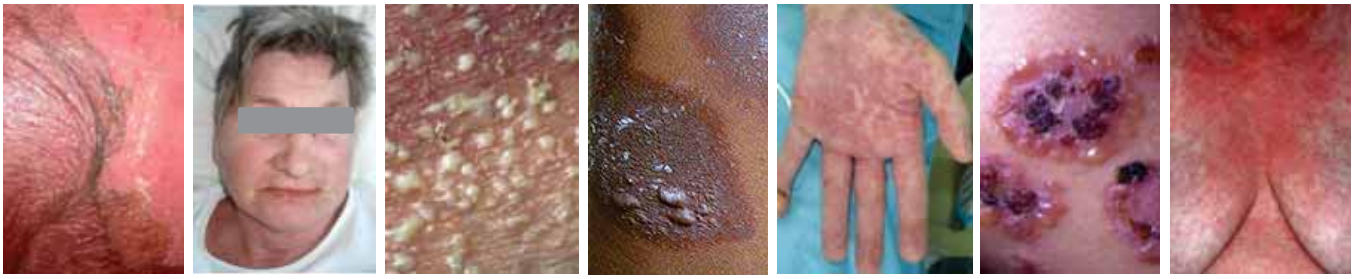


Toxidermies Sévères

Prise en charge

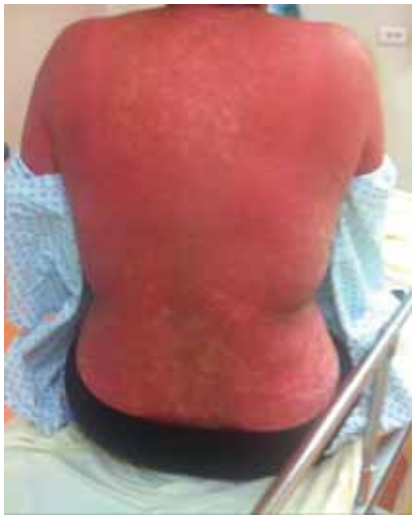
Dr Benoît BEN SAID
Centre de REFERENCE
Dermatoses Bulleuses Toxiques
UF Toxidermie Sévère
PAM medecine/Dermatologie
CHU GH Centre LYON

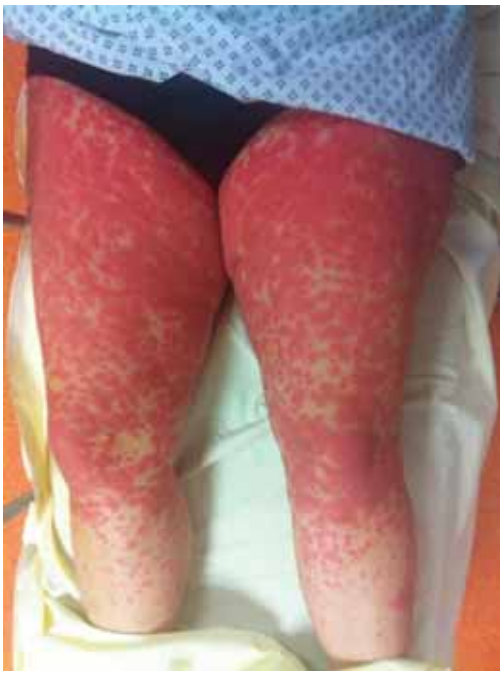
Histoire de la maladie

- 59 ans
- **Atcd** : Allergie au TOTAPEN
- 23/07/17 : découverte lésion cérébelleuse sous tentoriel responsable HTIC nécessitant une ventriculo-cisternostomie
- 05/08/17: exérèse de la lésion (médulloblastome multifocale desmoplastique)
  - Traitement par radiotherapie entre temps
- 11/08/17: dérivation ventriculo-peritoneale
- 11/09/2017 désunion de la cicatrice nécéssitant une reprise chirurgicale avec prélèvement retrouvant E cloacae et staphyloccus Aureus
- La patiente est mise sous MERONEME VANCOMYCINE et OFLOCET
- Arret VANCOMYCINE et OFLOCET le 06/10/17 et relais par MERONEME/FOSFOMYCINE

Histoire de la maladie

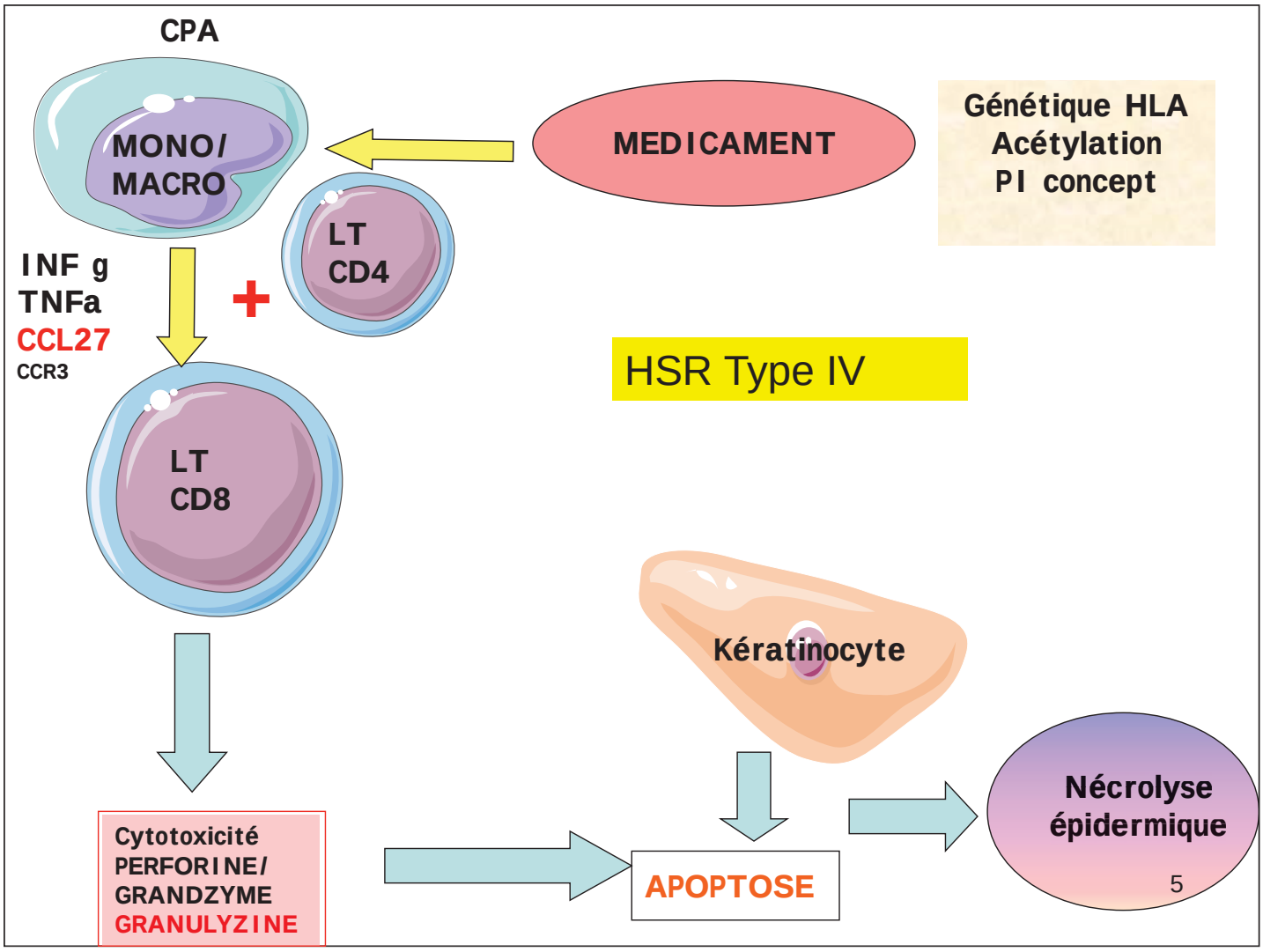
- Le 6/10/2017 survenue d'un tableau comprenant
  - Eruption fébrile à 40





Plan

1. Préciser le type de toxidermie
   - Clinique
   - Epidémiologie/Génétique
   - Physiopathologie
2. Préciser la Gravité
3. Enquête étiologique
4. Prise en charge thérapeutique
5. Prise en charge à distance



centre de référence
maladies rares

Plan

1. Préciser le type de toxidermie
   - Clinique
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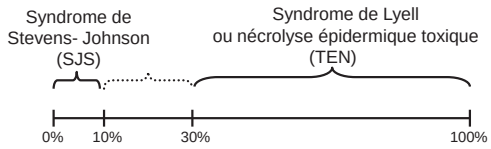
Nécrolyse épidermique

Une maladie unique avec des degrés divers de sévérité



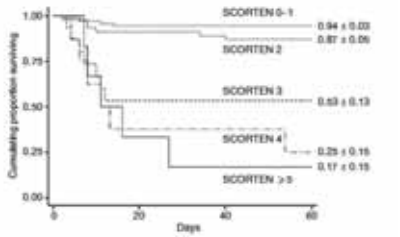
- **Physiopathologie:** apoptose kératinocytaire médiée par les LT
- **Incidence:** 1 à 3 cas/million/an.
- **Délai** : 1 à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre
  - Erosions muqueuses (>2 sites)
  - Décollements cutanés superficiels (S. de Nikolski +)
- **Biologie:** lymphopénie fréquente
- **Atteinte viscérale:** rénale, pulmonaire, digestive, foie
- **Histologie:** nécrolyse épidermique totale
- **Médicaments: allopurinol+++,** lamotrigine, carbamazépine, sulfamethoxazole, AINS (oxicams), nevirapine,…
- **Mortalité:** 30-35% (estimée par le SCORTEN)

Nécrolyse épidermique

Une maladie unique avec des degrés divers de sévérité

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

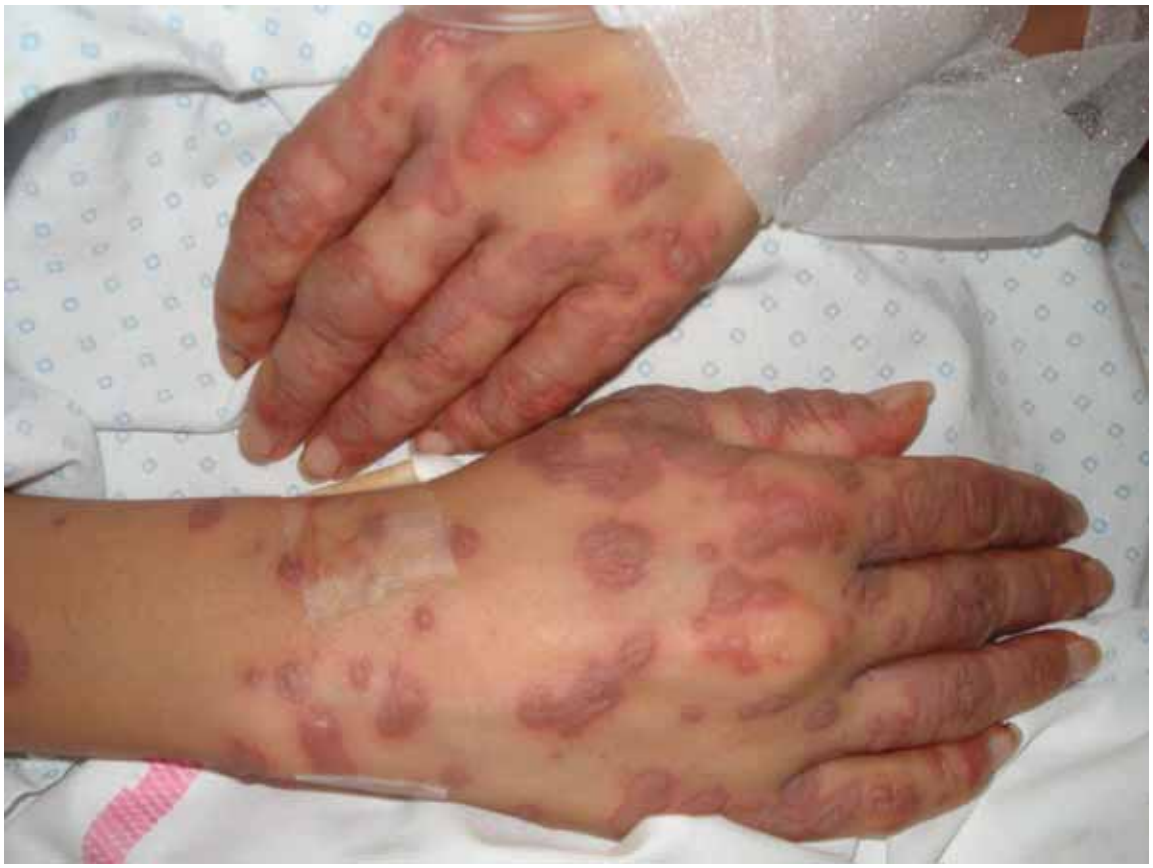
Independent prognosis factors		Weight
Age	⩾40 years	1
Malignancy	Yes	1
Body surface area detached	⩾10%	1
Tachycardia	⩾120/min	1
Serum urea	>10 mmol/l	1
Serum glucose	>14 mmol/l	1
Serum bicarbonate	<20 mmol/l	1
SCORTEN		7



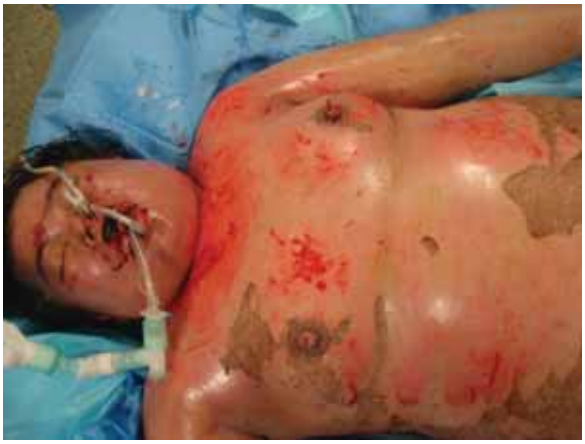
SJS/TEN
CLINIQUE

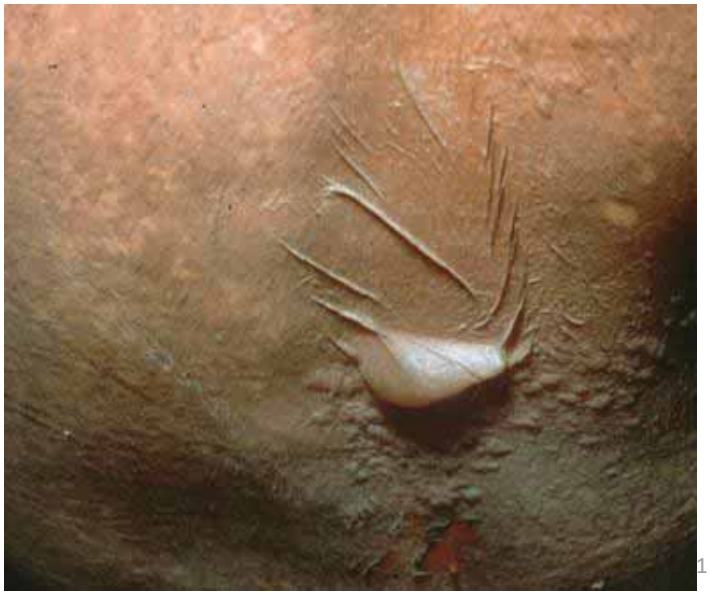
- Début symptômes peu spécifiques +++ mais aigus
  = fièvre, AEG importante, picotements oculaires
- Lésions muqueuses parfois précessives (1/3 cas)
  - Au moins 2 sites muqueux dans >80% des cas
  - 90-100% buccaux
  - Ophtalmologiques 80%
  - Genitaux
- Eruption maculo-papuleuse douloureuse du visage,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

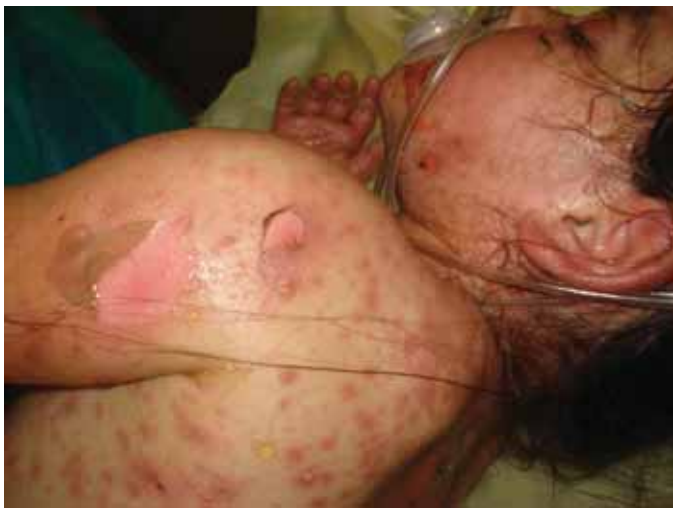
- Puis extension et décollements cutanés avec Nikolsky pendant quelques jous

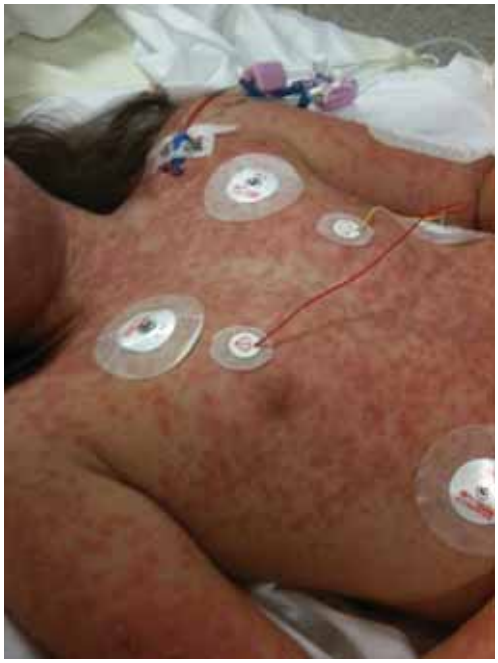


NECROLYSE EPIDERMIQUE TOXIQUE (NET)









SJS/TEN

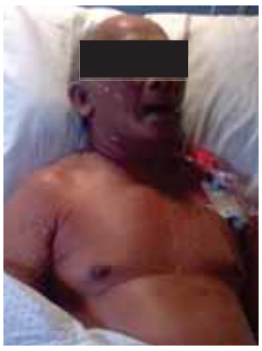
ATTEINTES EXTRA CUTANÉES

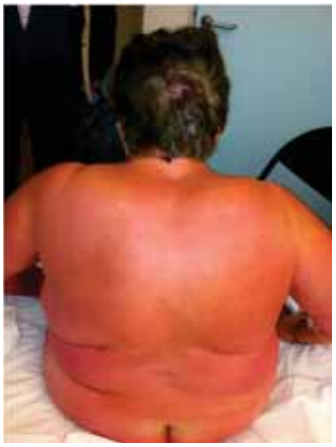
- Anomalies Hémato-biologiques
  - ✧ Anémie**,** **Neutropénie** (mauvais pronostic), lymphopénie, hypoalbuminéme, hypophosphorémie, cytolyse hépatique, pancréatite (amylasemie :salivaire)…
  - ✧ Insuffisance rénale aigue (NIA, NTIA, NTA..)
  - ✧ Auto-immunité: facteur de risque et conséquences
- Atteinte 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%)

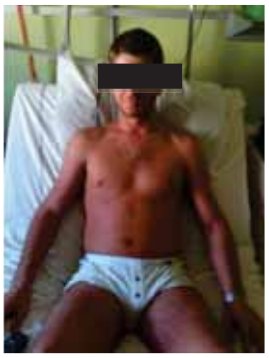
Lebargy et al. Intensive Care Med, 1997
De Prost et al , Vrit Care Med, 2014

DRESS

Drug Rash with Eosinophilia and Systemic Symptoms
Sd d'Hypersensibilité Médicamenteuse





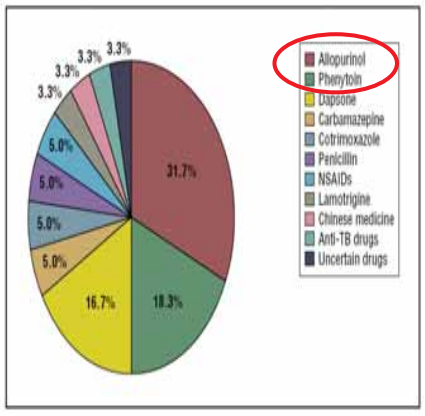


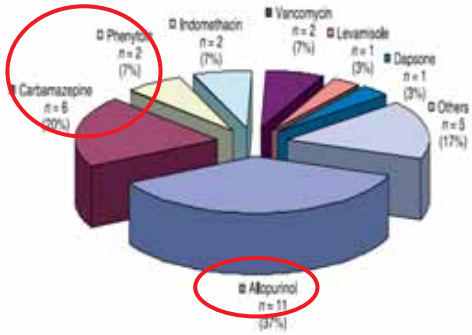
- Incidence inconnue
- Délai survenue: 3s à 3 mois après début de la prise
- Clinique:
  - AEG, T°
  - Œdème visage (périorbitaire) et cou, pharyngite précessive
  - polyADP, HPSMG
  - Evolution persistante>15 jours
- Bio:
  - Hyperéosinophilie (>1500, parfois absentes), lymphocytes hyperbasophiles, SAM
  - Réactivation virale Herpes virus (EBV, CMV, HHV6-7)
- Physiopathologie: hypersensibilité retardée médiée par les LT aux médicaments associée à des réactivation de virus latent type herpes virus
- Médicaments responsables : allopurinol,sulfamides antiépileptique, antibiotiques
- Pronostic: 10% †

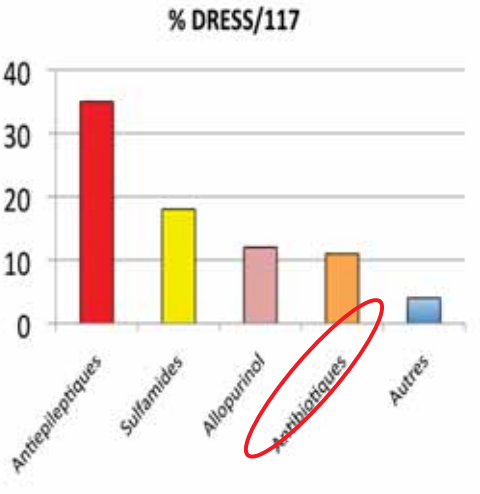
centre de référence maladies rares

DRESS

Épidémiologie-médicaments imputables







Chu et coll. JAAD, 2009
Chen et coll. Arch Derm, 2010
Allanore et Coll. Arch Derm,2011
Walsh et Coll. BJD,2012Kardaun et al , BJD,2013

DRESS

Médicaments imputables-CNR

Allopurinol	16
Fluindione	5
Amoxicilline	15
Vancomycine	20
Pristinamycine	2
Antiepileptiques	20
Deferasirox	1
Ran strontium	1
Trimetroprime	5
Verapamil	2
Imipeneme/Meroneme	8
Trimebutine	1
mequitazine	1
Lanzoprazole	2
Tazocilline/C3G	19
Targocid	1
Spiramycine	2
Clindamycine	6
salazopyrine	1
Fucidine	1
Oflocet	1
Antituberculeux	8
Xarelto	3

<u>Médicaments le plus souvent imputable</u>

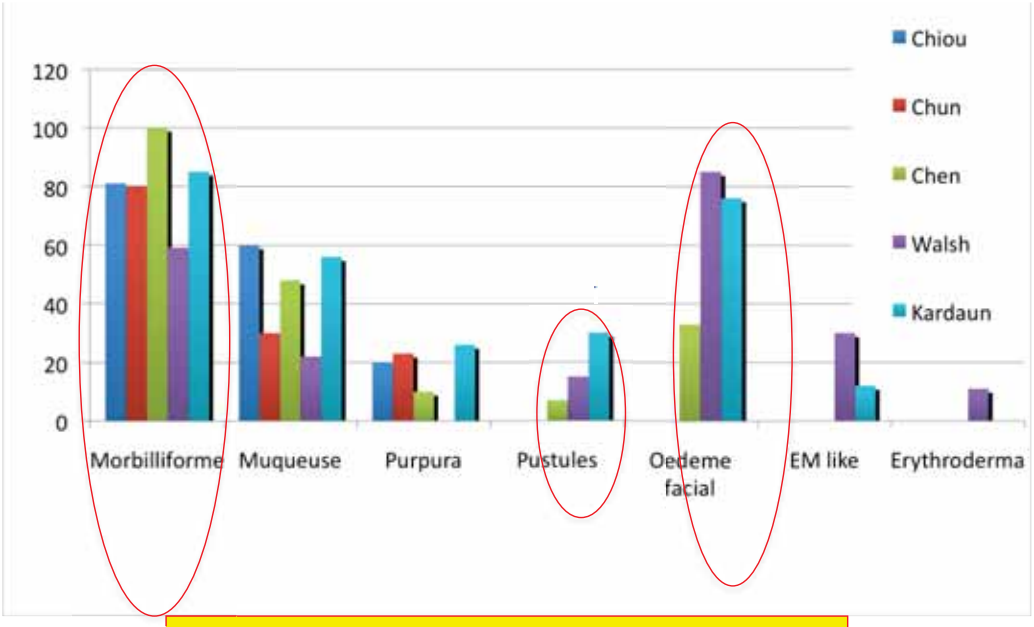
1. Amoxicilline/Betalactamines

   42/141- 30%
2. Vancomycine
3. Antiépileptique
4. Allopurinol
5. Clindamycine

N=141

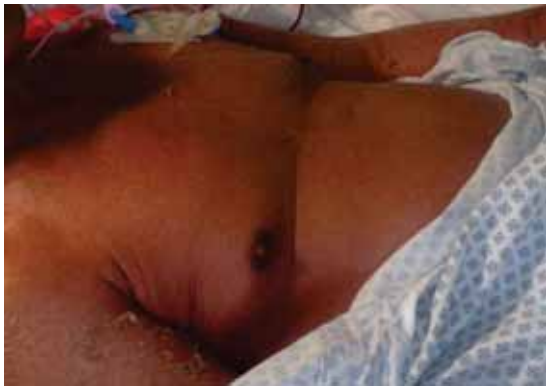
DRESS

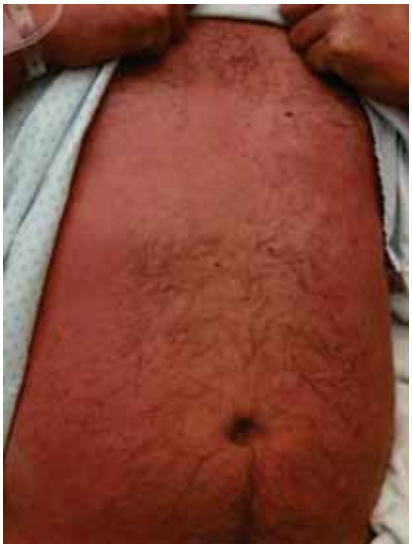
Signes cutanés



N=60
N=30
N=27
N=27
N=117

Chu et coll. JAAD, 2009
Chen et coll. Arch Derm, 2010
Chiou et coll. JEADV, 2008
Walsh et coll, BJD, 2012
Kardaun et al , BJD, 2016





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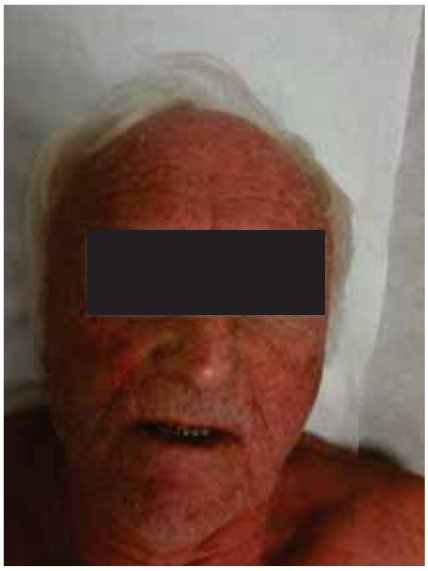

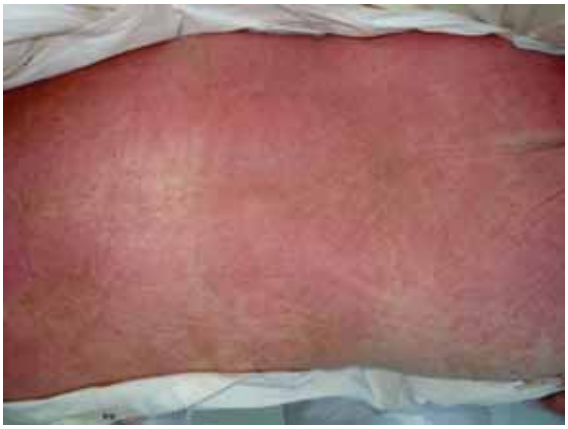

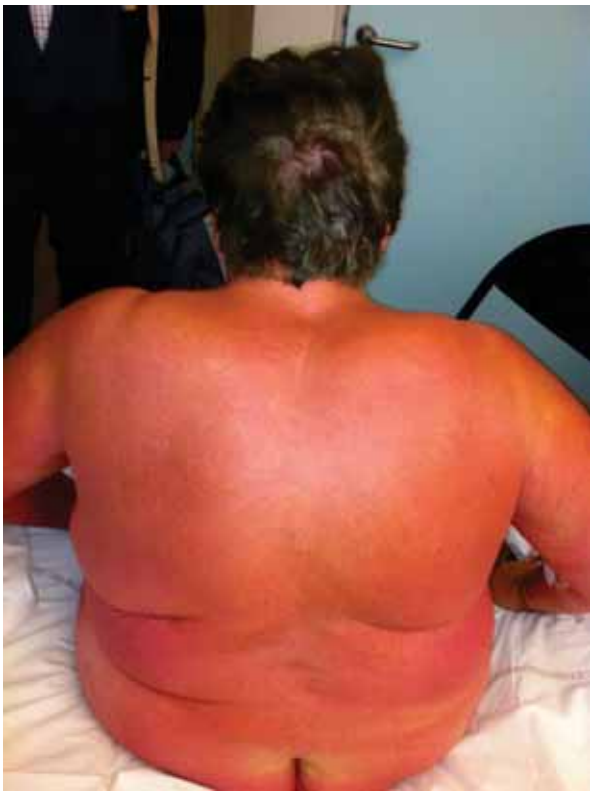

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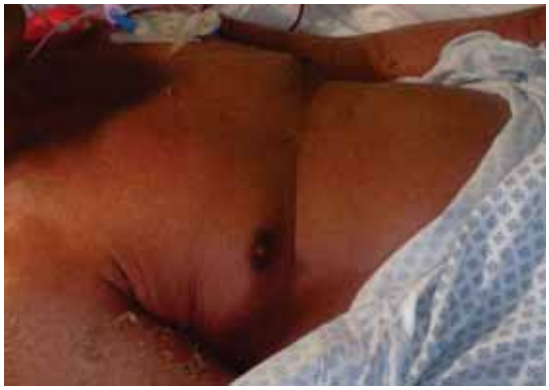
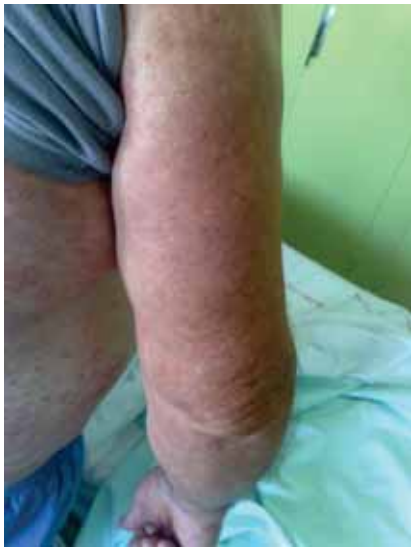
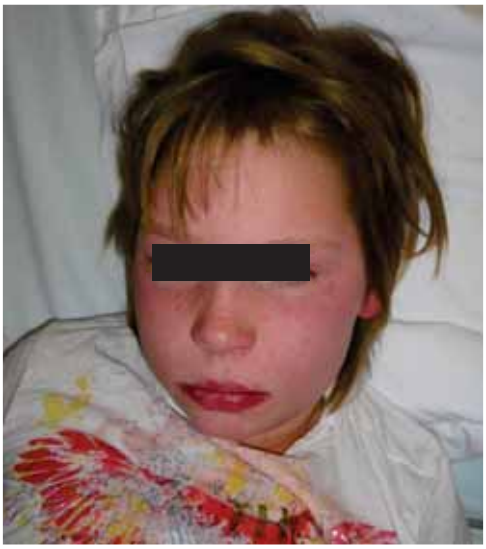
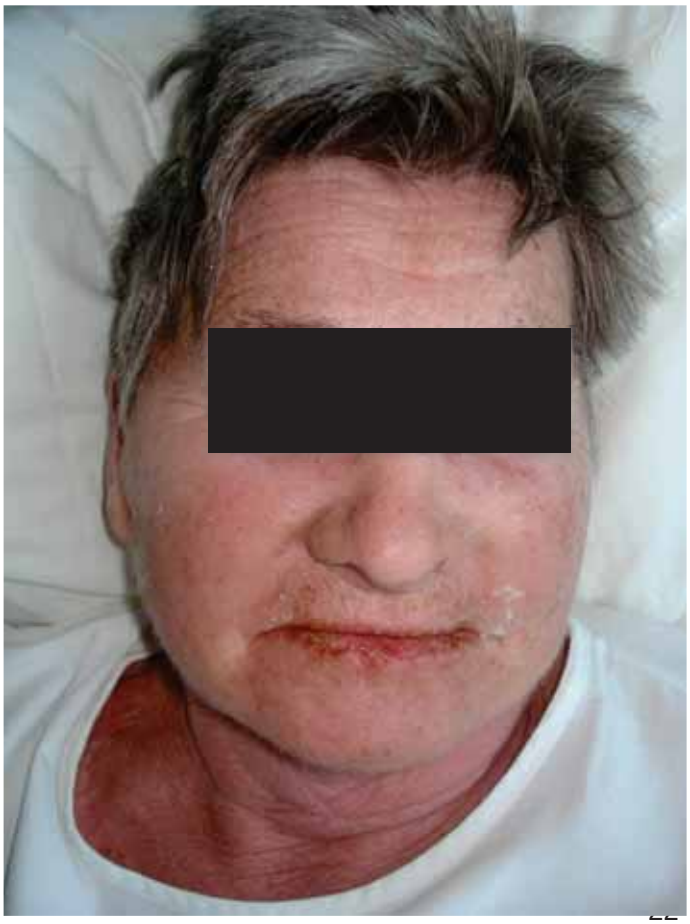
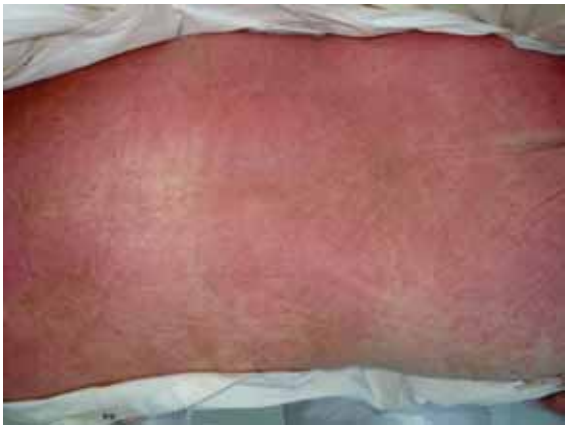




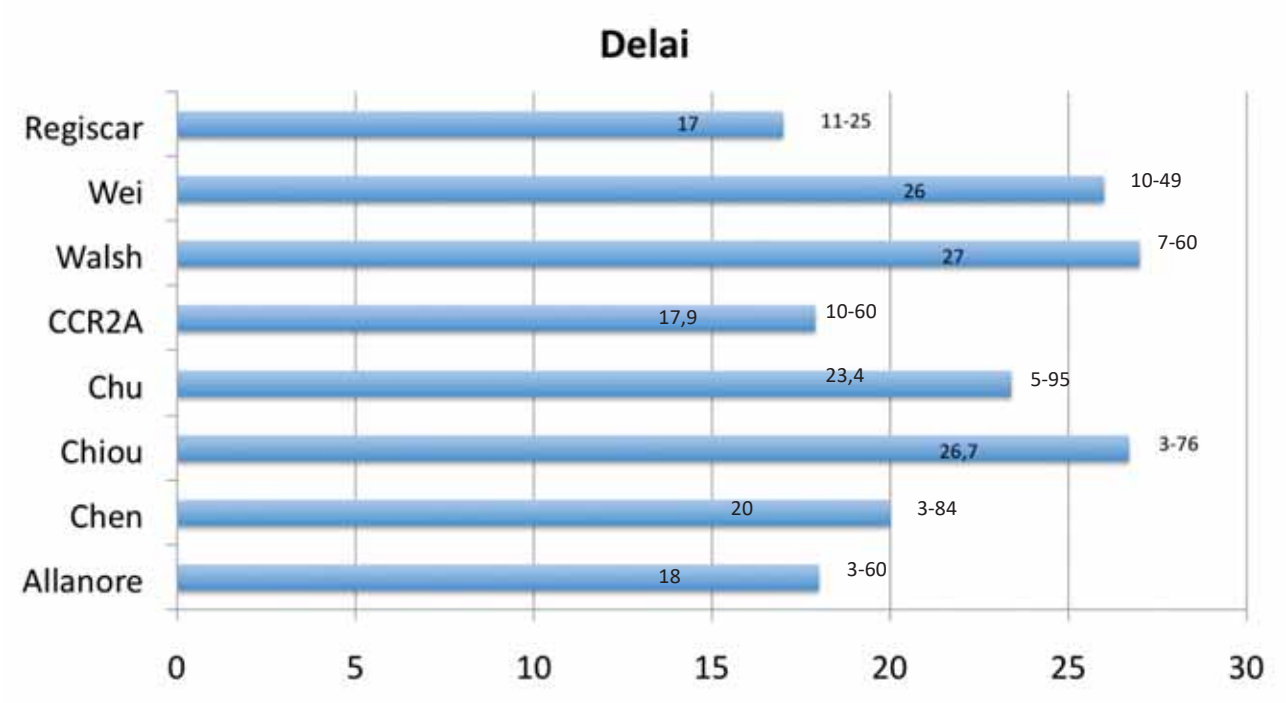
21







DRESS
Délai de survenue



centre de référence maladies rares

Diagnostic du DRESS
Score diagnostique

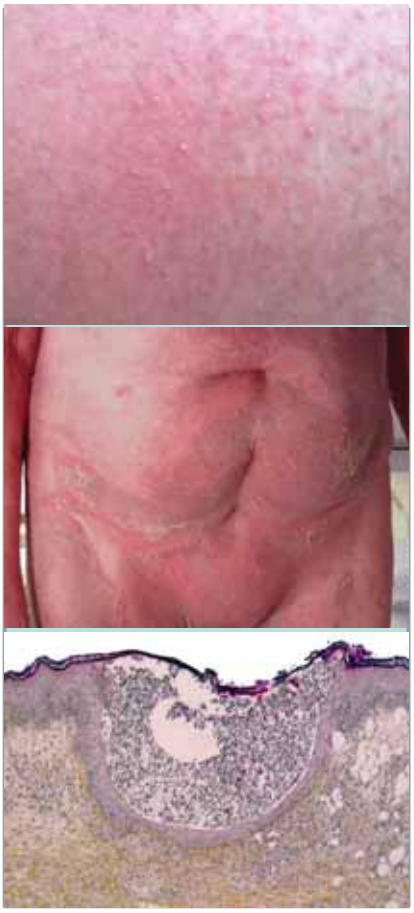
- **Critères Cliniques**
  - Eruption >50% +1
  - Eruption évocatrice DRESS +1
  - Adénopathies +1
  - Atteinte viscérale(foie, rein, poumons, cœur ou autres)
    - 1 atteinte 0
    - 2 atteintes ou plus +2
- **Critères Biologiques sanguins**
  - Lymphocytes atypiques ou activés +1
  - Eo >700/mm3 ou 10-19,9% si leuco<4g +1
  - Eo>1500/mm3 +2
  - ACAN/séro Mycoplasme ou chlamydia/Hémocultures/séro hépatites
    - Si au moins trois négatif +1
- **Critères Négatifs**
  - Si fièvre <38,5 -1
  - Si résolution <15j -1
  - Biopsie non compatible -1
  - Eruption non compatible -1

INTERPRÉTATION Score
<2 pas de DRESS
2-3 DRESS possible
4-5 DRESS probable
>5 DRESS définit

Score=7

PEAG

Pustulose Exanthématique Aigue Généralisée



- **Physiopathologie:** hypersensibilité retardée médiée par des LT spécifiques du médicament, rôle de l'IL 8
- **Incidence** inconnue
- **Délai :** quelques heures à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre,
  - Eruption pustuleuse des plis sur un fond érythémateux puis extension.
- **Biologie:**
  - Hyperleucocytose à PNN ou PNE,
  - Hypocalcémie
- **Atteinte viscérale:** foie, rein
- **Histologie:** pustules intraépidermiques ou sous cornées
- **Médicaments :** pénicillines, macrolides, carbamazépine, inhibiteurs calciques, terbinafine
- **Guérison** rapide (7 jours)
- **Mortalité:** 5%
- ATTENTION AU DRESS PUSTULEUX

PEAG

Pustulose Exanthématique Aigue Généralisée

- Médicaments+++: 90% des cas

Drug or coalition	AGEP (n = 97) n (%)	Controls (n = 1009) n (%)	OR[a]	95% CI		% of cases with recent use of other 'highly suspected' drugs[b]
Pristinamycin	10 (10)	0	∞	26	∞	10
Aminopenicillins	18 (19)	17 (2)	23	10	54	17
Quinolones	9 (9)	5 (0·5)	33	8·5	127	33
(Hydroxy)chloroquine	7 (7)	2 (0·2)	39	8·0	191	0
Sulphonamides	4 (4)	0	∞	7·1	∞	0
Terbinafine	4 (4)	0	∞	7·1	∞	25
Diltiazem	7 (7)	10 (1)	15	5·0	48	0

[a]Multivariate OR if at least three cases and three controls exposed, otherwise univariate; [b]recent use of other 'highly suspected' drugs (i.e. any other drug listed in the table).
AGEP, acute generalized exanthematous pustulosis; OR, odds ratio; CI, confidence interval.

