) and FasL (d). (e,f) Skin biopsies from a subject with maculopapular exanthema (e) and a healthy person (f) were stained with RC-8 antibody against granulysin. Scale bars, 200 μm.

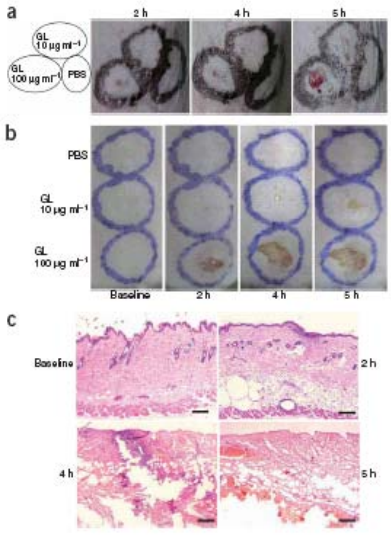
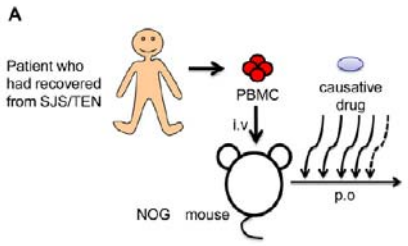


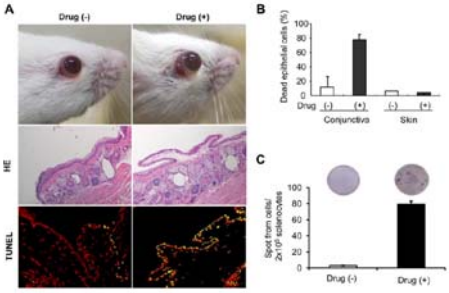
Figure 6 Intradermal injection of 15-kDa granulysin in mice.

- Injection intra-dermique de granulysine
- Obtention en 5 heures de bulles
- Extension avec reproduction histologie necrolyse epidermique

Chung et al. Nature Medecine 2008

SJS/TEN





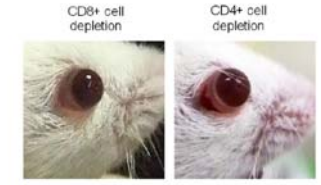


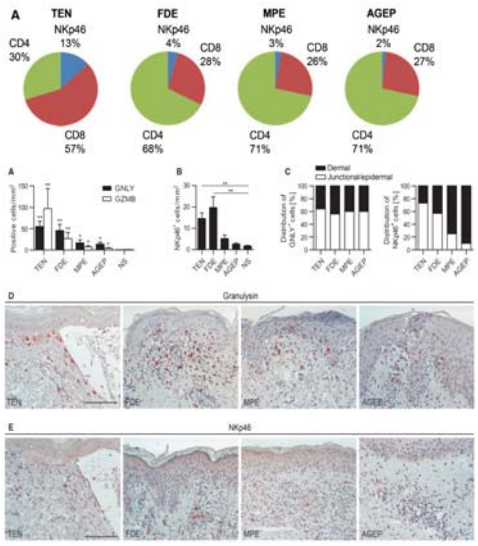
FIG E5. At 12 days after injection of CD4$^+$ T lymphocyte–depleted PBMCs from patients with SJS/TEN and causative drug intake, significant conjunctival congestion and conjunctival chemosis were noticed, whereas this was not the case with CD8$^+$ T lymphocyte–depleted PBMCs from patients with SJS/TEN. Samples from patient 2 with SJS/TEN were analyzed.

Dans un modèle SOURIS de SJS TEN reproduisant les signes de SJS TEN à j12

La déplétion des LTCD8 empêche la survenue des lésions

Saito et al, JACI, 2013

Role clef des LT cytotoxiques



Les cellules NK participent à majorer la cytotoxicite dans les toxidermies sévères

Schalpbach et al, Allergy, 2011

SJS/TEN
PHYSIOPATHOLOGIE

- Role des LT CD8/NK
- Granulysine/Cytotoxicité
- Nécroptose
- T reg
- Th17
- Rôle du métabolite
- Rôle de la clairance du médicament
- Rôle Hla

25

Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis

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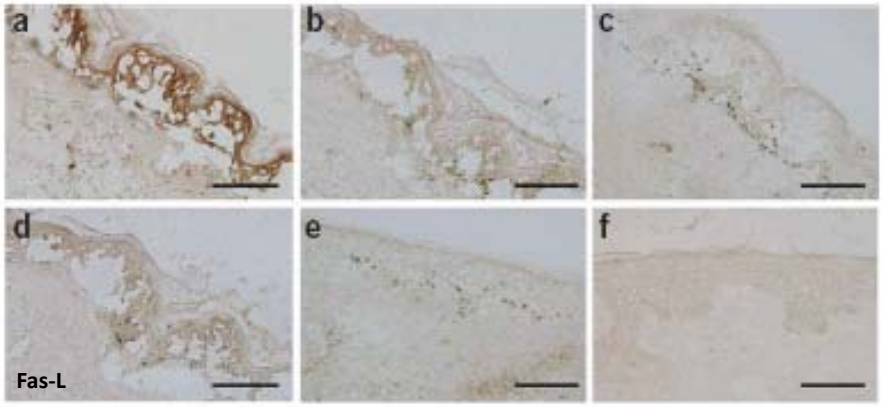
Chung et al. Nature Medecine 2008

Granulysin **Granzyme B** **Perforin**



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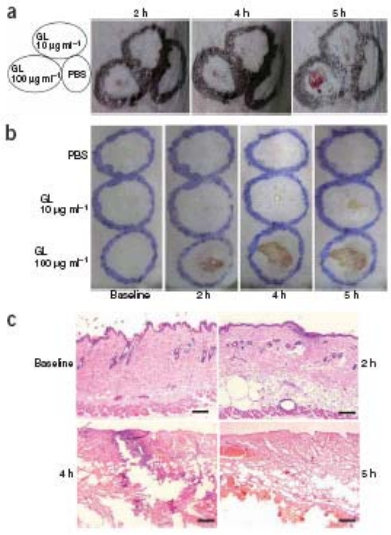


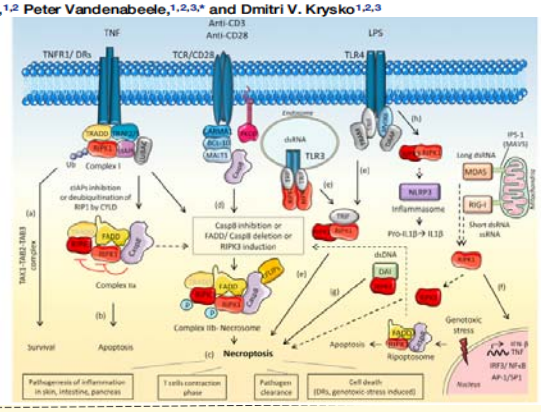
Figure 6 Intradermal injection of 15-kDa granulysin in mice.

- Intradermal injection of granulysin
- Cinetic of developpemnt of blisters
- Developpment of extensive dermal and epidermal necrosis at H5 after injection

28

Necroptosis: The Release of Damage-Associated Molecular Patterns and Its Physiological Relevance

Agnieszka Kaczmarek,[1,2] Peter Vandenabeele,[1,2,3,*] and Dmitri V. Krysko[1,2,3]



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SJS/TEN
PHYSIOPATHOLOGIE

centre de référence maladies rares

- Role des LT CD8/NK
- Granulysine/Cytotoxicité
- Nécroptose
- T reg
- Th17
- Rôle du métabolite
- Rôle de la clairance du médicament
- Rôle Hla

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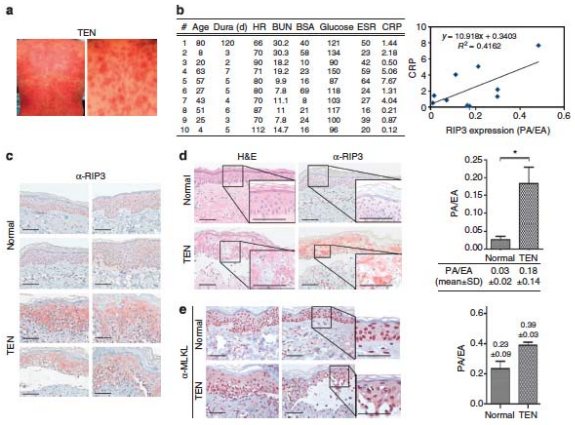
Upregulated RIP3 Expression Potentiates MLKL Phosphorylation–Mediated Programmed Necrosis in Toxic Epidermal Necrolysis

Sue Kyung Kim[1,6], Woo-Jung Kim[2,3,6], Jung-Ho Yoon[2,3], Jae-Hoon Ji[4], Michael J. Morgan[5], Hyeseong Cho[2,3], You Chan Kim[1] and You-Sun Kim[2,3]



