
XXXI CONGRESO
INTERNACIONAL
SCAI 2025
SOCIEDAD CHILENA DE ALERGIA E INMUNOLOGIA

TOXICODERMIAS RECURRENTES: CUÁL ES EL ROL DE LOS MICROORGANISMOS?

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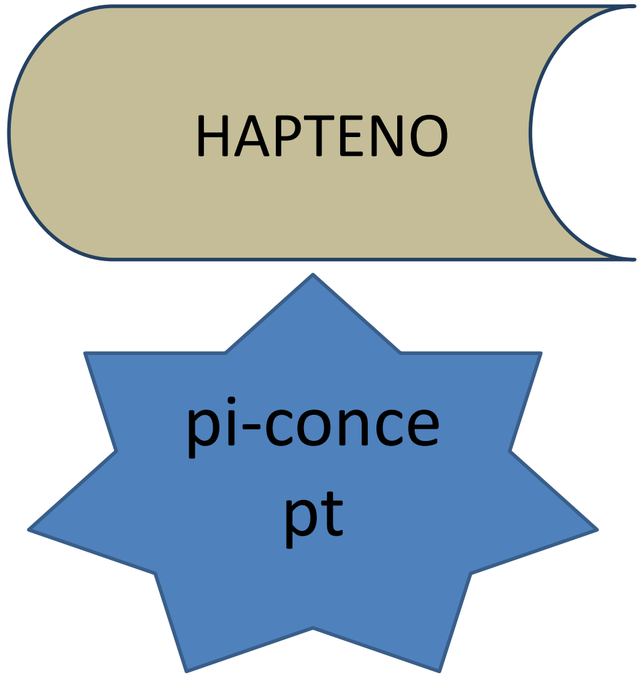
INMUNÓLOGA
CLÍNICA SANTA MARÍA