Antibiotics
Ampicillin [11, 12, 19, 34-36]
Amoxicillin [11, 12, 19, 34-36]
Amoxicillin/clavulanic acid [34]
Clindamycin [34, 35]
Cotrimoxazole [12, 34, 35]
Erythromycin [11, 12, 19, 34-36]
Metronidazole [3, 11, 34, 35, 37]
Penicillin [11, 12, 19, 34, 35, 37]
Pristinamycin [12, 19, 34, 35]
Spiramycin [12, 19, 34, 35]
Anticonvulsants
Carbamazepine [3, 12, 19, 34, 35, 38]
Antifungal agents
Nystatin [3, 11, 34, 36, 37]
Terbinafine [3, 11, 12, 19, 34, 36, 37]
Antihypertensives
Diltiazem hydrochloride [11, 12, 19, 34-36]
Antimalarial agents
Hydroxychloroquine [3, 12, 19, 34, 35, 39]

Sidoroff et al , BJD, 2007

PEAG

Pustulose Exanthématique Aigue Généralisée

- Infections
  - Bactéries
    - E coli
    - Mycoplasmes
    - Chlamydiae pneumoniae
    - Ecchinococcose
  - Virus: parfois réactivation au décours comme dans le DRESS
    - CMV
    - Parvovirus B19
    - EBV
    - Entérovirus
    - Hépatite B
- Mercure
- Herbes chinoises
- Araignées piqure venimeuse
- Radiothérapie/PUVA
- Huiles essentielles
- Vaccinations

Fernando, Aus J Derm, 2012/Speeckaert et al, EJD, 2010

Table 1 Diagnostic score for validation of acute generalised exanthematous pustulosis

Morphology	
Pustules	
Typical	+2
Compatible with disease	+1
Insufficient	0
Erythema	
Typical	+2
Compatible with disease	+1
Insufficient	0
Distribution	
Typical	+2
Compatible with disease	+1
Insufficient	0
Post-pustular desquamation	
Yes	+1
No	0
Course	
Mucous membrane involvement	
Yes	−2
No	0
Acute onset	
Yes	0
No	−2
Resolution	
Yes	0
No	−4
Fever ≥ 38°C	
Yes	+1
No	0
Polymorphonuclear cells ≥ 7/μL	
Yes	+1
No	0
Histology	
Other disease	−10
Not representative	0
Exocytosis of polymorphonuclear cells	+1
Subcorneal and/or intraepidermal non-spongiform pustules or	+2
NOS pustules with papillary edema or subcorneal and/or	
intraepidermal spongiform pustules or NOS pustules without papillary oedema	
Spongiform subcorneal and/or intraepidermal pustules with papillary oedema	+3

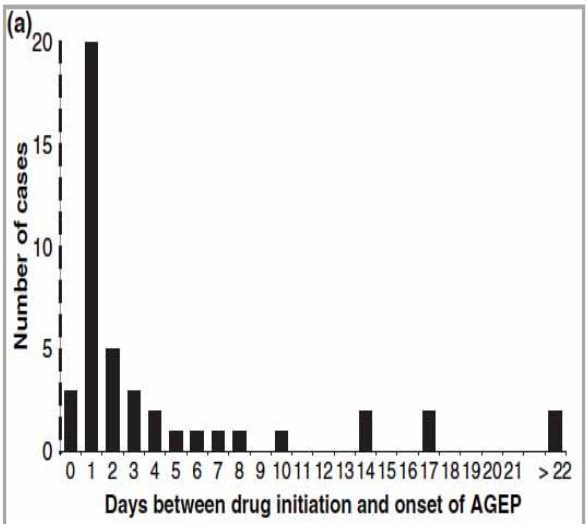
≤0; excluded, 1–4: possible, 5–7: probable, 8–12: definite. NOS, not otherwise specified.

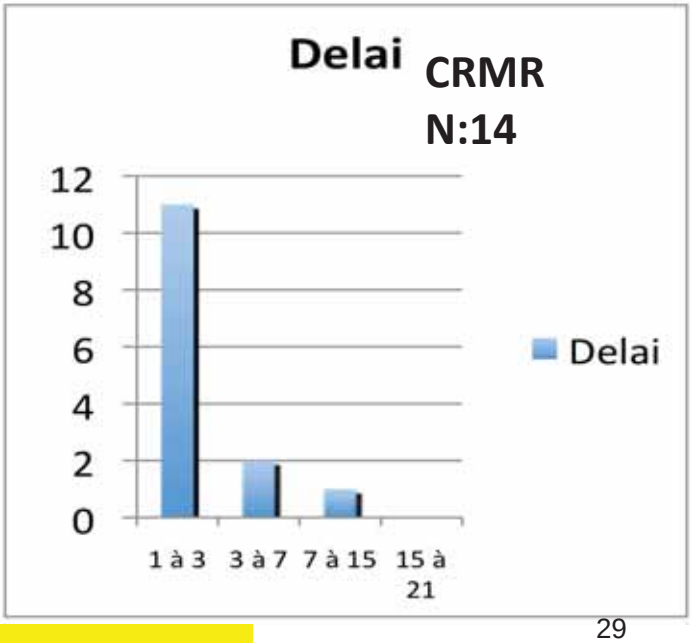
Score diagnostic

Sidoroff et al, J cut pathol ,2001

PEAG
Délai de survenue

- Survenue aigue (<48h)++++



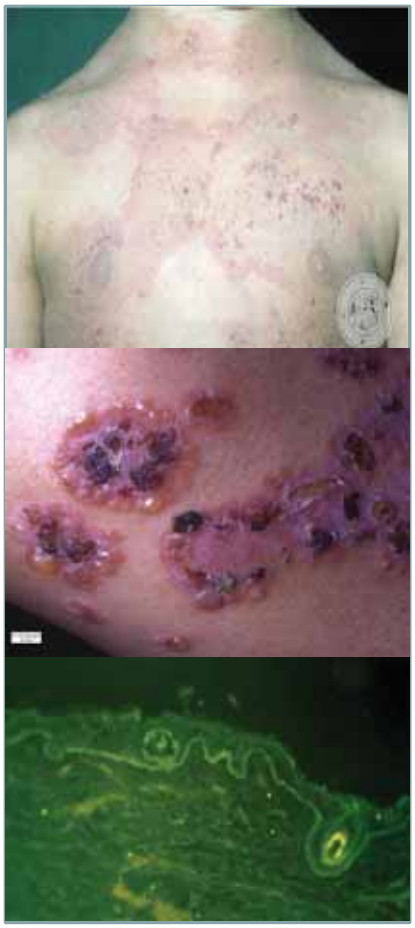


Sidoroff et al, BJD, 2007

Erythème pigmenté fixe bulleux

- **Physiopathologie:** hypersensibilité retardée médiée par les LT CD8+ spécifiques du médicament
- **Incidence :** inconnue
- **Délai :** Quelques heures à 2 jours
- **Clinique:**
  - Lésions arrondies uniques ou multiples parfois bulleuses
  - Laissent une cicatrice pigmentée séquellaire
  - Récidive sur le meme site
  - Pas d'atteinte pluri muqueuse
- **Biologie :** non spécifique
- **Atteinte viscérale:** possible extension TEN-like
- **Histologie** : proche de celle du SJS-TEN. Rôle des LT CD8+ intradermiques.
- **Médicaments :** barbituriques, carbamazepine, sulfamides, cyclines, antalgiques (pyrazolés, aspirine, paracétamol)
- **Guérison :** rapide (7 jours)
- **Mortalité:** non connue

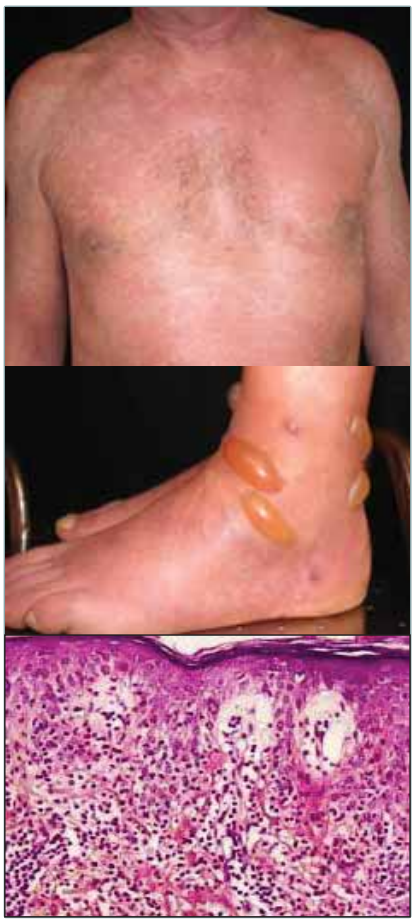
Dermatose à IgA linéaire médicamenteuse



- **Physiopathologie :** non connue
- **Incidence :** inconnue
- **Délais :** 1 à 21 jours
- **Clinique :**
  - Dermatose prurigineuse
  - Bulles tendues en peau érythémateuse ou urticarienne
  - Parfois Lyell like avec decollement
  - Disposition en rosette prédominant dans les régions péribuccales /génitales/palmoplantaire
- **Biologie (IFI)** : IgA1 anti collagène VII et BP 180
- **Atteinte viscérale**: rare
- **Histologie (IFD):** dépôts linéaires IgA +/- C3 en péri lésionnel
- **Médicaments :** AINS, antibiotiques, vancomycine, IEC
- **Guérison :** 5 semaines après arrêt du médicament
- **Mortalité :** non connue mais risque de séquelles

Toxidermie érythémateuse

Autres manifestations cutanées graves aux médicaments



- **Physiopathologie:** hypersensibilité retardée médiée par les LT
- **Incidence :** inconnue
- **Délai** : 1 à 21 jours
- **Clinique:**
  - Fièvre possible
  - Eruption maculo-papuleuse prurigineuse parfois bulleuse
  - Début au niveau des plis puis extension, jusqu'à l'érythrodermie
- **Biologie :** hyperéosinophilie
- **Histologie** : infiltrat dermique lymphocytaire et à éosinophiles, vacuolisation de la membrane basale, nécrose kératinocytaire, exocytose lymphocytaire, spongiose.
- **Médicaments :** pénicillines, sulfamides, céphalosporines, antituberculeux, anticomitiaux, allopurinol, sel d'or, captopril, AINS, phénothiazine
- **Guérison :** 1 à 3 semaines avec desquamation
- **Mortalité :** non connue

Plan

1. Préciser le type de toxidermie
   - Clinique
   - Epidémiologie/Génétique
   - Physiopathologie
2. Préciser la Gravité
3. Enquête étiologique
4. Prise en charge thérapeutique
5. Prise en charge à distance

Génétique

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

Génétique

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* = 30)	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^{-13}
*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^{-9}
*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.

Xing et al , The Pharmacogenomics Journal (2015), 1-5

Génétique

Background: Methazolamide (MTZ) has been occasionally linked to the lethal Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are associated with HLA-B*59:01. However, some MTZ-induced SJS/TEN (MTZ-SJS/TEN) cases are negative for HLA-B*59:01, implying that other genetic factors besides HLA-B*59:01 are contributing to MTZ-SJS/TEN.

Objectives: To comprehensively identify HLA and non-HLA genetic susceptibility to MTZ-SJS/TEN in Han Chinese.

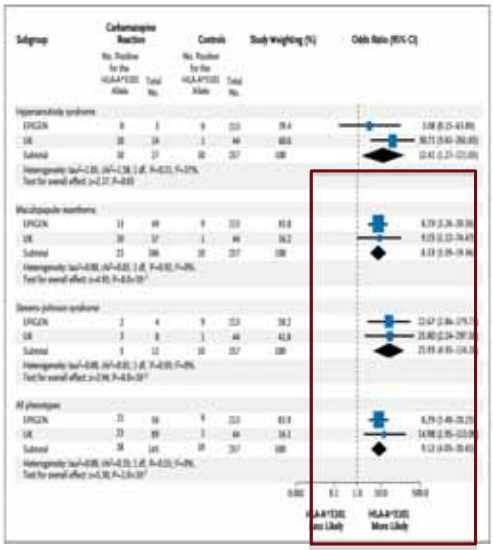
Methods: Eighteen patients with MTZ-SJS/TEN, 806 subjects of the population control and 74 MTZ-tolerant individuals were enrolled in this study. Both exome-wide and HLA-based association studies were conducted. Molecular docking analysis was employed to simulate the interactions between MTZ and risk HLA proteins.

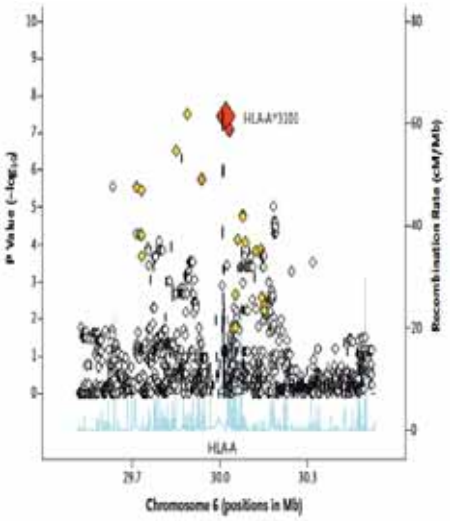
Results: We found a strong signal in the major histocompatibility complex region on chromosome 6 with 22 SNPs reaching exome-wide significance. Compared with MTZ-tolerant controls, a significant association of HLA-B*59:01 with MTZ-SJS/TEN was validated [odds ratio (OR) = 146.00, 95% confidence interval (CI): 16.12-1321.98; $P = 6.19 \times 10^{-10}$]. Moreover, 66.7% of MTZ-SJS/TEN patients negative for HLA-B*59:01 were carriers of HLA-B*55:02, whilst 2.7% of the tolerant individuals were observed with HLA-B*55:02 (OR = 71.00, 95% CI: 7.84-643.10; $P = 1.43 \times 10^{-4}$). Within HLA-B protein, the E45–L116 motif could completely explain the association of HLA-B*59:01 and HLA-B*55:02 with MTZ-SJS/TEN (OR = 119.33, 95% CI: 29.19-1227.96; $P = 4.36 \times 10^{-13}$). Molecular docking analysis indicated that MTZ binds more stably to the pocket of HLA-B*59:01 and HLA-B*55:02 than to that of non-risk alleles of HLA-B*40:01 and HLA-C*01:02.

Conclusions: This study confirmed the association of HLA-B*59:01 with MTZ-SJS/TEN and identified HLA-B*55:02 as a novel risk allele in Han Chinese with the largest sample size to date. Notably, the rs41562914(A)-rs12697944(A) haplotype, encoding E45–L116, is capable of serving as a powerful genetic predictor for MTZ-SJS/TEN with a sensitivity of 89% and specificity of 96%.

Xing et al , JEADV, 2022

Génétique





Mc Cormack. NEJM 2011

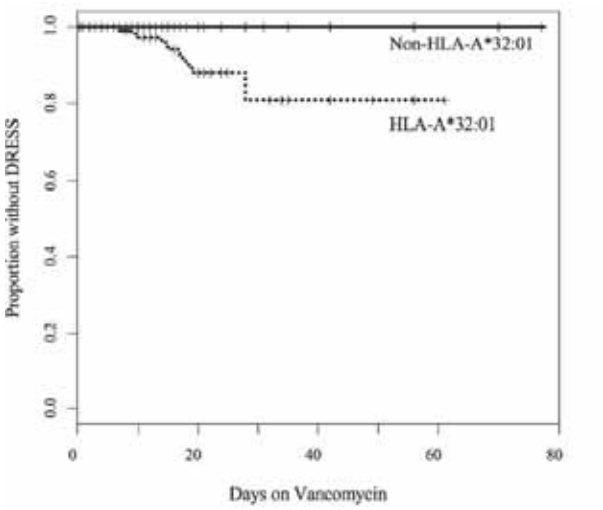
Génétique

Table 1: Associations of SCARs and delayed-type drug hypersensitivity and HLA alleles.

Causative drug	HLA allele	Hypersensitivity reactions	Ethnicity	Odds ratio (95% CI)	Reference
Abacavir	B*57:01	Abacavir hypersensitivity	Caucasians	117 (29–481)	[48]
Allopurinol	B*58:01	SJS/TEN/DRESS	Asians	74.18 (26.95–204.14)	[34]
			Non-Asians	101.45 (44.98–228.82)	[34]
Carbamazepine	B*15:02	SJS/TEN	Han Chinese	115.32 (18.17–732.13)	[17]
			Thai	54.43 (16.28–181.96)	[17]
			Malaysians	221.00 (3.85–12694.65)	[17]
			Indians	54.60 (2.25–1326.20)	[17]
	B*15:08		Indians	nd	[15]
	B*15:11		Japanese	16.3 (4.76–55.61)	[23]
			Koreans	18.0 (2.3–141.2)	[22]
			Mainland China Han Chinese	31.00 (2.74–350.50)	[24]
	B*15:18		Japanese	13.58 (nd)	[25]
	A*31:01	DRESS	Han Chinese	23.0 (4.2–125)	[20]
			Europeans	57.6 (11.0–340)	[20]
		SJS/TEN	Europeans	4.4 (1.1–17.3)	[20]
			All populations	3.94 (1.4–11.5)	[20]
		SJS/TEN	Europeans	25.93 (4.93–116.18)	[19]
		DRESS	Europeans	12.41 (1.27–121.03)	[19]
		MPE	Europeans	8.33 (3.59–19.36)	[19]
		SJS/TEN/DRESS	Japanese	10.8 (5.9–19.6)	[18]
Dapsone	B*13:01	DRESS	Mainland China Han Chinese	20.53 (11.55–36.48)	[61]
Lamotrigine	B*15:02	SJS/TEN	Han Chinese	3.59 (1.15–11.22)	[27]
Nevirapine	DRB1*01:01	DRESS/MPE	Australians	depend on CD4 T-cells count	[56]
	B*14:02		Sardinians	nd	[58]
	B*35:05		Thai	18.96 (4.87–73.44)	[57]
	Cw8		Sardinians, Japanese	nd	[58, 59]
Oxcarbazepine	B*15:02	SJS/TEN	Taiwan Han Chinese	80.7 (3.8–1714.4)	[30]
Phenytoin	B*15:02	SJS/TEN	Han Chinese	4.26 (1.93–9.39)	[27]

Chung et al , J Immunol , 2021

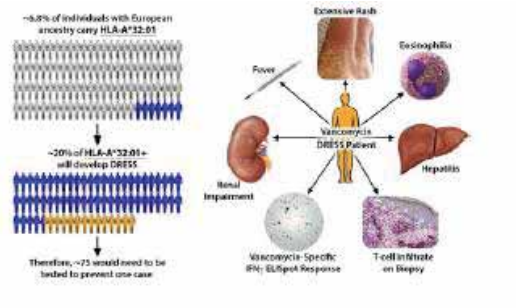
Génétique



HLA A 32 01 19/23 DRESS vs 0/46 NON DRESS

Européens

$P<10^{-8}$++++



Philips et al , JACI , 2019

Génétique

Table 1

Clinical characteristics and HLA-A genotyping of the cases group.

Patient	Sex	Age (years)	Indication	Dose of carbamazepine (mg/day)	Duration of treatment (days)	Imputability according RECIVAR	HLA typing	HLA-A*31:01
P1	M	33	Peripheral neuropathy	100	8	probable	ND	ND
P2	M	29	Bipolar disorder	400	7	possible	ND	ND
P3	F	36	Bipolar disorder	400	27	Probable	HLA- A1, A30, B51, B41 (BW4, BW6)	–
P4	M	38	Peripheral neuropathy	200	36	Probable	**HLA - A23, A31; B40, B35(BW4, BW6)**	+
P5	M	34	Epilepsy	400	66	probable	ND	ND
P6	F	40	Bipolar disorder	400	21	Definite	**HLA - A1, A31; B51, B37 (BW4)**	+
P7	F	33	Peripheral neuropathy	300	42	probable	HLA- A2, A3; B51, B62 (BW4, BW6)	–
P8	M	33	Epilepsy	400	11	Definite	**HLA- A31, A blanc; B35, B51 (BW4,BW6)**	+
P9	M	54	Peripheral neuropathy	400	45	Probable	ND	ND
P10	M	56	Bipolar disorder	400	11	Definite	**HLA - A68, A31; B61, B50 (BW4,BW6)**	+
P11	F	37	Epilepsy	400	11	probable	ND	ND
P12	F	46	Bipolar disorder	400	116	probable	ND	ND
P13	M	63	Peripheral neuropathy	100	6	Probable	HLA - A1, A1; B7, B37 (BW6, BW6)	–
P14	M	74	Peripheral neuropathy	200	27	Definite	ND	ND

Patients with HLA-A31 allele have been in bold.

Afrique du Nord

RR 52

HLA A 31

DRESS Carbamazépine

Table 2

Clinical characteristics and HLA-A genotyping of the controls group.

Patient	Sex	Age (years)	Indication	Dose of carbamazepine (mg/day)	Duration of treatment (years)	HLA typing	HLA-A*31:01
P1	M	25	Epilepsy	800	2	HLA- A3, A29; B62, B22 (BW6)	–
P2	M	37	schizophrenia	1200	5	HLA- A31, A33; B51, B14 (BW4,BW6)	–
P3	F	25	Epilepsy	300	7	HLA- A2, A29; B44, B45 (BW4,BW6)	–
P4	M	47	Epilepsy	200	13	HLA- A1, A1; B8, B44 (BW4,BW6)	–
P5	M	60	Peripheral neuropathy	300	½ (6 months)	HLA- A2, A10; B8, B blanc (BW4, BW6)	–
P6	M	57	schizophrenia	1200	30	HLA- A2, A24; B45, B50 (BW4, BW6)	–
P7	F	63	Peripheral neuropathy	300	11	HLA - A66, A24; B40, B blanc (BW6)	–
P8	M	22	Epilepsy	600	9	HLA- A2, A9; B44, B45 (BW4,BW6)	–
P9	M	52	Bipolar disorder	800	12	HLA- A30, A33; B51, B14 (BW4,BW6)	–
P10	M	48	Epilepsy	800	15	HLA - A3, A blanc; B7, B14 (BW6)	–
P11	F	56	Epilepsy	1000	23	HLA - A1, A23; B44, B07 (BW4)	–
P12	M	35	Epilepsy	1200	17	HLA - A3, A blanc; B7, B14 (BW6)	–
P13	M	68	Bipolar disorder	800	14	HLA- A2, A68; B44, B35 (BW4, BW6)	–
P14	F	70	Peripheral neuropathy	200	3	HLA- A2, A24; B50, B63 (BW4, BW6)	–
P15	M	23	Schizophrenia	800	7	HLA- A2, A23; B44, B42 (BW4, BW6)	–
P16	M	54	Epilepsy	800	30	HLA A3, A32; B7,B44 (BW4,BW6)	–
P17	M	32	Epilepsy	400	15	HLA- A24, A blanc; B45, B35 (BW4, BW6)	–
P18	F	36	Peripheral neuropathy	200	3	HLA- A2, A blanc; B51, B50 (BW4, BW6)	–
P19	M	51	Epilepsy	400	20	HLA- A1, A29, B8, B44 (BW4, BW6)	–
P20	M	30	Epilepsy	600	7	HLA- A2, A9; B40, B35 (BW4, BW6)	–
P21	M	32	Epilepsy	600	7 et ½	HLA- A2, A11; B17, B35 (BW4, BW6)	–
P22	M	52	Epilepsy	400	12	HLA- A28, A24; B35, B blanc (BW4, BW6)	–
P23	M	34	Bipolar disorder	600	6	**HLA- A1, A31; B35, B blanc (BW4, BW6)**	+
P24	M	31	Epilepsy	300	4	HLA- A2, A32; B44, B50 (BW4, BW6)	–
P25	M	69	Peripheral neuropathy	200	2	HLA- A1, A74; B17, B blanc	–

Ksouza et al , Seizure, 2017

Génétique

Table 2 The results of patch testing and genetic polymorphism in patients and controls

Subjects	Genetic polymorphism		Patch test
	CYP2C9*2	CYP2C9*3 (heterozygous)	Positive reactions
Total number	218	218	108
Diphenylhydantoin-induced patients	0/10	3/10*	3/10
Diphenylhydantoin-exposed controls	0/39	0/39	0/40
Non-exposed controls	0/169	1/169	1/58

- CYP2C9: association avec le métabolisme DPH
- FDR significatif CADR à phénytoïne
- Présent chez as Lee et al , Eur J Pharmacol, 2004 opéens
- Rôle dans la maladie+++

Génétique Autre

Table 2 Association test results for risk alleles for maculopapular exanthema (MPE) across ethnicities

		European				Han Chinese			
Drug	Marker	MPE Homozygosity/ heterozygosity/ reference (MAF)	Control Homozygosity/ heterozygosity/ reference (MAF)	OR (95% CI)	*p* Value	MPE Homozygosity/ heterozygosity/ reference (MAF)	Control Homozygosity/ heterozygosity/ reference (MAF)	OR (95% CI)	*p* Value
CBZ	*HLA-B*15:02*	0/0/95 (0)	0/0/869 (0)	—	—	0/2/21 (0.04)	3/22/162 (0.07)	0.6 (0.1–2.8)	0.53
CBZ	*HLA-A*31:01*	0/16/79 (0.08)	0/27/841 (0.02)	5.5 (3.0–10)	1.47×10^{-10}	0/1/22 (0.02)	0/10/156 (0.03)	0.8 (0.1–6.8)	0.81
LTG	*HLA-A*24:02*	2/14/102 (0.08)	8/122/681 (0.09)	0.9 (0.5–1.5)	0.71	0/4/12 (0.12)	1/7/20 (0.16)	0.7 (0.1–3.5)	0.62
PHT	*CYP2C9*3*	0/10/42 (0.1)	0/51/421 (0.05)	1.8 (0.9–3.8)	0.08	0/1/21 (0.02)	0/2/56 (0.02)	0.9 (0.1–12)	0.92
PHT	rs7823978 4	2/8/42 (0.12)	0/14/458 (0.02)	8.8 (4.0–19)	2.94×10^{-10}	0/0/22 (0)	0/0/58 (0)	—	—

Abbreviations: CBZ = carbamazepine; CI = confidence interval; LTG = lamotrigine; MAF = mean allele frequency; OR = odds ratio; PHT = phenytoin.
Representative risk alleles from previous genome-wide association study findings and this report for antiepileptic drug–induced skin rash studies (CBZ, LTG, and PHT) were assessed for association in our study. *p* Values from logistic regression model with sex and 5 principal components as covariates.

Mutation of voie du facteur H complément constitue un FDR de MPE à la phénytoïne chez les EUROPEENS

Mc Cormack et al , Neurology, 2018

Génétique

centre de référence
maladies rares

Abstract

Importance: Acute generalized exanthematous pustulosis (AGEP) is a rare and severe type of drug eruption. Dihydrocodeine phosphate is a semisynthetic opioid analgesic. Recently, recessive mutations in IL36RN have been identified in generalized pustular psoriasis (GPP). To date, 4 cases of AGEP and IL36RN mutation without previous history of psoriasis vulgaris (PV) have been reported.

Observations: A woman in her 60s with PV presented with diffuse erythema, nonfollicular pustules, and fever. She had been treated with dextromethorphan hydrobromide hydrate, amoxicillin hydrate, clarithromycin, dihydrocodeine phosphate, tipepidine hibenzate, and tulobuterol tape for a cough and common cold. Based on histopathologic results and a positive result in a drug provocation test with dihydrocodeine phosphate, she was diagnosed with AGEP. A heterozygous IL36RN mutation c.28C>T (p.Arg10X) was also confirmed by mutation analysis.

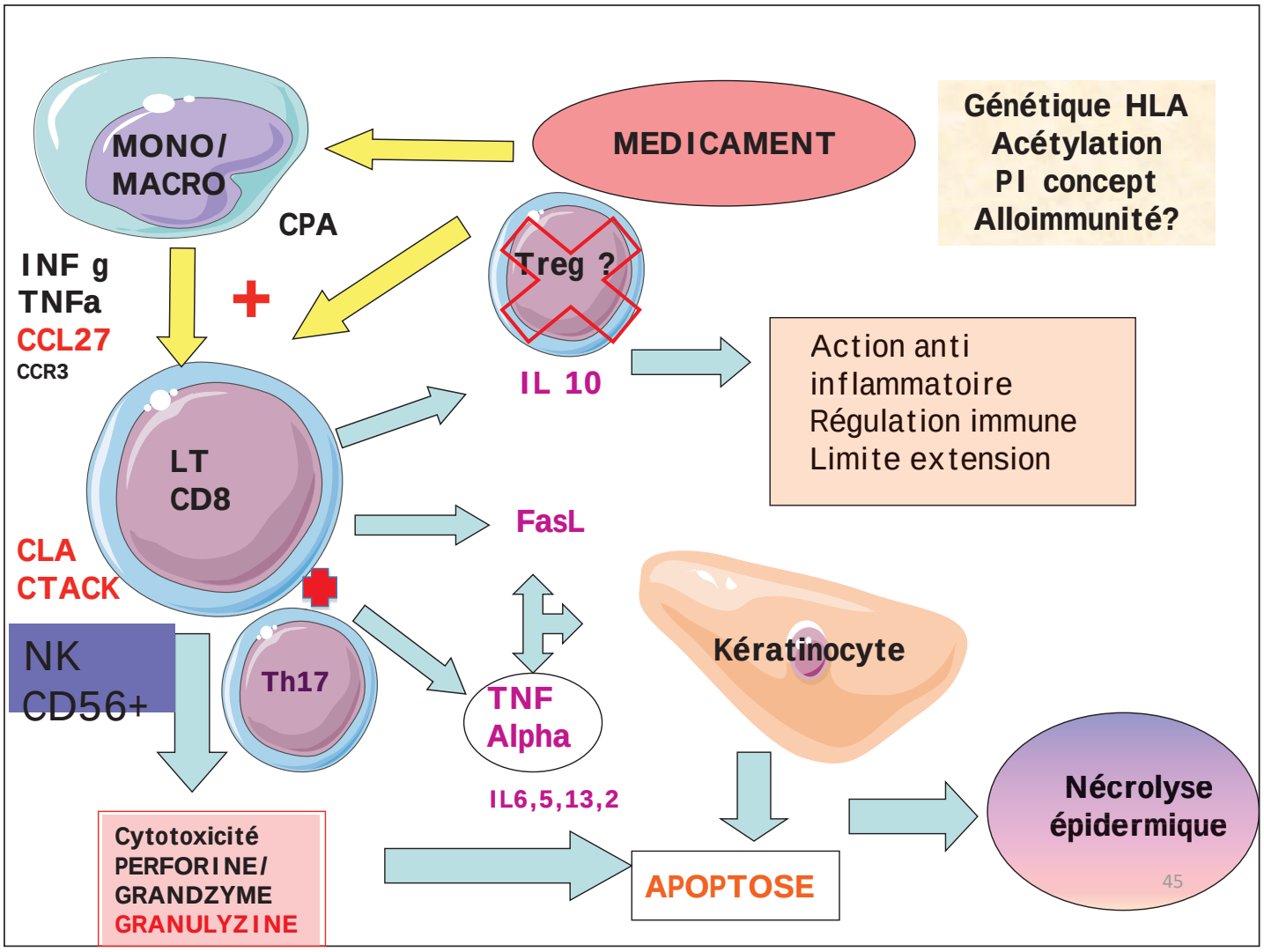
Conclusions and relevance: This is the first report of dihydrocodeine phosphate–induced AGEP. In this case, helper T cells, type 17, might have been activated because of morphine and underlying PV, followed by increased production of interleukin (IL) 36. However, because of the IL36RN mutation, IL-36 signaling was uncontrolled, which might have resulted in the occurrence of AGEP. An IL36RN mutation might underlie several different pustular skin eruptions, including AGEP and GPP, and further accumulation of patient data is required.