La nécroptose participe à la réaction inflammatoire au cours des NET

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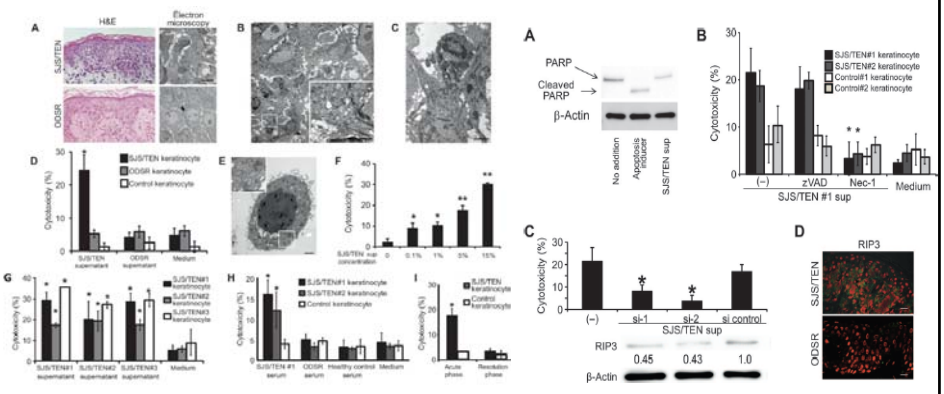
CUTANEOUS DRUG REACTIONS

An annexin A1–FPR1 interaction contributes to necroptosis of keratinocytes in severe cutaneous adverse drug reactions

Nao Saito,[1] Hongjiang Qiao,[1] Teruki Yanagi,[1] Satoru Shinkuma,[1] Keiko Nishimura,[1] Asuka Suto,[1] Yasuyuki Fujita,[1] Shotaro Suzuki,[1] Toshifumi Nomura,[1] Hideki Nakamura,[1] Koji Nagao,[2] Chikashi Obuse,[2] Hiroshi Shimizu,[1]* Riichiro Abe[1]*



Il existe deux phénomènes de morts cellulaires au cours des SJS TEN : Apoptose et nécroptose

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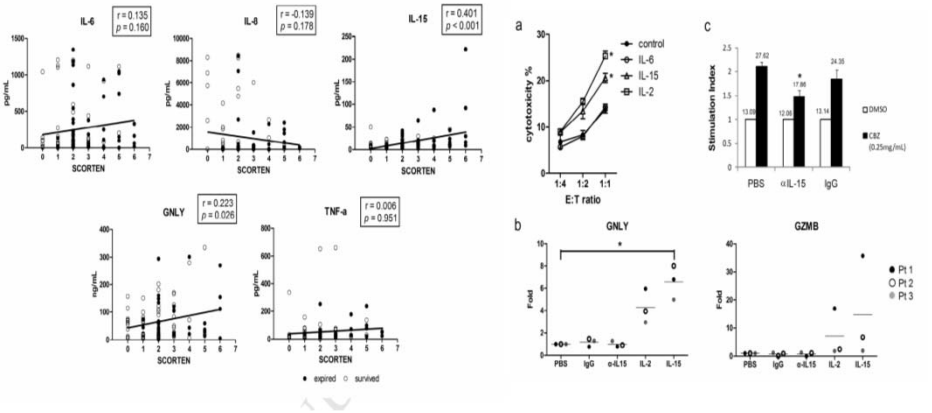
centre de référence maladies rares

Interleukin-15 is associated with severity and mortality in Stevens-Johnson syndrome/toxic epidermal necrolysis

Shih-Chi Su, Maja Mockenhaupt, Pierre Wolkenstein, Ariane Dunant, Sabine Le Gouvello, Chun-Bing Chen, Olivier Chosidow, Laurence Valeyrie-Allanore, Teresa Bellon, Peggy Sekula, Chuang-Wei Wang, Martin Schumacher, Sylvia H. Kardaun, Shuen-Iu Hung, Jean-Claude Roujeau, Wen-Hung Chung



IL15 joue un rôle dans la physiopathologie du TEN et est corrélé à la sévérité de la maladie

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SJS/TEN

PHYSIOPATHOLOGIE

- Role des LT CD8/NK
- Granulysine/Cytotoxicité
- Nécroptose
- T reg
- Th17
- Rôle du métabolite
- Rôle de la clairance du médicament
- Rôle Hla

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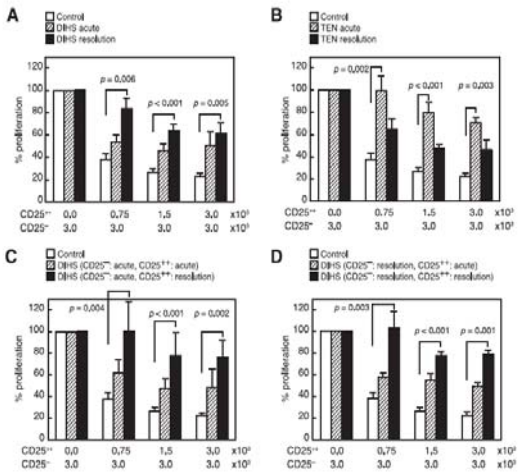
TEN et LT Régulateur

Défaut de régulation:

- Shiohara et coll. J Immunol, 2009



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SJS/TEN
PHYSIOPATHOLOGIE

- Role des LT CD8/NK
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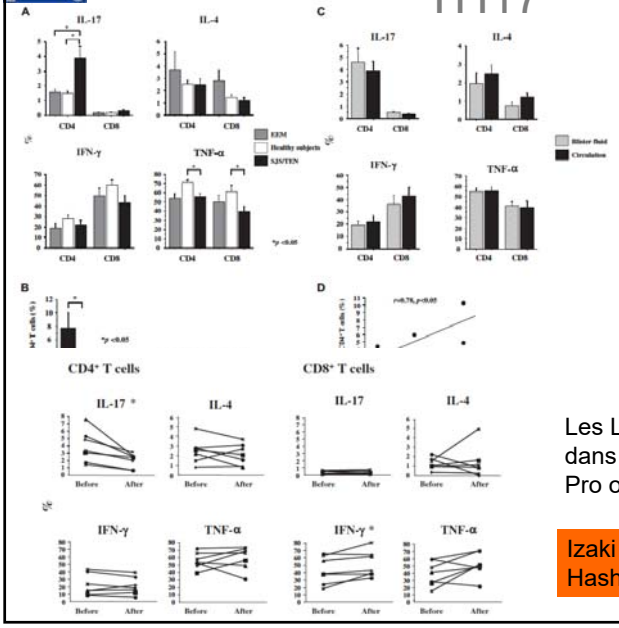
SJS/TEN
TH17



Les LT TH17 semblent avoir un role dans le SSJS NET
Pro ou anti Inflammatoire?

Izaki et al , JACI, 2012
Hashizume, As Pac Al, 2015

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SJS/TEN
PHYSIOPATHOLOGIE

centre de référence maladies rares

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- Rôle Hla

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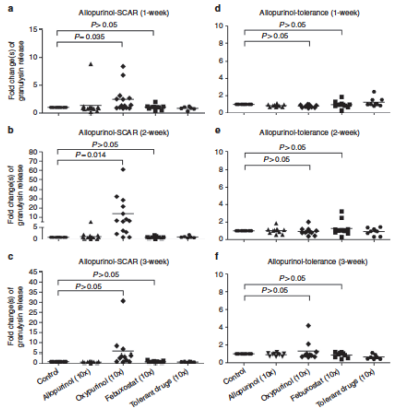
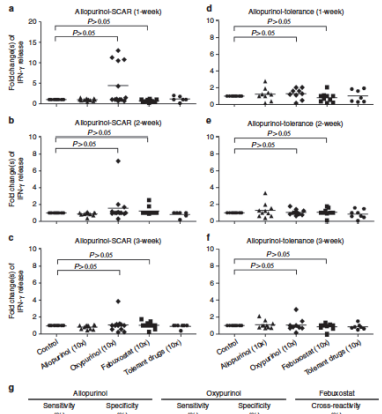
Oxypurinol-Specific T Cells Possess Preferential TCR Clonotypes and Express Granulysin in Allopurinol-Induced Severe Cutaneous Adverse Reactions

Wen-Hung Chung[1,2,6], Ren-You Pan[3,6], Mu-Tzu Chu[4], See-Wen Chin[1,2], Yu-Lin Huang[1,2], Wei-Chi Wang[5], Jen-Yun Chang[5] and Shuen-Iu Hung[3,4]





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	Allopurinol		Oxypurinol		Febuxostat
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Cross-reactivity (%)
1 week	7	100	43	100	0
2 week	14	100	86	91	0
3 week	0	100	64	80	0

	Allopurinol		Oxypurinol		Febuxostat
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Cross-reactivity (%)
1 week	0	89	38	78	0
2 week	0	90	15	100	10
3 week	0	90	8	89	0

L'oxypurinol est le meilleur antigène pour la réalisation des tests immunobiologiques lors des SCARS Allopurinol/La GLN le meilleur marqueur

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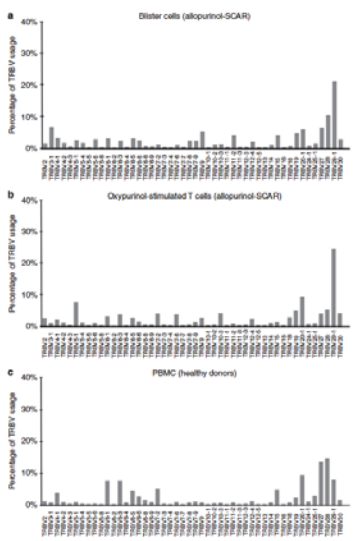
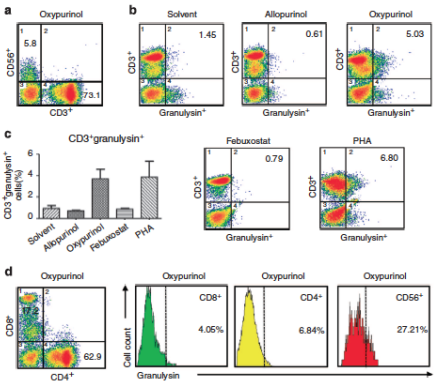
Oxypurinol-Specific T Cells Possess Preferential TCR Clonotypes and Express Granulysin in Allopurinol-Induced Severe Cutaneous Adverse Reactions