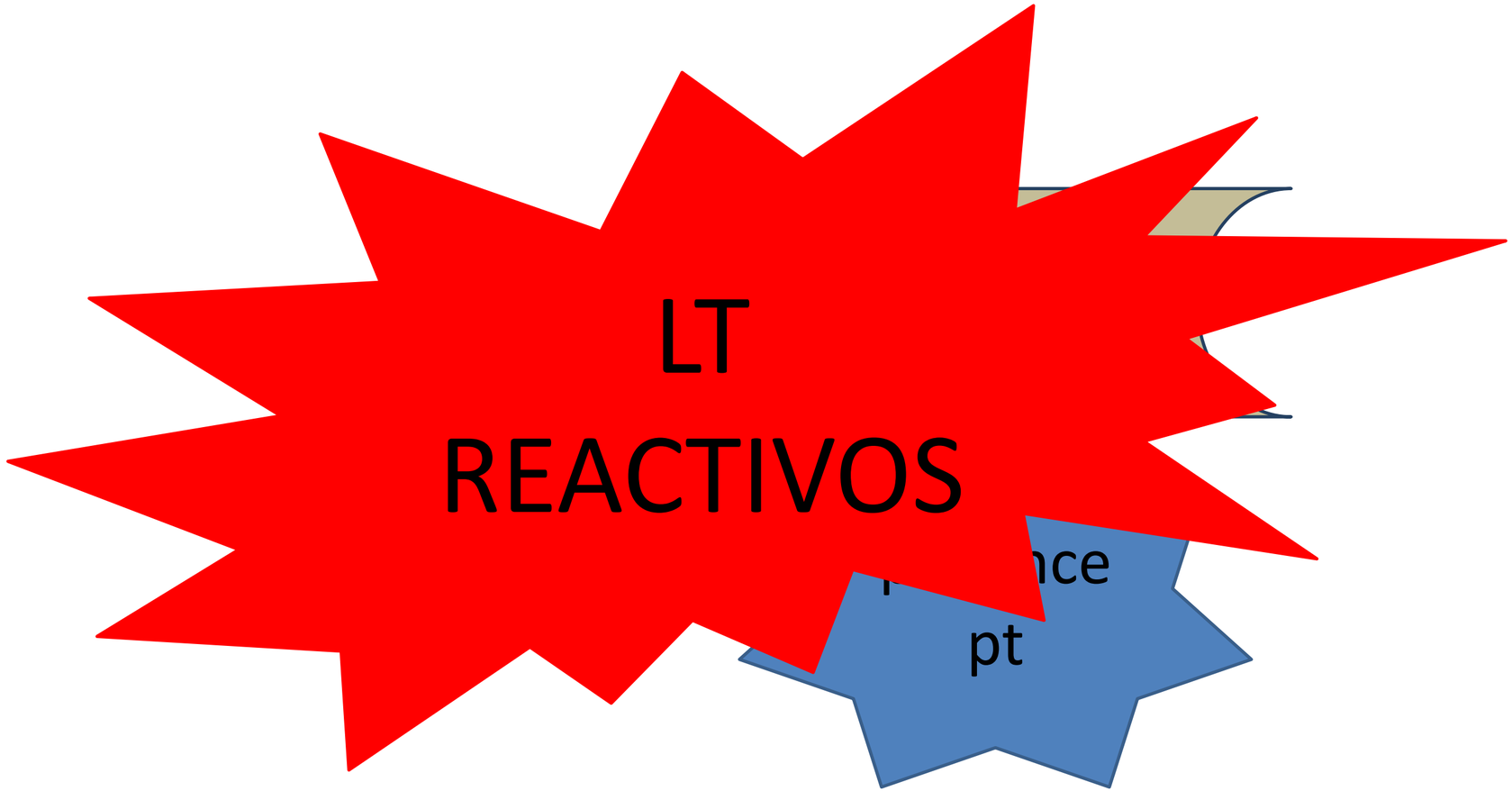

Antiinflamatorios
no esteroideos (aines)


Antibiotics

IgE

LT

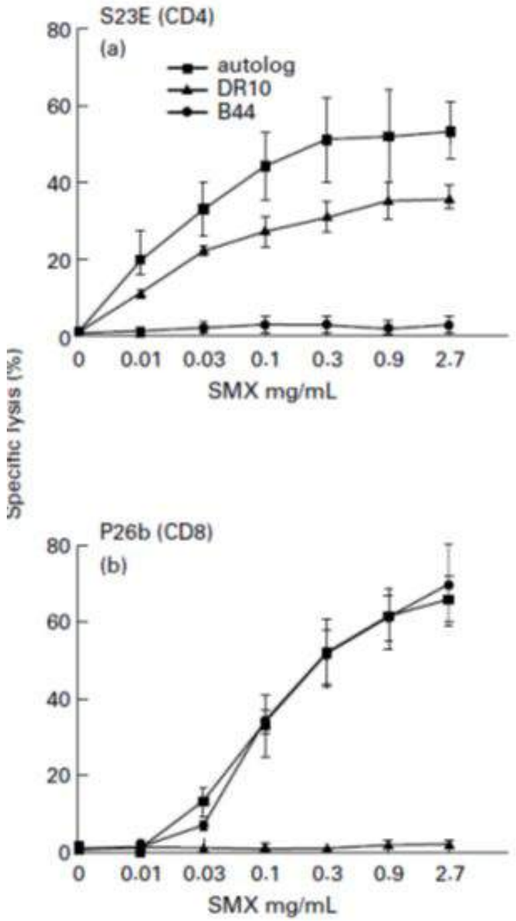



LT
REACTIVOS
nce
pt

EXANTEMAS EN ALERGIA FÁRMACOS

- Más típico: exantemas o Exantema MP (vesiculares)
  - Mayoría leves y transitorios
  - Mayor superficie corporal y de mayor duración en contexto virus
  - Más EMP con alza transitoria GOT/GPT