Nakai et al , JAMA Dermatol, 2015

centre de référence
maladies rares

Plan

1. Préciser le type de toxidermie
   - Clinique
   - Epidémiologie/Génétique
   - Physiopathologie
2. Préciser la Gravité
3. Enquête étiologique
4. Prise en charge thérapeutique
5. Prise en charge à distance



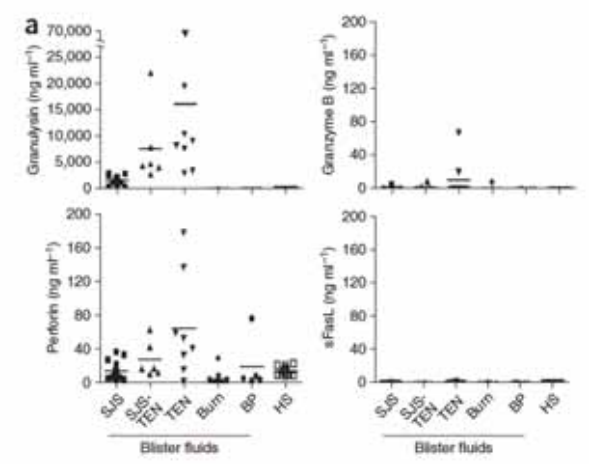
SJS/TEN

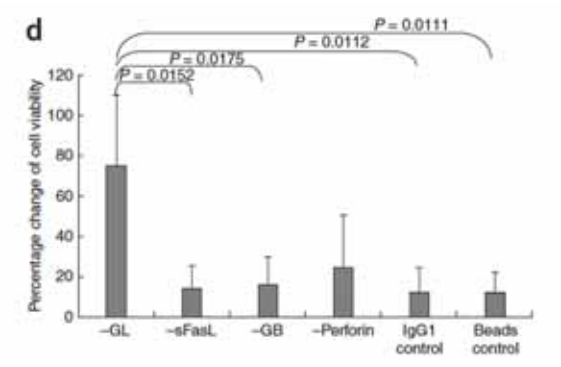
PHYSIOPATHOLOGIE

centre de référence
maladies rares

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

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

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

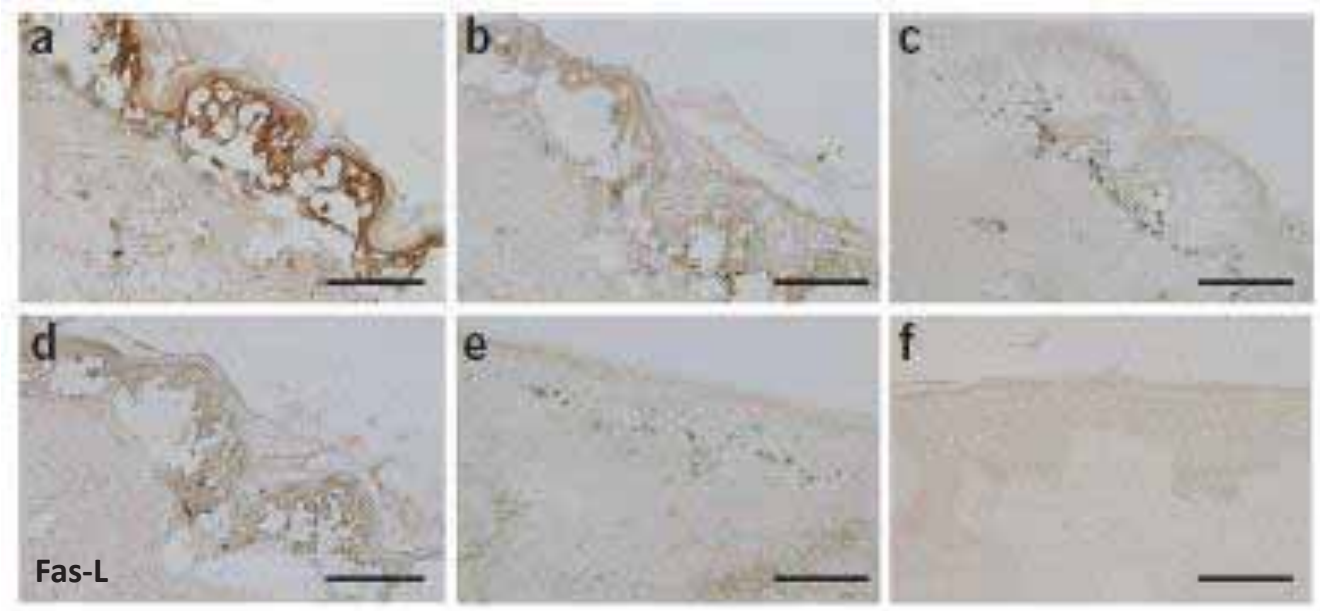


Figure 3 Immunohistochemistry staining of cytotoxic proteins in skin biopsies. (a–d) Serial sections of a skin biopsy from a subject with TEN were stained with antibodies against granulysin (a), granzyme B (b), perforin (c) and FasL (d). (e,f) Skin biopsies from a subject with maculopapular exanthema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

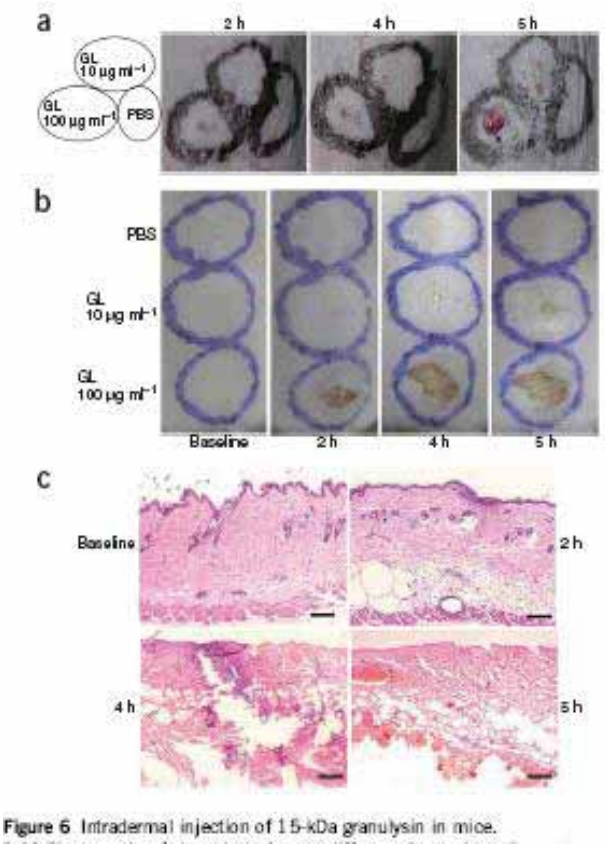
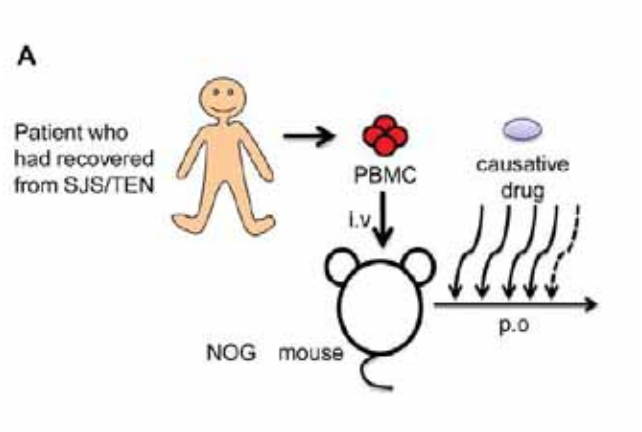


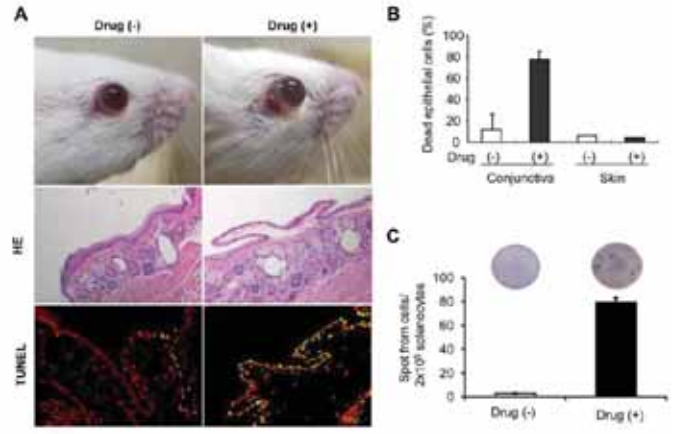
Figure 6 Intradermal injection of 15-kDa granulysin in mice.

- 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





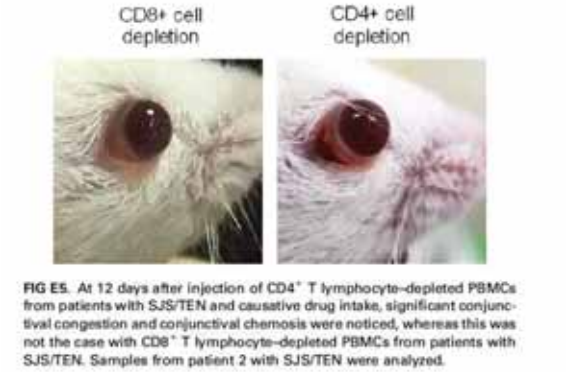


FIG E5. At 12 days after injection of CD4⁺ T lymphocyte–depleted PBMCs from patients with SJS/TEN and causative drug intake, significant conjunctival congestion and conjunctival chemosis were noticed, whereas this was not the case with CD8⁺ T lymphocyte–depleted PBMCs from patients with SJS/TEN. Samples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

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.
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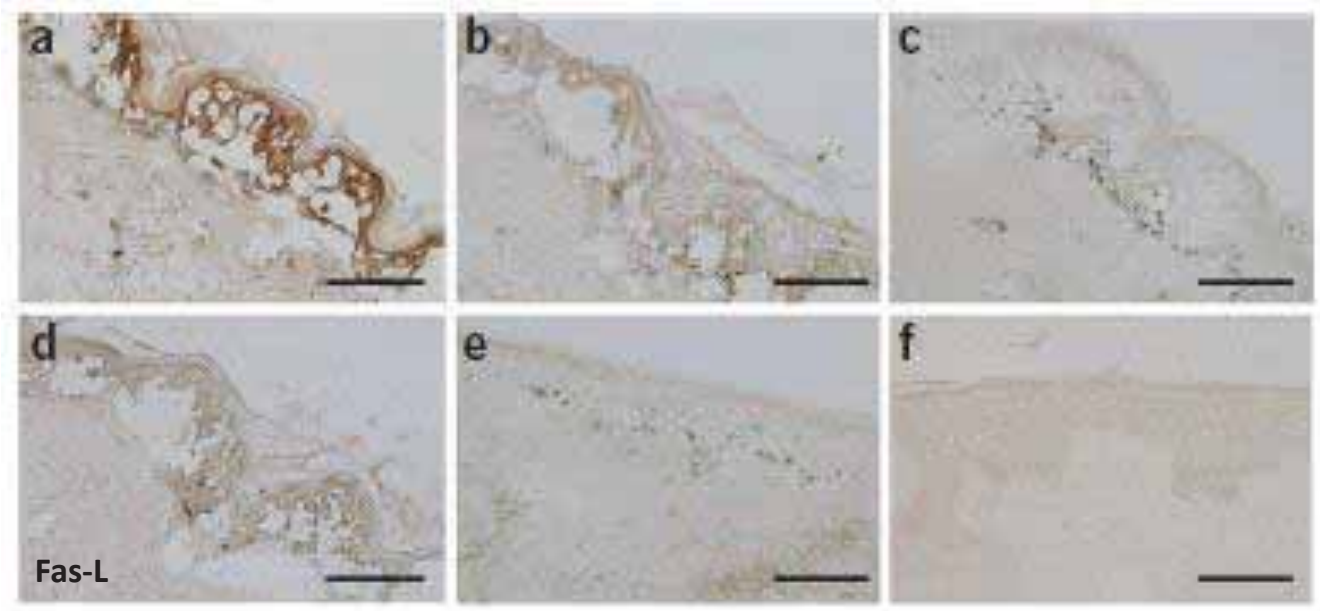


Figure 3 Immunohistochemistry staining of cytotoxic proteins in skin biopsies. (a–d) Serial sections of a skin biopsy from a subject with TEN were stained with antibodies against granulysin (a), granzyme B (b), perforin (c) and FasL (d). (e,f) Skin biopsies from a subject with maculopapular exanthema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

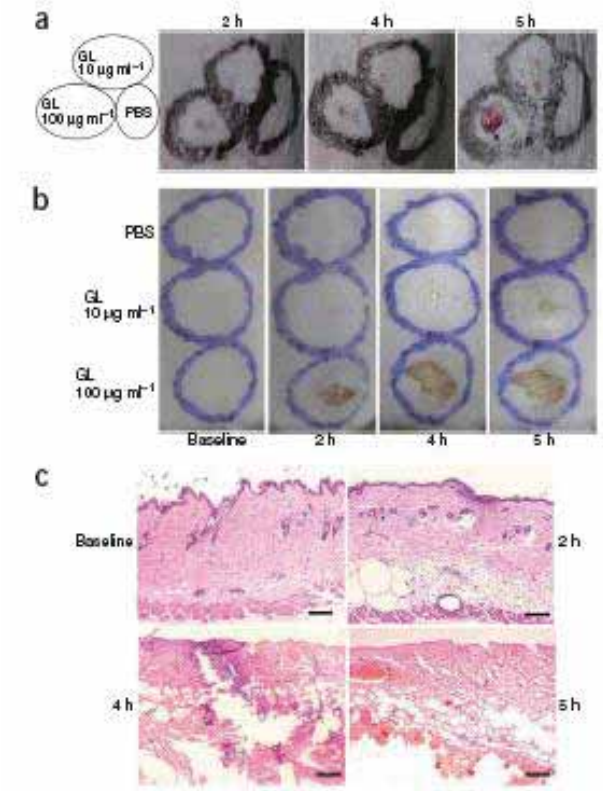
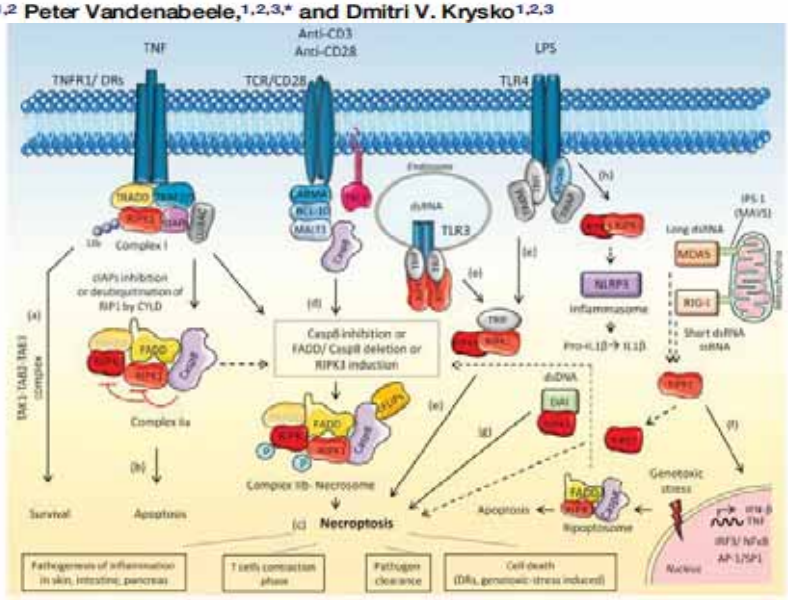


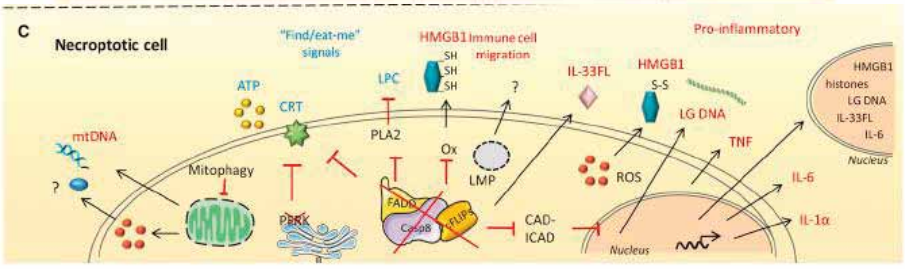
Figure 6 Intradermal injection of 15-kDa granulysin in mice.

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

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]





SJS/TEN
PHYSIOPATHOLOGIE

centre de référence maladies rares

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- Nécroptose
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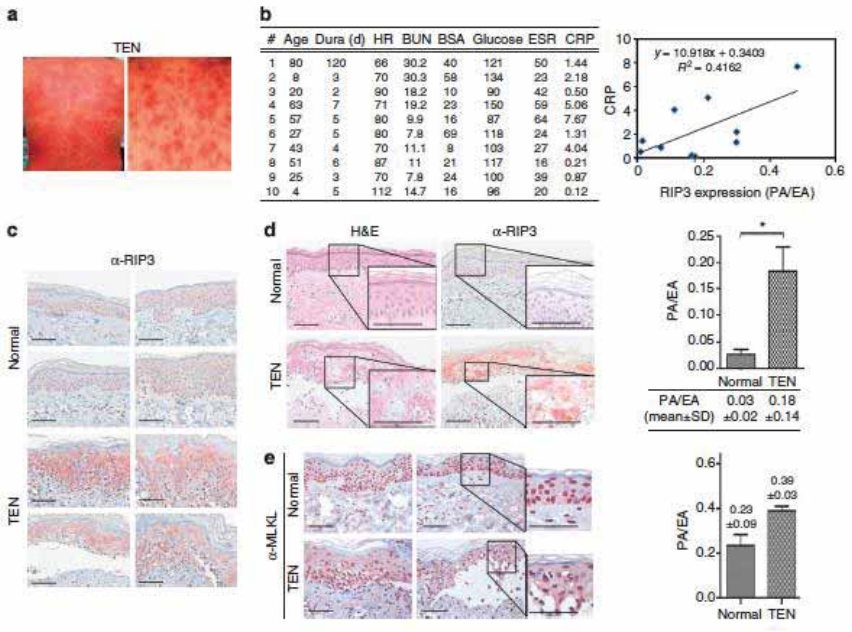
- Rôle du métabolite
- Rôle de la clairance du médicament
- Rôle Hla

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]

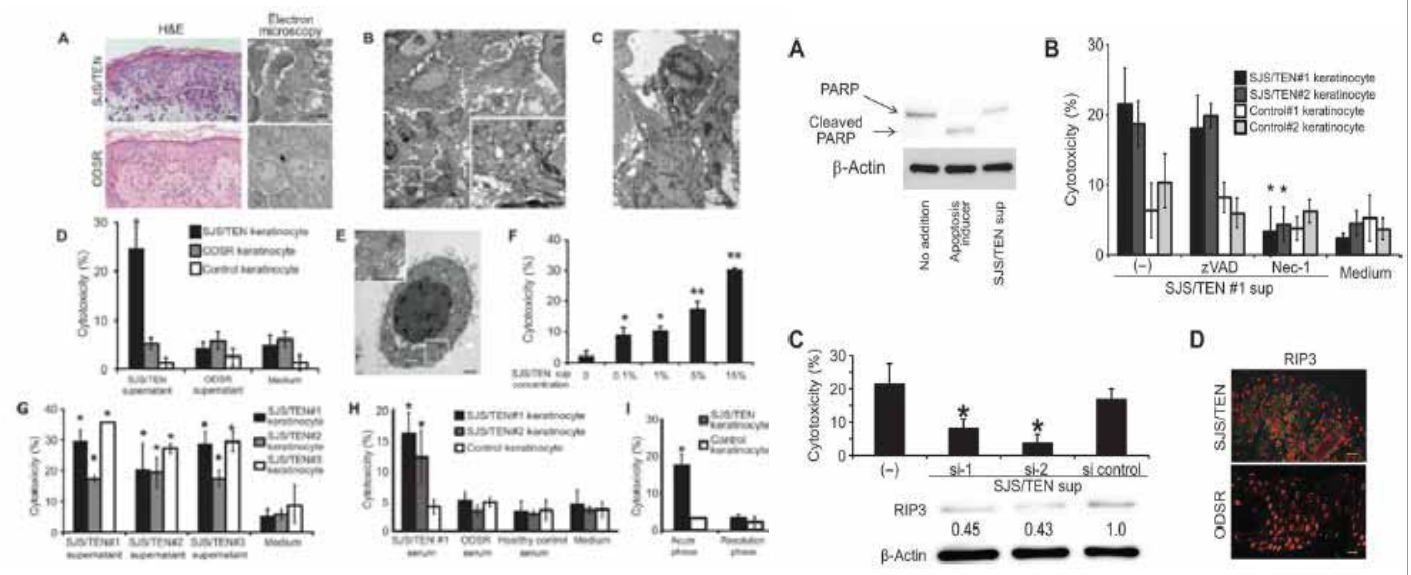


La nécroptose participe à la réaction inflammatoire au cours des NET

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

SJS/TEN

PHYSIOPATHOLOGIE

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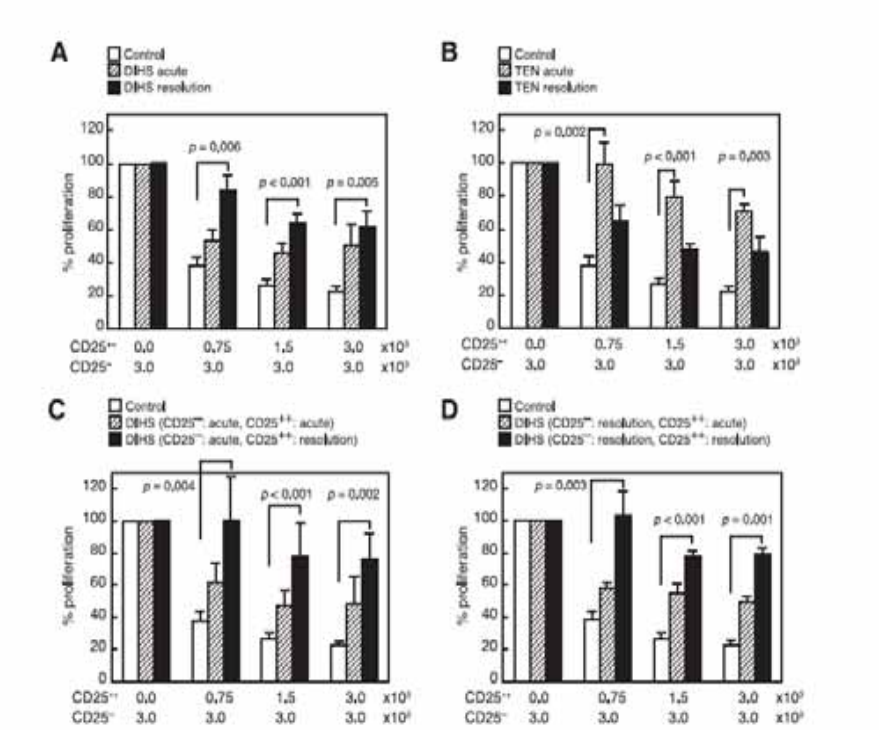
TEN et LT Régulateur

Défaut de régulation:

- Shiohara et coll. J Immunol, 2009



SJS/TEN

PHYSIOPATHOLOGIE

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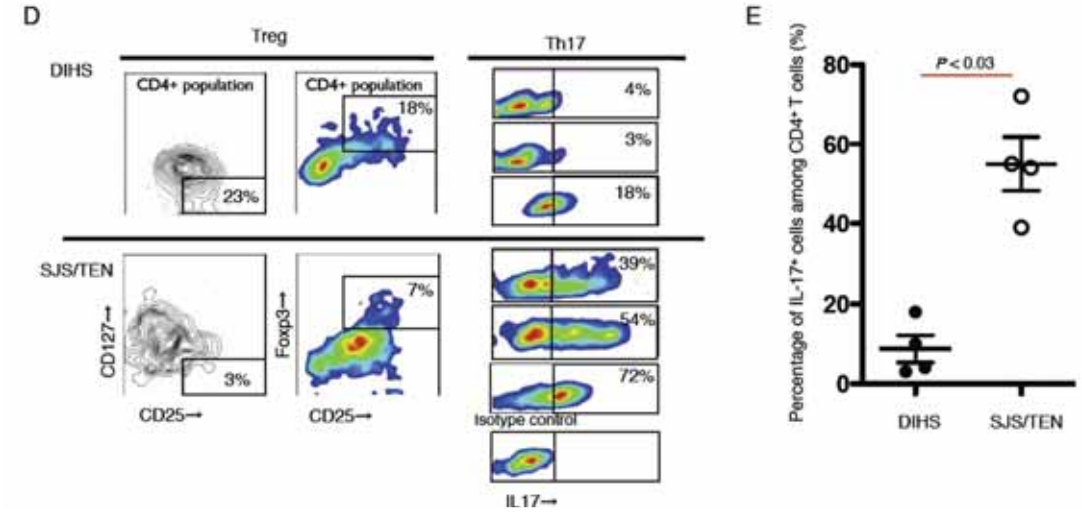
Physiopathologie
TH17



TH17 joue un rôle dans la phase aigue du Lyell dans une population asiatique Shiohara et al ,CEA, 2018

SJS/TEN
PHYSIOPATHOLOGIE

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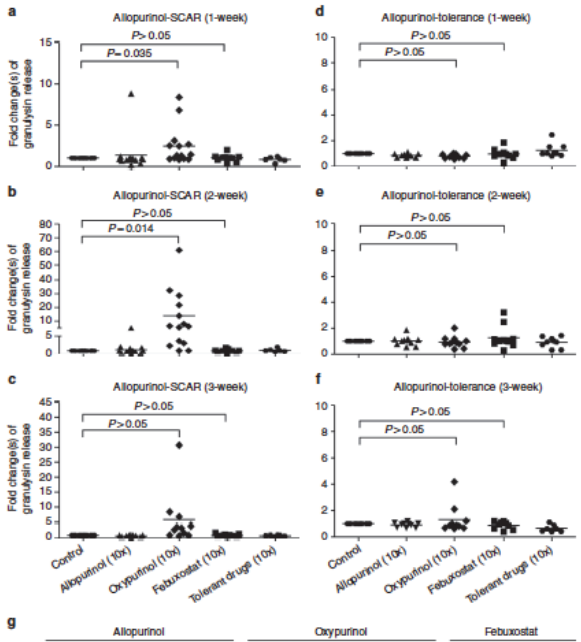
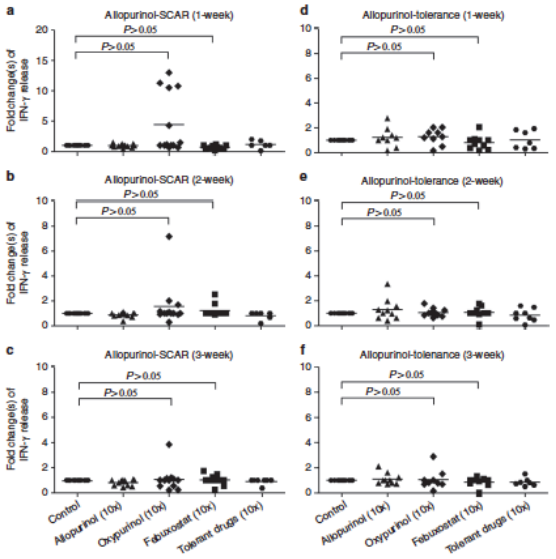
- Rôle Hla

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

g

	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

SJS/TEN
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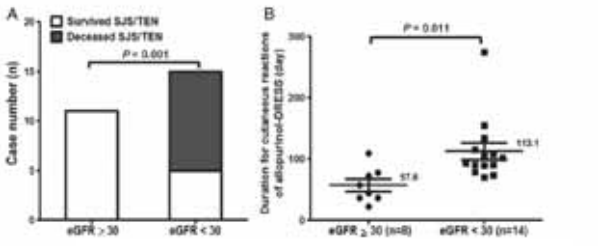
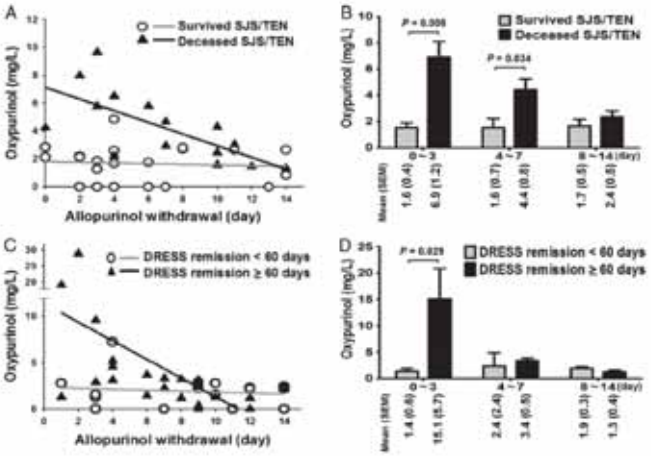
SJS/TEN

Role de la clairance du metabolite





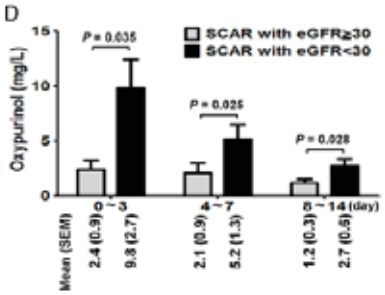


Table 2 Delayed clearance of oxypurinol in patients with allopurinol-SCAR*

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

SJS/TEN

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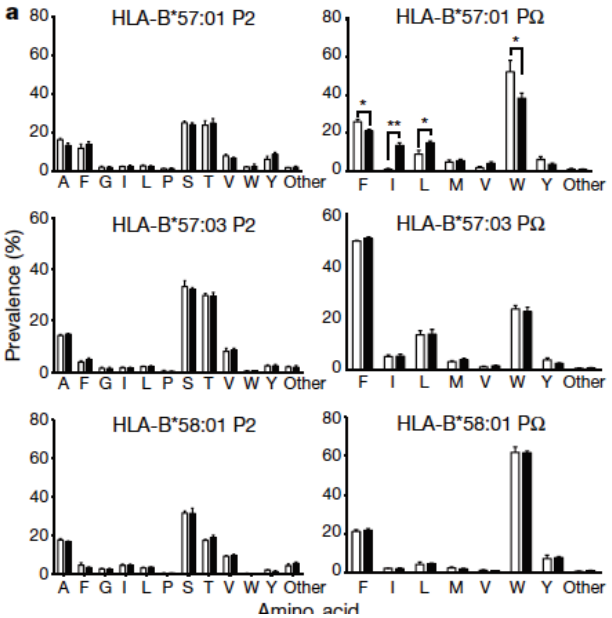
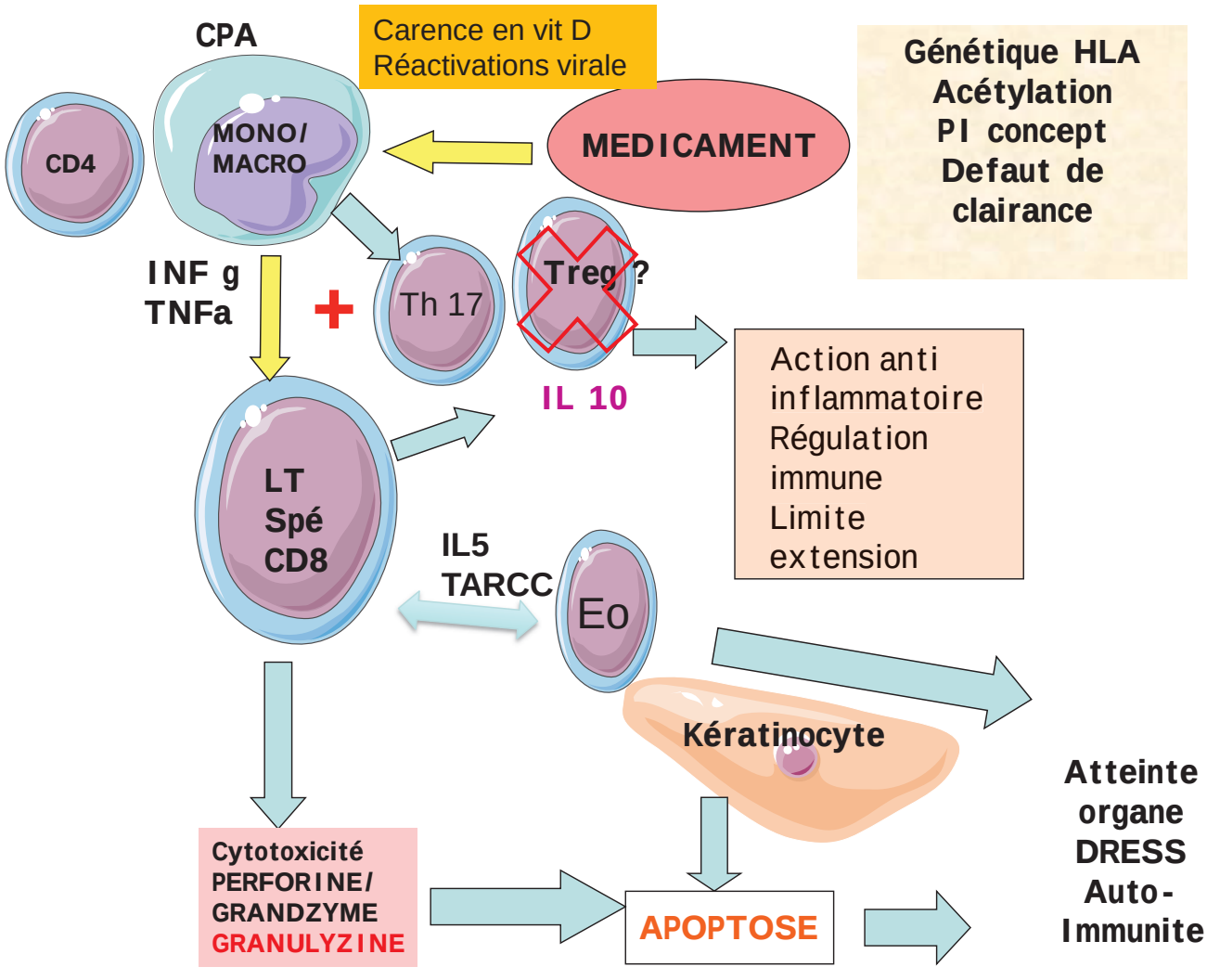
SJS/TEN

Rôle HLA

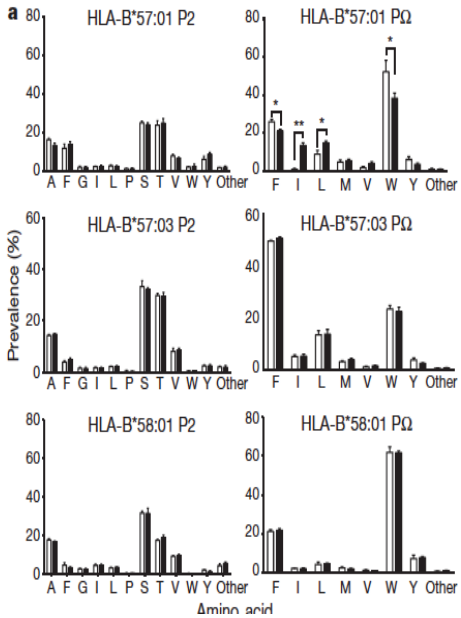


La fixation du médicament sur un HLA spécifique entrainerait la modification de la molécule HLA à l'origine de la formation de 5 néo peptides au moins responsable d'une allo immunisation et de la sévérité de la réaction immune

Mc Cluskey et al , nature, 2012



HLA restriction et intensité de la réponse immune



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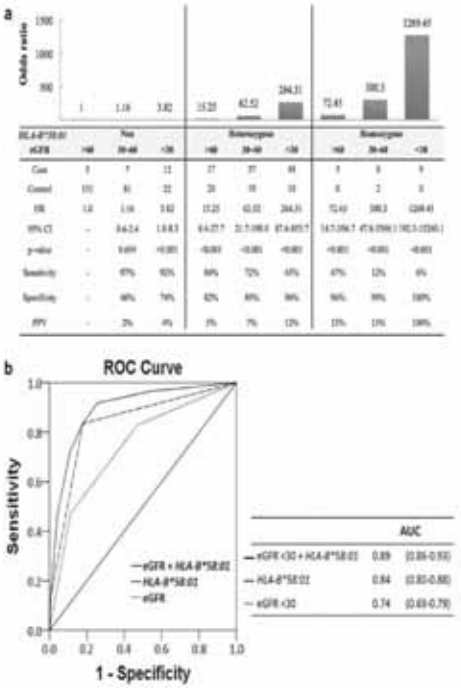
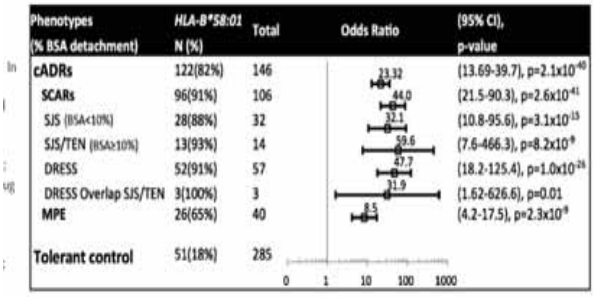
Mc Cluskey et al , nature, 2012

Rôle HLA et DRESS

HLA B58 01 est un facteur de risque de SCARS Allopurinol Association insuffisance rénale augmente le risque