Wen-Hung Chung[1,2,6], Ren-You Pan[3,6], Mu-Tzu Chu[4], See-Wen Chin[1,2], Yu-Lin Huang[1,2], Wei-Chi Wang[5], Jen-Yun Chang[5] and Shuen-Iu Hung[3,4]





Les clones TCR détectés sont spécifiques de l'OXYPURINOL

Les cellules responsables de la sécrétion de GLN sont en majorité des NK

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SJS/TEN
PHYSIOPATHOLOGIE

centre de référence maladies rares

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SJS/TEN
Role de la clairance du metabolite

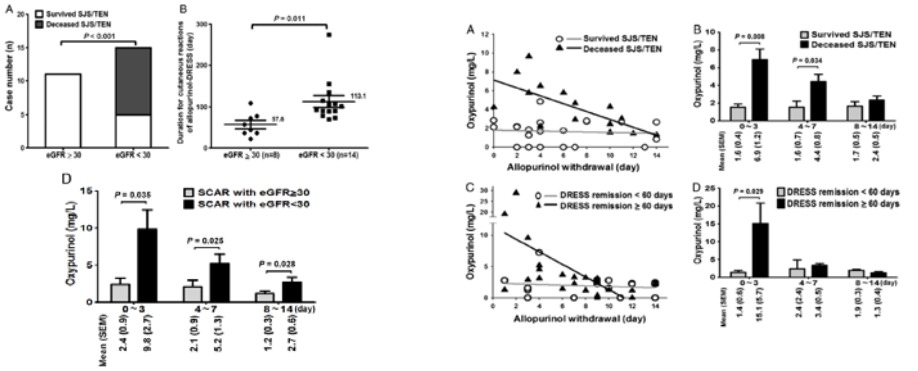

Table 2 Delayed clearance of oxypurinol in patients with allopurinol-SCAR*

Groups	Severity of renal impairment	CKD stage†	Delayed clearance of oxypurinol			
			No	Yes	Per cent	p Value
Group 1 (eGFR ≥30)†	Moderate to normal	3, 2, 1	8	10	56	0.002
Group 2 (eGFR <30)§	Kidney failure to severe	5, 4	1	24	96	

Chung WH et al , Ann Rheum Dis, 2015

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SJS/TEN
PHYSIOPATHOLOGIE

- Role des LT CD8/NK
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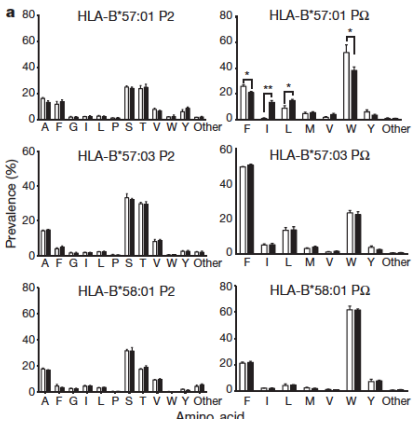
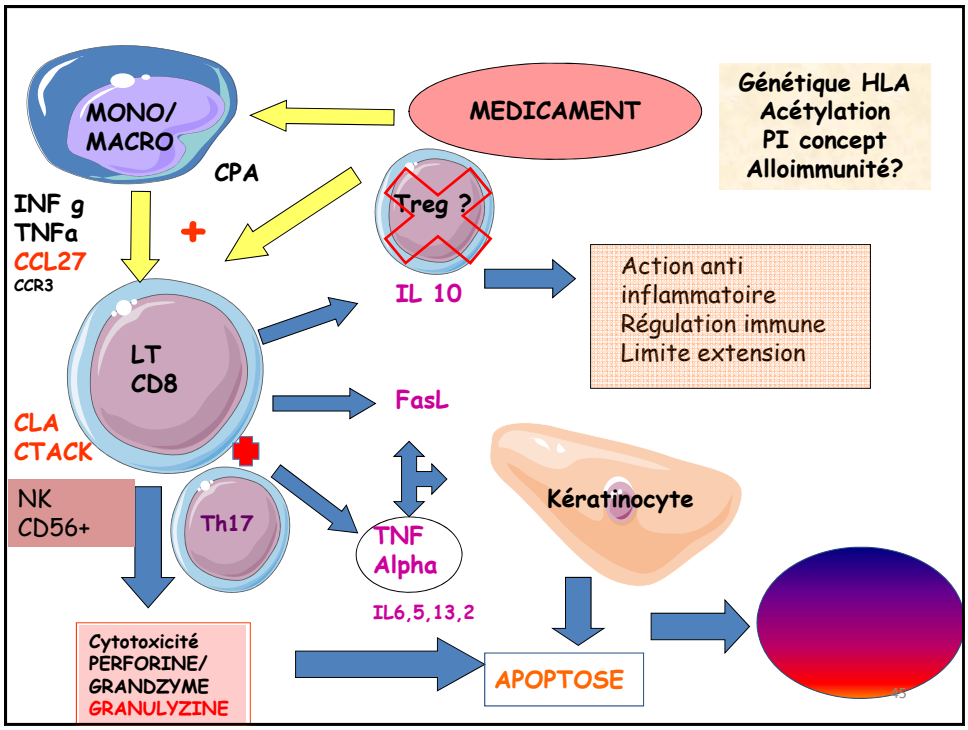
SJS/TEN
Rôle HLA



La fixation du médicament sur un HLA spécifique entrainerait la modification de la molécule HLA à l'origine de la formation de 5 néo peptides au moins responsable d'une allo immunisation et de la sévérité de la réaction immune

Mc Cluskey et al , nature, 2012

44

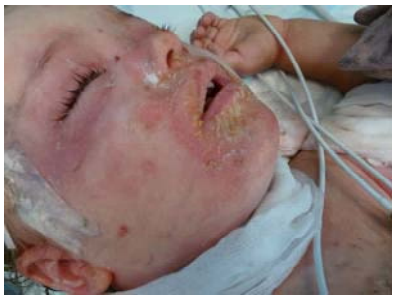


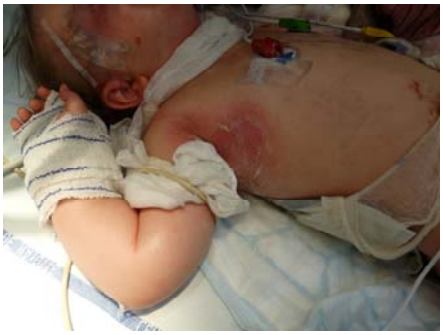
DIAGNOSTIC DIFFÉRENTIEL

Table II. Differential diagnosis of TEN

Bullous disease	Fever	Mucositis	Morphology	IF	Onset	Miscellaneous features
Drug-induced pemphigoid	No	Rare	Tense bullae (sometimes hemorrhagic)	+	Acute	Diuretics a common cause, especially spironolactone; often pruritic
Staphylococcal scalded skin syndrome	Yes	Absent	Erythema, skin tenderness, periorificial crusting	−	Acute	Affects children under 5, adults on dialysis, and those on immunosuppressive therapy
Drug-induced pemphigus	No	Usually absent	Erosions, crusts, patchy erythema (resembles pemphigus foliaceous)	±	Gradual	Commonly caused by penicillamine and other "thiol" drugs; resolves after inciting agent is discontinued
Drug-triggered pemphigus	No	Present	Mucosal erosions, flaccid bullae	+	Gradual	Caused by "non-thiol" drugs; persists after discontinuation of drug; may require long-term immunosuppressive therapy
Paraneoplastic pemphigus	No	Present (usually severe)	Polymorphous skin lesions, flaccid bullae	+	Gradual	Resistant to treatment; associated with malignancy, especially lymphoma
Acute graft-versus-host disease	Yes	Present	Morbilliform rash, bullae and erosions	−	Acute	Closely resembles TEN
Acute generalized exanthematous pustulosis	Yes	Rare	Superficial pustules (resembles pustular psoriasis)	−	Acute	Self-limiting on discontinuation of drug
Drug-induced linear IgA bullous dermatosis	No	Rare	Tense, subepidermal bullae (resembles pemphigoid)	+	Acute	Vancomycin most commonly implicated drug; pruritus often present

EPF BULLEUX GENERALISE





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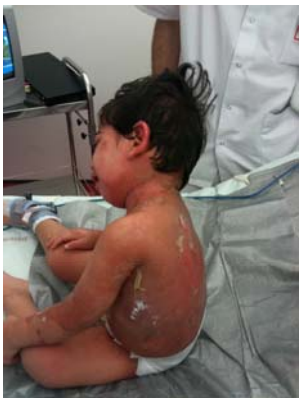