LT donantes sanos
LT EMP SMX



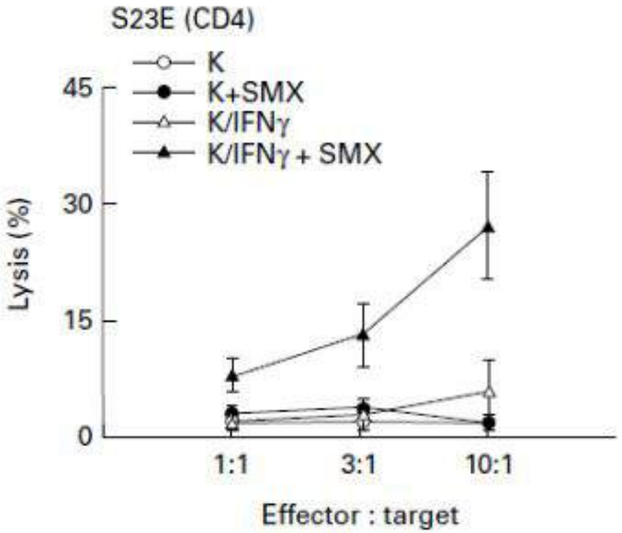
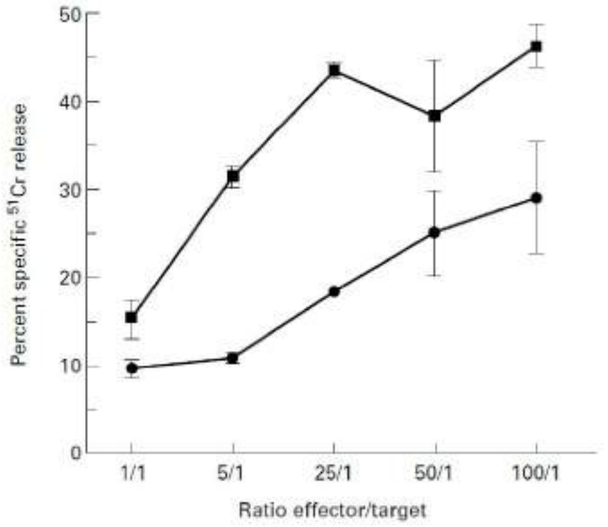


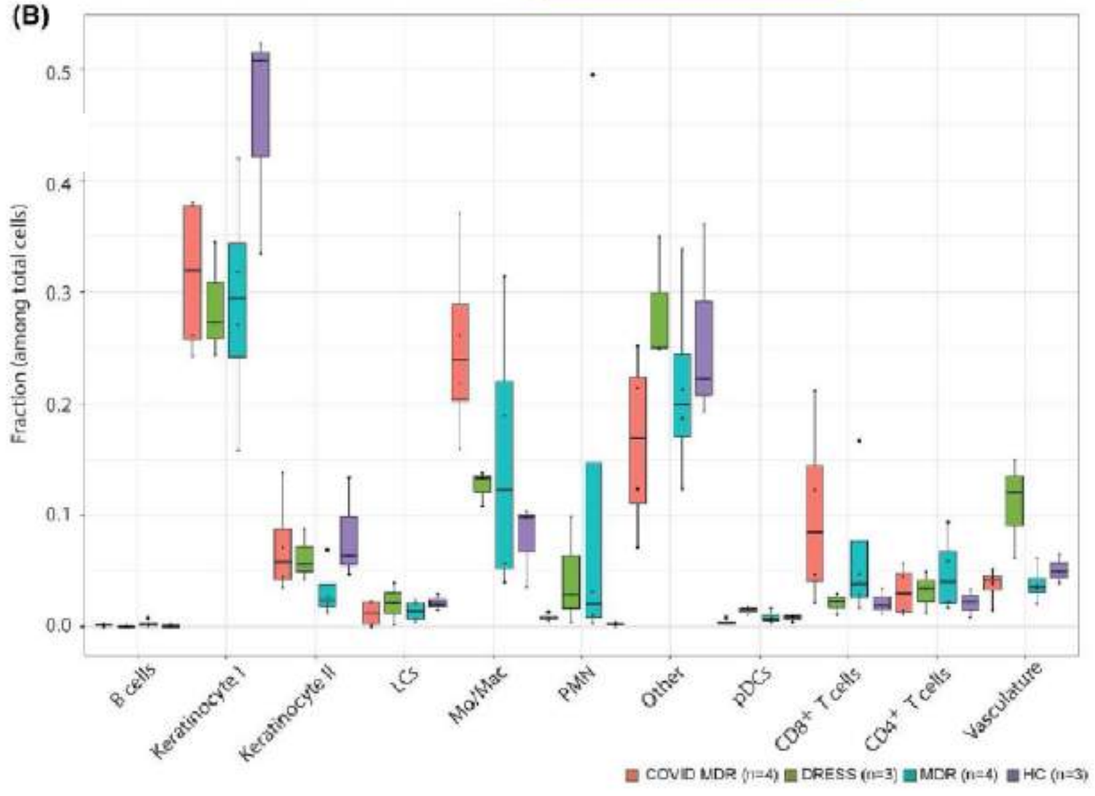
Table 2. Flow cytometric analysis of gated blister fluid lymphocytes