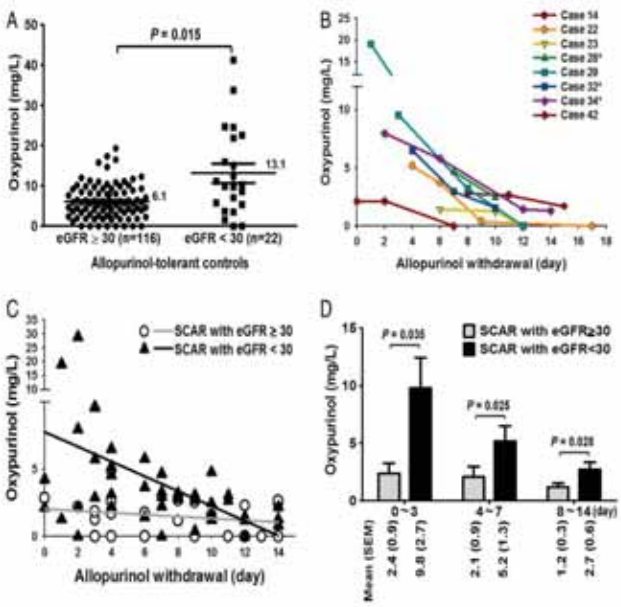


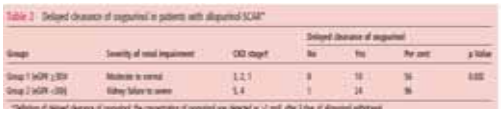
CHUNG WH et al , JID,2016

centre de référence maladies rares

Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin

Wen-Hung Chung,[1,2,3] Wan-Chun Chang,[4] Sophie L Stocker,[5,6] Chiun-Gung Juo,[7] Garry G Graham,[5,6] Ming-Han H Lee,[5,6] Kenneth M Williams,[5,6] Ya-Chung Tian,[3,8] Kuo-Chang Juan,[3,8] Yeong-Jian Jan Wu,[3,9] Chih-Hsun Yang,[2,3] Chee-Jen Chang,[10,11] Yu-Jr Lin,[10,11] Richard O Day,[5,6] Shuen-Iu Hung[4]





La clairance de l'oxypurinol aggravée par Insuffisance renale augmente le risque de SCAR

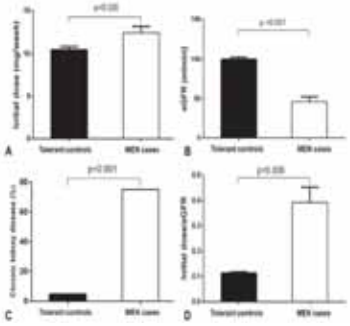
Chung W-H, et al. Ann Rheum Dis 2014

centre de référence maladies rares

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

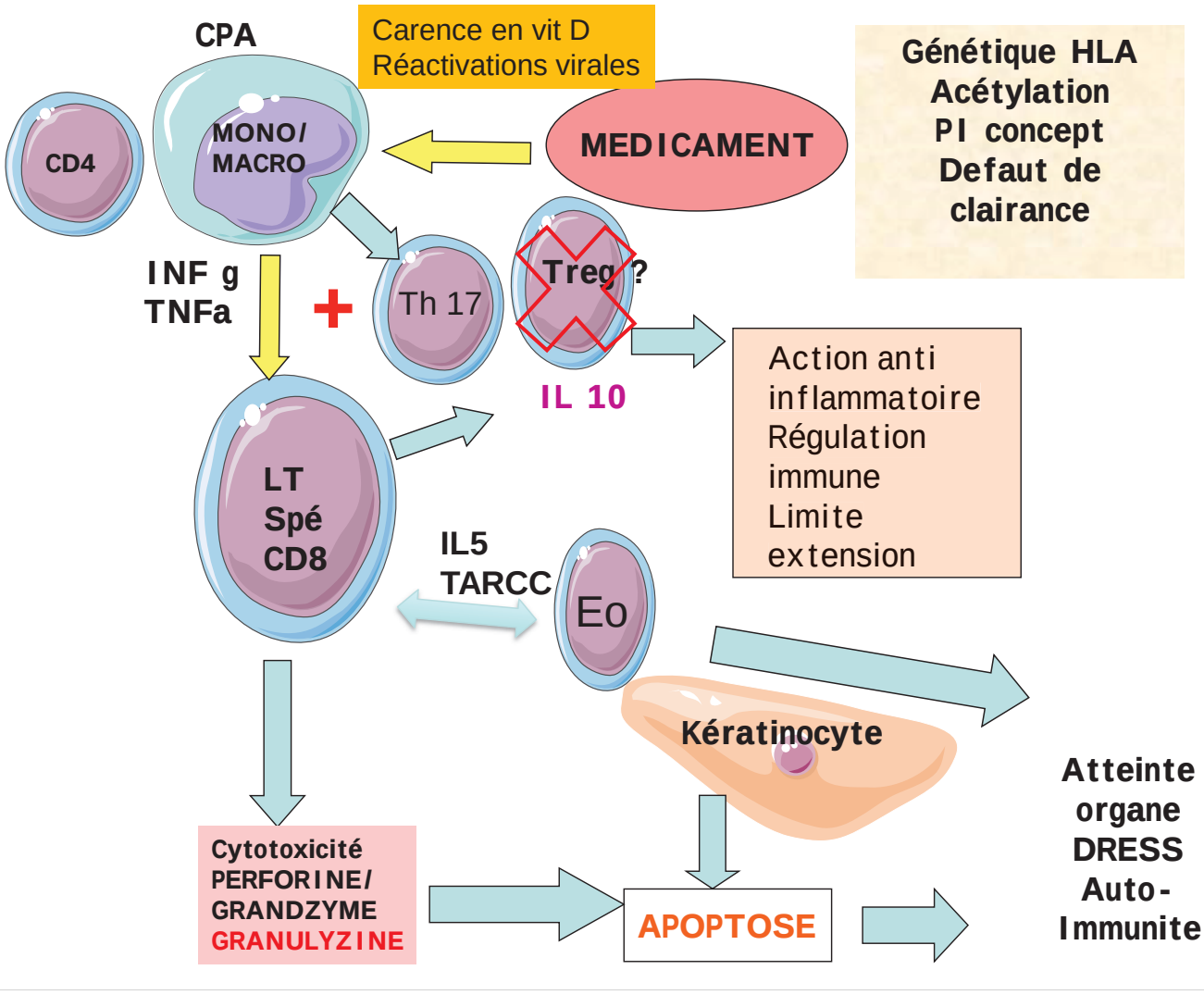
Ting-Jui Chen, MD,[a,b] Wen-Hung Chung, MD, PhD,[c,d] Chun-Bing Chen, MD,[c,d] Rosaline Chung-Yee Hui, MD, PhD,[c,d] Yu-Huei Huang, MD,[c,d] Yueh-Tsung Lu, MD,[c] Chang-Wei Wang, PhD,[c] Kuo-Hsien Wang, MD,[b] Li-Cheng Yang, MD,[c] and Shuen-Iu Hung, PhD[a]
Taipei, Linkou, Keelung, and Taoyuan, Taiwan

	MTX-induced epidermal necrosis (N = 24)	MTX-tolerant controls (N = 150)	*P* value	Odds ratio (95% CI)
Gender, male/female	13/11	86/64	1	
Age, y (mean ± SD)	65.8 ± 10.7	40.7 ± 13.4	<.001	
>60 y, n (%)	16 (66.7)	11 (7.3)	<.001	25.3 (8.87-72.0)
Mortality, n (%)	4 (16.7)	0	—	
Underlying disease psoriasis/psoriatic arthritis, n (%)	22 (91.7)	148 (98.7)	.092	
Skin detachment (% TBSA), mean ± SD (range)	33.2 ± 20.8 (8-80)	0	—	
Mucosal involvement, n (%)	14 (58.3)	0	—	
Leukopenia, <3000 WBC/μL, n (%)	14 (58.3)	0	—	
<1000 WBC/μL, n (%)	9 (37.5)	0	—	
Thrombocytopenia <150,000 platelets/μL, n (%)	16 (66.7)	0	—	
Liver function (transaminases) (IU/L)				
AST, mean ± SD (range)	36.2 ± 38.5 (7-184)	28.7 ± 10.2 (8-49)	.396	
ALT, mean ± SD (range)	37.1 ± 39.9 (12-193)	30.2 ± 9.8 (8-51)	.427	
Hypoalbuminemia (plasma albumin <3.5 g/dL), n (%)	18 (85.7)	30 (20)	<.001	
Methotrexate exposure				
Duration (range)	34 (3-90) days	> 3 months	<.001	
Initial dosage, mg/week (mean ± SEM)	12.4 ± 0.8	10.5 ± 0.3	.026	
No slow titration upward, initial dosage >10 mg/week, n (%)	15 (62.5%)	55 (36.7%)	.024	2.88 (1.18-7.01)
Without folic acid supplement	23 (95.8%)	108 (72.0%)	.010	8.94 (1.17-68.4)
Concomitant drugs				
NSAID use, n (%)	5 (20.8%)	45 (30.0%)	.47	
Renal function				
eGFR, mL/min (mean ± SEM)	46.1 ± 6.2	100.0 ± 2.5	<.001	
Chronic kidney disease (eGFR <60 mL/min) n (%)	17 (70.8%)	7 (4.7%)	<.001	49.6 (15.5-159)
Ratio of MTX initial dosage/eGFR [(mg/week)/(mL/min)], mean ± SEM	0.39 ± 0.06	0.11 ± 0.01	.006	



Les MEN sont associés à une mortalité accrue surtout chez le patient

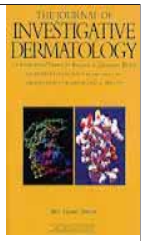
Chen et al, J Am Acad Dermato

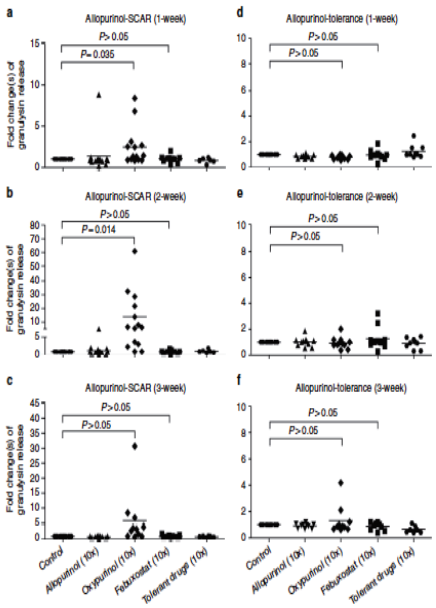


centre de référence maladies rares

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

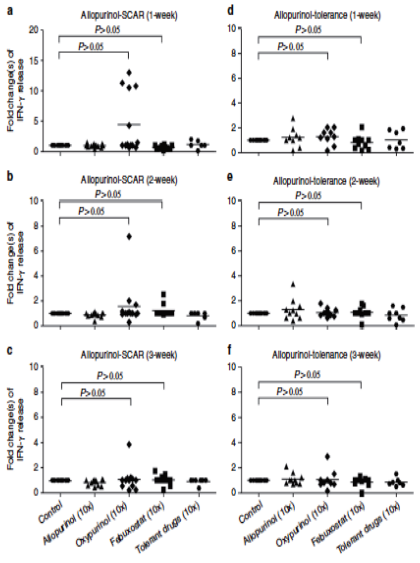
Wen-Hung Chung[1,2,6], Ren-You Pan[3,6], Mu-Tzu Chu[4], See-Wen Chin[1,2], Yu-Lin Huang[1,2], Wei-Chi Wang[5], Jen-Yun Chang[5] and Shuen-Iu Hung[3,4]





g

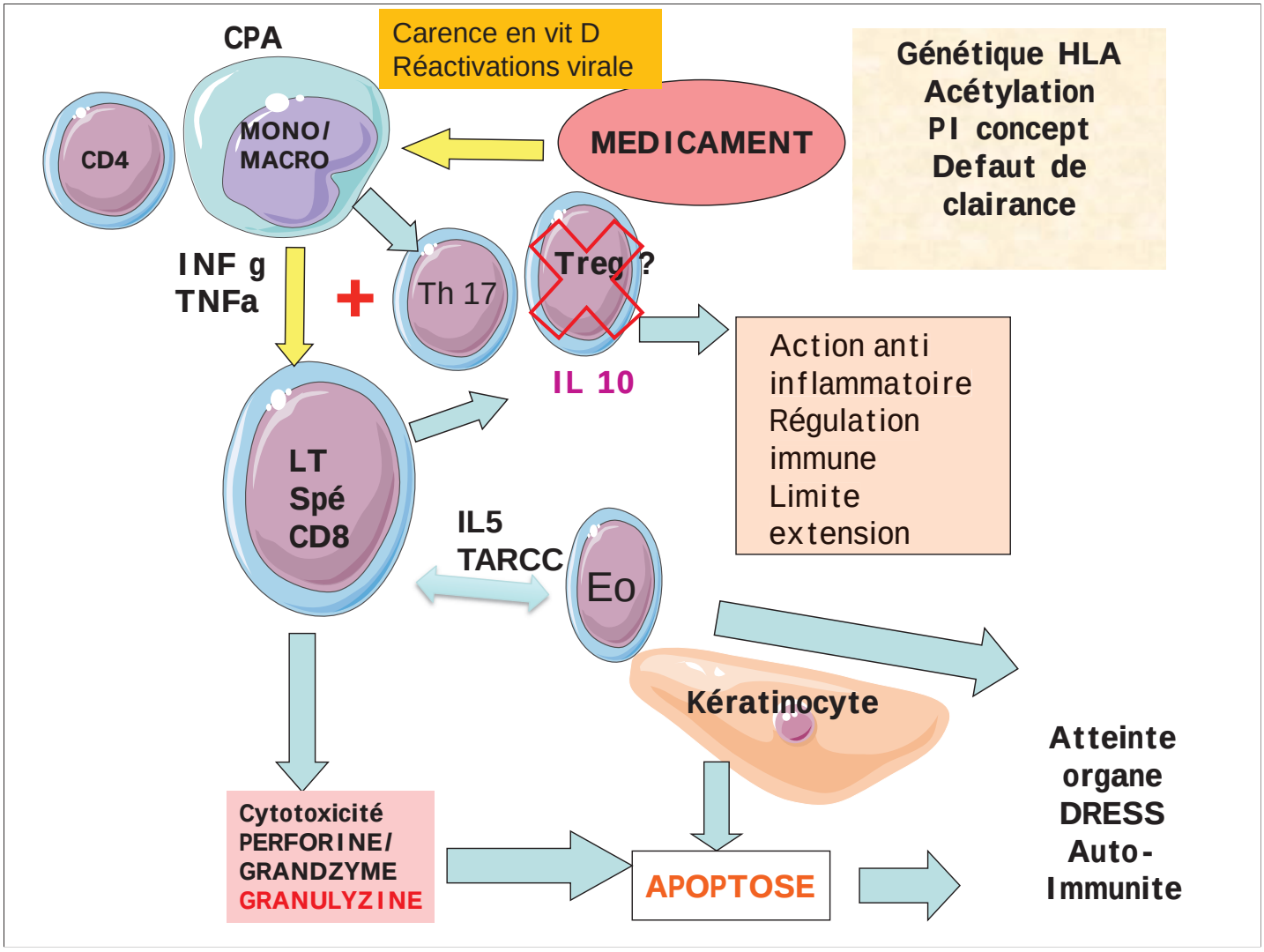
	Allopurinol		Oxypurinol		Febuxostat
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Cross-reactivity (%)
1 week	7	100	43	100	0
2 week	14	100	86	91	0
3 week	0	100	64	80	0



g

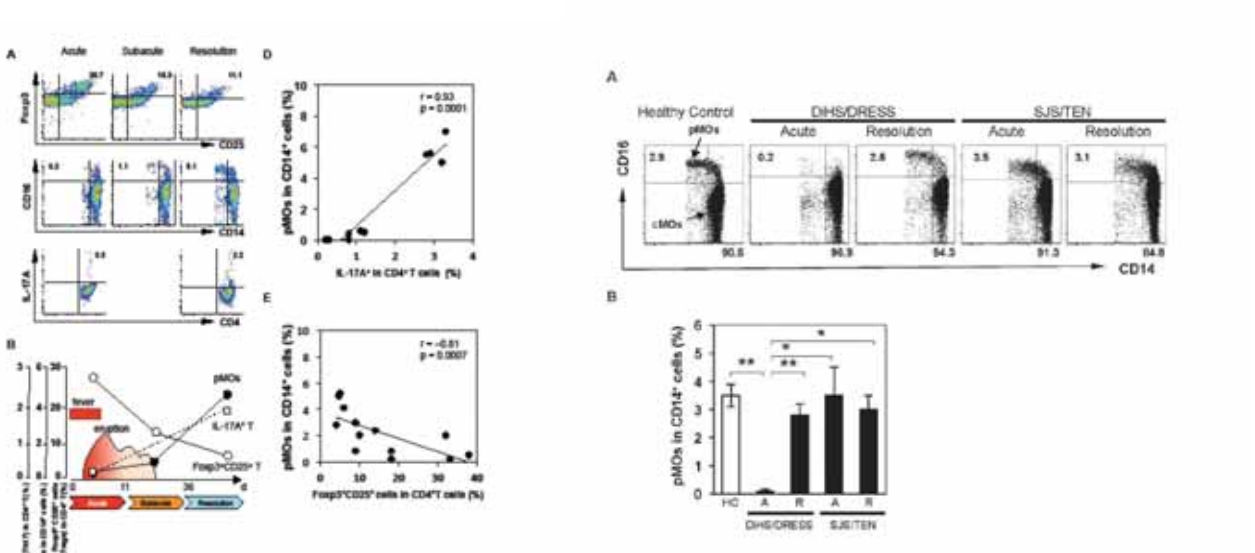
	Allopurinol		Oxypurinol		Febuxostat
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Cross-reactivity (%)
1 week	0	89	38	78	0
2 week	0	90	15	100	10
3 week	0	90	8	89	0

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



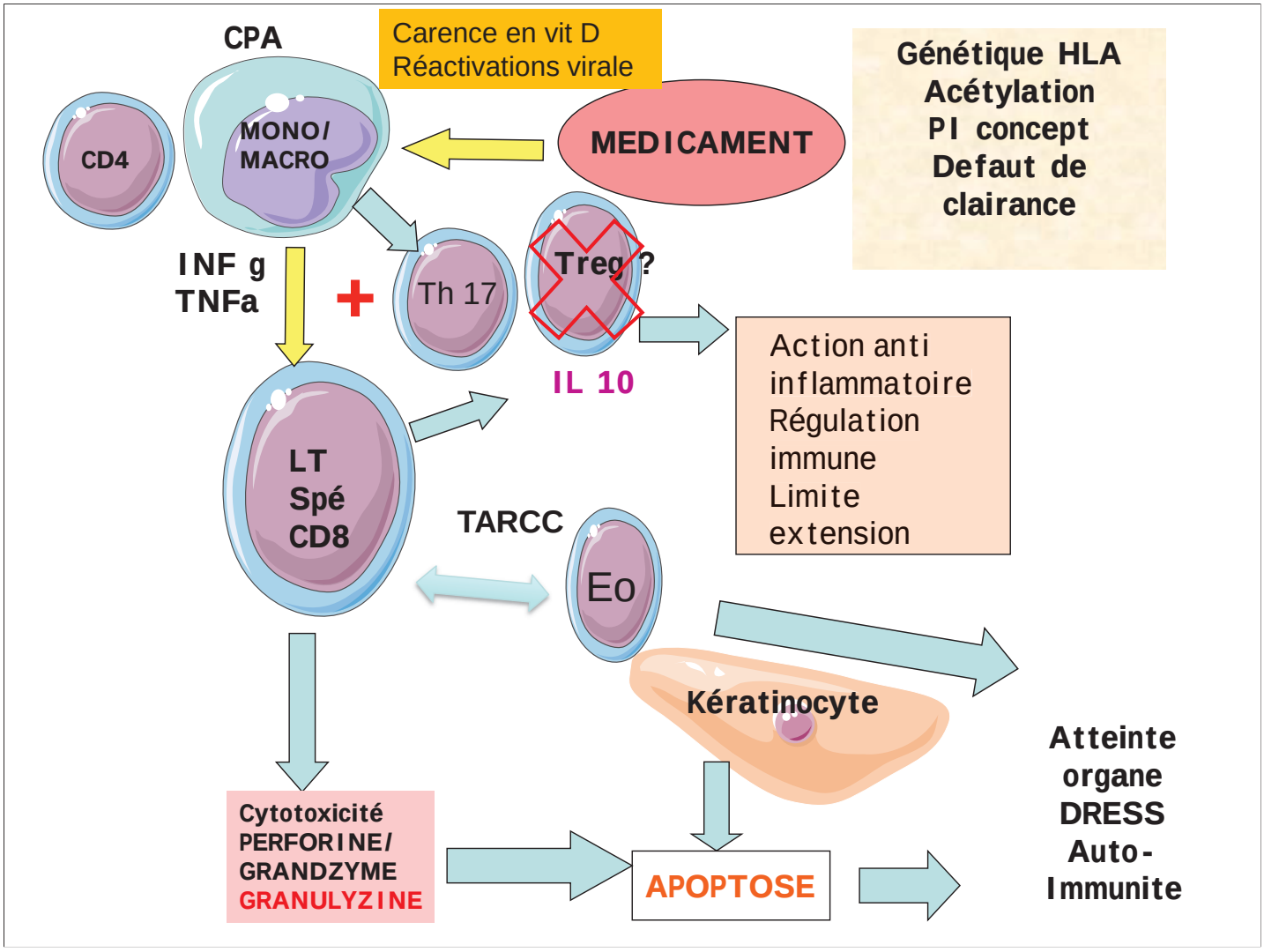
centre de référence maladies rares

DRESS Th17



Les Monocytes se differentient en macrophage pro Infl apres Un DRESS

Shiohara et al ,CEA, 2018



Physiopathologie
Elimination metabolite

centre de référence maladies rares

Table 1. Characteristics of patients with minocycline-induced DRESS

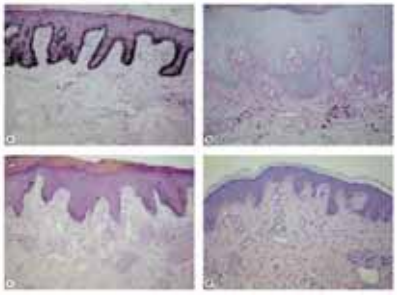
Case	Sex	Age years	Photo-type	Time to onset, days	Total dose, g	Organ dysfunction	Eosinophilia/ atypical lymphocytes	Treatment of DRESS	Duration of DRESS, months
1	F	45	V	60	n.d.	Liv, Kid, Lu, Per	14,000 eo/λ+	prednisone, α-interferon	18 (dead[1])
2	F	31	VI	30	3	Liv, Kid	0 eo/λ+	topical steroid	1
3	F	24	V	25	1.2	Liv, Kid, Lu	2,200 eo/λ+	prednisone	8
4	M	22	V	30	3	Liv, Kid, Lu	4,130 eo/λ+	prednisone	5
5	F	24	V	21	n.d.	Kid, Per, Myo	2,500 eo/n.d.	n.d.	n.d.
6	F	15	VI	16	2.4	Liv, Kid, Lu	8,730 eo/λ+	prednisone	6 (dead[1])
7	F	34	VI	21	3	Liv, Kid, Lu	3,200 eo/λ+	prednisone	3
8	F	19	V	19	3.15	Liv, Kid, Lu	1,660 eo/λ+	topical steroid	1
9	F	29	V	60	6.75	Liv, Lu	3,300 eo/λ+	topical steroid	3

Table 2. Minocycline assay and glutathione S-transferase genotypes

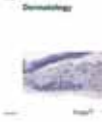
Case	Minocycline assay			Genotyping		
	interval	plasma, mg/l	skin	GSTT1	GSTM1	GSTP1
1	M12	0.79	+	n.d.	+	A/G
	M17	0.037	+			
2	D11	0.015	–	+	+	A/G
3	D6	–	–	–	+	A/A
4	D18	0.299	–	+	–	A/G
5		n.d.	n.d.	–	+	A/G
6	D17	1.18	–	–	–	A/A
	M3	+	n.d.			
	M5	–	n.d.			
7	M12	2.89	+	–	+	A/G
	M17	–	n.d.			
8	D18	0.025	n.d.	+	–	G/G
	D36	–	+			
9	M3	–	+	+	–	A/A

Accumulation minocycline
Peau et sang phototype V
Complexe mélanine
Forme prolongée 4/9
Rôle polymorphisme enzymatique

Rôle origine génétique

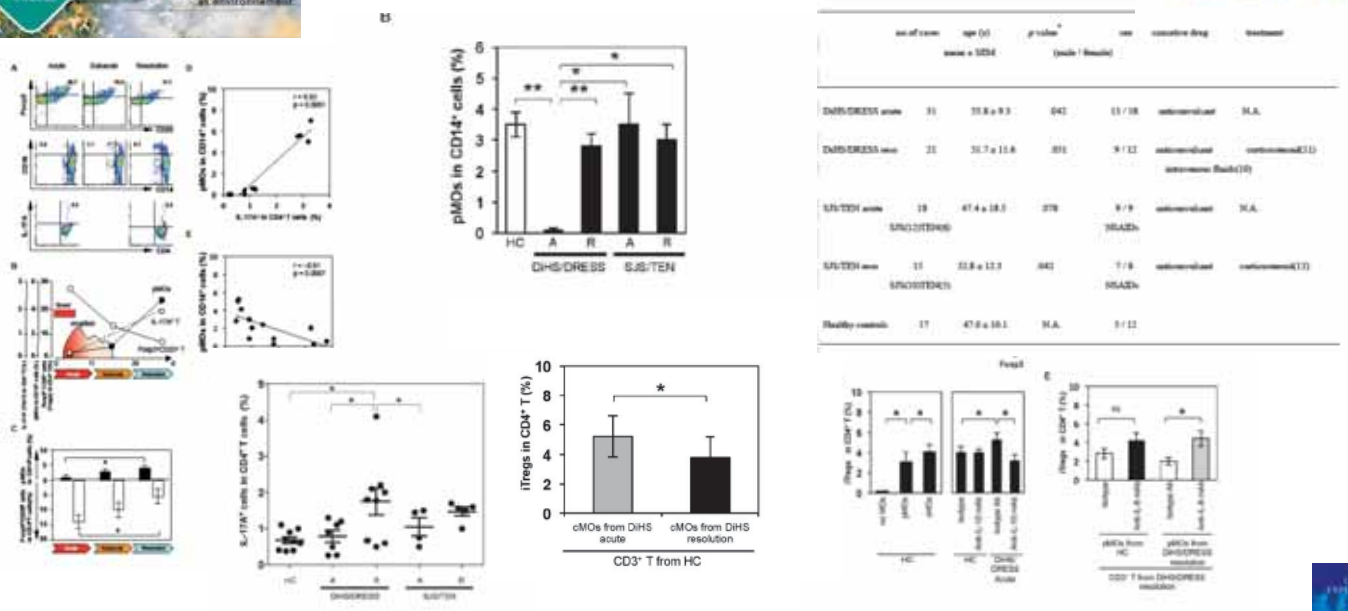


Maubec et al, Dermatology, 2008



Physiopathologie
TH17

centre de référence
maladies rares

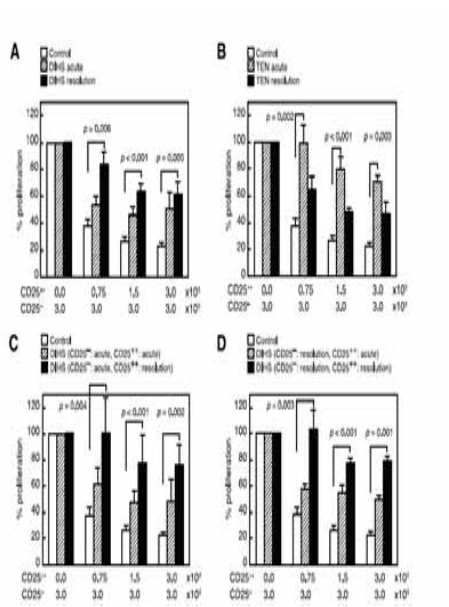


Les Monocytes polarisent vers une réponse TH17 chez une pop asiatique

Shiohara et al ,CEA, 2018

centre de référence
maladies rares

Physiopathologie
LT Régulateurs



- Il existe un défaut de régulation chronique après un DRESS

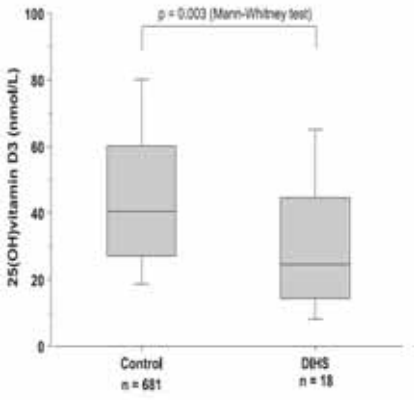
- Rôle dans
  - Réactivations virales
  - Auto-immunité
  - Hypersensibilité

Shiohara et al, J Immunol, 2009

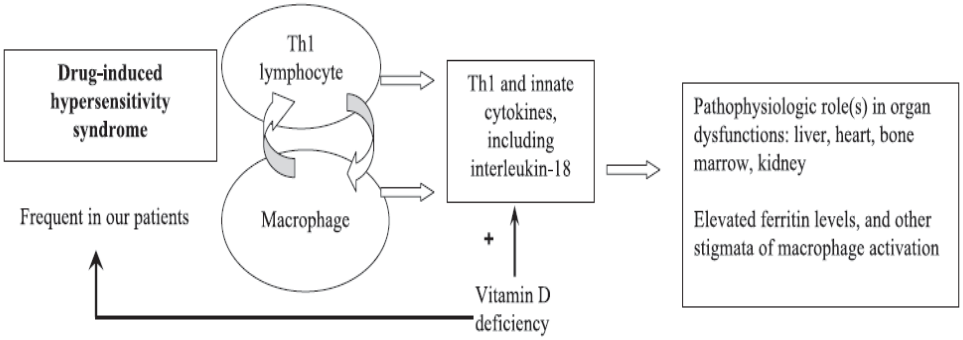
centre de référence maladies rares

Physiopathologie DRESS

Rôle de la carence en Vitamine D



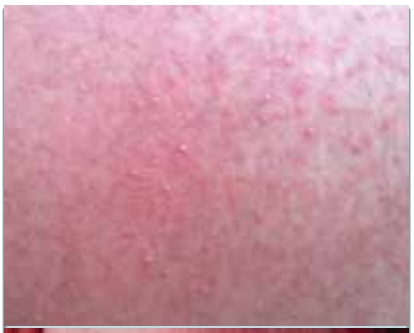
Quel rôle?
- Immuno-modulation
- Cause ou conséquence?

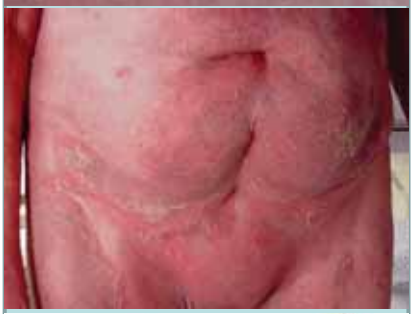


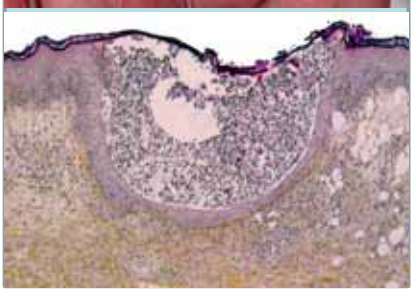
Ben Mrad et coll. Medicine 2009

PEAG

Pustulose Exanthématique Aigue Généralisée

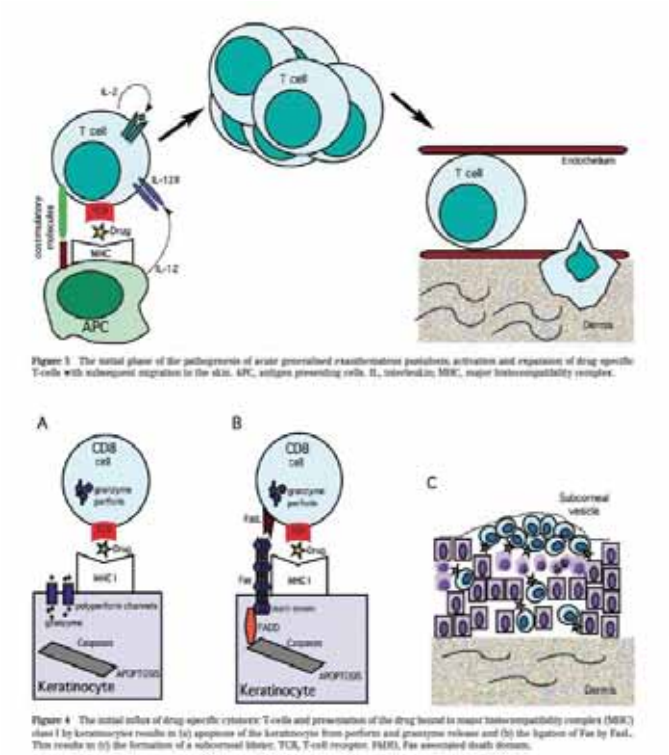






- **Physiopathologie:** hypersensibilité retardée médiée par des LT spécifiques du médicament, rôle de l'IL 8
- **Incidence** inconnue
- **Délai :** quelques heures à 21 jours
- **Clinique:**
  - Altération de l'état général, fièvre,
  - Eruption pustuleuse des plis sur un fond érythémateux puis extension.
- **Biologie:**
  - Hyperleucocytose à PNN ou PNE,
  - Hypocalcémie
- **Atteinte viscérale:** foie, rein
- **Histologie:** pustules intraépidermiques ou sous cornées
- **Médicaments :** pénicillines, macrolides, carbamazépine, inhibiteurs calciques, terbinafine
- **Guérison** rapide (7 jours)
- **Mortalité:** 5%
- ATTENTION AU DRESS PUSTULEUX

Physiopathologie-1



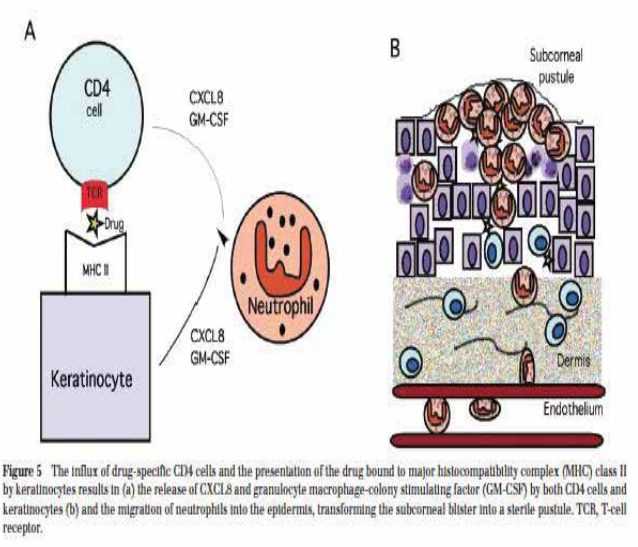
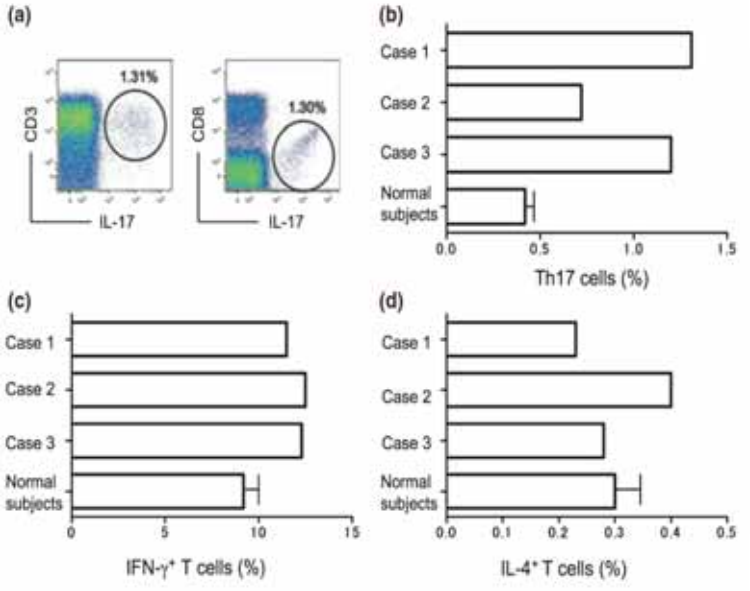


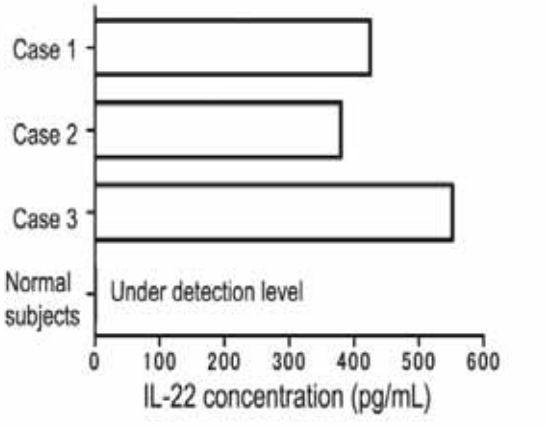
Figure 5 The influx of drug-specific CD4 cells and the presentation of the drug bound to major histocompatibility complex (MHC) class II by keratinocytes results in (a) the release of CXCL8 and granulocyte macrophage-colony stimulating factor (GM-CSF) by both CD4 cells and keratinocytes (b) and the migration of neutrophils into the epidermis, transforming the subcorneal blister into a sterile pustule. TCR, T-cell receptor.