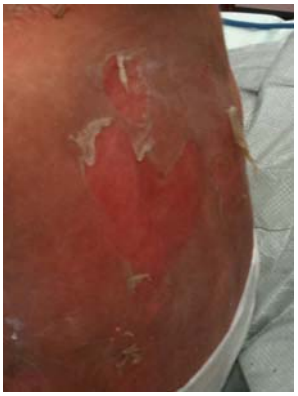

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SJS/TEN
PRONOSTIC

- MORTALITE (Sepsis, Atteinte pulmonaire, Digestif)
  - ➢ 5% SJS
  - ➢ 33% NET global
  - ➢ 23% etude EUROSCAR, 34% à 1an

- Score pronostique dans les 3 premiers jours = SCORTEN

  - ❖ âge>40ans
  - ❖ cancer récent,
  - ❖ S>30%,
  - ❖ FC>120/mn
  - ❖ Urée>10, bicar<20 mmol/
  - ❖ Glycémie >14 mmol/l

Table I. SCORTEN level and predicted mortality

SCORTEN	Mortality
0-1	3.2%
2	12.1%
3	35.3%
4	58.3%
5 or greater	90.0%

Bastuji Garin et al, J Invest dermatol, 2000
Sekula et al, BJD, 2013

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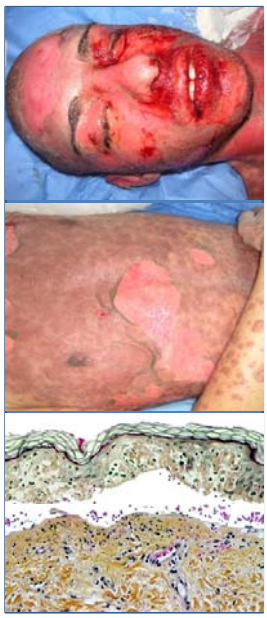
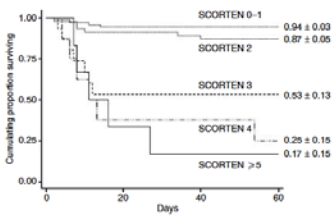


MORTALITE (Sepsis, Atteinte pulmonaire, Digestif)
- ➢ 5% SJS
- ➢ 15-33% NET global
- ➢ 34% à 1an

Table 1. Seven independent prognosis factors of Stevens–Johnson syndrome and toxic epidermal necrolysis are included in the SCORTEN

Independent prognosis factors		Weight
Age	⩾40 years	1
Malignancy	Yes	1
Body surface area detached	⩾10%	1
Tachycardia	⩾120/min	1
Serum urea	>10 mmol/l	1
Serum glucose	>14 mmol/l	1
Serum bicarbonate	<20 mmol/l	1



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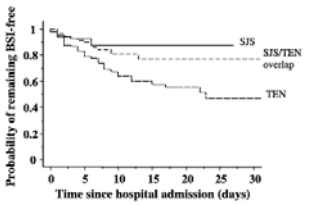
SJS/TEN

SEPSIS

Medicine

TABLE 4. Predictors on Hospital Admission of Bloodstream Infection During the Hospital Stay

Variable	N	BSI No. (%)	Univariate Analysis HR (95% CI)	P	Multivariate Analysis HR (95% CI)	P
Age >40 yr						
No	83	15 (18)	1	0.005	1	0.004
Yes	96	33 (35)	2.4 (1.30–4.46)		2.5 (1.35–4.63)	
Diabetes						
No	164	41 (25)	1	0.077	—	NS
Yes	15	7 (47)	2.1 (0.92–4.69)			
Cancer/hematologic malignancy						
No	159	41 (26)	1	0.374	—	NS
Yes	20	7 (35)	1.6 (0.58–4.18)			
HIV infection						
No	145	37 (25)	1	0.895	—	NS
Yes	34	11 (32)	1.0 (0.52–2.11)			
Temperature >39°C						
No	94	21 (21)	1	0.910	—	NS
Yes	85	27 (32)	1.0 (0.54–1.72)			
Shock						
No	143	28 (20)	1	0.467	—	NS
Yes	36	20 (55)	1.5 (0.52–4.20)			
Serum urea level >10 mM						
No	148	33 (22)	1	0.002	—	NS
Yes	31	15 (48)	2.6 (1.42–4.84)			
White blood cells >10,000/mm³						
No	150	35 (23)	1	0.042	1	0.064
Yes	29	13 (45)	1.9 (1.02–3.68)		1.9 (0.96–3.61)	
Bronchial ulcerations						
No	162	42 (26)	1	0.594	—	NS
Yes	17	6 (35)	1.3 (0.53–3.00)			
Body surface area involved, %						
<10	78	11 (14)	1		1	
10–29	68	22 (32)	1.8 (0.89–3.70)	0.099	1.8 (0.86–3.61)	0.12
>30	33	15 (45)	2.8 (1.35–6.77)	0.006	2.5 (1.13–5.47)	0.023



Bonne VPP culture cutanée et surface cutanée pour sepsis

TABLE 6. Association Between Skin Colonization and Bloodstream Infection for the Main Pathogens Recovered in Patients With a Maximal Detached Body Surface Area ≥10% (n = 126)

Pathogen	Skin Culture	BSI +	BSI −	Odds Ratio [95% CI]	Sensitivity [95% CI]	Specificity [95% CI]	NPV [95% CI]	PPV [95% CI]	P*
P. aeruginosa	+	13	46	18.6 [2.36–147.58]	0.93 [0.661–0.998]	0.59 [0.492–0.681]	0.98 [0.920–0.999]	0.22 [0.123–0.347]	<0.001
	−	1	66						
MRSA	+	8	31	22.2 [2.67–184.69]	0.89 [0.517–0.997]	0.73 [0.645–0.812]	0.99 [0.938–0.999]	0.20 [0.093–0.365]	<0.001
	−	1	86						
MSSA	+	6	29	3.6 [1.01–12.54]	0.54 [0.234–0.832]	0.75 [0.658–0.824]	0.94 [0.876–0.982]	0.17 [0.065–0.336]	0.038
	−	5	86						
EB	+	8	55	1.0 [0.35–2.85]	0.50 [0.246–0.753]	0.50 [0.403–0.597]	0.87 [0.765–0.943]	0.13 [0.056–0.235]	NS
	−	8	55						
Other GPP	+	1	27	0.4 [0.04–3.05]	0.10 [0.002–0.445]	0.77 [0.680–0.841]	0.91 [0.833–0.957]	0.03 [0.001–0.183]	NS
	−	9	89						

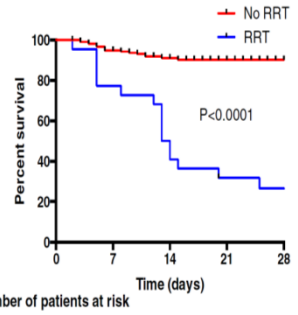
DEPROST et al, Medicine, 2010

centre de référence maladies rares

Renal replacement therapy during Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective observational study of 238 patients

M. Papo[1], L. Valeyrie-Allanore[3], K. Razazi[1,2], G. Carteaux[1,2], P. Wolkenstein[3], O. Chosidow[3], C. Brun-Buisson[1,2], A. Mekontso Dessap[1,2], N. de Prost[1,2]

Variables	All (n=238)	No RRT (n=216)	RRT (n=22)	p
ICU admission	81 (34.0)	59 (27.3)	22 (100.0)	<0.0001
Duration of hospital stay, d	14 [9-23]	14 [9-23]	13 [7-27]	0.93
Maximal detached BSA, %	20 [5.7-45]	20 [5-35]	70 [33-86]	<0.0001
≤10% (SJS)	83 (34.8)	82 (38.0)	1 (4.4)	<0.0001
11-30% (overlap syndrome)	76 (31.9)	72 (33.3)	4 (18.2)	
31-100% (TEN)	79 (33.2)	62 (28.7)	17 (77.3)	
Shock	64 (26.8)	43 (19.9)	21 (95.4)	<0.0001
Mechanical ventilation	69 (28.9)	48 (22.2)	21 (95.4)	<0.0001
Bloodstream infection	75 (31.5)	64 (29.6)	11 (50)	0.05
Antibiotic treatment	145 (60.9)	124 (57.4)	21 (95.4)	0.0005
Adjuvant therapies				
Cyclosporine	78 (32.7)	75 (34.7)	3 (13.6)	0.044
Immunoglobulins	38 (15.9)	36 (16.6)	2 (9.0)	0.35
In-hospital mortality	37 (15.5)	19 (8. 8)	18 (81.8)	<0.0001



L a dialyse est un facteur de gravite et n'améliore pas le pronostic

Papo M, Br J Dermatol. 2017 May;176(5):1370-1372

centre de référence maladies rares

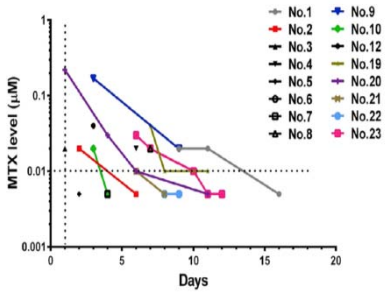
Methotrexate-induced epidermal necrosis: A case series of 24 patients

Ting-Jui Chen, MD,[a,b] Wen-Hung Chung, MD, PhD,[c,d] Chun-Bing Chen, MD,[c,d] Rosaline Chung-Yee Hui, MD, PhD,[c,d] Yu-Huei Huang, MD,[c,d] Yueh-Tsung Lu, MD,[c] Chang-Wei Wang, PhD,[c] Kuo-Hsien Wang, MD,[b] Li-Cheng Yang, MD,[c] and Shuen-Iu Hung, PhD[e]
Taipei, Linkou, Keelung, and Taoyuan, Taiwan