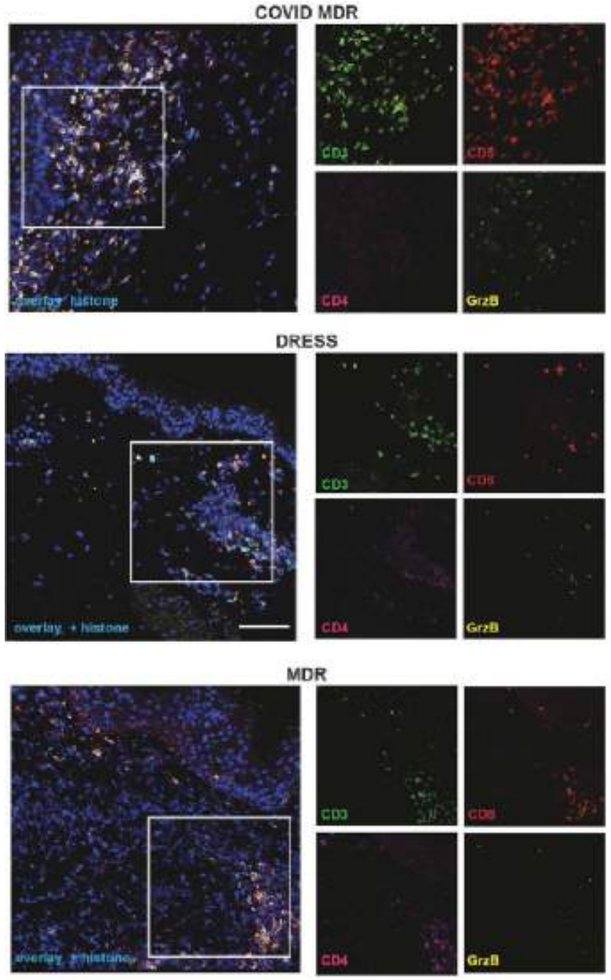
	Patients					
	1	2	3	4a	4b	Mean
CD3/CD8, %	69	72	61	56	64	65
CD4, %	21	34	8	10	ND	18
CD3/CD4, %	15	10	6	ND	ND	10
CD56, %	23	19	14	24	22	20
CD3CD56, %	3·5	3·8	4	9	5·4	52
CD8, %	10	54	13	10	ND	
CD28, %	0	4·4%	28	18	ND	13
CLA, %	60	76	82	69	ND	72
CD101, %	3	19	60	77	ND	
CD3/CD101, %	ND	13	58	77	ND	
HLA-DR, %	26	76	79	80	ND	65