Fernando et al, Aus J Derm,2012

Role IL36 RN POLYMORPHISME POUR Amoxicilline Roujeau et al JID 2013

Physiopathologie -2





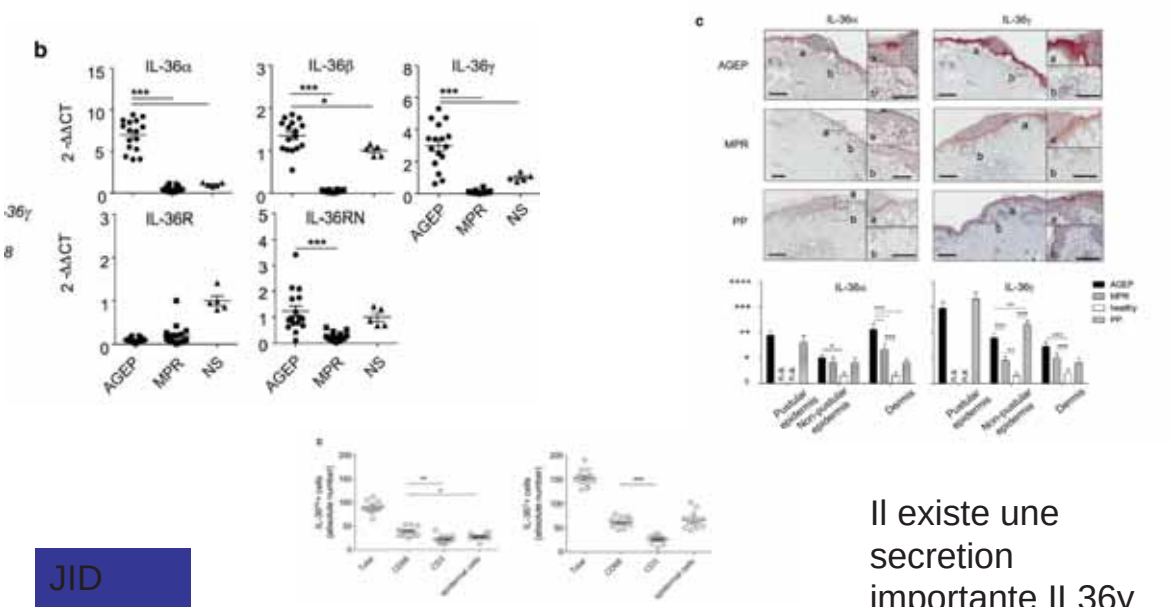
Tokura et al ,JEADV , 2011

LT Th17 sont augmentés dans la PEAG vs contrôle(N:12) ainsi que la sécrétion d'IL22

centre de référence
maladies rares

Culprit Drugs Induce Specific IL-36 Overexpression in Acute Generalized Exanthematous Pustulosis

Barbara Meier-Schiesser[1,2], Laurence Feldmeyer[3], Dragana Jankovic[1,3], Mark Mellett[1], Takashi K. Satoh[1], Daniel Yerly[1], Alexander Navarini[1,3,4], Richiro Abe[5], Nikhil Yawalkar[3], Wen-Hung Chung[6], Lars E. French[1,2,7,8] and Emmanuel Contassot[1,2,8]

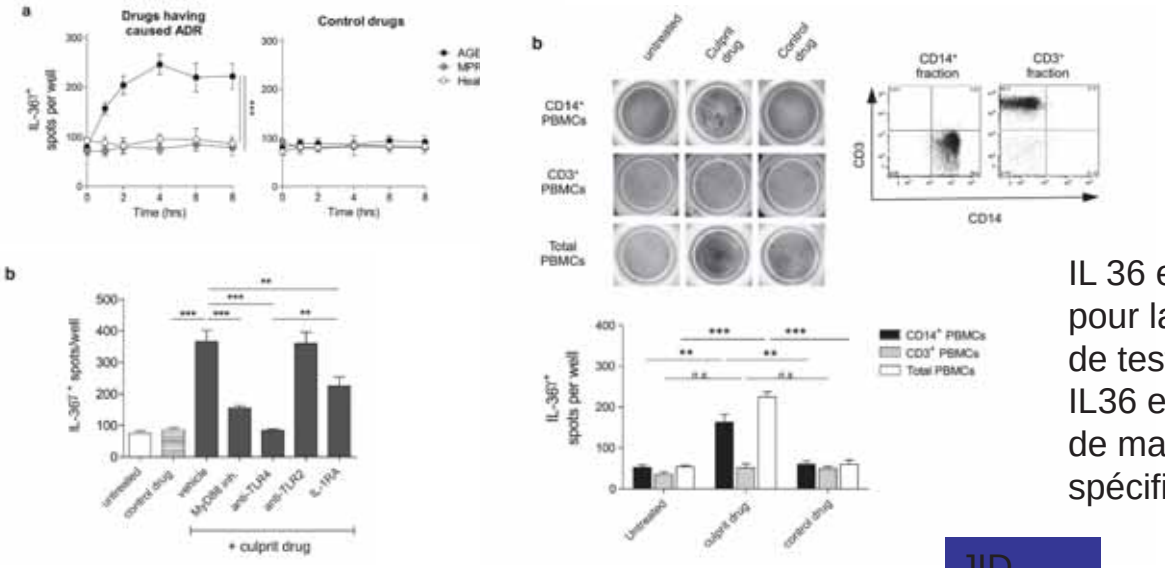


JID 2018

Il existe une secretion importante IL36y dans les AGEP

centre de référence
maladies rares

Culprit Drugs Induce Specific IL-36 Overexpression in Acute Generalized Exanthematous Pustulosis



IL 36 est une cible pour la réalisation de tests ELISPOT IL36 est secrété de manière spécifique

JID 2018

centre de référence maladies rares

Hypersensitivity and cardiovascular risks related to allopurinol and febuxostat therapy in Asians: A population-based cohort study and meta-analysis

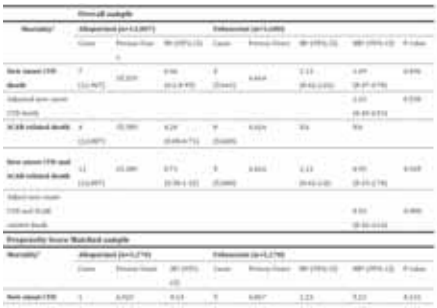
Table 1. Baseline characteristics of the new allopurinol and febuxostat users

	Before Propensity Matching			After Propensity Matching		
	Allopurinol (n=12,007)	Febuxostat (n=5,680)	SMD	Allopurinol (n=5,270)	Febuxostat (n=5,270)	SMD
Age (years), Mean ± SD	61.0±17.1	64.8±15.2	0.23	65.0±15.1	65.5±15.2	0.04
Sex, No. (%)						
Male	9,250 (77.0)	4,170 (73.4)	-0.08	3,870 (73.5)	3,864 (72.8)	-0.01
Female	2,757 (23.0)	1,510 (26.6)		1,400 (26.5)	1,434 (27.2)	
Underlying diseases, No. (%)						
Gout	7,901 (65.8)	2,951 (52.0)	0.28	2,951 (55.9)	2,951 (55.9)	0.00
Hypertension	4,539 (37.8)	2,809 (49.5)	0.24	2,567 (47.5)	2,620 (49.8)	0.05
CKD	2,416 (21.8)	2,329 (41.0)	0.42	1,927 (36.5)	1,927 (36.5)	0.00
Diabetes mellitus	2,740 (22.8)	1,718 (30.2)	-0.17	1,572 (29.8)	1,572 (29.8)	0.00
Hyperlipidemia	3,349 (27.9)	1,876 (33.0)	-0.11	1,734 (32.9)	1,766 (33.5)	-0.01
CVD*	40 (0.3)	17 (0.3)	0.01	21 (0.4)	16 (0.3)	0.02

Abbreviations: SMD, standardized mean difference; CKD, chronic kidney disease; CVD, cardiovascular

Table 2. Incidence of allopurinol- and febuxostat-related hypersensitivity reactions

Year	New Allopurinol Users, No.	New Febuxostat Users, No.	Allopurinol Hypersensitivity† No. (‰)	Febuxostat Hypersensitivity† No. (‰)	Allopurinol SCAR† No. (‰)	Febuxostat SCAR† No. (‰)	P value*	P value§
2012	3,914	NA	14 (3.6)	NA	6 (1.5)	0		
2013	3,647	1,396	11 (3.0)	0 (0)	5 (1.4)	0	0.678	0.597
2014	2,751	2,556	3 (1.1)	0 (0)	1 (0.4)	0	0.251	1.000
2015	1,675	2,918	5 (3.0)	1 (0.3)	4 (2.4)	0	0.098	0.042
Total	12,007	5,680	33 (2.7)	1 (0.2)	16 (1.3)	0	<0.001	0.003



Febuxostat semble moins toxique que l'allopurinol

WH CHUNG et al, Clin Pharma and Ther, 2019

centre de référence maladies rares

1-Preciser le type de Toxidermie

Quels sont les éléments cliniques et biologiques A visée diagnostic et pronostic faites vous?

Signes de gravité/Clinique

- Oedème du visage
- Adénopathies multiples
- Fièvre élevée en plateau
- Purpura/pustules

DRESS/PEAG

- Atteintes muqueuses
  - Deux sites au moins (Lyell)
- Bulles
- AEG/Douleurs intenses
- Signes de Nikolski
- Extension rapide

NET/EPF

Éléments biologiques nécessaires

- NFP+ frottis sanguin
- Bilan hépatique
- Bilan rénal
- Recherche de Ly actives
- Bilan inflammatoire
- Sérologies VIH VHB VHC
- Sérologies Mycoplasme IgM et IgG
- Auto-immunité (ACAN ENA Anticorps anti peau , anti TPO)
- Biopsie cutanée , IFD si bulles
- Autres en fonction des atteintes

DRESS

Anomalies Hématologiques

	Roujeau *et al.* [2, 3]	Peyrière *et al.* [14]	Chen *et al.* [9]	Ang *et al.* [15]	Cacoub *et al.* [16]	Wei *et al.*	KARDAUN
Case number	53	446	60	27	172	91	117
LAP	75%	18.1%	30.9%	NA	56%	11%	81%
Eosinophilia	30%	57%	52%	81.5%	66%	69%	95%
Atypical Lymphocyte	NA	7%	63.3%	NA	27%	73%	67%

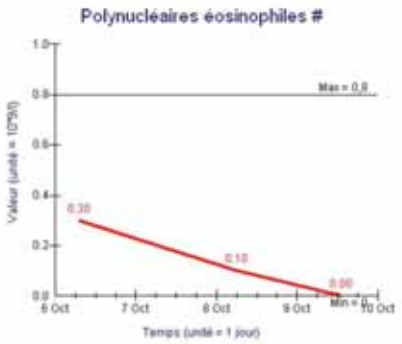
L'éosinophilie dans le DRESS est inconstante ET retardée

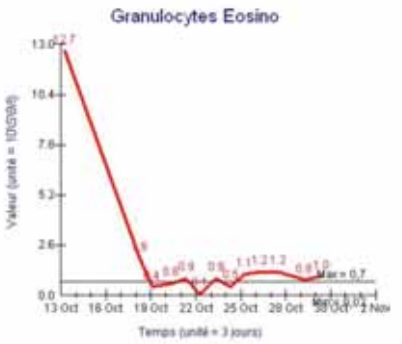
Peut être remplacée par une lymphocytose atypique

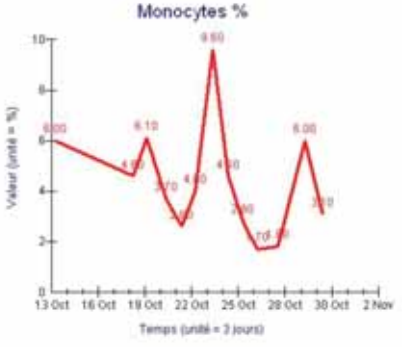
Wei et al , EJD, 2011
Kardaun et al , BJD, 2013

Biological specificities

Eosinophilia is often delayed







DRESS
Pustuleux

Evolution :
Healing within
Two months
under
corticosteroids

DRESS

Anomalies Hématologiques

TABLE 3. Laboratory Features of Patients With DIHS and Patients With AOSD, With or Without Hemophagocytosis

Characteristic	DIHS (Present Report) No. (%)	AOSD and Hemophagocytosis (Ref. 2) No. (%)	AOSD (Ref. 28) No. (%)
No. of patients	24	6	72
Age, yr (range)*	50.4 ± 17.1 (29–84)	43.3 ± 16.6 (22–72)	35.2 ± 13.5
No. with leukocytosis (>10,000/μL)	14 (58)	2 (33)	64 (89)
Mean leukocyte count ± SD	18,514 ± 7,581/μL	†	
No. with ≥80% neutrophils	9	2/6 (33)	
C-reactive protein (mg/L) (nl < 5)			
Mean ± SD (range)	131 ± 111 (14–467)	236 ± 131 (39–355)	
Lactate dehydrogenase (IU/L) (nl < 200)			
No. tested	22	6	
Mean ± SD (range)	1044 ± 1084 (306–4788)	1544 ± 1398 (350–3600)	
No. with value >2N	13/22 (59)	4/6 (67)	
Triglycerides (mmol/L) (nl <1.5–<1.6)			
No. tested	14	6	
Mean ± SD (range)	2.3 ± 1.3 (1.27–5.7)	3.1 ± 1.0 (1.9–4.24)	
No. with value >N	11/14 (79)	6/6 (100)	
Ferritin (μg/L) (nl 20–250)			
No. tested	19	6	72
No. with value >20N	3/19‡ (16)	5/6 (83)	
No. with value >5N	9/19 (47)	5/6 (83)	28/72 (39)
No. with value >N	14/19 (74)	6/6 (100)	50/72 (69)
Glycosylated ferritin (%) (nl > 50)			
No. tested	11	5	
No. with value <20%	4/11 (36)	4/5 (80)	52 (72)
No. with value <50%	8/11 (73)	5/5 (100)	

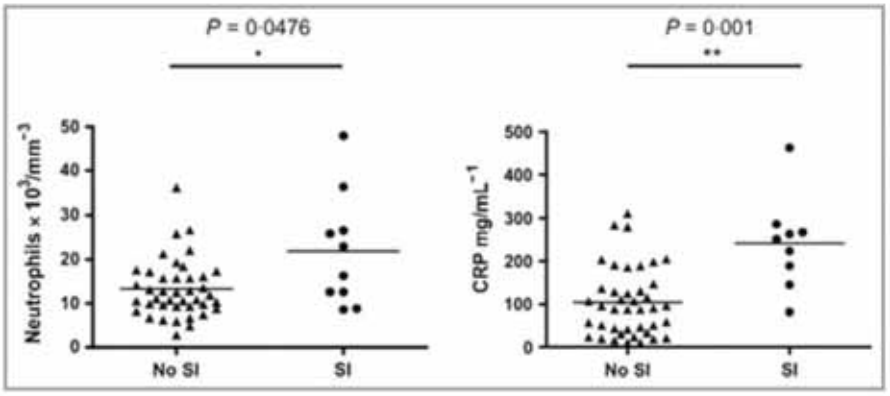
Abbreviations: N, upper limit of the normal value; nl, normal value; No. tested, number of patients with level tested.
*Mean ± SD (range).
†Two patients had leukocytosis: 13,730/μL and 27,600/μL, respectively.
‡Excluding 1 patient who had received multiple blood transfusions.

Il existe souvent des critères de SAM mais le SAM vrai est rare

Ben m'rad. Médicine, 2009

NOVARTIS

PEAG
Biologie



La neutrophilie est associée au pronostic et aux atteintes viscerales
Une eosinophilie modérée >730 est presente dans 80% des cas

Choi et al , Ann Derm, 2012
Hotz et al , BJD, 2013

Clinique et Biologie

Clinique

- Fièvre à 40
- Érythème prurigineux diffus avec oedeme facial
  - Muqueuses normales
  - Elements purpuriques
- ADP cervicales indolores bilatérales
- Dyspnée mais Auscultation cardio-pulmonaire normale
- Persistance 1 mois avec desquamation finale

Biologie

NFP:
•Lymphocytes activés au frottis
•Lymphocytose à 5470/mm3
•Eosinophilie à 1840/mm3

•Syndrome inflammatoire biologique (CRP 75, PCT 0.3)

•Bilan hépatique normal sauf ALAT à 80

•Sérologies hépatites/VIH/mycoplasme négatives

•Histologie: toxidermie avec infiltrat lymphocytaire peri-vasculaire riche en éosinophiles et lymphocytes stimulés

- 1-Preciser le type de Toxidermie
- Quel est votre diagnostic final?

Diagnostic du DRESS
Score diagnostique

- **Critères Cliniques**
  - Eruption >50% +1
  - Eruption évocatrice DRESS +1
  - Adénopathies +1
  - Atteinte viscérale(foie, rein, poumons, cœur ou autres)
    - 1 atteinte 0
    - 2 atteintes ou plus +2
- **Critères Biologiques sanguins**
  - Lymphocytes atypiques ou activés +1
  - Eo >700/mm3 ou 10-19,9% si leuco<4g +1
  - Eo>1500/mm3 +2
  - ACAN/séro Mycoplasme ou chlamydia/Hémocultures/séro hépatites
    - Si au moins trois négatif +1
- **Critères Négatifs**
  - Si fièvre <38,5 -1
  - Si résolution <15j -1
  - Biopsie non compatible -1
  - Eruption non compatible -1

INTERPRÉTATION Score
<2 pas de DRESS
2-3 DRESS possible
4-5 DRESS probable
>5 DRESS définit

Score=7

Plan

1. Préciser le type de toxidermie
2. Préciser la gravité
3. Enquête étiologique
4. Prise en charge thérapeutique
5. Prise en charge à distance

- 2- Préciser la gravité
- Recherchez vous des atteintes viscérales?
- Si oui lesquelles?

DRESS
Les atteintes viscérales sont fréquentes

Table 2. Comparison of Clinical Features of DRESS Between Different Studies[a]

Clinical Feature	Source: Roujeau and Stern[13]	Peyrière et al[9]	Chiou et al[14]	Present Cases
Common culprit drugs	Aromatic anticonvulsants, sulfonamides	Aromatic anticonvulsants, abacavir	Allopurinol, carbamazepine	Allopurinol, phenytoin, dapsone
Fever	87	69	72	87
Skin eruption	Exanthematous	Exanthematous	Exanthematous	Exanthematous
Lymphadenopathy	75	18	50	31
Eosinophilia	30	57	48	52
Atypical lymphocytes	NA	7	45	63
Hepatic involvement	51	52	87	80
Renal involvement	11	10	53	40
Mortality rate	10	10-40	10	10

Allanore et al

50% foie
66%

Internal organ involvement	107/117	91	85–96
1 organ involved	42	36	
2 organs involved	41	35	
> 2 organs involved	24	21	
Liver	86/114	75	
Kidney	40/108	37	
Lung	33/104	32	
Muscle/heart	13/99	13	
Spleen	12/79	15	
Pancreas	3/77	4	
Other[c]	13/117	11	

Kardaun et coll. BJD, 2013

Wei *et al.*	
91	
Chang Gung Memorial Hospital Health System, Taiwan	
84%	Liver
57%	Kidney
14%	Death

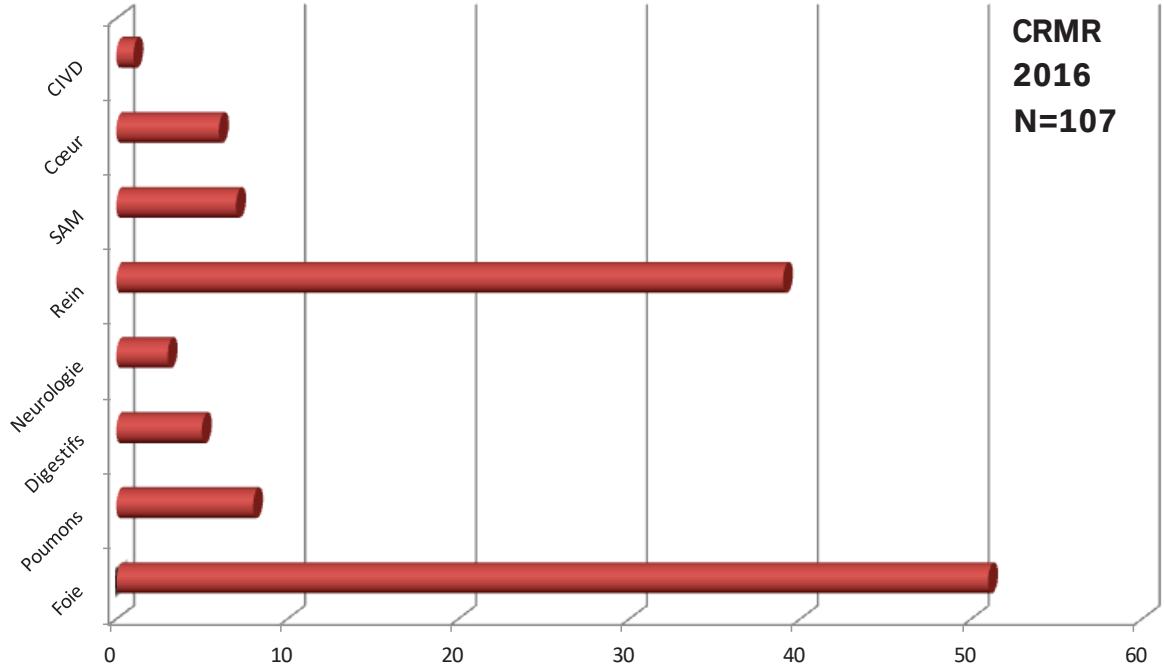
Wei et coll. EJD, 2011

Major organ dysfunction	
Liver‡	13 (54)
Kidney§	4 (17)
Heart	5 (21)
Biliary tract	2 (8)
Other organ affected	
Lung	4 (17)
Pharynx	7 (29)
Joints	4 (17)
Brain	4 (17)
Pancreas	1 (4)

Ben M'Rad et coll. Medicine, 2009

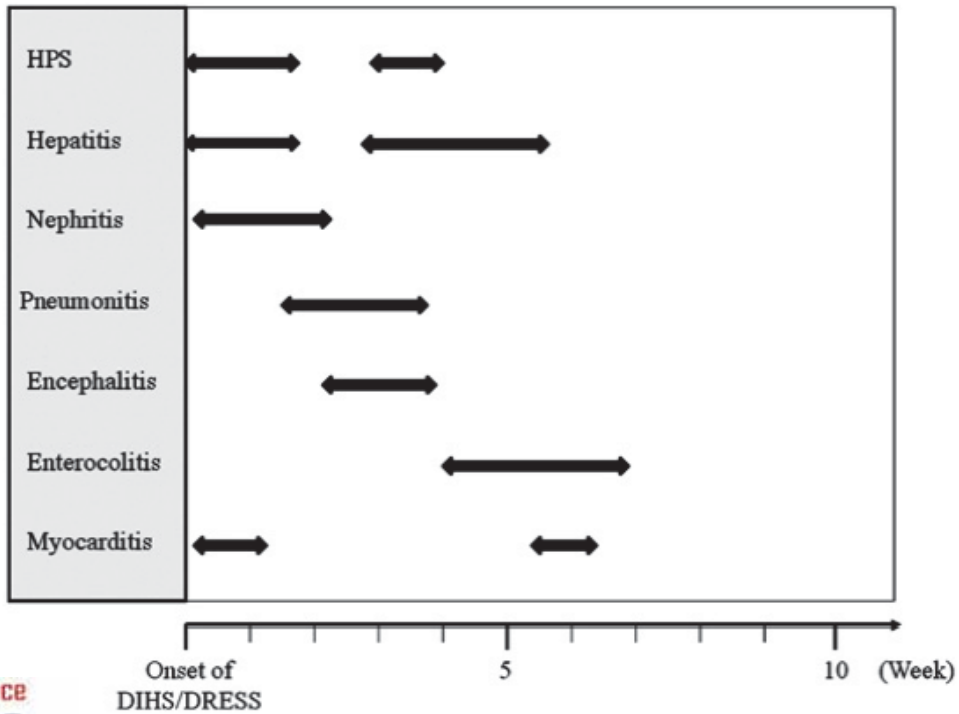
DRESS- Atteintes Viscérales

Les atteintes viscérales sont fréquentes et variées



centre de référence maladies rares

Les atteintes viscérales sont retardées dans les Toxidermies sévères (DRESS/PEAG)



centre de référence maladies rares

Kano et al. Med Clin North America, 2010

centre de référence maladies rares

ORIGINAL ARTICLE

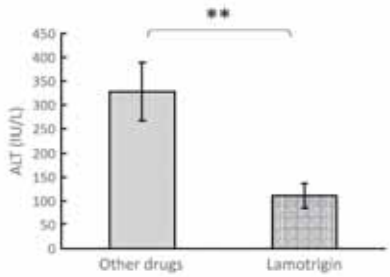
Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms due to lamotrigine differs from that due to other drugs

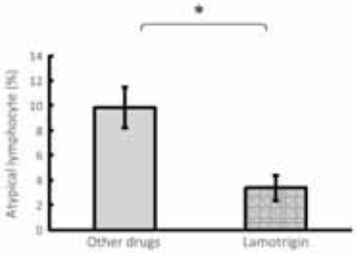
Yasuya TASHIRO,[1] Hiroaki AZUKIZAWA,[2] Hideo ASADA,[2] Hiroyuki NIIHARA,[3]

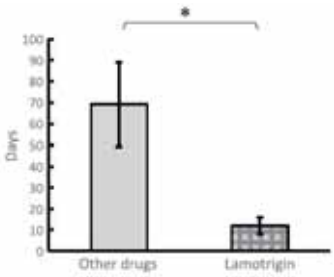
centre de référence maladies rares

Table 1. Characteristics of the patients

	Other drugs	Lamotrigine
Numbers of patients	32	12
Sex (male/female)	21/11	5/7
Age (years, mean ± SE)	49.3 ± 2.81	40.9 ± 4.37
Causative drug (numbers of patients)	Carbamazepine (15) Allopurinol (4) Phenobarbital (3) Mexiletine (2) Salazosulfapyridine (2) Zonisamide (2) Dapsone (1) Febuxostat (1) Phenytoin (1) Trichloroethylene (1)	Lamotrigine (12)







Il existe une différence clinique des DRESS en fonction des médicaments ainsi que sur les résultats du bilan allergologique

Tashiro et al,J Dermatol. 2019 Mar;46(3):226-233

NOVARTIS

PEAG
Atteintes viscérales

BJD

Parameter	Without SI (n = 48)	With SI (n = 10)	P-value
Age, year	52 ± 20	56 ± 18	0·5[a]
Female	28 (58·3%)	5 (50%)	0·7[b]3
Amoxicillin	7 (14·5%)	4 (40%)	0·08[b]
Amoxicillin rechallenge	0	2 (20%)	0·03[b]
Pristinamycin	8 (16·7%)	0	0·32[b]
Antibiotics	21 (43·8%)	5 (50%)	0·74[b]
Hospitalization, days	6·8 ± 4·4	8·4 ± 2·7	0·03[a]
Neutrophil count, × 10^3/mm^3	13·3 ± 6·5	21·9 ± 12·8	0·04[a,c]
C-reactive protein, mg/mL	103·3 ± 79·8	241·6 ± 106·2	0·001[a,c]

Reference	Patients (n, sex, age)	Comorbidities	Drug exposure	Systemic involvement	Outcome after drug withdrawal
Series					
Roujeau *et al.*[1]	n = 63: 52 without psoriasis history, 11 with psoriasis; 33 F/30 M; age (49·3 ± 21 y)	Preexisting kidney disease in 1	Mercury (n = 8); antibiotics (n = 45): β-lactams (n = 28), macrolides (n = 11), others (n = 6); other drugs (n = 10)	Acute renal insufficiency: 32% (n = 47); mean creatinine clearance: 1·21 ± 0·44 mL/s	nd

N=58

*10/58=29%

*Rein :6/10 Foie:7/10 Poumons:2/10

Hotz et al, BJD,

centre de référence maladies rares

DRESS
Pronostic

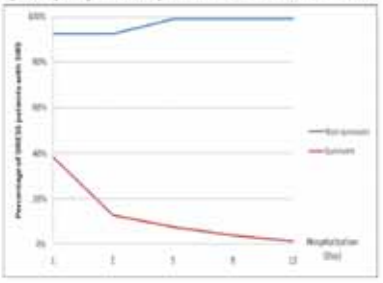
Table 3 Prognostic factors analysis at disease early stage (on the day of admission)

	Non-survivors (n=13)	Survivors (n=78)	OR	95%CI	P-value(<0.01)
SAPS variables					
Age(≥40)	10/13	60/78	1	0.2-4.0	1
Heart rate (>90)	12/13	20/78	20.3	2.5-164.1	0.0004
Systolic blood pressure (<100 or >200 mmHg)	1/13	5/78	1.2	0.1-11.3	1
Temperature (>38 ℃ or <36℃)	10/13	41/78	3.0	0.8-11.8	0.13
Oliguresis	1/13	0/10	x		1
BUN (>28mg/dl)	11/13	31/78	8.3	1.7-40.2	0.0051
WBC (white blood cells) (<4000 or >12000 /mm³)	11/13	25/78	11.7	2.4-56.8	0.0005
WBC <4000	1/13	5/78			1
WBC >12000	10/13	20/78	3	1.1-7.8	0.0006
K(<3 or >5)	2/13	7/71	1.7	0.3-9.1	0.62
Na(<125 or >145)	0/13	5/71	x		1
Bicarbonate(<20mmol/L)	5/13	3/10	1.5	0.3-8.4	1
Bilirubin (>4)	1/11	4/64	1.5	0.2-14.8	1
Glasgow coma scale (<14)	0/13	0/78	x		1
Chronic disease (metastatic cancer or hematologic malignancy)	0/13	10/78	x		0.35
Other variables					
Glucose(>212mg/dl)	3/13	5/61	3.4	0.7-16.3	0.14
P(<0.8 or >1.35)	9/13	10/21	2.5	0.6-10.6	0.30
AST(>40)	11/13	63/74	1	0.2-5.0	1
ALT(>40)	11/13	69/73	0.3	0.1-2.0	0.22
PaO₂ (<70mmHg)	3/13	1/10	2.7	0.2-30.8	0.60
Respiratory rate (>30/min)*	8/13	6/78	8	2.4-26.8	0.001

Table 5. The comparison of DRESS patients with SIRS between non-survivors and survivors

Hospitalization day	DRESS patients with SIRS		OR	95%CI	P-value (<0.01)
	Non-survivors	Survivors			
Day 1*	12/13	30/78	19.2	2.4-155.3	0.0004
Day 2	12/13	10/78	81.6	9.5-697.3	<0.000001
Day 5	13/13	6/78	300	15.8-5714.0	<0.000001
Day 8	10/10[#]	3/78	475	22.1-10223.1	<0.000001
Day 12	10/10[#]	1/78	1463	46.0-46599.0	<0.000001

Figure 1 The percentage rates of DRESS patients with SIRS between non-survivors and survivors during hospitalization



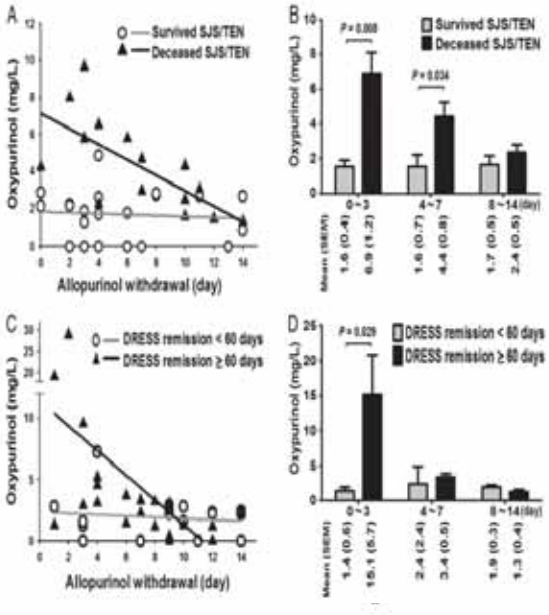
La présence d'un SIRS est un facteur pronostic au cours du DRESS

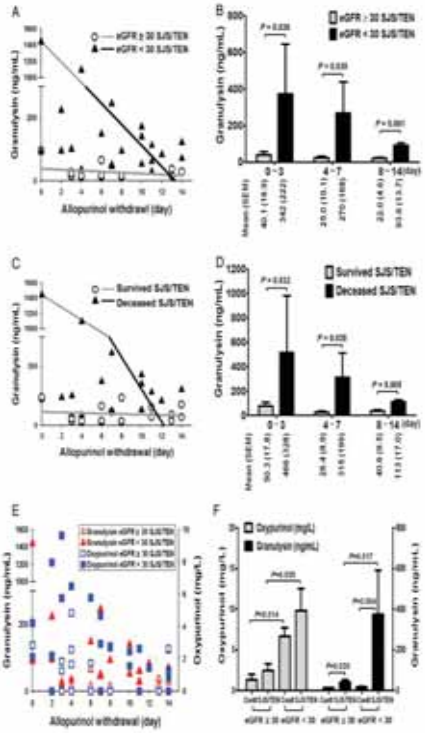
Wh chung et al , EJD 2011

centre de référence maladies rares

Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin

Wen-Hung Chung,[1,2,3] Wan-Chun Chang,[4] Sophie L Stocker,[5,6] Chiun-Gung Juo,[7] Garry G Graham,[5,6] Ming-Han H Lee,[5,6] Kenneth M Williams,[5,6] Ya-Chung Tian,[3,8] Kuo-Chang Juan,[3,8] Yeong-Jian Jan Wu,[2,9] Chih-Hsun Yang,[2,3] Chee-Jen Chang,[10,11] Yu-Jr Lin,[10,11] Richard O Day,[5,6] Shuen-Iu Hung[4]





L'insuffisance rénale ralentie la clairance de l'oxypurinol et de la granulysine, aggrave le pronostic

Chung W-H, et al. Ann Rheum Dis 2015

SCARS et AKI: rôle pronostic

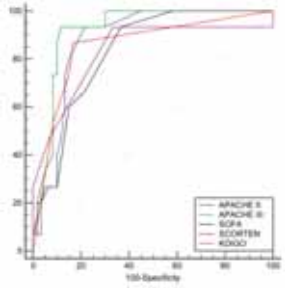


Table 5. Properties of discrimination and reclassification for combining KDIGO with other individual models in predicting in-hospital mortality.