JAAD

Table II. Prognostic factors for survival of methotrexate-induced skin necrosis

	Deceased cases (n = 4)	Surviving cases (n = 20)	*P* value	Odds ratio (95% CI)
Age, y (mean ± SD)	71.8 ± 3.0	64.7 ± 11.3	.38	—
Sex, male/female	1/3	12/8	.30	—
Dosage				—
Starting dose, mg/week (mean ± SD)	10.6 ± 5.2	12.8 ± 3.3	.33	
Slow titration upward, n (%)	2 (50.0)	7 (35.0)	.49	—
Skin detachment (% TBSA), mean ± SD	45.0 ± 8.7	30.4 ± 4.8	.17	—
Albumin plasma level (g/dL), mean ± SD	2.0 ± 0.1	2.9 ± 0.6	.40	—
Renal function				—
eGFR, mL/min (mean ± SEM)	22.1 ± 2.6	50.9 ± 7.0	<.001	
Severe renal diseases (eGFR <30), n (%)	4 (100)	5 (25.0)	.012	25.4 (1.17-551)
WBC count (cells/μL), mean ± SEM	830 ± 370	3980 ± 690	<.001	—
WBC <1000/μL, n (%)	3 (75.0)	2 (10.0)	.018	27.0 (1.83-399)
Hemoglobin (g/dL)	10.5 ± 1.53	10.6 ± 0.52	.93	—
Hemoglobin <10, n (%)	2 (50.0)	10 (50.0)	1	—
Platelet count (1000/μL)	98.8 ± 17.8	149.2 ± 24.5	.38	—
Platelet count <150,000/μL, n (%)	4 (100)	12 (60.0)	.26	
SCORTEN criteria, n (%)				
Age ≥40 y	4 (100)	20 (100)	1	
Cancer/hematologic malignancy	2 (50)	3 (15)	.18	
Heart rate ≥120 beats/min	1 (25)	2 (10)	.44	
Skin detachment ≥10% TBSA	4 (100)	15 (75)	.54	
Serum BUN >10 mmol/L	4 (100)	8 (40)	.09	
Serum bicarbonate <20 mmol/L	0	0	1	
Serum glucose >14 mmol/L	0	1 (5)	1	



Une insuffisance rénale et un retard dans l'élimination du MTX sont des FDR de MEN

Chen et al, J Am Acad Dermatol. 2017 Aug;77(2):247-255

53

SJS/TEN
PRONOSTIC-SEQUELLES

centre de référence maladies rares

- Atteinte oculaire: Fonctionnelle +++
  = 65-89 % de séquelles/ RISQUE DE CECITE
  - ✓ Kératites, ulceres cornéens
  - ✓ Symblépharons.synechies
  - ✓ Métaplasie malpighienne conjonctive ou cornée.
  - ✓ Cils dystrophiques.

- Attention séquelles cutanées:70% des cas
  - ✓ si infection herpétique +++
  - ✓ Cicatrices rétractiles / dépigmentations /hyperpigmentations
  - ✓ Eruption de naevi

- Autres séquelles
  - ✓ Psychiatriques (92% des cas, Sd de stress post traumatique)
  - ✓ Pulmonaire (BPCO, IRCO), trouble diffusion
  - ✓ Gynécologique (synéchies, adénose vaginale)
  - ✓ Dentaire (déchaussement, gingivite)

Morales et al ,J Am Ohtalm, 2010
Duong TA et al, BJD, 2018

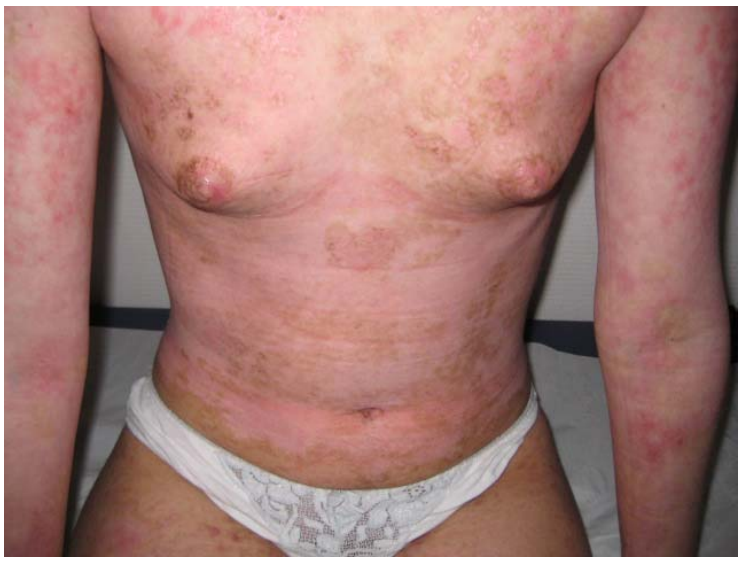
54

SEQUELLES

Expérience du CCR2A 01/2009-05/2012

Séquelles	N=17	Cut	Ophtal	Psy	Gyn	Pulm	Stoma	Neuro	Uro
Sd Lyell	17 11F/ 6H	12/17	10/17	5/17	0/11	2/17	5/17	1/17	1/17

55



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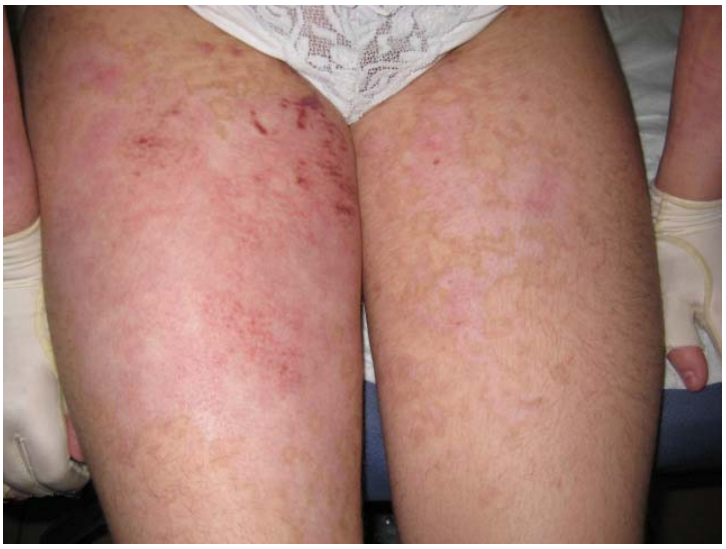
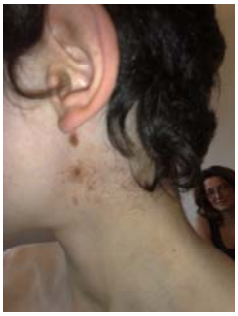
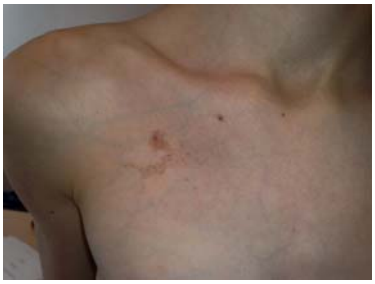
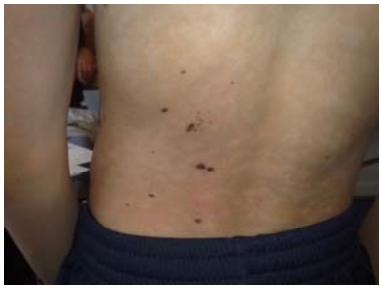


57

Naevi







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SJS/TEN

TRAITEMENT

Arrêter le médicament +++

→ pronostic moins grave (baisse de la mortalité) si arrêt précoce et ½ vie d'élimination du médicament < 24h.

Au delà de 2 mois de prise: Non imputable

Garcia-Doval I et al. Arch dermatol, 2000

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SJS/TEN

TRAITEMENT SYMPTOMATIQUE LOCAL

- **Cutané:** laisser épiderme nécrosé en place +/- pansements gras sur zones décollées associés à Flammazine/vaseline
  - Allogreffe cutanée ou xénogreffe
  - Hydrocellulaire
  - Aquacel Ag
- **Oeil** : Corticoides locaux, Vitabact/4h, méthylcellulose/2h, décoller les synéchies. Anneaux corneens+++
  - Membrane amniotique
  - Immunosupresseurs? discuter
  - Greffe cornéenne: plutot non
- **Muqueuse génitale**: Vaseline/ Dermocorticoides pour traiter adénose vaginale/Conformateur
- **ORL:**Emollients/antimycosique

Huang SH. Burns,2008
Hszu et al ,Cornea, 2012
Kaser et al, Rev Obste Gynecol,2013

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SJS/TEN
TRAITEMENT SPECIFIQUE

centre de référence maladies rares

des essais mais pas beaucoup de certitude

1. **Corticoides**
2. **Ig IV**
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4. **Dialyse:**
5. **Thalidomide** = non
6. **GCSF**
7. **N acétylcystéine**
8. Anti TNF alpha
9. Cyclosporine

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Pediatric Dermatology Vol. 31 No. 6 664–669, 2014

Mycoplasma-Associated Stevens–Johnson Syndrome in Children: Retrospective Review of Patients Managed With or Without Intravenous Immunoglobulin, Systemic Corticosteroids, or a Combination of Therapies