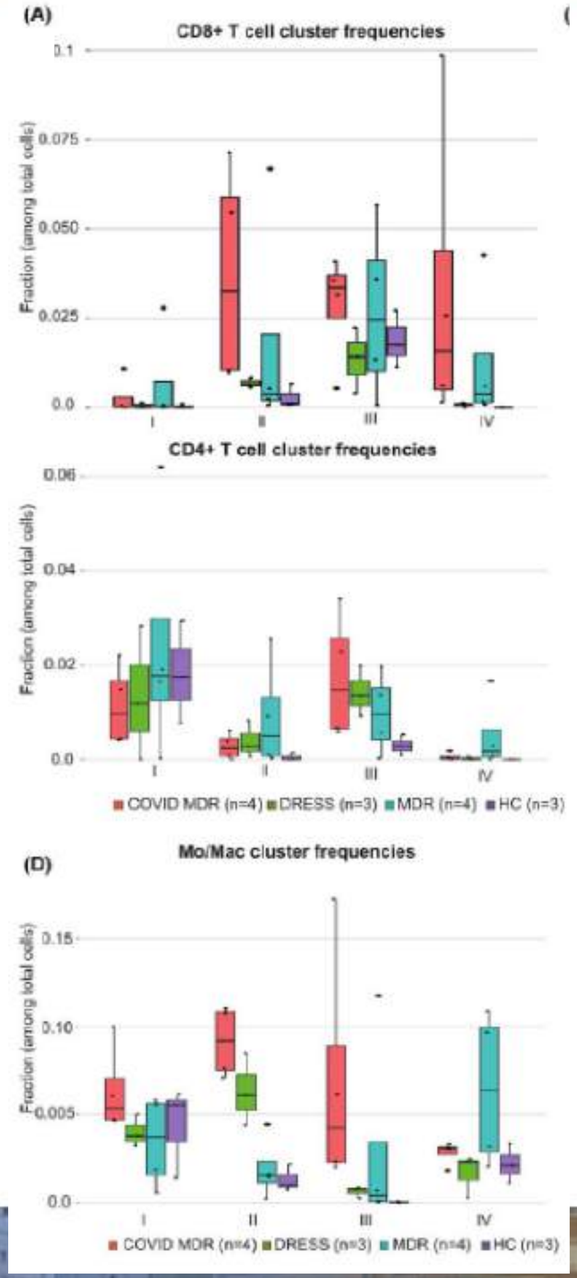


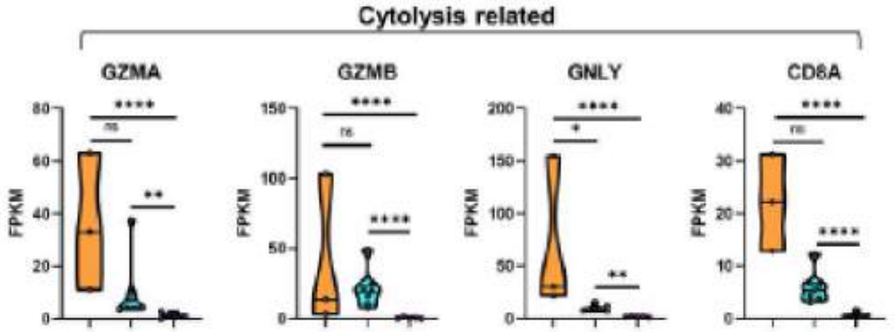
Cleach, Clin Exp Immunol, 119
Schnyder, Clin Exp Allergy, vol 28

Infecciones COVID-19 potencia LTCD8


(B)
Fraction (among total cells)
0.0
0.1
0.2
0.3
0.4
0.5
B cells
Keratinocyte I
Keratinocyte II
LCS
Mo/Mac
PMN
Other
pDCS
CD8+ T cells
CD4+ T cells
Vasculature
COVID MDR (n=4)
DRESS (n=3)
MDR (n=4)
HC (n=3)