Model	IDI (95% CI)	*P* value	NRI (95% CI)	*P* value
APACHE II	15.9% (2.4%, 29.4%)	0.021	133% (89%, 177%)	<0.001
APACHE III	7.8% (-2.9%, 18.3%)	0.152	117% (68%, 165%)	<0.001
SOFA	20.7% (6.0%, 35.4%)	0.006	130% (86%, 174%)	<0.001
SCORTEN	14.2% (5.5%, 22.9%)	0.001	100% (49%, 151%)	0.0005

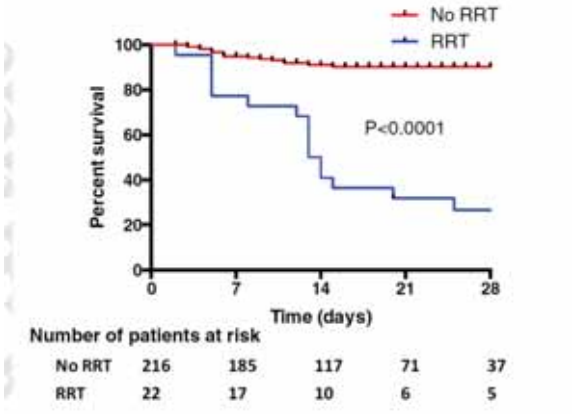
L'AKI est un facteur pronostic majeur
La stratification par de scores combinés semblent plus efficace

Mendela et al,PLOSone,2018

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

Séminaire ALLERGOLYON 2018

Transplantation

Acute Liver Failure/Injury Related to Drug Reaction With Eosinophilia and Systemic Symptoms: Outcomes and Prognostic Factors

At admission	
Median age (years)	35.8 (17-74)
Gender (n, females)	11
Origin (n)	
Africa	11
Asia	1
Caribbean islands	2
South America	1
Western Europe	1
Incriminated drug	
Carbamazepine	2
Allopurinol	2
Levetiracetam	1
Flunarizine	1
Sulazopyrine	1
Isoniazid	1
Isoniazid and/or pyrazinamide	2
Rabeprazole	2
Nevirapine	1
Beta-lactams	2
Beta-lactams/Clavulanic acid	1
Duration of treatment with the incriminated drug (days), n=13	31 (26-38)
Fever (°C)	39°C (39-40)
Skin rash	
Generalized erythematous rash	16
Erythematous rash > 50% body surface area	14
Facial oedema	5
Exanthem	4
Adenopathy	10
Hypereosinophilia	16
Eosinophilia (x10⁹ L)	1400 (580-2100)
Organ involvement	
Liver	16
Lung	1
Heart	0
Kidney	7
Pancreas	1
Muscle	4
HIV positive	4
PCR HHV6 (n=6)	5
RegiSCAR scoring	
Probable cases of DRESS (RegiSCAR score: 4-5)	3
Definite cases of DRESS (RegiSCAR score ≥ 6)	13

	Total	Patients who improved spontaneously (n=9)	Patients who died or were transplanted (n=7)	p
Age (median, Q1-Q3, years)	35.8 (28.6-43.6)	34.3 (25-44)	40.8 (30.2-42.9)	0.54
Gender (n, females)	11	6	5	1
Temperature (°C)	39 (39-39)	39 (39-39.5)	39 (38.9-39)	0.56
Duration of treatment with the incriminated drug (days), n=13	31 (26-38)	31 (26.5-36.5)	31 (17.5-37)	0.84
IV/oral corticosteroid therapy	9	5	4	1
Topic corticosteroids	4	3	1	0.58
Time between onset of rash-initiation of corticosteroid (days, n=9)	11 (6-19)	13 (6-19)	8.5 (4.5-13.5)	0.81
HIV positive	4	4	0	0.09
Hepatic encephalopathy	7	0	7	< 0.005
Creatinine $_{ad}$ (µmol/L), n= 14	85 (65-195.2)	80 (63.75-141.2)	131 (78.0-264.2)	0.48
Bilirubin $_{ad}$ (µmol/L)	105 (21-242)	41 (17.5-141.5)	163 (133-242)	0.22
INR$_{ad}$	2.19 (1.87-4.69)	1.90 (1.86-2.20)	5.12 (2.19-7.30)	0.16
PT$_{ad}$ (%)	37 (20.5-42.8)	42 (37-43)	13 (11-36)	0.019
Factor V$_{ad}$ (%)	58 (45-80)	73 (50.8-89.5)	45 (20-58)	0.079

16/36 cas de ALI :44,4%

25% mortalité
40% si transplanté= 6/16

Ichai P et al, Transplantation. 2017;101:1830-1837I

centre de référence maladies rares

Éléments biologiques nécessaires

- NFP+ frottis sanguin
- Bilan hépatique
- Bilan rénal et protéinurie 24h/CBU/ éosinophilurie
- Bilan thyroïdien
- Marqueurs cardiaques (troponine, BNP)
- PCR virales EBV CMV HHV6 HHV7
- lipasémie
- LDH, ferritinémie, triglycéridémie (SAM)
- Électrophorèse des protéines, calcémie
- Marqueurs inflammations (CRP, PCT)
- Sérologies VIH VHB VHC
- Sérologies Mycoplasme
- Auto-immunité (ACAN ENA Anticorps anti peau , anti-TPO)
- Biopsie cutané , IFD si bulles
- Autres en fonction des atteintes

Descamps et al , Ann Derm Venereol, 2010

DRESS
Réactivations virales

- Etude prospective 2002-2005 sur 40 DRESS
- Sérologies, PCR quantitatives sur sérum et cellules mononuclées sanguines
- réactivation virale= PCR sérum + et/ou charge virale importante dans les PBMCs (>1500 copies /µg d'ADN)

	EBV	HHV-6	HHV-7	CMV
Sérologie	EBNA: 38/38	IgG: 38/38 IgM: 16/38	-	IgG: 27/38 IgM: 0/38
Réactivation virale	16/38	17/38	12/38	0/38

13 patients (34%) =multiples réactivations virales

- 12 réactivent EBV et HHV-6 ou HHV-7

- Présence d'EBV intracellulaire dans les cellules mononuclées chez tous les patients

76% des patients réactivation virale

Picard et al, Sci Transl Med, 2010

ith Eosinophilia and Systemic Symptoms (DRESS): A
iral T Cell Response
t al.
Sci Transl Med 2, 46ra62 (2010);

DRESS
Réactivations virales

Table 3 Demographic, Clinical, and Treatment Characteristics Associated with DRESS

	n	%
Age (years)		
Mean ± SD (range)	40.7 ± 20.9 (0.1-84)	–
Sex		
Male	87/165	53
Female	78/165	47
Onset (weeks)*		
Mean ± SD (range)	3.9 ± 2.3 (0.5-16)	–
Skin rash	167/172	97
Maculopapular rash	101/167	60
Generalized erythematous rash	90/167	54
Facial edema	65/167	39
Internal organ involvement	151/172	88
Liver	142/151	94
Elevation of liver function tests	84/142	59
Hepatomegaly	17/142	12
Kidney	12/151	8
Lung	7/151	5
Central nervous system	3/151	2
Heart	3/151	2
Hypereosinophilia (>0.7 × 10^9 L^{-1})	114/172	66
Eosinophils (10^9 L^{-1})		
Mean ± SD (range)	3.5 ± 4.1 (0.4-30)	–
Fever >38.5°C	111/172	64
Lymphadenopathy	96/172	56
Atypical lymphocytes	47/172	27
HHV-6 infection		
Detection	70/172	41
Positive	56/70	80
Treatment		
Corticosteroids	134/172	78
Intravenous immunoglobulin	16/172	9

DRESS = Drug Reaction with Eosinophilia and Systemic Symptom; HHV-6 = human herpesvirus 6.
*Time between the initiation of drug therapy and the occurrence of symptoms.

Métanalyse
2012

172 DRESS

80% de positivité HHV6(basé sur élévation titre IgG dans majorités des cas)

35% 117 DRESS
Regiscar Study

Cacoub et al, JAMA, 2012
Kardaun et al, BJD, 2013

DRESS
Virus reactivation

DRESS Are Not Virus-Related Diseases In The Majority Of Cases

Benoit Ben Said[1], Jean Francois Nicolas[2], Denis Jullien[1]
1.SCARS National Reference Center, Dermatology, GH Lyon Centre, Lyon, France
2.Allergology and Clinical Immunology department, GH Lyon Sud, Lyon, France

Background

DRESS is one of the most severe SCARS associated with a mortality of 5 to 10%. During the last decade the role herpes virus reactivation (HHV6-7-cmv-ebv) in the development of DRESS was discussed. In this work we have evaluated in common practice the frequency of viral reactivation during DRESS syndrome detected by whole blood PCR.

Materials and methods

Between 01/2012 AND 01/2015 all patients seen for DRESS confirmed by KARDAUN score> 5 were evaluated for reactivation of the HERPES group viruses (HHV6, EBV, CMV) by blood PCR evaluated at diagnosis (D0) and repeatedly later (D7 to D42) and in the resolution phase (> 6 months) when possible

Results

During the study 85 DRESS patients were included.Among them 12% had a positive viral PCR at diagnosis (D0). Of these 85 cases, 55 cases were evaluated for these viruses several times. Of these 55 cases, 16% had remote reactivation (D7-D42) bringing the total viruses reactivation to 28% in acute phase. These late reactivations were dominated by CMV (80%) and HHV6 (20%). Of these 85 cases 65 were evaluated for these viruses in the resolution phase with a reactivation rate of 20% and blood levels remains identical to the initial level in all cases.In the resolution phase, the skin tests with the attributable drugs (score> I3) (Patch tests) found a positivity of patch tests in 60% of cases

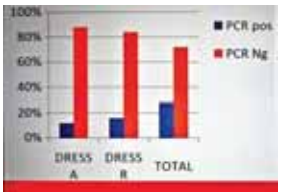
Discussion:

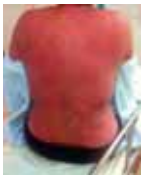
In contrast of previous, we find very rare viral reactivations during DRESS

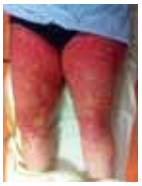
These data do not mean that the virus can not play a role in DRESS but suggests that virus are not the initial event or the cause of the disease. Viruses such as CMV seems to play a prognosis role in DRESS during evolution as has already been observed in dysimmune diseases such as GVH. Among the 65 cases evaluated, the skin tests were found to be positive in 60% of cases, confirming the role of drug delayed hypersensitivity during DRESS

Conclusion

The role of virus in the pathophysiology of DRESS is discussed. Our study confirms that viral reactivations detected, according to our method of detection and the virus searched, are positive in a minority of DRESS and that these viruses are not in our study, the original mechanism of the disease.







N=85

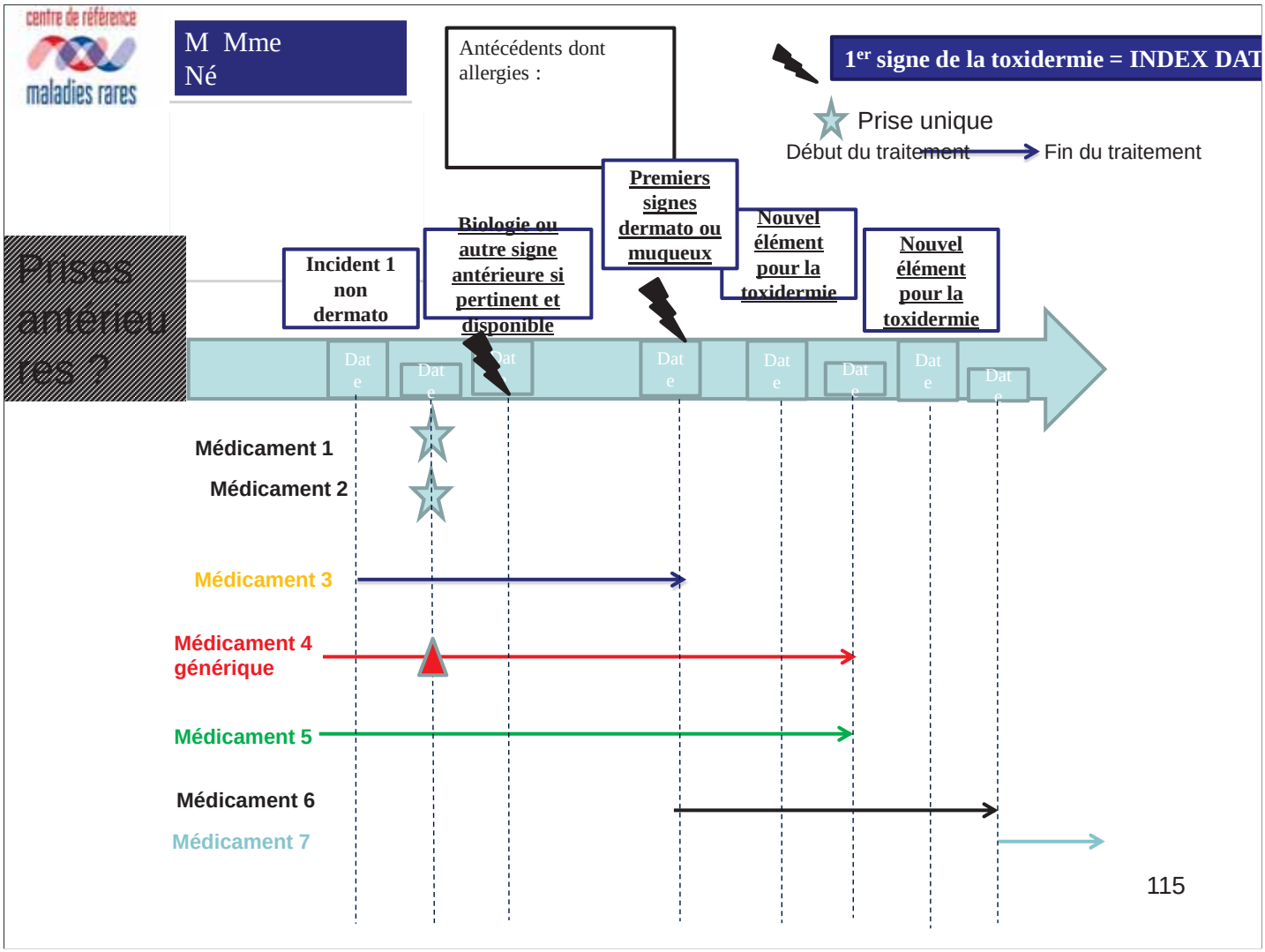
CMV EBV HHV6

28% virus

12% very acute
16% after Day 7 (CMV+++)

Plan

1. Préciser le type de toxidermie
2. Préciser la Gravité
3. Enquête étiologique
4. Prise en charge thérapeutique
5. Prise en charge à distance



Éléments à ne pas oublier dans le raisonnement d'imputabilité…

- « Index date »: jour des premiers signes:
  - !! peuvent être NON dermatologiques
  - syndrome pseudo grippal/conjonctivite/mal à la gorge dans un SJS/Lyell, fièvre dans un DRESS…
- Terrain du patient: immunodépression (VIH…), corticothérapie générale, immunosuppresseurs, insuffisance rénale chronique: peuvent modifier les délais d'imputabilité
- Demi-vie du médicament si déjà arrêté avant les premiers signes (règle des 5 demi-vies)

Méthodes d'imputabilité

- Méthode française (« Bégaud ») *Begaud B et al. Imputabilité des effets inattendus ou toxiques des médicaments. Actualisation de la méthode utilisée en France. Thérapie 1985;40:111-8; Arimone Y et al. Updating the French method for the causality assessment of adverse drug reactions. Therapie. 2013;68:69-76*
  - Imputabilité intrinsèque: critères chronologiques (C), sémiologiques (S) → score I (I0 à I6)
  - Imputabilité extrinsèque: score B (B1 à B4)

- Score de Naranjo *Naranjo CA et al. "A method for estimating the probability of adverse drug reactions". Clin. Pharmacol. Ther. 1981;30: 239–45.*

- Score ALDEN (spécifique SJS/Lyell) *Sassolas, B et al. ALDEN, an Algorithm for Assessment of Drug Causality in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Comparison With Case-Control Analysis, Clin Pharmacol Ther. 2010;88:60-68*
  - Prise en compte de l'imputabilité intrinsèque ET de la notoriété du médicament dans le même score

Méthode française pour CHAQUE médicament:

Critères chronologiques

Critères sémiologiques

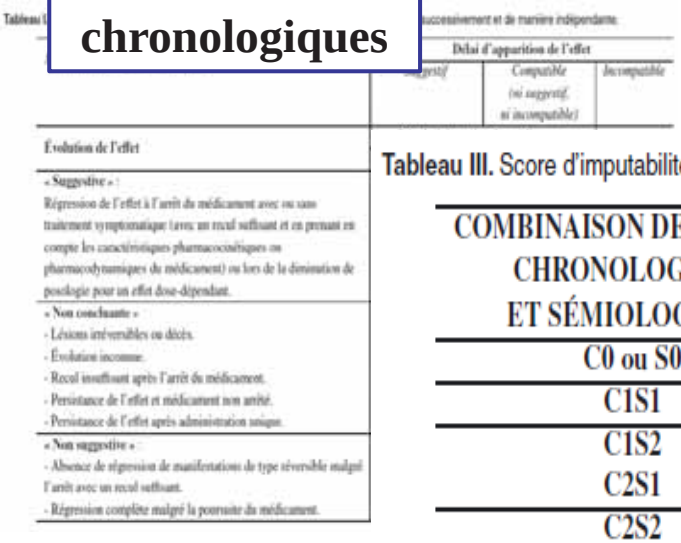
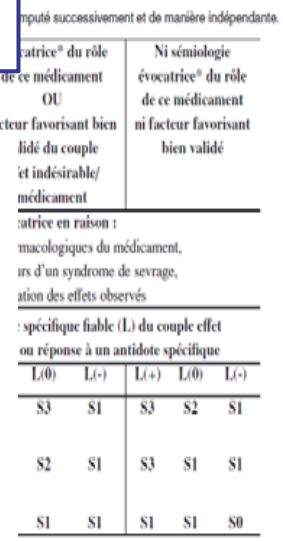
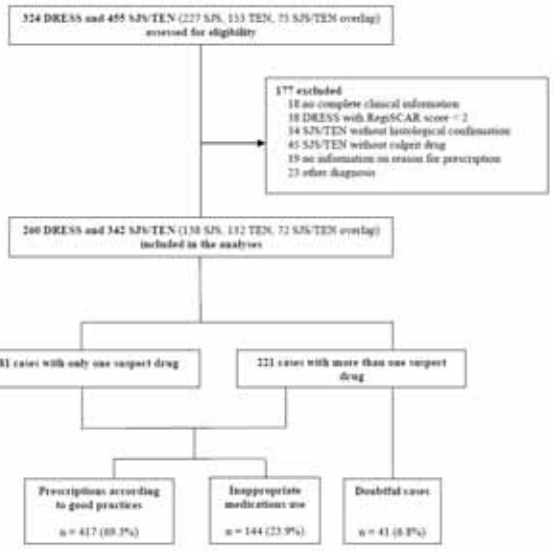


Tableau III. Score d'imputabilité intrinsèque.

COMBINAISON DES SCORES CHRONOLOGIQUE ET SÉMIOLOGIQUE	SCORE D'IMPUTABILITÉ INTRINSÈQUE
C0 ou S0	I 0
C1S1	I 1
C1S2	I 2
C2S1	I 2
C2S2	I 3
C1S3	I 4
C3S1	I 4
C2S3	I 5
C3S2	I 5
C3S3	I 6





Une mise à jour des pratiques médicales et un respect des indications
Permettrait de diminuer l'incidence des SCARS

Charby et al, Br J Dermatol. 2018

Is acetaminophen associated with a risk of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis? Analysis of the French Pharmacovigilance database.

Bénédicte Lebrun-Vignes MD[1], Claire Guy MD[2], Marie-Josèphe Jean-Pastor MD[3], Valérie Gras-Champel PharmD, PhD[4], Marie Zenut MD[5], the French Network of Regional Centres of Pharmacovigilance and the French Investigators for Adverse Skin Reactions to Drugs.

Il existe aucune preuve objective d'un sur-risque de SJ NET sous paracétamol

Biais avec autres causes le plus souvent

Lebrun-vignes B et al, Br J Clin Pharmacol. 2018;84(2):331-338

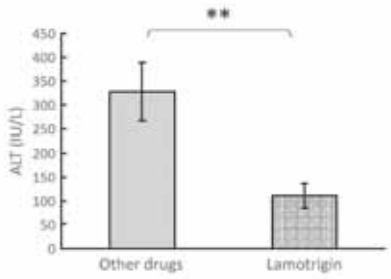
ORIGINAL ARTICLE

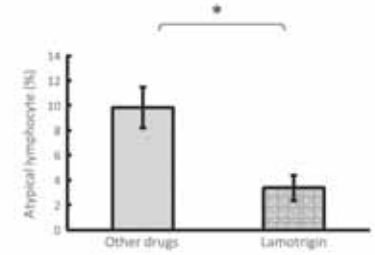
Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms due to lamotrigine differs from that due to other drugs

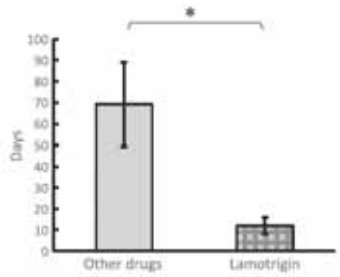
Yasuya TASHIRO,[1] Hiroaki AZUKIZAWA,[2] Hideo ASADA,[2] Hiroyuki NIIHARA,[3]

Table 1. Characteristics of the patients

	Other drugs	Lamotrigine
Numbers of patients	32	12
Sex (male/female)	21/11	5/7
Age (years, mean ± SE)	49.3 ± 2.81	40.9 ± 4.37
Causative drug (numbers of patients)	Carbamazepine (15) Allopurinol (4) Phenobarbital (3) Mexiletine (2) Salazosulfapyridine (2) Zonisamide (2) Dapsone (1) Febuxostat (1) Phenytoin (1) Trichloroethylene (1)	Lamotrigine (12)







Il existe une différence clinique des DRESS en fonction des médicaments ainsi que sur les résultats du bilan allergologique

Tashiro et al,J Dermatol. 2019 Mar;46(3):226-233

- Mais toujours penser que tout est possible et rester factuel: délai compatible→arrêt

Syndrome toxidermie sévère secondaires à des maladies infectieuses

- Coxsackie B4
- CMV
- Parvo B19++ (3 cas)
- Ecoli
- Chlamydiae
- Mycoplasme (Lyell+++)
- Herpes Virus (DRESS+++)

Feio AB, Acta Med. Port. 1997
Haro-Gabaldon V. Int. J. Dermatol. 1996
Naides SJ. Dis. Clin. North Am. 1998
Manzano S, Arch Pediatrie, 2006
Klein et al, Hautarzt 2009
Fernando SL, Australas Dermatol, 2012

SJS/TEN
CAUSES

- 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

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

SJS/TEN
Idiopathique

centre de référence maladies rares

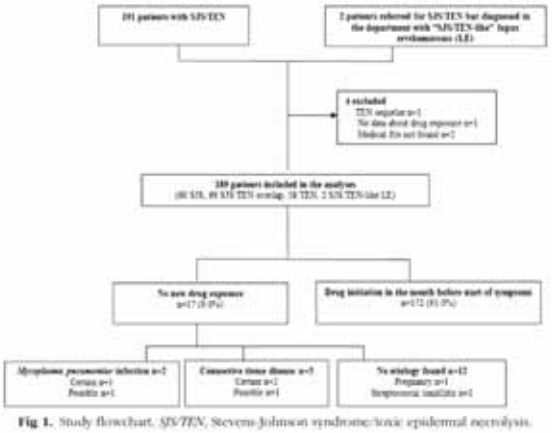


Fig. 1. Study flowchart. *SJS/TEN*, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table 1. Patients' characteristics

Characteristic	Idiopathic SJS/TEN (n = 12)	Drug-induced SJS/TEN (n = 172)	*P* value
Median age, y (IQR)	31 (23-43)	47 (35-61)	.004
Female, n (%)	9 (75.0)	89 (51.7)	.10
Median Scorten score at admission (IQR)[a]	0.5 (0-2)	1 (1-2)	.04
Median temperature at admission, °C (IQR)	39.1 (37.6-40.1)	38.3 (37.4-39.2)	.21
Median skin detachment, % (IQR)			
At admission	6 (2-13)	10 (2-20)	.39
At day 1	6 (2-12)	13 (4-25)	.09
At day 5	3 (1-9)	16 (4-35)	.02
Median biologic parameters at admission (IQR)			
Urea level (mmol/L)	3.7 (3.4-4.7)	5.3 (3.5-8.0)	.05
Creatinine level (μmol/L)	57 (49-75)	82 (64-99)	.008
Glucose level (mmol/L)	7.3 (5.7-7.7)	6.1 (5.1-7.9)	.50
AP level (IU/L)	51 (38-63)	64 (49-85)	.04
ALT level (IU/L)	35 (22-51)	38 (24-79)	.30
AST level (IU/L)	36 (27-57)	40 (25-68)	.50
GGT level (IU/L)	29 (19-46)	52 (26-108)	.05
LDH level (IU/L)	250 (129-355)	291 (184-415)	.35
Leukocyte count (10^9/L)	5800 (3600-8400)	5850 (4450-7950)	.59
Hemoglobin level (gm/dL)	11.7 (10.5-12.4)	11.9 (10.7-13.1)	.82
Platelet count (10^9/L)	184 (131-253)	210 (168-291)	.25
ICU admission, n (%)	4 (33.3)	54 (31.4)	1.0
In-hospital mortality, n (%)	0 (0)	17 (9.9)	.61

Chaby G et al , BJD,2019

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[c]	
		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			

<0 Very unlikely, 0–1 unlikely, 2–3 possible, 4–5 probable, >6 very probable

Sassolas et al, Clin Pharm Ther, 2010

centre de référence
maladies rares

Plan

1. Préciser le type de toxidermie
2. Préciser la Gravité
3. Enquête étiologique
4. Prise en charge thérapeutique
5. Prise en charge à distance

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

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

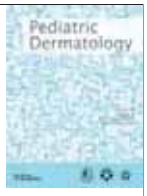
Huang SH. Burns,2008
Hszu et al ,Cornea, 2012
Kaser et al, Rev Obste Gynecol,2013

SJS/TEN
TRAITEMENT SPECIFIQUE

des essais mais pas beaucoup de certitude

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

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

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

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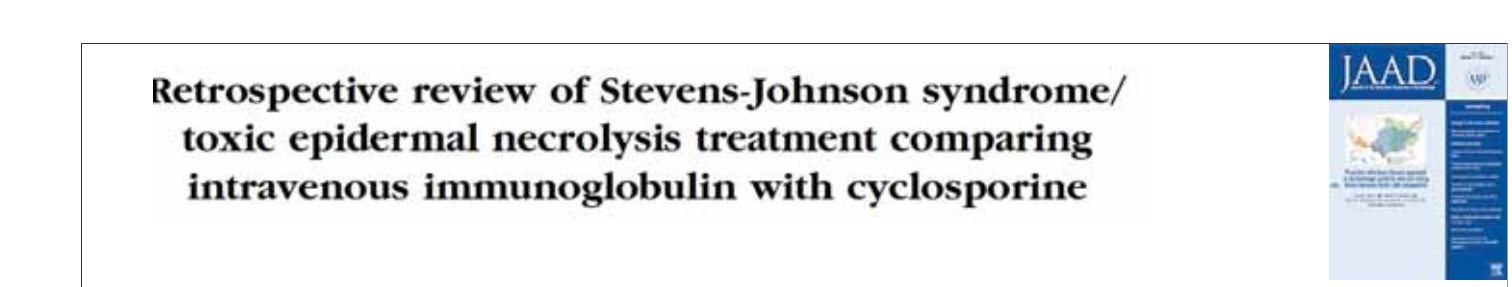
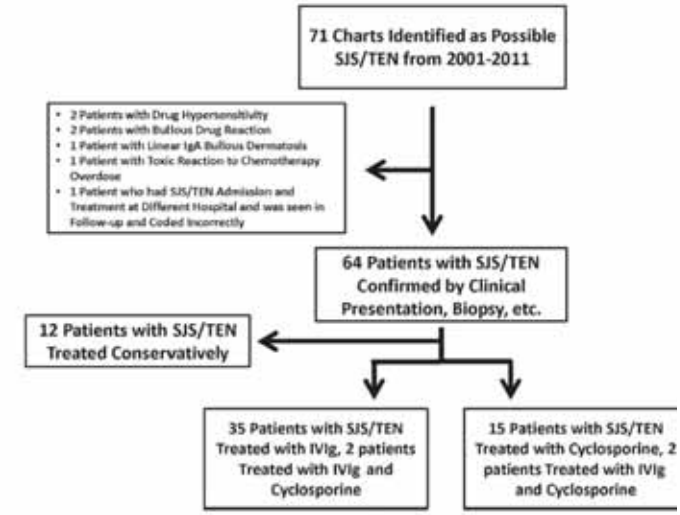
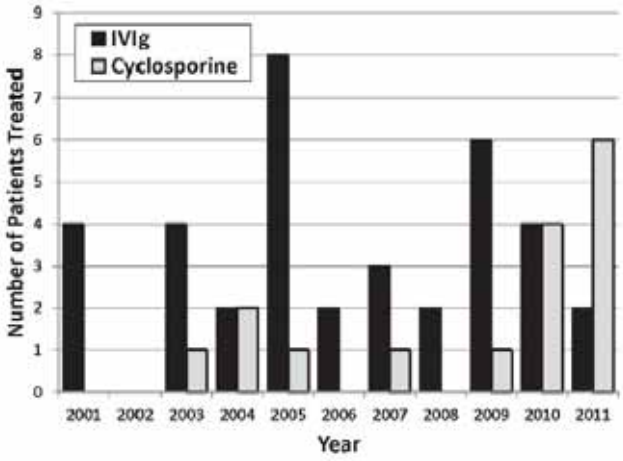
6. **GCSF**
7. **N acétylcystéine**
8. Anti TNF alpha
9. Cyclosporine

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







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

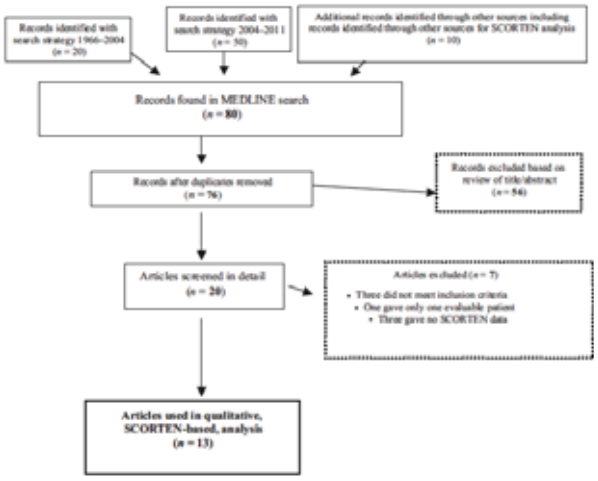
Bénéfice cyclosporine mais peu de patient peu grave

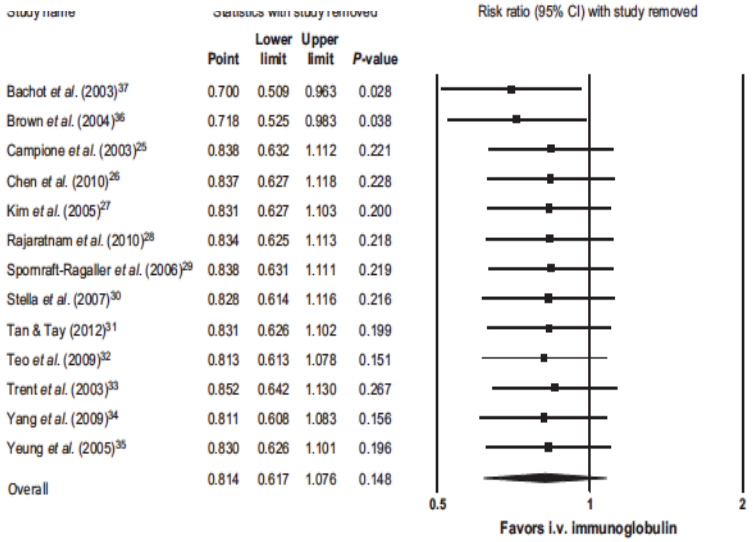
HM peu d'effet

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



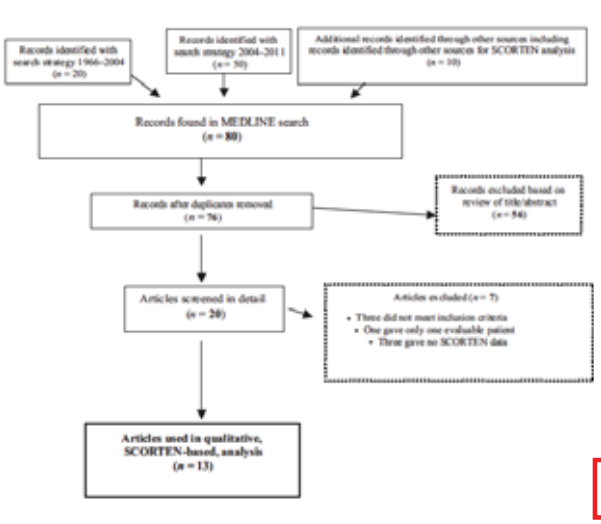


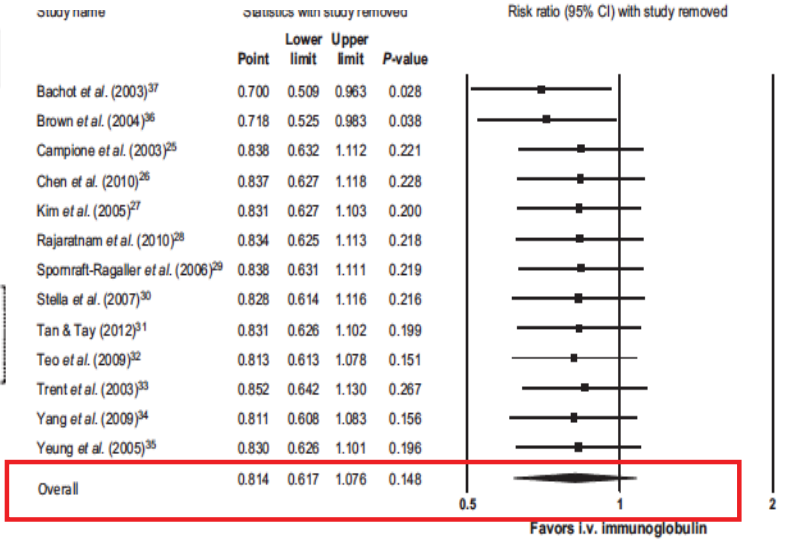
Il y a un effet des Ig IV sur la mortalité dans les SJS/TEN

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





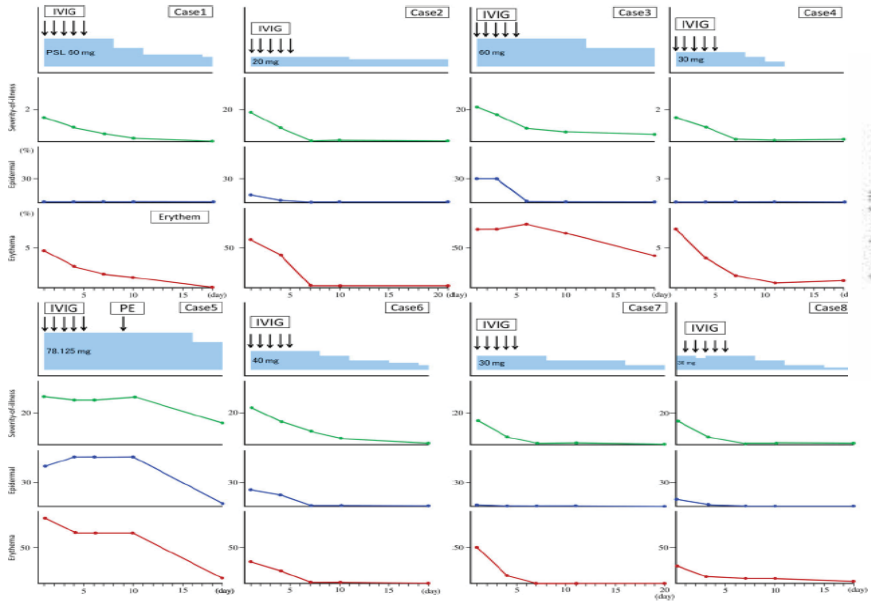
CONFIRME l'absence d'effet des IgIV sur la mortalité dans les SJSTEN

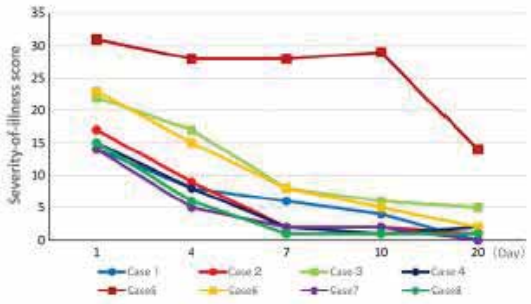
doi: 10.1111/1346-8138.12925 *Journal of Dermatology* 2015; **42**: 1–10

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, alloputinol	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

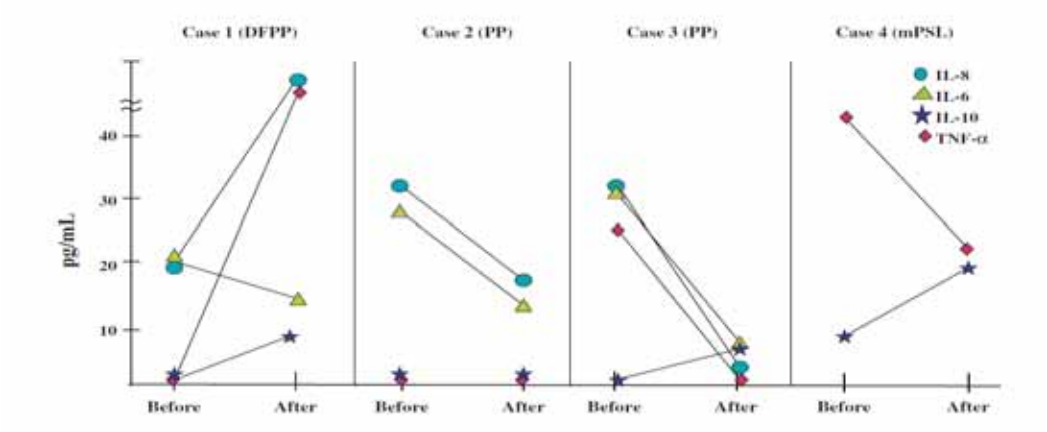
SJS/TEN

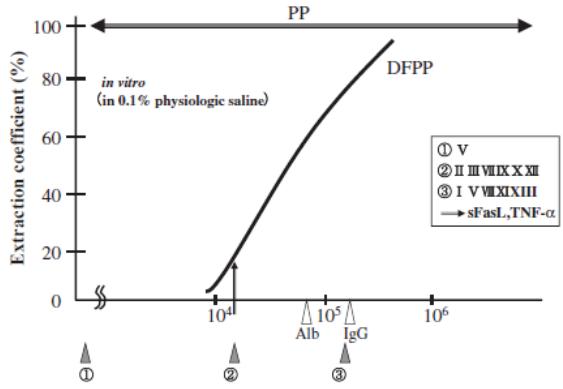
TRAITEMENT SPECIFIQUE

des essais mais pas beaucoup de certitude

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

SJS/TEN
PLASMAPHERESE





Pas d'etude
Quelques cas interessants

Narita et al ,J dermatol, 2011

SJS/TEN
TRAITEMENT SPECIFIQUE

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SJS/TEN

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9. Cyclosporine

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

SJS/TEN
TRAITEMENT SPECIFIQUE

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9. Cyclosporine

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

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

Etanercept therapy for toxic epidermal necrolysis

Andrea Paradisi, MD,[a] Damiano Abeni, MD,[a] Fabio Bergamo, MD,[b] Francesco Ricci, MD,[c]
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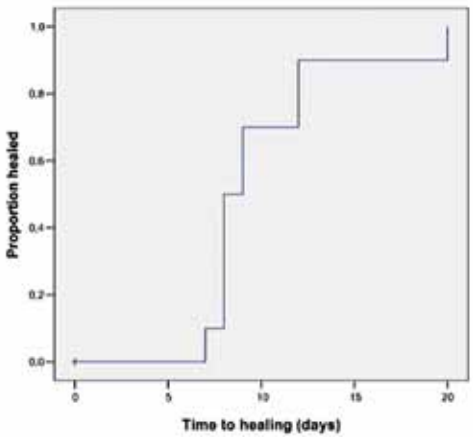


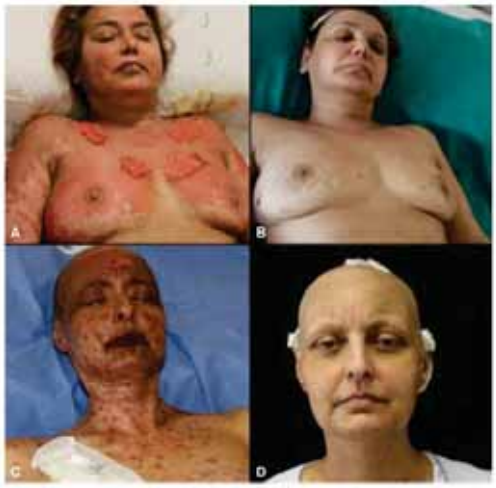


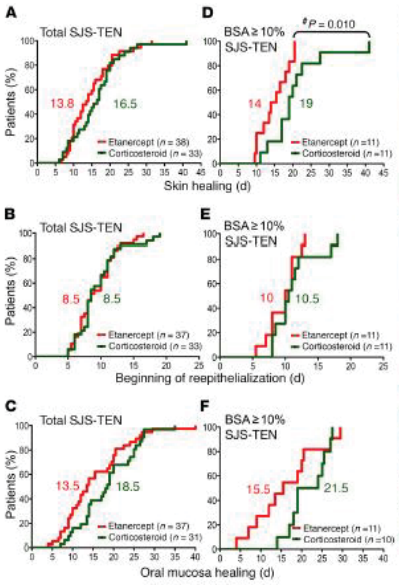
Fig 1. Two patients with toxic epidermal necrolysis before (A and C) and after treatment with a 50 mg single-dose subcutaneous injection of etanercept (B and D), respectively.