Jusleen Ahluwalia, B.A.,* Joy Wan, M.D.,† Diana H. Lee, M.D., Ph.D.,‡ James Treat, M.D.,* and Albert C. Yan, M.D.*

Markers of baseline disease characteristics	IVIG and corticosteroids ($n = 3$)	IVIG alone ($n = 3$)	Supportive therapy ($n = 3$)	CS alone ($n = 1$)	IVIG + CS vs IVIG – CS p-Value	IVIG – CS vs supportive therapy p-Value
Days between onset of rash or mucosal involvement and hospitalization, median	2 (2–4)	1 (1–2)	5 (3–8)	7	0.20*	0.10*
Mucosal involvement, %						
Oral	100	100	100	100		
Ocular	67	100	67	100		
Genital	33	0	33	100	>0.99†	>0.99†
Number of febrile days before hospitalization, median (range)	4 (4–8)	5 (1–7)	1 (1–2)	7	>0.99*	0.40*
Proxies of disease severity						
Length of stay after initiation of therapy in days, median (range)	7 (7–17)	15 (11–15)	8 (3–11)	3	0.70*	0.07*
Number of febrile days after initiation of therapy, median (range)	0 (0–2)	2 (2–3)	0 (0–3)	0	0.20*	0.36*

TABLE 5. *Post-Stevens-Johnson Syndrome (SJS) Sequelae Upon Follow-Up in the Intravenous Immunoglobulin (IVIG) and Non-IVIG Groups*

Post-SJS sequelae	IVIG group ($n = 5$), n (%)	Non-IVIG group ($n = 3$), n (%)
Blurred vision	1 (20)	1 (33)
Epiphora	2 (40)	0 (0)
Bronchiectasis	1 (20)	0 (0)
Tachycardia	1 (20)	0 (0)
Rhinorrhea	1 (20)	0 (0)
Otitis media	0 (0)	1 (33)
Pain		
Oral	1 (20)	0 (0)
Lumbar	0 (0)	1 (33)
Arthralgia	1 (20)	0 (0)

TABLE 3. *Comparisons of Intravenous Immunoglobulin (IVIG) and Non-IVIG Groups ($N = 10$)*

Markers of baseline disease characteristics	IVIG group ($n = 6$)	Non-IVIG group ($n = 4$)	p-Value
Days between onset of rash or mucosal involvement and hospitalization, median (range)	2 (1–4)	6 (3–8)	0.02*
Mucosal involvement, %			
Oral	100	100	
Ocular	83	75	
Genital	17	25	>0.99†
Number of febrile days before hospitalization, median (range)	4.5 (1–8)	1.5 (1–7)	0.26*
Proxies of disease severity, median (range)			
Length of stay after initiation of therapy in days	13 (7–17)	5.5 (3–11)	0.11*
Number of febrile days after initiation of therapy	2 (0–3)	0 (0–3)	0.48*

†Fisher exact test.

Les corticoïdes semblent avoir une tendance à l'amélioration des SJS TEN à mycoplasme

Les Ig IV seules semblent délétère

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SJS/TEN
CORTICOIDES

Table 1 Baseline characteristics in cases and controls

Parameters (frequencies and percentages if not stated otherwise)	Patients with prior steroid use (n = 92)	Patients without prior steroid use (n = 321)	P-value
Disease classification			
SJS	37 (40)	150 (47)	0·07
SJS/TEN overlap	43 (47)	109 (34)	
TEN	12 (13)	62 (19)	
Sex, male	47 (51)	127 (40)	0·05
Age, years (mean ± standard deviation)	53·6 ± 18·7	49·0 ± 24·4	0·05
Liver disorders (8 missing values)	13 (14)	28 (9)	0·12
Kidney disorders (7 missing values)	19 (21)	26 (8)	< 0·01
Recent malignancy (8 missing values)	49 (55)	21 (7)	< 0·01
In-hospital development of skin reaction	25 (27)	39 (12)	< 0·01
Country			
Germany	56 (61)	167 (52)	0·31
France	22 (24)	98 (31)	
Other countries[a]	14 (15)	56 (17)	

[a]Other countries: Italy n = 32, Israel n = 20, the Netherlands n = 10, Austria n = 8. SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

La maladie dure plus longtemps sous corticoides et il ya une surmortalite en analyse univariée non retourvé en univarié

Resultats discordants

Lee et al. BJD, 2012

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SJS/TEN
TRAITEMENT SPECIFIQUE

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des essais mais pas beaucoup de certitude

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7. **N acétylcystéine**
8. Anti TNF alpha
9. Cyclosporine

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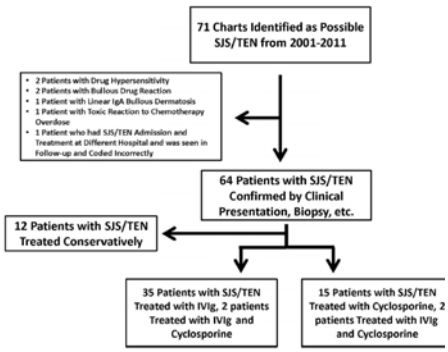
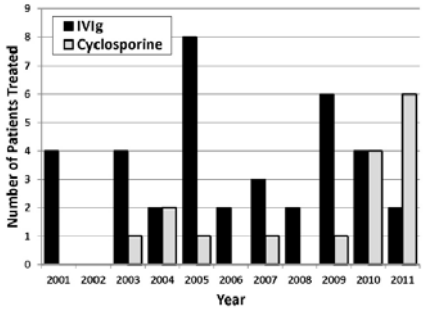
Retrospective review of Stevens-Johnson syndrome/ toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine





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Retrospective review of Stevens-Johnson syndrome/ toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine

	IVIg (N = 37)	Cyclosporine (N = 17)	*P* value
Average age, y	54.6, SD 20.6	53.2, SD 22.2	.83
Male sex	48.6% (N = 18)	41.2% (N = 7)	.61
Average SCORTEN on day 1	2.08, SD 1.23	1.65, SD 1.22	.24
Causative drug withdrawn within 24 h of hospital presentation	81.1% (N = 30)	64.7% (N = 11)	.19
Disease classification based on initial BSA involvement			
SJS	45.9% (N = 17)	64.7% (N = 11)	.20
SJS/TEN overlap	32.4% (N = 12)	23.5% (N = 4)	.51
TEN	21.6% (N = 8)	11.8% (N = 2)	.39
Disease classification based on maximum BSA involvement			
SJS	29.7% (N = 11)	58.8% (N = 10)	.04
SJS/TEN overlap	37.8% (N = 14)	23.5% (N = 4)	.30
TEN	32.4% (N = 12)	17.6% (N = 3)	.26
Average maximum BSA involvement	28.7%, SD 26.6%	16.3%, SD 19.6%	.06
Average time from onset of symptoms to hospital presentation, d	4.3, SD 5.9	8.2, SD 13.2	.25
Average time from admission to initiation of systemic treatment, h	50.1, SD 98.7	26.8, SD 25.3	.19
Average length of hospital stay, d	26.6, SD 28.0	16.8, SD 8.2	.06
Patients receiving corticosteroids before IVIg or cyclosporine	46% (N = 17)	47% (N = 8)	1.00
Patients with pre-existing renal dysfunction	14% (N = 5)	6% (N = 1)	.41

	No. of patients	
SCORTEN	IVIg	Cyclosporine
0	2	3
1	12	6
2	11	3
3	6	4
4	5	1
5	1	0
Predicted mortality	7.7	2.4
Observed mortality	11	1
Standardized mortality ratio	1.43 (95% CI 0.71-2.56)	0.42 (95% CI 0.11-2.32)

Rétrospectif

Confirme peu intérêts IgIV

Bénéfice cyclosporine mais peu de patient peu grave

HM peu d'effet

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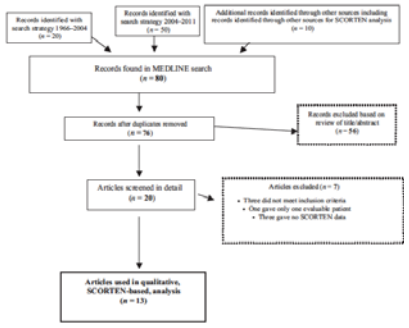
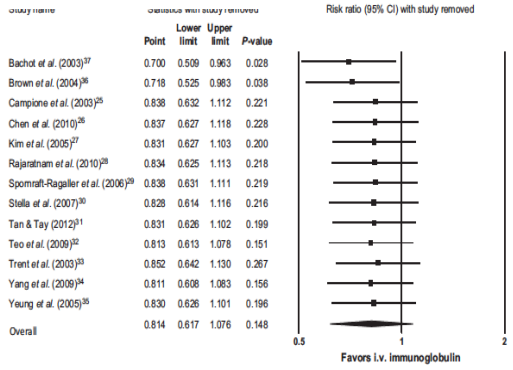
Pharmacology and therapeutics

Intravenous immunoglobulin in the treatment of Stevens–Johnson syndrome and toxic epidermal necrolysis: a meta-analysis with meta-regression of observational studies

Stacy J. Barron[1], MD, Michael T. Del Vecchio[2], MD, and Stephen C. Aronoff[2], MD





Il y a un effet des Ig IV sur la mortalité dans les SJS/TEN

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Pharmacology and therapeutics