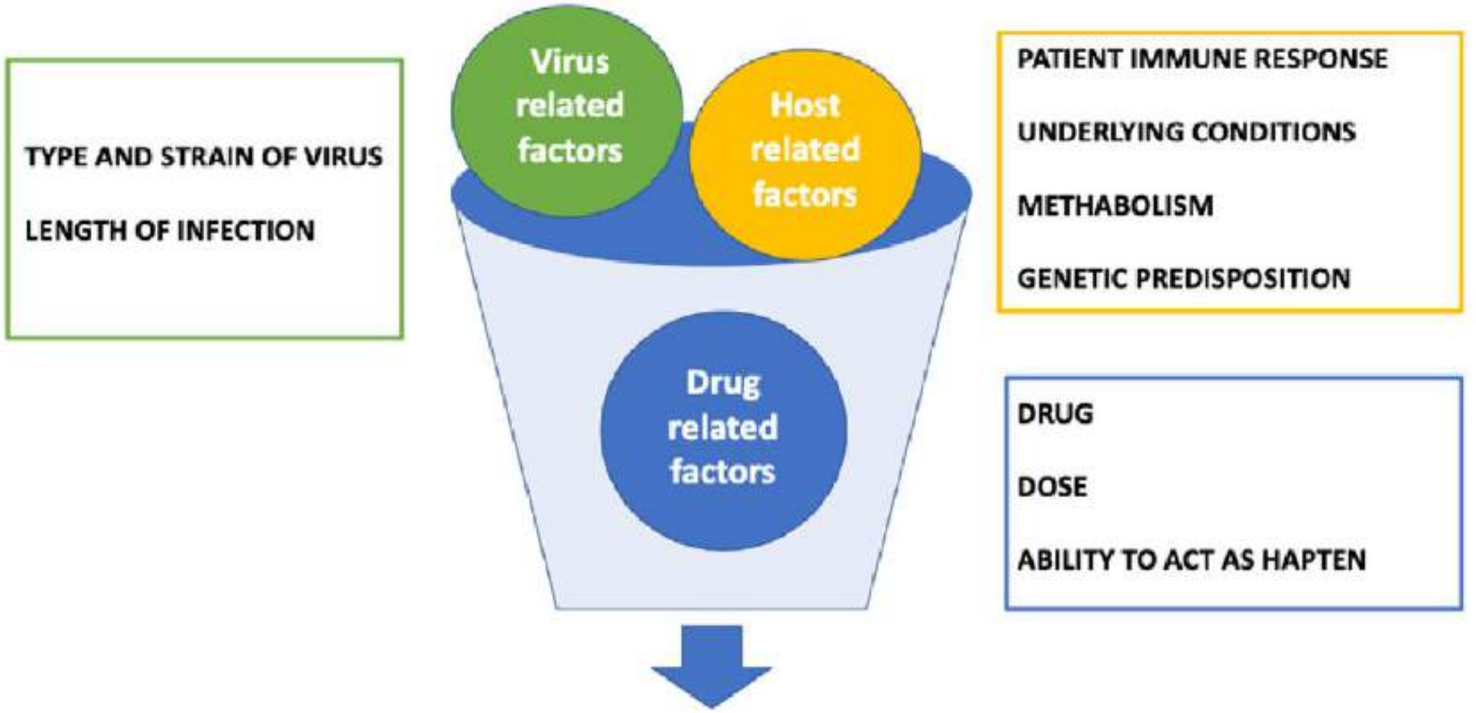

COVID MDR
CD3
CD8
CD4
GrzB
DRESS
CD3
CD8
CD4
GrzB
MDR
CD3
CD8
CD4
GrzB





Mitamura, Allergy 2021