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

Donc efficacité potentielle à confirmer

SJS/TEN TRAITEMENT

ANTI TNFa



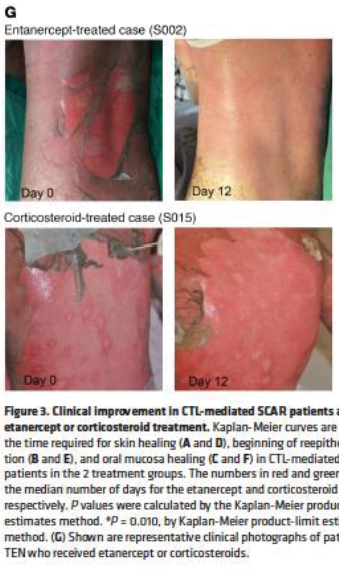


Figure 3. Clinical improvement in CTL-mediated SCAR patients after etanercept or corticosteroid treatment. Kaplan-Meier curves are shown for the time required for skin healing (**A** and **D**), beginning of reepithelialization (**B** and **E**), and oral mucosa healing (**C** and **F**) in CTL-mediated 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.

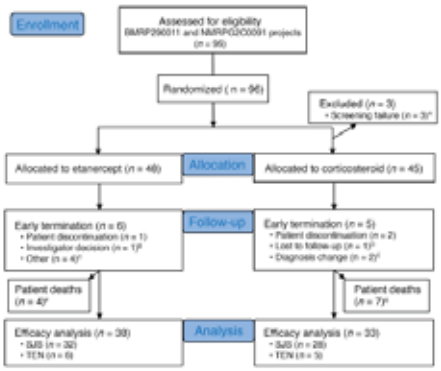


Table 4. Observed mortality rates for patients with CTL-mediated SCARs in the etanercept and corticosteroid treatment groups

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

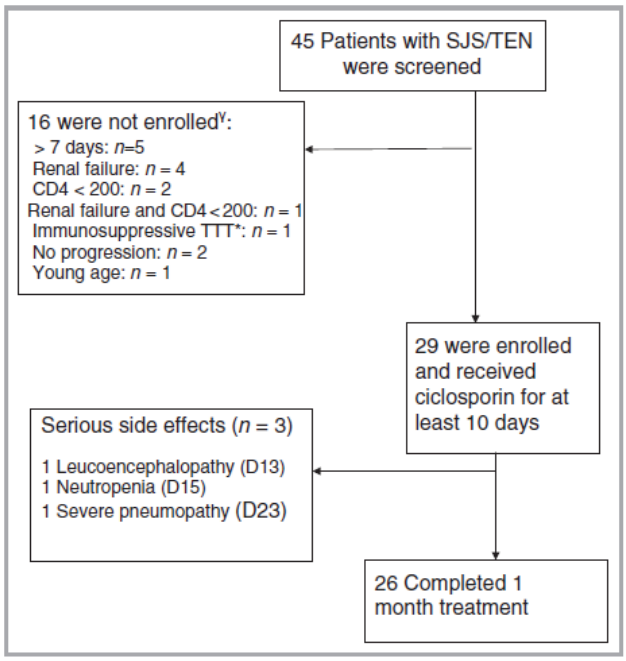
[A]Reference group. *P* values are based on an unconditional *z*-pooled test.

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

CHUNG Wh et al, JCI ,2018

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

Cyclosporine

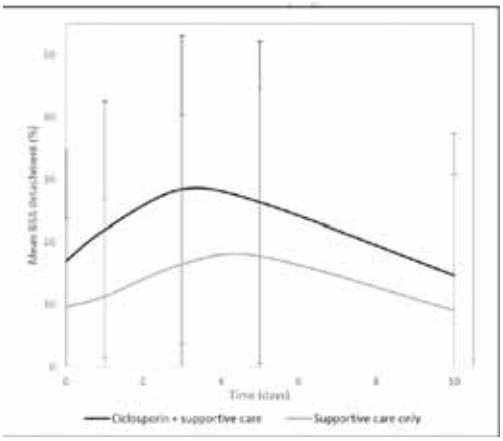
Table 2 – Baseline characteristics of patients not receiving or receiving ciclosporin — after propensity-score matching

	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 hospitalization	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 immunosuppressive 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

SJS/TEN

TRAITEMENT SPECIFIQUE

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

centre de référence maladies rares

Improving mortality outcomes of Stevens Johnson syndrome/toxic epidermal necrolysis: A regional burns centre experience

*M. Nizamoglu *, J.A. Ward, Q. Frew, H. Gerrish, N. Martin, A. Shaw, D. Barnes, O. Shelly, B. Philp, N. El-Muttardi, P. Dziewulski*

BURNS

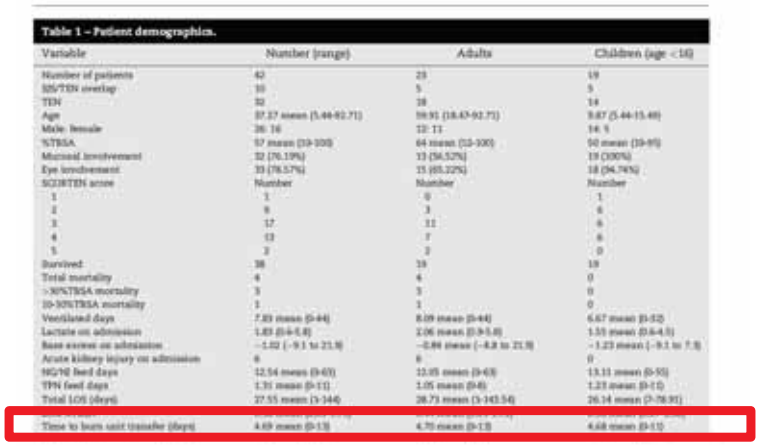


Table 1 – Patient demographics.

Variable	Number (range)	Adults	Children (age <16)
Number of patients	42	23	19
SJS/TEN overlap	10	5	5
TEN	32	18	14
Age	37.17 mean (5.44-92.71)	59.91 (18.47-92.71)	9.87 (5.44-15.48)
Male: female	26: 16	12: 11	14: 5
%TBSA	57 mean (10-100)	64 mean (10-100)	50 mean (10-95)
Mucosal involvement	32 (76.19%)	13 (56.52%)	19 (100%)
Eye involvement	33 (78.57%)	15 (65.22%)	18 (94.74%)
SCORTEN score	Number	Number	Number
1	1	0	1
2	9	3	6
3	17	11	6
4	13	7	6
5	2	2	0
Survived	38	19	19
Total mortality	4	4	0
>30%TBSA mortality	3	3	0
10-30%TBSA mortality	1	1	0
Ventilated days	7.83 mean (0-44)	8.09 mean (0-44)	6.67 mean (0-32)
Lactate on admission	1.83 (0.4-5.8)	2.06 mean (0.9-5.8)	1.55 mean (0.4-4.1)
Base excess on admission	−1.02 (−9.1 to 21.9)	−0.84 mean (−4.8 to 21.9)	−1.23 mean (−9.1 to 7.9)
Acute kidney injury on admission	6	6	0
NG/NJ feed days	12.54 mean (0-63)	12.05 mean (0-63)	13.11 mean (0-55)
TPN feed days	1.31 mean (0-11)	1.05 mean (0-6)	1.23 mean (0-11)
Total LOS (days)	27.55 mean (3-144)	28.73 mean (3-143.54)	26.14 mean (7-78.91)
Time to burn unit transfer (days)	4.69 mean (0-13)	4.70 mean (0-13)	4.68 mean (0-11)

10% de mortalité
sur 42 patients
4 versus 16 attendu
selon le SCORTEN

La mortalité des NET baisse lorsqu'ils sont pris en charge dans des centres spécifiques

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Nizamoglu Met al, Burns. 2017: S0305-4179(17)30504

Pourquoi? Pas de traitement spécifique

centre de référence maladies rares

Quelle prise en charge proposez vous?

Indications des traitements dans les toxidermies

- **Arrêt du ou des médicaments imputables**

- **Absence de signes de gravité** : dermocorticoïdes (classe II ou classe I), émollients.

- **présence de signes de gravité atteinte viscérale menaçante**
  - **Corticoïdes généraux à discuter avec centre expert**
  - **Dermocorticoïdes fortes doses (PHRC en cours)**
- **Lyell**
  - Pas de traitement efficace à ce jour
  - PHRC CNR Lyon (2019)

- **Autres : Pas de codification**
  - PEAG grave (rare) corticoïdes

Descamps et al , Ann Derm Venereol, 2010
Joly et al ,JAMA Dermatol, 2013

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Plan

1. Préciser le type de toxidermie
2. Préciser la Gravité
3. Enquête étiologique
4. Prise en charge thérapeutique
5. Prise en charge à distance

DRESS

Séquelles

Table I. Summary of demographic and clinical characteristics for 6 surviving patients with sequelae

Patient No. sex/age, y	Culprit drug	Follow-up period/onset	Underlying disease	Internal organ involvement†	Sequelae	Diagnostic aids
1/M/27	Ampicillin	9.7 y/36 d*	None	Liver, lung	Graves disease, alopecia areata	Laboratory data, echogram, elevated TBII
2/F/33	Carbamazepine	3 y/8.7 mo*	None	Liver, lung	Graves disease	Laboratory data, echogram, exophthalmos
3/F/47	Dapsone	7 y/48 d*	Pulmonary TB, cutaneous vasculitis	Liver, lung	Fulminant type 1 DM	Acute DKA, low C-peptide
4/F/35	Dapsone	3.5 y/14 d‡	Suspect LE	Liver	AIHA	Anemia, low haptoglobin, positive Coombs test result
5/F/52	Allopurinol	2.7 y/10 d§	DM, HTN, CRI	Liver, kidney	ESRD	HD
6/M/79	Allopurinol	5.6 y/2.7 y§	DM, HTN, CRI, gout	Liver, kidney	ESRD	HD

N=66

11.5% séquelles défaillance organe

N=145

Table II. Newly developed disease

Newly developed disease	Number of patients	Age or mean age (years)	Interval†	Published cases
Autoimmune thyroiditis				
Graves' disease	2 (M1:F1)	30.0	2 m, 9 m	Chen *et al.*[20]
Hashimoto's thyroiditis	3 (F)	67.0	6 m-3 yr	Ushigome *et al.*[21]
Painless thyroid disease	2 (M1:F1)	61.5	2 m, 2 yr	
Thyroid dysfunction††	2 (F)	53.0	1 m, NA	
DM				
Fulminant type 1 DM	5 (M3:F2)	56.6	1–2 m	Chiou *et al.*[16], Chen *et al.*[20]
Type 2 DM	1 (F)	64	3 m	
Herpes zoster	5 (M3:F2)	59.6	2 m-3 yr	Ushigome *et al.*[21], Kano *et al.*[26]
Drug eruption	4 (M2:F2)	60.5	2-6 yr	Ushigome *et al.*[21]
Arthritis				
Reactive arthritis	1 (F)	63	3 m	Morito *et al.*[25]
Rheumatoid arthritis	1 (F)	48	10 yr	
Arthralgia	1 (F)	67	11 m	
Pneumonia	2 (M)	70.5	8 m, 1.5 yr	Ushigome *et al.*[21]
Thrombotic infarction‡	2 (M)	63.5	2 m	Hashizume *et al.*[27]
Alopecia§	1 (F)	45	4 m	Ushigome *et al.*[21]
Systemic lupus erythematosus¶	1 (M)	36	3.5 yr	Aota *et al.*[19]
Vitiligo	1 (F)	45	4.5 m	

Chen et al, JAAD, 2013
Kano et al, J Dermatol,

Clinical specificities

Autoimmune Disease

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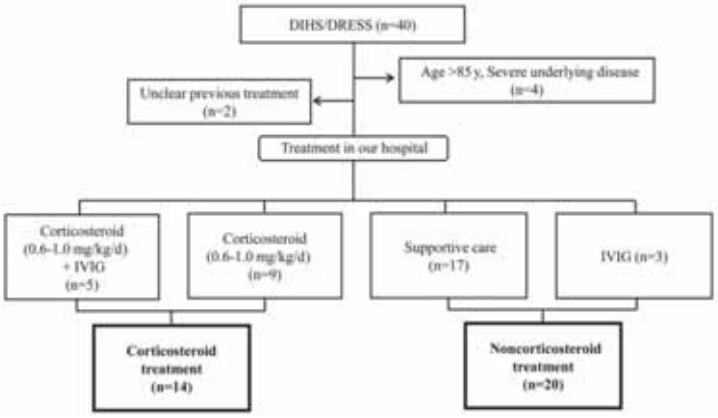
Chen et al, JAAD, 2013
Kano et al, J Dermatol, 2015

Clinical specificities

Autoimmune Disease



N=34

Corticoids?

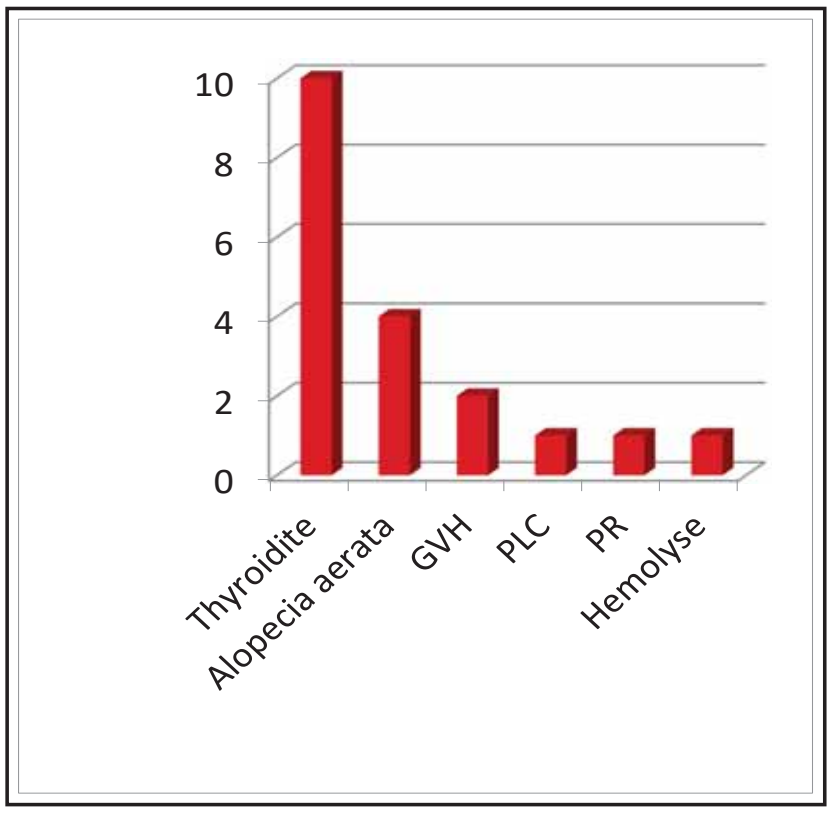
Table III. Detection of autoantibodies

	Detection of autoantibody	
	Frequency Detected antibodies (No. of cases)	
Treatment group (No. of cases)	Early phase	Late phase
Corticosteroid (6)	0% (0/6)	16.7% (1/6) ANA (1)
Noncorticosteroid (10)	20.0% (2/10) ANA (2)	70.0% (7/10) ANA (2) ATGA (4) ATPOA (3)

Ushigome et al, JAAD, 2013

Clinical specificities

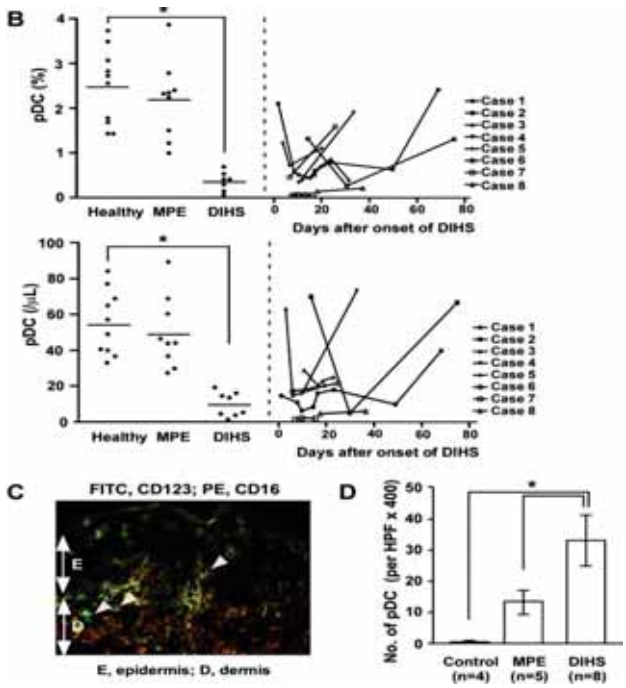
Autoimmune Disease



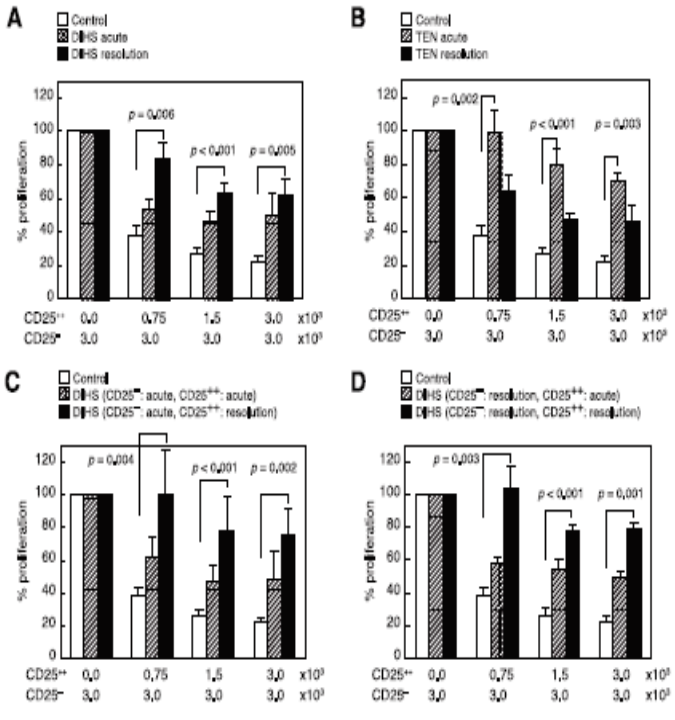
- Frequent
- 21/64
- Systemic assay was negative at the acute phase in all cases
- Confirming link to DRESS

Clinical specificities

Autoimmune Disease



Sugita et al , JACI, 2010



Shiohara et al, J Immunol, 2009

SJS/TEN
PRONOSTIC-SEQUELLES

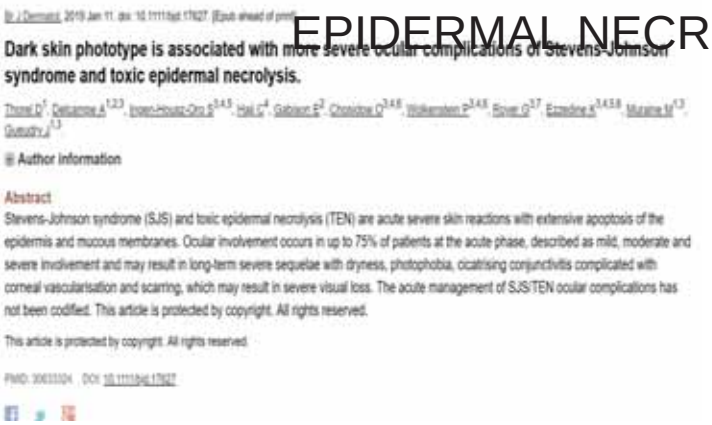
- Atteinte oculaire: Fonctionnelle +++
  = 65-89 % de séquelles/ RISQUE DE CECITE
  - ✓ Kératites, ulceres cornéens
  - ✓ Symblépharons.synechies
  - ✓ Métaplasie malpighienne conjonctive ou cornée.
  - ✓ Cils dystrophiques.

- 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

DARK SKIN PHOTOTYPE IS ASSOCIATED WITH MORE SEVERE OCULAR COMPLICATIONS OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS


Dark skin phototype is associated with more severe ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Author information

Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute severe skin reactions with extensive apoptosis of the epidermis and mucous membranes. Ocular involvement occurs in up to 75% of patients at the acute phase, described as mild, moderate and severe involvement and may result in long-term severe sequelae with dryness, photophobia, cicatrising conjunctivitis complicated with corneal vascularisation and scarring, which may result in severe visual loss. The acute management of SJS/TEN ocular complications has not been codified. This article is protected by copyright. All rights reserved.

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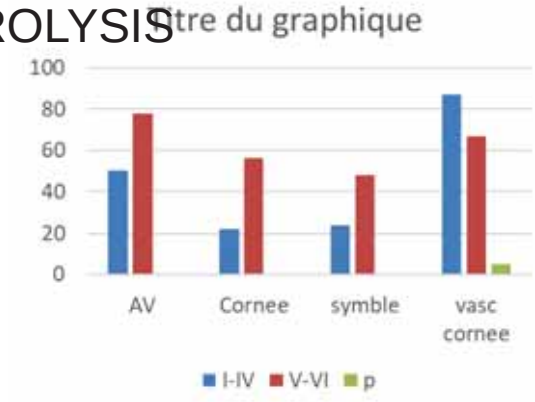
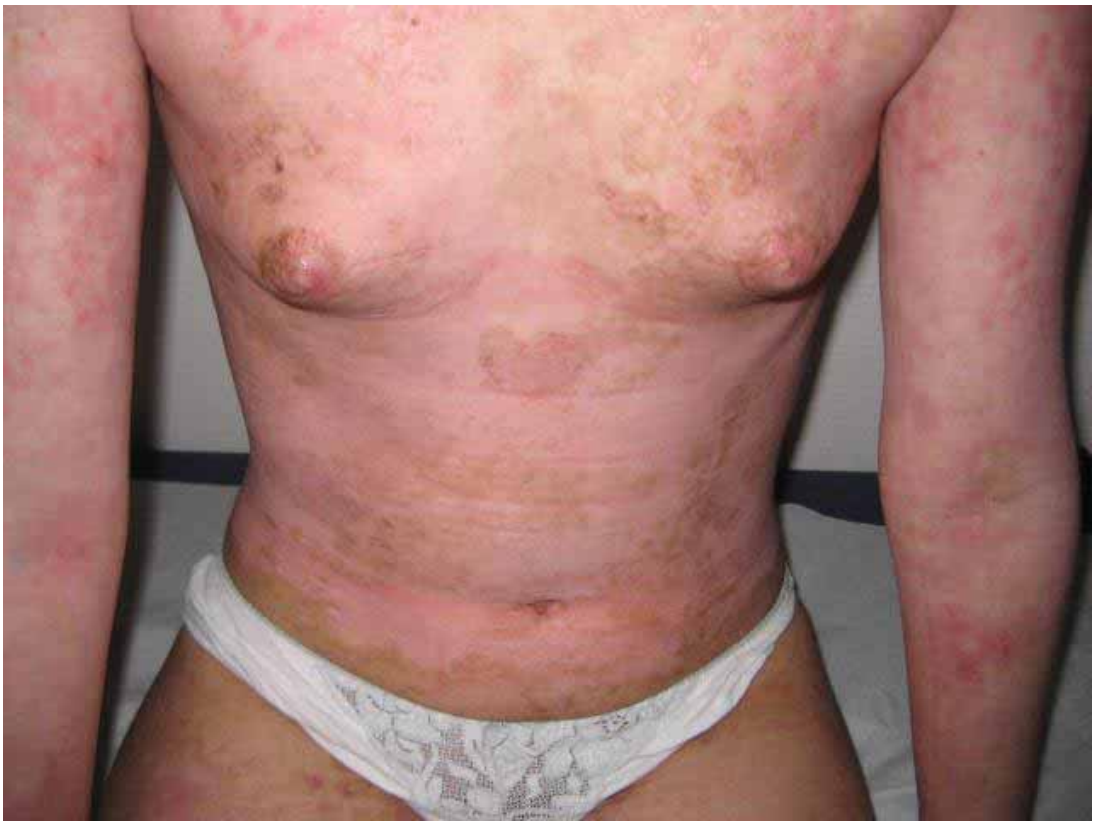


Gueudry et al, BJD, 2019



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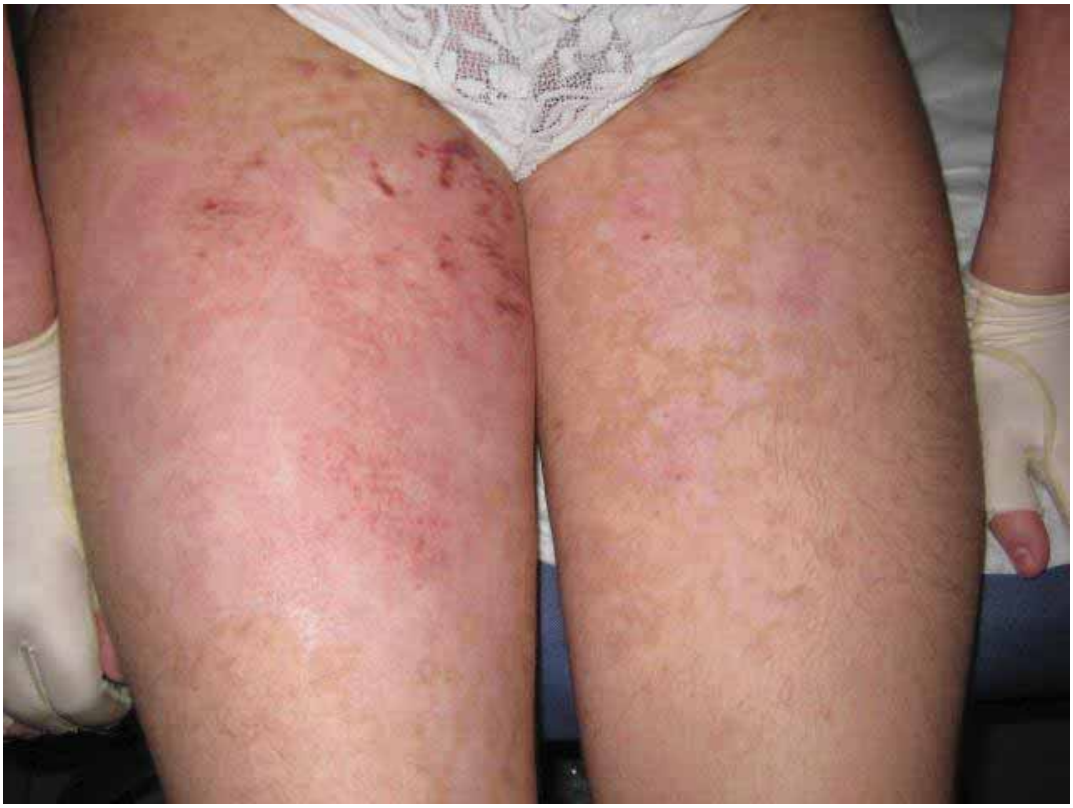

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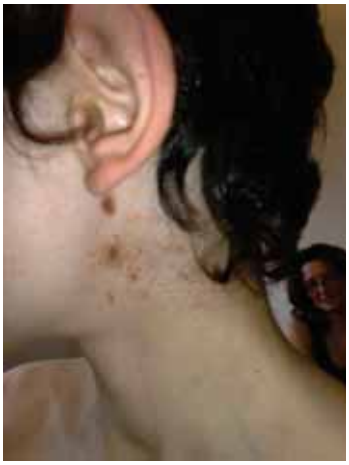
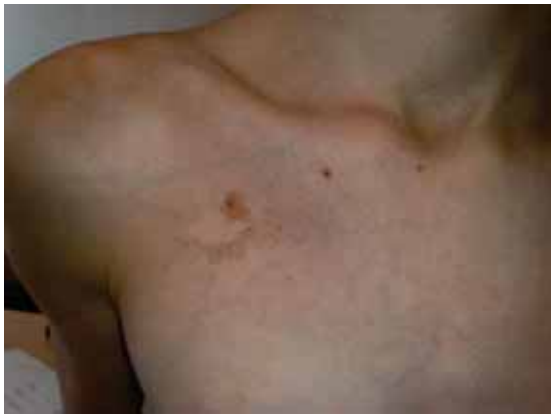
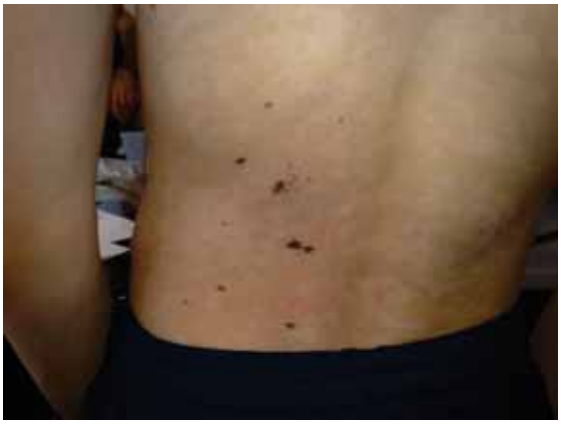
Naevi







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Bilan Allergologique

Dr Benoit BEN SAID
CHU Lyon Centre
Service de Dermatologie
Centre de référence sur les dermatoses bulleuses toxiques

CLINIQUE CONCORDANTE
SJS TEN DRESS AGEP MPE
OTHERS

IMPUTABILITE MEDICAMENTEUSE

TESTS CUTANES (patch/IDR)
TESTS IMMUNOBIOLOGIQUES

TESTS CUTANÉS

- Réalisation tests cutanés selon les méthodes ERGCD
  - Lecture 48-72h

- Au moins 6 semaines après la résolution complète
  - 6 mois pour les DRESS

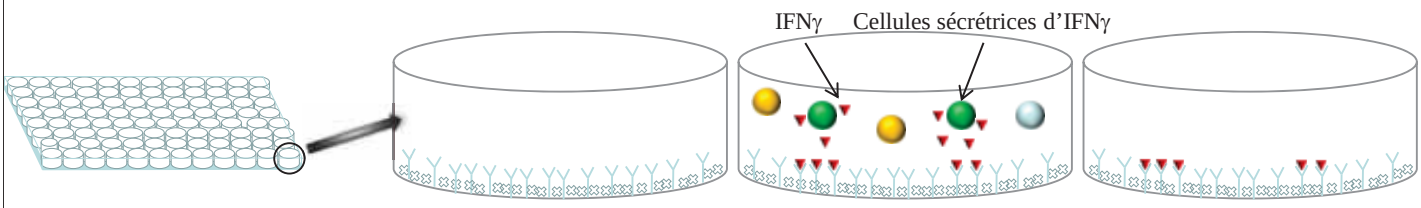
ANALYSE DE LA RÉPONSE T

– Faire la différence entre irritation et réaction allergique

– Avant la réalisation des patchs tests:

Détection des LT spécifique d'antigène circulant.
Sécrétion d'IFNg (méthode ELISPOT)

TEST ELISPOT - METHODE

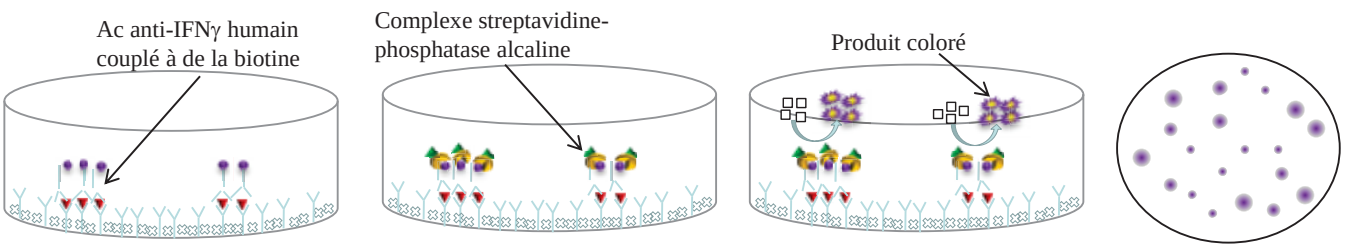


a/ plaque ELISpot 96 puits avec membrane de nitrocellulose

b/ coating de la plaque avec des Ac anti-IFNγ humain

c/ culture PBMCs/puits en présence du médicament.

d/ lavage de la plaque



e/ fixation de l'Ac de détection sur les cytokines captées.

f/ liaison du complexe streptatvidine-phosphatase alcaline à la biotine

g/ révélation des spots par l'action de la phosphatase alcaline sur un substrat.

h/ numération des spots (1 spot = 1 cellule sécrétrice d'IFNγ).