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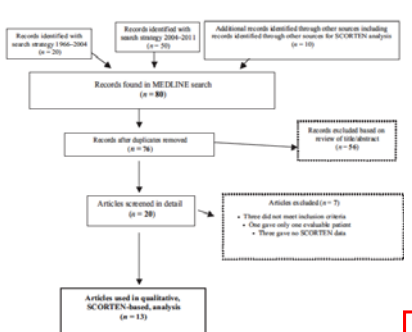
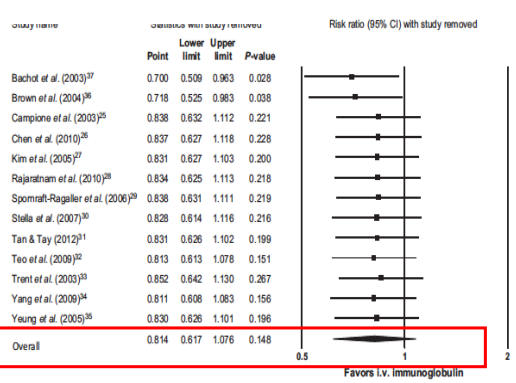




CONFIRME l'absence d'effet des IgIV sur la mortalité dans les SJSTEN

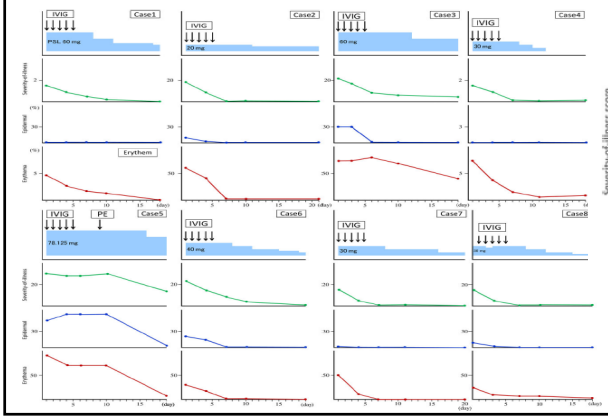
68

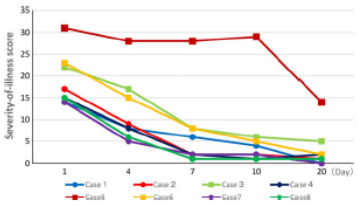
doi: 10.1111/1346-8138.12925 *Journal of Dermatology* 2015; **42**: 1–10

ORIGINAL ARTICLE

Efficacy of additional i.v. immunoglobulin to steroid therapy in Stevens–Johnson syndrome and toxic epidermal necrolysis

No.	Age (years)	Sex	Type of disease	Suspected drug	Severity-of-illness score (points)†	Extent of epidermal detachment (%)†	Extent of erythema (%)†	Lip/oral lesions†	Ophthalmic lesions†	Fever (°C)†	SCORTEN†
Case 1	51	Male	SJS	Anticonvulsants	14	0	45	Yes	Yes	35.4	1
Case 2	41	Male	SJS	None‡	17	9	60	Yes	No	35.8	1
Case 3	53	Male	TEN	Cold medicine	22	30	75	Yes	Yes	37.0	3
Case 4	78	Male	SJS	Supplements	15	0	75	Yes	Yes	36.4	1
Case 5	65	Female	TEN	Allopurinol	31	50	90	Yes	Yes	36.8	3
Case 6	52	Male	TEN	Fenofibrate, allopurinol	23	18	30	Yes	Yes	36.6	2
Case 7	67	Female	SJS	Antibiotics, cold medicine	14	0.1	50	Yes	Yes	36.0	1
Case 8	57	Male	SJS	Carbamazepine	15	9	25	Yes	Yes	37.2	1





8 patients
7/8 efficace

discutable

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SJS/TEN

TRAITEMENT SPECIFIQUE

des essais mais pas beaucoup de certitude

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8. Anti TNF alpha
9. Cyclosporine

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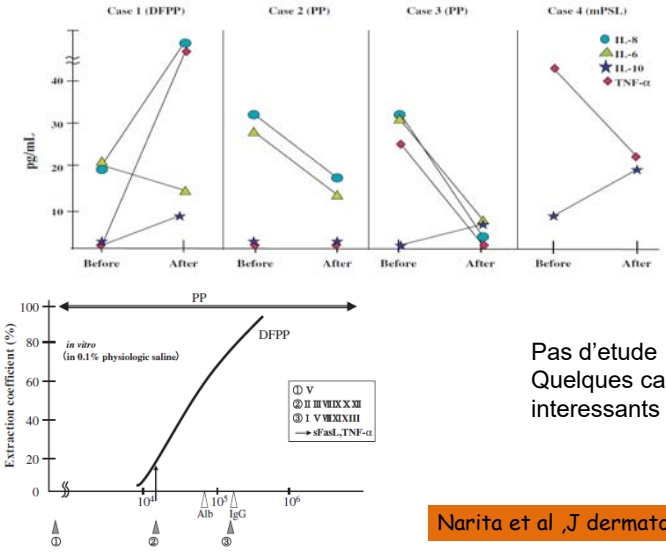
SJS/TEN
PLASMAPHERESE



Pas d'etude
Quelques cas interessants

Narita et al ,J dermatol, 2011

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SJS/TEN
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SJS/TEN
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SJS/TEN
GCSF

Table 2 Patient demographics.

Patient	Age	Comorbidities/ initial presentation	Sex	TBSA	Medication	IVIG (days)	IVC (days)	G-CSF (days)	Skin stage	Mucosal involvement	SCORTEN/Apache II/MOD/predicted mortality	Complications	Days in hospital	Follow up (months)
1	61	Epilepsy/ Addisonian-like crisis	F	95%	Phenytoin, phenobarbitone, teichoplanin	30	17	2	3	Oral, eyes	5/14/9/90%	–	32	24
2	47	Arthritis, hypertension, gout/rash	M	50%	Sulfasalazine	9	9	3	1 & 2	Oral	5/11/6/90%	Chest sepsis	14	24
3	50	Single kidney/rash	F	60%	Teicoplanin, gentamycin, acyclovir	27	7 (renal impairment)	2	2	Eyes, genitalia	5/13/7/90%	Chest sepsis	32	18
4	35	Epilepsy, psoriasis/rash	F	95%	carbamazapine	3	10	1	1 & 2	Oral, genitalia	2/6/5/12.1%	Chest sepsis	12	16
5	55	SLE	F	80%	Prednisolone, hydroxychloroquine	11	11	–	1, 2 & 3	Oral, eyes, genitalia	2/13/0/12.1%	–	20	12

Nombreux cas cliniques plutôt utilisé en association sauf l'etude princeps

Notre experience sur 20 cas traités deux deces (scorten jusqu'à 5) mais d'une comorbidite

Abela et al, Jof plastic surgery, 2014
Chapman et al , BJD, 2010

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SJS/TEN
TRAITEMENT SPECIFIQUE

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SJS/TEN TRAITEMENT
ANTI TNFa

- Nombreux cas rapportent efficacité
- Rationnel:
  - augmentation TNFa dans sérum (montré dans trois cas)
  - Infliximab et autres anti TNF

Mess et al, JEADV, 2007

  - Lutte contre effet apoptique du TNF
  - Attention au risque infectieux
  - Mais aussi cas de SJS/NET sous traitement

centre de référence maladies rares

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Etanercept therapy for toxic epidermal necrolysis

Andrea Paradisi, MD,[a] Damiano Abeni, MD,[a] Fabio Bergamo, MD,[b] Francesco Ricci, MD,[c]
Dario Didona, MD,[d] and Biagio Didona, MD[b]
Rome, Italy

Table II. Patients with toxic epidermal necrolysis treated with etanercept: Sex, age, comorbidities, culprit drugs, and time to healing

	Patient no.									
	1	2	3	4	5	6	7	8	9	10
Gender	F	M	F	F	M	M	F	F	M	F
Age, y	57	70	28	62	73	78	72	50	71	55
Culprit drug	Carbamazepine	Ofloxacin	Lansoprazole, azathioprine	Methylprednisolone	Ciprofloxacin	Carbamazepine	Phytotherapy product	Carbamazepine	Carbamazepine	Diclofenac
Time to healing (days)	12	8	8	12	8	7	8	20	9	9
Comorbidities	Cerebral neoplasm	Bronchopneumonia	Systemic lupus erythematosus	Pemphigus vulgaris	Bronchopneumonia	Cerebral neoplasm	—	Cerebral metastases (breast cancer)	Intracranial hemorrhage (head trauma)	Periarthritis

F, Female; *M*, male.