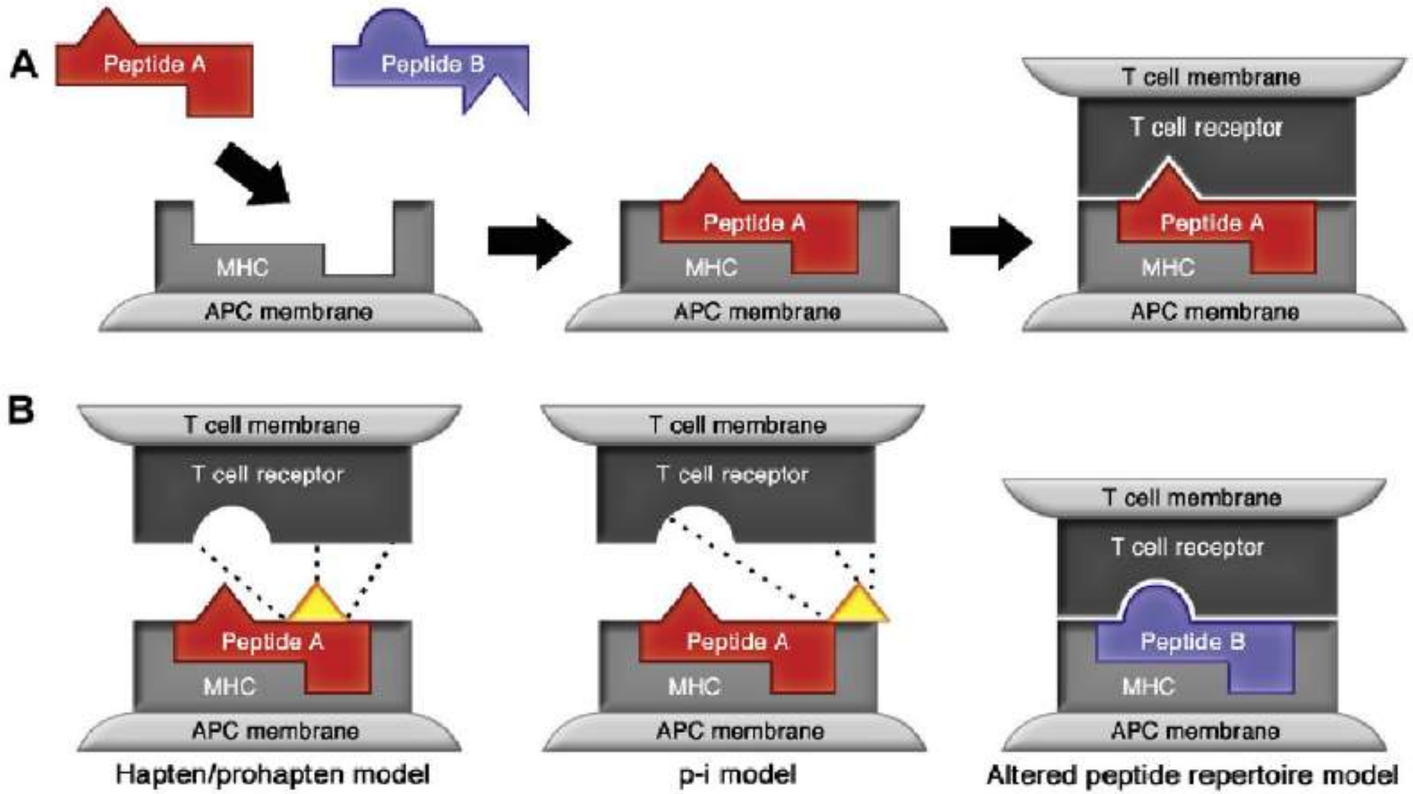
POR QUÉ LOS VIRUS EXACERBAN REACCIONES DROGAS MÁS QUE OTRO TIPO DE INFECCIONES?