CLINIQUE CONCORDANTE
SJS TEN DRESS AGEP MPE
OTHERS

↓

IMPUTABILITE MEDICAMENTEUSE

↓

TESTS CUTANES (patch/IDR)
TESTS IMMUNOBIOLOGIQUES

RÉSULTATS-TESTS

Maladie/ test	Positif	Négatif ST	Total (N-134)
SJS TEN	7/26(27%)	19/26(73%)	26
DRESS	42/73(58%)	31/73(42%)	73
AGEP	6/10(60%)	4/10(40%)	10
EPF	2/7(27%)	5/7(73%)	7
DIGAL	1/5(20%)	4/5(80%)	5
TE	8/13(61.5%)	5/13(38.5%)	13

24/42 positifs antibiotiques

Dont 16 pénicillines

RÉSULTATS-TESTS

Maladie/ test	Positif	Négatif ST	Total (N-134)
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MDH 6/42 pos in DRESS: 14%
Dans tous les cas deux antibiotiques associés

RÉSULTATS-TESTS

Maladie/ test	Positif	Négatif ST	Total (N-134)	Relapse
SJS TEN	7/26(27%)	19/26(73%)	26	0
DRESS	42/73(58%)	31/73(42%)	73	9
AGEP	6/10(60%)	4/10(40%)	10	0
EPF	2/7(27%)	5/7(73%)	7	0
DIGAL	1/5(20%)	4/5(80%)	5	
TE	8/13(61.5%)	5/13(38.5%)	13	0

MDH 6/42 pos in DRESS: 14%

TESTS CUTANES

Maladie/Etudes	Wolkenstein 1996	Barbaud 2013	CCR2A 2013	Santiago 2009	Chung
DRESS	?	46/72(64%)	42/73(58%)	18/56(32%)	70%
AGEP	7/14(50%)	26/45(57%)	6/10(60%)	NF	NF
MPE	6/23 (26%)	?	8/13(61%)	NF	NF
SJS TEN	2/22(9%)	4/17(23%)	7/26(23%)	NF	60%
Multipos		24%	14%		

Nous confirmons

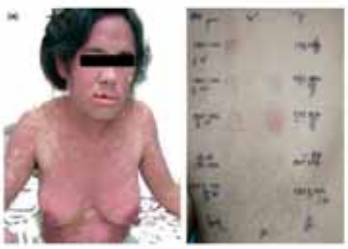
-la bonne valeur prédictive positive des tests au cours des DRESS , MPE or AGEP
la mauvaise VPP dans les SJS EPF DIGAL
-La valeur négative des tests n'est pas connue mais semble imparfaite dans les DRESS
-Il existe un risque d'exantheme maculo-papuleux par extension dans les DRESS
-la présence de multi-positivité des tests dans les DRESS sans présumé de la signification

Santiago et al , Contact Derm, 2009
Wolkenstein et al, Contact Derm, 1996
Barbaud et al ,BJD, 2013

Les patchs tests sont utiles dans l'exploration des toxidermies sévères à la carbamazépine

Lin et al. JEADV 2012

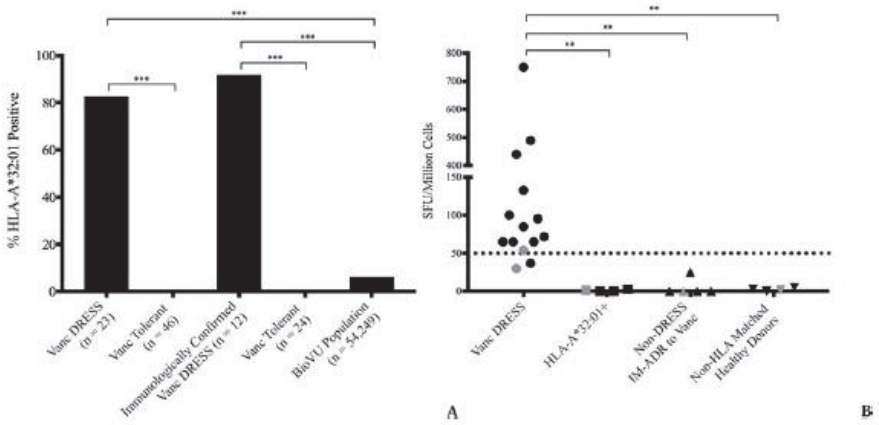
Case no.	Interval between resolution and patch test	CBZ 10%	CBZ 30%	OXC 10%	OXC 30%	CBZ-E 10%	CBZ-E 30%	PHT 10%	PHT 30%	LTG 10%	LTG 30%
1	17 months	++	++	–	–	+	+	+	+	–	–
2	17 months	++	++	+	+	+	+	+	+	–	–
3	7 months	+	++	–	–	+	++	–	–	–	–
4	4 weeks/13 months	–	?+	–	–	–	–	–	–	–	–
5	5 weeks	?+	+	–	–	NA	NA	–	–	–	–
6	4 months	++	++	+	+	+	+	+	+	–	–
7*	2 months	–	+	–	–	NA	NA	–	–	–	–
8	1 month	+	+	–	–	NA	NA	+	+	–	–
9*	1 month	+	+	–	–	–	–	–	–	–	–
10	6 months	?+	?+	?+	?+	–	–	+	+	–	–
11	1 month	+	+	+	+	+	+	+	+	+	+
12	1 month	?+	?+	–	–	–	–	–	–	–	–
13	6 weeks	+	+	–	?+	+	+	–	–	+	+
14	1 month	?+	?+	–	–	–	–	–	–	–	–
15	1 month	–	–	–	–	–	–	–	–	–	–
16	1 month	–	–	–	–	+	–	–	–	–	–
Positive reaction (+ or ++)		50% (8/16)	62.5% (10/16)	18.8% (3/16)	18.8% (3/16)	53.8% (7/13)	46.2% (6/13)	37.5% (6/16)	37.5% (6/16)	12.5% (2/16)	12.5% (2/16)



- **62.5 % de positivité dans les SJS TEN**
- **Positivité plus franche si dilué dans vaseline à 30%**
- **Réaction croisée fréquente12-53%% des cas**
- **HLA et structure chimique comme explication de la positivité des PT(13/16)**
- **Pas de récidive pendant PT**

Allergologie

centre de référence maladies rares



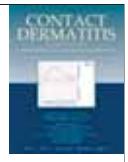
Les Elispots sont nettement plus rentables en cas d'HLA A 3201

Donc variabilité en fonction de l'origine HLA

Konvinse et al , JACI, 2019

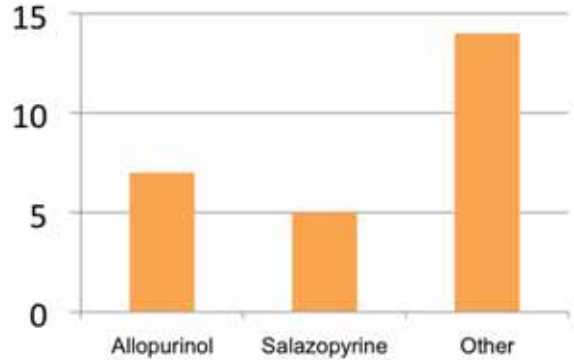
centre de référence maladies rares

LES TESTS DÉPENDENT DES MOLÉCULES



Culprit drugs	Patients tested	Positive patch tests	% positive patch tests
Antiepileptics	33	17	51.5
Carbamazepine (1%, 5%, 10%, 20%[a] pet.)	18	13	72.2
Phenytoin (5%, 10% pet.)	7	1	14.3
Lamotrigine (1%, 10% pet.)	5	2	40
Phenobarbital (5%, 10% pet.)	2	0	0
Topamax® (topiramate, 30% in water and pet.)	1	1	100
Allopurinol (1%, 10%, 20% pet.)[b]	19	0	0
Oxypurinol (5%, 10% pet.)[b]	9	0	0

Santiago et al, Contact Dermatitis,2010



Dans notre étude 10 cas sont liées à l'ALLOPURINOL et reste négatif

Barbaud et al, BJD, 2013

CLINIQUE CONCORDANTE
SJS TEN DRESS AGEP MPE
OTHERS

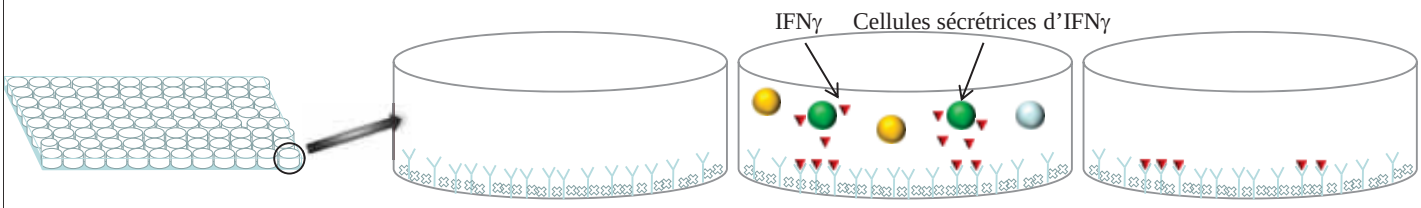
↓

IMPUTABILITE MEDICAMENTEUSE

↓

TESTS CUTANES (patch/IDR)
TESTS IMMUNOBIOLOGIQUES

TEST ELISPOT - METHODE

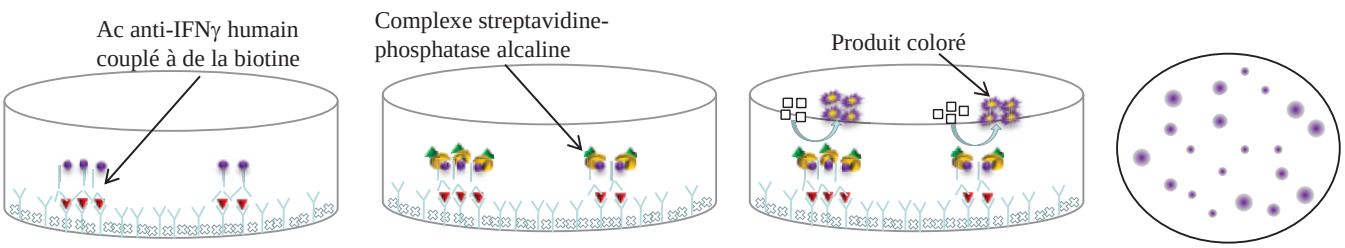


a/ plaque ELISpot 96 puits avec membrane de nitrocellulose

b/ coating de la plaque avec des Ac anti-IFNγ humain

c/ culture PBMCs/puits en présence du médicament.

d/ lavage de la plaque



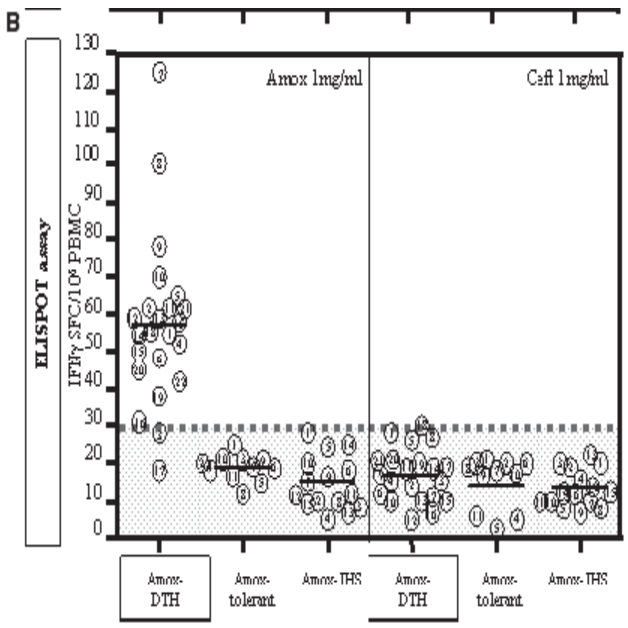
e/ fixation de l'Ac de détection sur les cytokines captées.

f/ liaison du complexe streptatvidine-phosphatase alcaline à la biotine

g/ révélation des spots par l'action de la phosphatase alcaline sur un substrat.

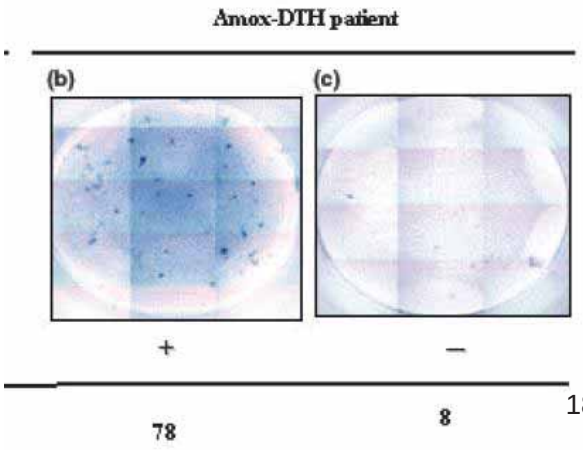
h/ numération des spots (1 spot = 1 cellule sécrétrice d'IFNγ).

ELISPOT
Exanthème maculo-papuleux



Sensibilité 91%
Spécificité 95%

n=22 EMP avec patch tests positifs



Rozieres et al, Allergy , 2010

Acta Derm Venereol 2013; 93: 66–69

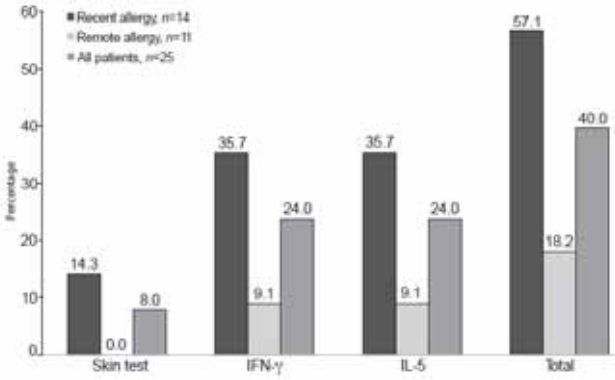
CLINICAL REPORT

The Potential of Using Enzyme-linked Immunospot to Diagnose Cephalosporin-induced Maculopapular Exanthems

Boonthorn TANVARASETHEE, Supranee BURANAPRADITKUN and Jettanong KLAEWSONGKRAM

Clinical characteristics	ELISPOT Positive (n=10)	ELISPOT Negative (n=15)	p
Gender, M/F, n	4/6	7/8	NS
Age, years, mean ± SD	59.5 ± 5.1	53.6 ± 4.5	NS
Underlying diseases, allergic/ malignancy/others, n	1/2/7	3/6/6	NS
Naranjo ADR, probable/definite, n	8/2	14/1	NS
Time from last exposure, weeks, mean ± SD	70.9 ± 19.5	96.3 ± 17.6	NS
Recent/remote allergy, n	8/2	6/9	0.04
Time to notice rash after drugs used, h, mean ± SD	180.6 ± 49.5	48.9 ± 8.4	0.00

NS: not significant; ADR: adverse drug reaction; SD: standard deviation.

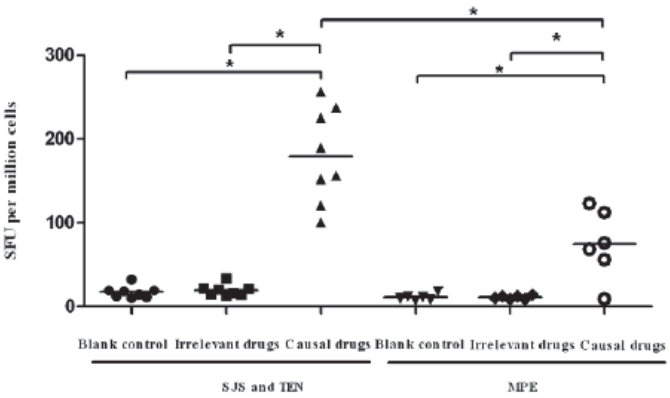


Les ELISPOTS sont utiles pour le diagnostic des toxidermies mais la combinaison des cytokines détectées optimisent les tests

Recovered Patients with Stevens–Johson Syndrome and Toxic Epidermal Necrolysis Maintain Long-Lived IFN-c and sFasL Memory Response

Table 1. Patient characteristic.

Patient	Age/ gender	Causal drugs	Irrelevant drug	Disease	LTT	Intervals*
1	32 years/f	CFZ (50 ug/ml)	NMS (7 ug/ml)	TEN	+	3 years
2	37 years/f	NMS (7 ug/ml)	CFZ (50 ug/ml)	TEN	+	2 years
3	57 years/f	AMX (40 ug/ml)	NMS (7 ug/ml)	SJS	+	1 year
4	80 years/m	PNC (40 ug/ml)	NMS (7 ug/ml)	TEN	+	1 year
5	64 years/m	NMS (7 ug/ml)	CFZ (50 ug/ml)	SJS	+	1 year
5	3 years/m	APAP (50 ug/ml)	CFZ (50 ug/ml)	TEN	+	1 year
6	77 years/m	AP (50 ug/ml)	CFZ (50 ug/ml)	TEN	+	3 month
7	26 years/m	AMX (40 ug/ml)	NMS (7 ug/ml)	SJS	+	2 months
8	15 years/f	HCQ (40 ug/ml)	CFZ (50 ug/ml)	TEN	+	1 month
9	48 years/f	CBZ (25 μg/mL)	AMX (40 ug/ml)	MPE	+	2 years
10	46 years/m	APAP (50 ug/ml)	CFZ (50 ug/ml)	MPE	+	1.5 years
11	21 years/f	AMX (40 ug/ml)	NMS (7 ug/ml)	MPE	+	1 year
12	45 years/m	PNC (40 ug/ml)	NMS (7 ug/ml)	MPE	+	1 year
13	34 years/f	CBZ (25 μg/mL)	AMX (40 ug/ml)	MPE	+	3 months
14	14 years/f	CFZ (50 ug/ml)	NMS (7 ug/ml)	MPE	+	1 month



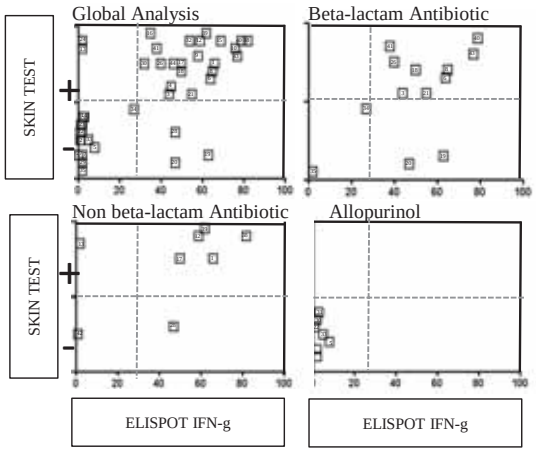
N=8 SJS TEN
N= 6MPE

Mais incubés 10 jours
Sensibilisation active?
Efficace dans ces cas

Fu et al , PLOS one ,

centre de référence maladies rares

RÉSULTATS- ANALYSE RÉPONSE T



- DRESS: Corrélation >90% entre ELISPOT et Tests confirmant qu'il existe une activation de LT spécifiques

Patch test / ELISPOT	Positif	Négatif	Total
Positif	2	1	3
Négatif	1	10	11
Total	3	11	14

Il existe aussi dans les SJS TEN une bonne corrélation ELISPOT /PT

Cependant les ELISPOT ne sont pas plus positif que les PT

Il existe des preuves d'une activation LT spécifiques dans les SJS NET

TESTS IMMUNOBIOLOGIQUES

- Sensibilité 52% Spécificité 100%
  - 19 patients Elispot IFN g

- 16 patients avec ELISPOT IFN g modifiés
  - 13/16 Positifs
  - Mais technique difficile en routine
  - Nécessité homogénéisation des pratiques

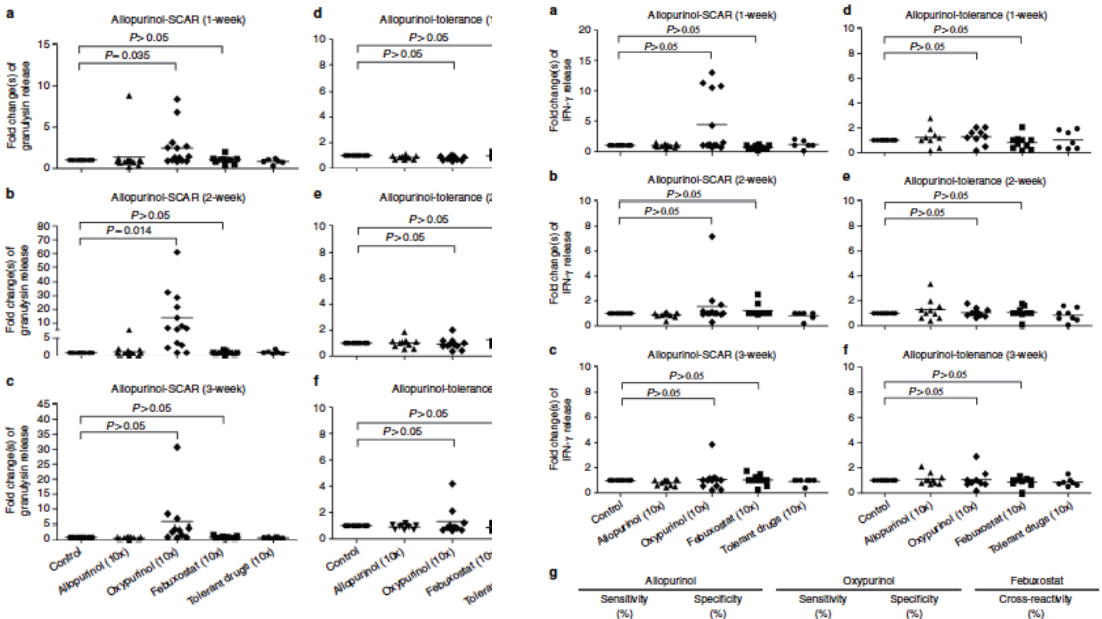
Srisuttiyakorn C, BJD ,2016
Philips EJ et al, JACIP, 2017
Kato K, J Derm Sci, 2017

LES TESTS DÉPENDENT DES MOLÉCULES

201
5

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]

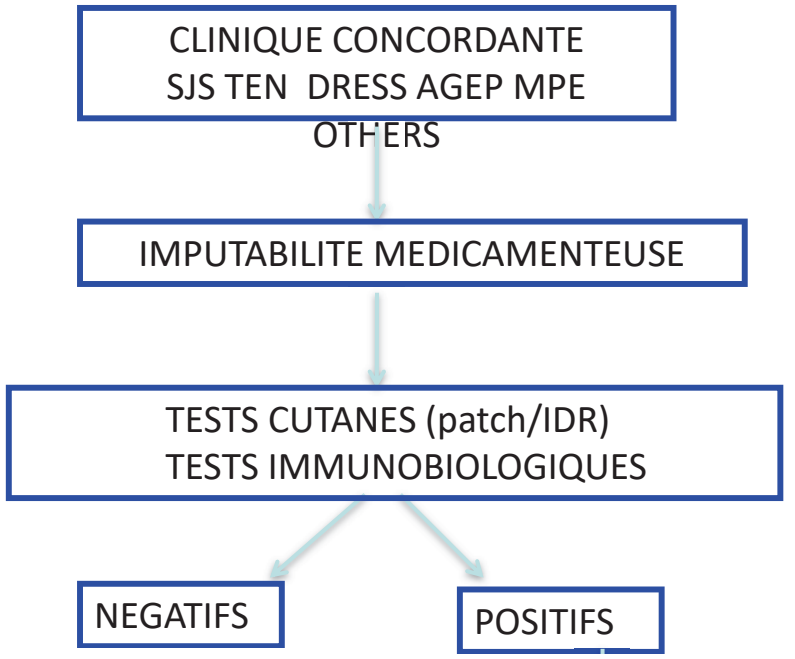


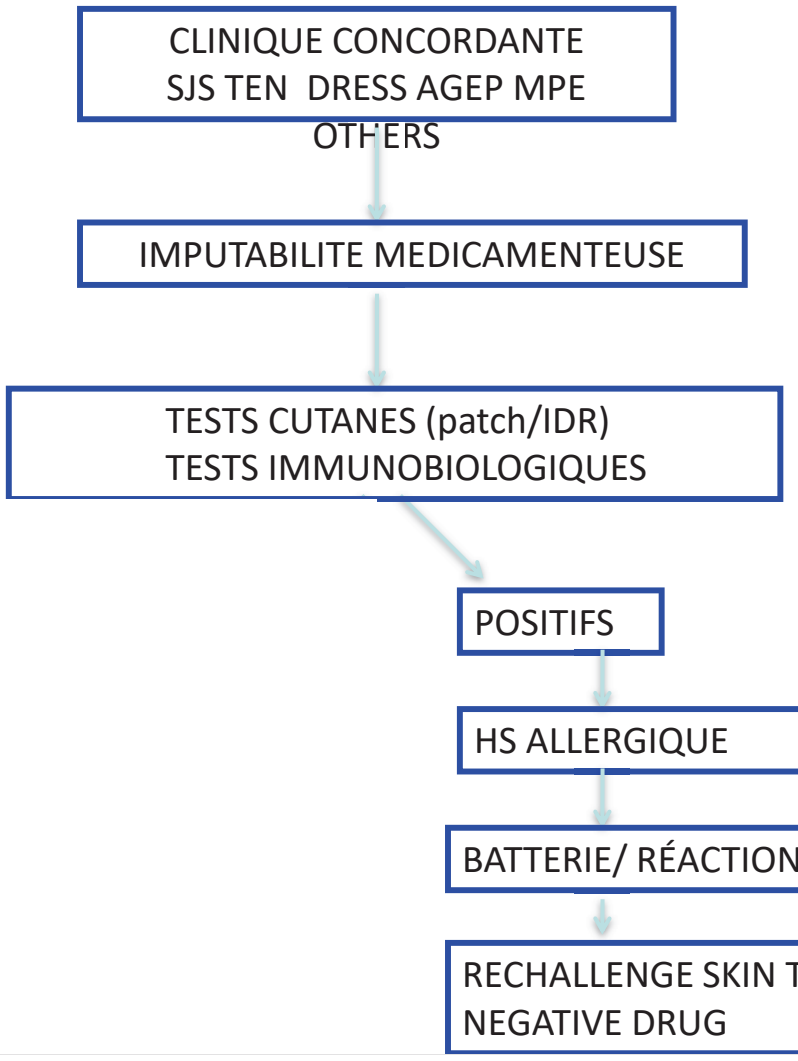
g

	Allopurinol		Oxypurinol		Febuxostat
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Cross-reactivity (%)
1 week	7	100	43	100	
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

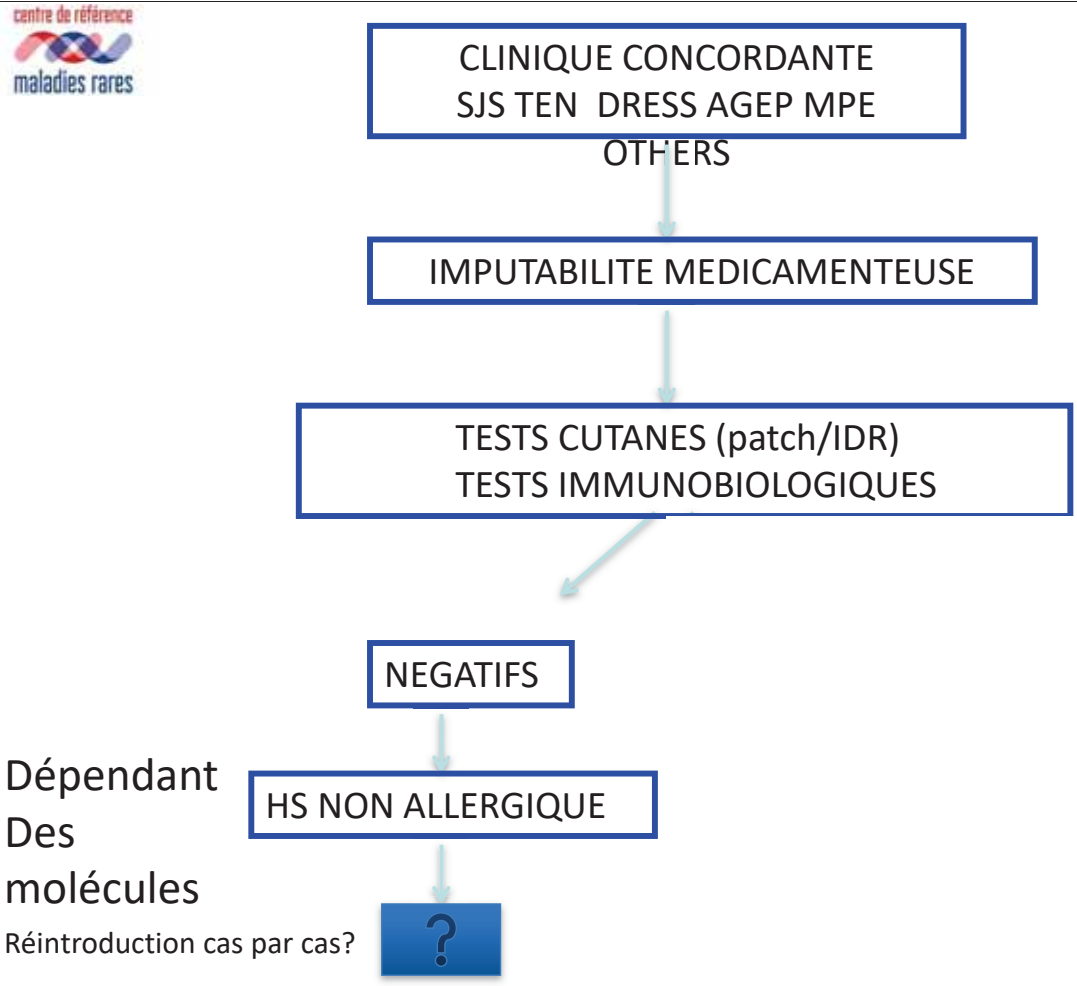

CLINIQUE CONCORDANTE
SJS TEN DRESS AGEP MPE
OTHERS
IMPUTABILITE MEDICAMENTEUSE
TESTS CUTANES (patch/IDR)
TESTS IMMUNOBIOLOGIQUES
NEGATIFS
POSITIFS


CLINIQUE CONCORDANTE
SJS TEN DRESS AGEP MPE
OTHERS
IMPUTABILITE MEDICAMENTEUSE
TESTS CUTANES (patch/IDR)
TESTS IMMUNOBIOLOGIQUES
POSITIFS
HS ALLERGIQUE
BATTERIE/ RÉACTION CROISEE
RECHALLENGE SKIN TEST
NEGATIVE DRUG

RÉSULTATS-TEST DE RÉINTRODUCTION

Maladie/test cutané	Positif	Réintroduction molécule même famille avec tests négatifs	Récidive
SJS TEN	7	7	0
DRESS	42	42	0
AGEP	6	6	0
FDE	2	2	0
DIGAL	1	1	0
MPE severe	8	8	0

La réintroduction de médicaments de la même famille avec des tests négatifs semble possible dans les toxidermies sévères
Seulement si nécessaire et vitaux



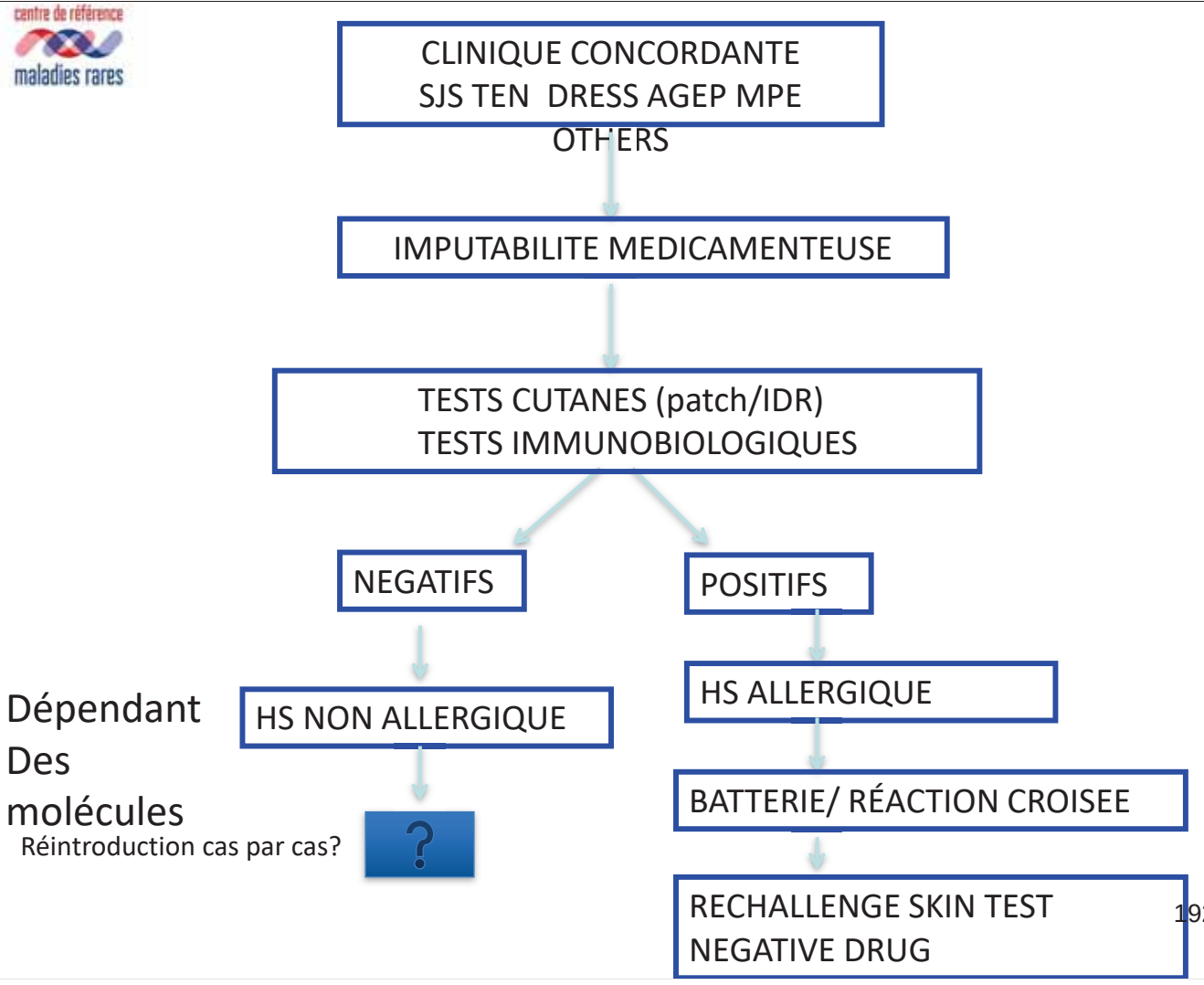
Dépendant Des molécules

Réintroduction cas par cas?

RÉSULTATS-TEST DE RÉINTRODUCTION

Maladie/test cutané	Négatif	Réintroduction Molécule Imputable	Récidive
SJS TEN	19	0	0
DRESS	31	4	4
AGEP	4	0	0
FDE	5	0	0
DIGAL	4	0	0
MPE sévère	5	0	0

La réintroduction de médicaments avec tests cutanés négatifs n'est pas recommandée dans les DRESS



Recurrence of drug-induced reactions in DRESS patients

D. Picard,[1,2] M. Vellar,[1] B. Janela,[3] A. Roussel,[1] P. Joly,[1,2] P. Musette[1,2,*]

Table 1 Characteristics of patients with history of multiple drug-induced reactions including DRESS

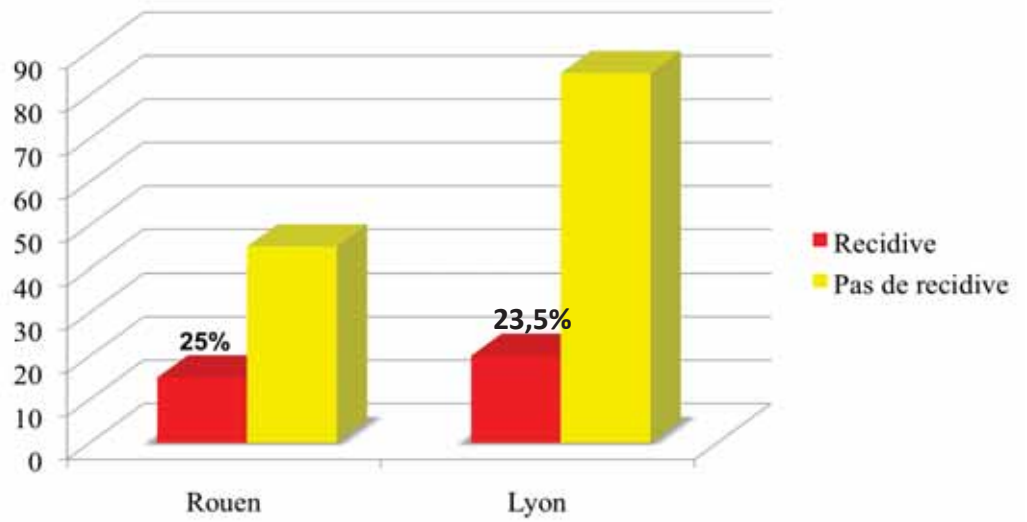
Patient #	Past history of drug allergy	DRESS culprit drugs	Type of initial DRESS eruption	Type of recurrence	Time after initial hypersensitivity reaction	Medication involved/ delay after intake	Clinical/biological manifestations
1		Minocycline	Erythroderma	ED MPE	M15 M19	Acetaminophen/D7 Acetaminophen/D3	Eosinophilia 1G/L
2		Oxcarbazepine	Erythroderma and purpura	MPE	M24	Aminopenicillin/D2	
3		Salazopyrine	Exfoliative dermatitis	MPE	M47	Aminopenicillin/D4	
4		Vancomycine	Erythroderma	Erythroderma	M8	Amitriptyline/D90	
5		Allopurinol/Ceftriaxone/ Lercanidipine/Glicazide/	Maculopapular Rash	MPE ED and urticarial dermatitis	D15 M5	Tygecycline/D3 corticosteroid tapering	Eosinophilia 1.3G/L
6	Penicillin	Cefotaxim	Maculopapular Rash	Flare up with facial oedema and worsening skin eruption	D2 D3	Vancomycin/D2 Teicoplanine/D1	
8		Acetaminophen	Erythroderma with pustules	Facial oedema and MPE Erythoderma	D33 D36	Penicillin M + Gentamycin/D3 Pristinamycin/D1	Eosinophilia 1.3G/l
9	Penicillin	Allopurinol	Erythroderma, blisters	Erythoderma Pustular erythroderma	D23 D37 D80	Ticarcilline/D2 Vancomycin/D15 Vancomycin/D6	Eosinophilia 4G/L RF/Eosinophilia 1.6G/L
10		Rifamicin	Exfoliative dermatitis	MPE MPE MPE	D65 D100 D175	Rifamicin/D2 Clarythromycin/D1	
11		Minocycline	Erythroderma with pustules	Pustular rash	D240	Fluoxetine/D72 and Ibuprofen/D3	Eosinophilia 0.9G/L
12		Vancomycin	Erythroderma	Facial and troncular rash	D90	Aminopenicillin/D3	
13		Amoxicillin/Telmisartan	Erythroderma	MPE	D184	Indapamide/D10	
14	Penicillin + contrast media	Vancomycin	Exfoliative dermatitis	Erythroderma	M49	Vancomycin/D3	RF/Eosinophilia 1.5G/L
15		Imatinib + Allopurinol	Maculopapular rash	MPE	D77	Imatinib/D1	Eosinophilia 4G/l

DRESS, Drug reaction with eosinophilia and systemic symptoms; ED, eczematous dermatitis; MPE, maculopapular exanthema; RF, renal failure.

Le DRESS est associé à un risque de récidive de type MINI DRESS avec des molécules différentes de la molécule causale

centre de référence maladies rares

HYPERSENSIBILITÉ ET DRESS



Récidive ne veut pas dire nouvelle HSR dans tous les cas

Picard et al ,JEADV, 2014

DRESS ET RISQUE DE RÉCIDIVE

- Notre étude est la première relatant un risque de récidive généralisée au cours des tests cutanés dans les DRESS

- Les molécules responsables étaient
  - les béta-lactamines dans 7/9 cas
  - Rôle des contacts antérieurs avec sensibilité accrue car dans 5 cas /9 survenue DRESS dans les 48h après la prise chez des patients aux ATCD de rash sous Amoxicilline

Conclusion

- **Il existe une bonne valeur des tests cutanés dans les toxidermies érythémateuses (DRESS-PEAG-TE)**
- **Moins bonne dans les toxidermies bulleuses**
- **Il existe un risque de récidive non grave dans les DRESS qui doit être pris en compte**
- **La valeur prédictive positive des tests semble bonne**
- **La valeur négative reste inconnue à ce jour**
- **Les tests Immunobiologiques peuvent être utile**
- **Une réintroduction de molécule semble faisable dans les cas de maladie avec tests cutanés positifs et avec une molécule de la même famille avec tests négatifs**
- **Le rapport bénéfice risque doit toujours être très positif pour le patient (médicaments nécessaires ou vitaux)**