SCORTEN components	1	2	3	4	5	6	7	8	9	10
Age >40 y	1	1	0	1	1	1	1	1	1	1
Heart rate >120 beats/min	1	0	1	1	1	1	0	0	0	0
Cancer or hematologic malignancy	1	0	0	0	0	1	0	1	0	0
>10% body surface area involvement	1	1	1	1	1	1	1	1	1	1
Serum urea level >10 mmol/L	1	1	0	0	0	0	0	1	0	0
Serum bicarbonate level <20 mmol/L	1	0	0	0	0	0	0	1	0	0
Serum glucose level >14 mmol/L	0	0	0	0	1	1	0	1	0	1
SCORTEN score	6	3	2	3	4	5	2	6	2	3

10 cas

Délai par rapport début non précisé
Adressé dans les 72h au centre

Délai prise médicament non connu

50 mg ETERNACEPT une fois

WH chung, JID, 2017

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Etanercept therapy for toxic epidermal necrolysis

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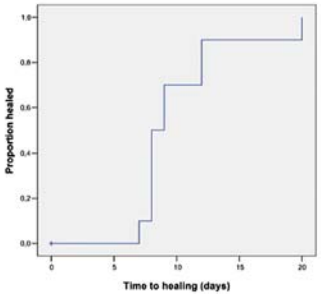

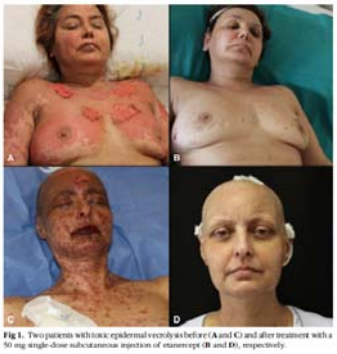

Fig 1. Two patients with toxic epidermal necrolysis before (A and C) and after treatment with a 50 mg single-dose subcutaneous injection of etanercept (B and D), respectively.

10 réponses
48,6% décès attendu/0 au total
Délai cicatrisation 8,5j moyenne mais 5-20j

Donc efficacité potentielle à confirmer

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SJS/TEN TRAITEMENT
ANTI TNFa

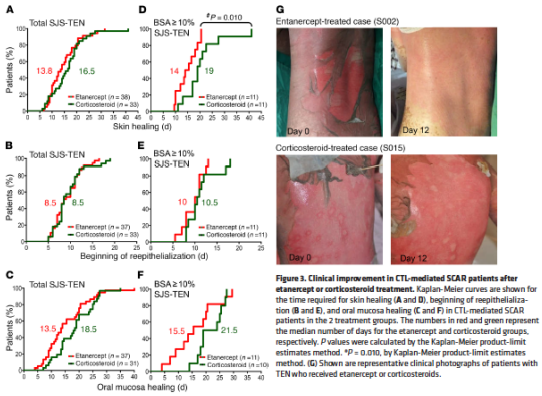

Figure 3. Clinical improvement in CTL-mediated SCAR patients after etanercept or corticosteroid treatment. Kaplan-Meier curves are shown for the time required for skin healing (**A** and **D**), beginning of reepithelialization (**B** and **E**), and oral mucosa healing (**C** and **F**) in CTL-mediated SCAR patients in the 2 treatment groups. The numbers in red and green represent the median number of days for the etanercept and corticosteroid groups, respectively. *P* values were calculated by the Kaplan-Meier product-limit estimates method. *$P = 0.010$, by Kaplan-Meier product-limit estimates method. (**G**) Shown are representative clinical photographs of patients with TEN who received etanercept or corticosteroids.

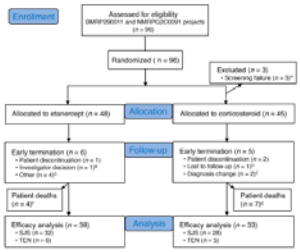

Table 4. Observed mortality rates for patients with CTL-mediated SCARs in the etanercept and corticosteroid treatment groups

	Etanercept		Corticosteroid[a]		OR (95% CI)	*P* value
	n	%	*n*	%		
Death	4	8.3	7	16.3	0.47 (0.13–1.72)	0.266
Survival	44		36			
Total	48		43			

[a]Reference group. *P* values are based on an unconditional *z*-pooled test.

Il existe une amelioration de la rapidite de la cicatrisation mais pas d'effet sur la mortalite

CHUNG Wh et al, JCI ,2018

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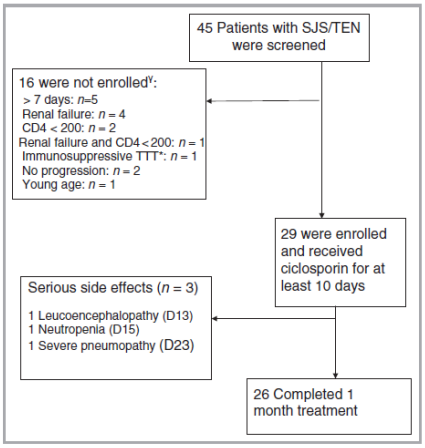
SJS/TEN TRAITEMENT
CYCLOSPORINE



	Ciclosporin (n = 29)	IVIG (n = 34)
Age (years), mean ± SD	34·2 ± 14·1	47 ± 21
BSA, day 0 (%), mean ± SD	12 ± 8	19 ± 16
SCORTEN (mean)	1·27	2·17
Predicted deaths	2·75	8
Observed deaths	0	11
Delay between onset and admission (days), mean ± SD	2·8 ± 1·8	4·1 ± 2·0
Progression, n (%)	11 (38)	22 (65)
Stabilization, n (%)	18 (62)	12 (35)

BSA, affected body surface area.

Pas d'effet

ALLANORE et al, BJD, 2018

AREVALO et al. J Trauma, 2000

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Cyclosporine

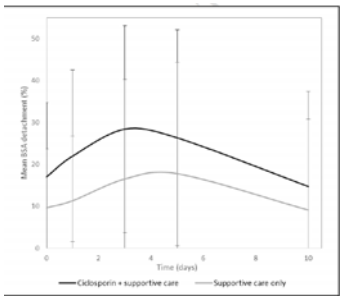
Table 2 – Baseline characteristics of patients not receiving or receiving ciclosporin — after propensity-score matching

	Not receiving ciclosporin N=37	Receiving ciclosporin N=37	Absolute standardized difference	p-value
Age, years	46 [36-63]	49 [34-60]	0.07	0.78
Female gender, n (%)	19 (51.3)	19 (51.3)	0	1.0
Calendar year	2009 [2006-2012]	2009 [2008-2013]	0.14	0.93
Time between probable onset and hospitalisation	3 [2-7]	4 [3-6]	0.13	0.28
Past history of, n (%)				
- lupus erythematosus	1 (2.7)	1 (2.7)	0	1.0
- malignancy	4 (10.8)	4 (10.8)	0	1.0
- HIV infection	7 (18.9)	6 (16.2)	0.07	0.76
Use of immunosuppresive therapy at admission *, n (%)	3 (8.1)	2 (5.4)	0.10	1.0
Epidermal detachment, BSA %	5 [1-15]	10 [1-20]	0.09	0.34
Heart rate ≥ 120/min, n (%)	5 (13.5)	7 (18.9)	0.15	0.75
Serum urea level > 10 mmol/l, n (%)	2 (5.4)	3 (8.1)	0.11	1.0
Serum bicarbonate level < 20 mmol/l, n (%)	1 (2.7)	2 (5.1)	0.14	0.49
Serum glucose level > 14 mmol/l, n (%)	2 (5.4)	3 (8.1)	0.11	1.0
SCORTEN at admission	1 [1-2]	1 [1-2]	0.17	0.65
Expected deaths using SCORTEN calculation, n (%)	3 (8.1)	3 (8.1)	0	1.0
Maximal temperature, °C	37.9 [37.0.-39.1]	38.0 [37.4-38.9]	0.08	0.51
Propensity score	0.49 [0.30-0.63]	0.48 [0.30-0.63]	0.004	0.98

BSA, body surface area; SCORTEN, SCORe of Toxic Epidermal Necrosis
Data are median (interquartile range) unless indicated
* for the underlying condition (e.g., glucocorticoids or azathioprine for lupus erythematosus)

	Before propensity score matching N=174			After propensity score matching N=74		
	sHR	95% CI	p-value	sHR	95% CI	p-value
Start of cutaneous re-epithelialization on day 5						
Crude analysis	0.90	0.95–1.25	0.54	0.76	0.48-1.19	0.23
Multivariable analysis*	0.85	0.61-1.18	0.33	0.79	0.51-1.24	0.31
Multivariable analysis**	-	-	-	0.75	0.48-1.18	0.22
Complete mucosal re-epithelialization on day 10						
Crude analysis	0.58	0.35-0.95	0.03	0.49	0.24-1.03	0.07
Multivariable analysis***	0.70	0.44-1.12	0.14	0.56	0.29-1.08	0.08
Multivariable analysis**	-	-	-	0.48	0.23-1.02	0.06
	HR	95% CI	p-value	HR	95% CI	p-value
Overall mortality						
Crude analyses	0.43	0.15-1.24	0.12	1.48	0.25-8.88	0.67
Multivariable analyses****	0.68	0.22-2.09	0.51	1.58	0.17-14.6	0.69
Multivariable analyses**	-	-	-	1.54	0.26-9.28	0.64

HR, hazard ratio sHR, sub-distribution hazard ratio 95% CI, 95% confidence interval



Pas d'efficacite de la cyclosporine dans cette large étude

Poizeau et al , BJD, 2018

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SJS/TEN
TRAITEMENT SPECIFIQUE

centre de référence maladies rares

des essais mais pas beaucoup de certitude

1. **Corticoides/ DISCUTE**
2. **Ig IV NON**
3. **Plasmaphérèse ?**
4. **Dialyse ?**
5. **Thalidomide** = non
6. **GCSF discute**
7. **N acétylcystéine NON**
8. Anti TNF alpha
9. Cyclosporine discuté

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Conclusion

- Le syndrome de LYELL est une pathologie complexe et grave
- Physiopathologie non élucidé notamment la raison de la sévérité
- Traitement peu codifie
- Nécessité d'une prise en charge dans des centres spécialisés

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