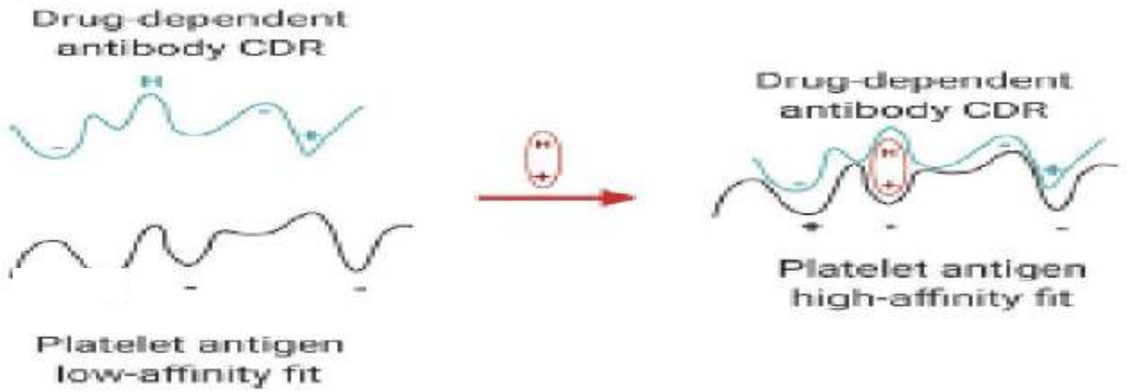


DRUG HYPERSENSITIVITY REACTION

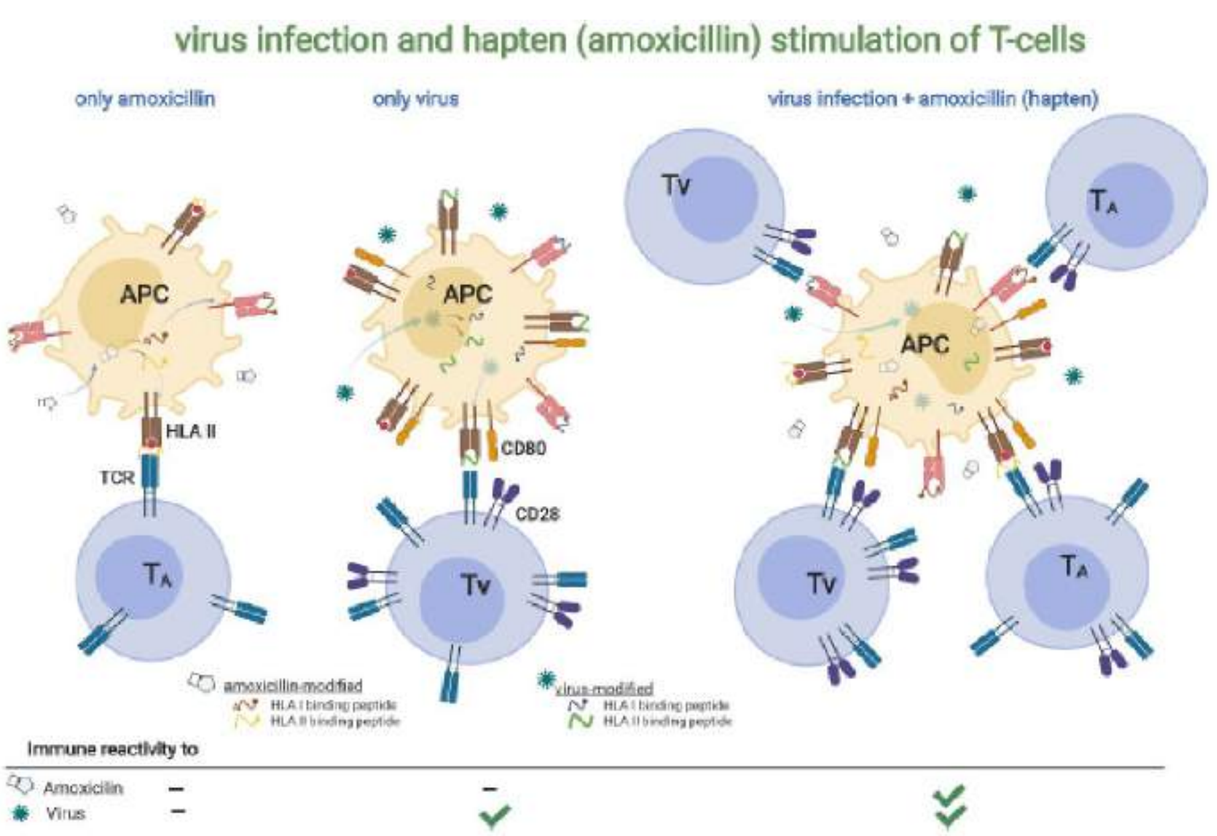
Inter-relación droga/virus/ sistema inmune

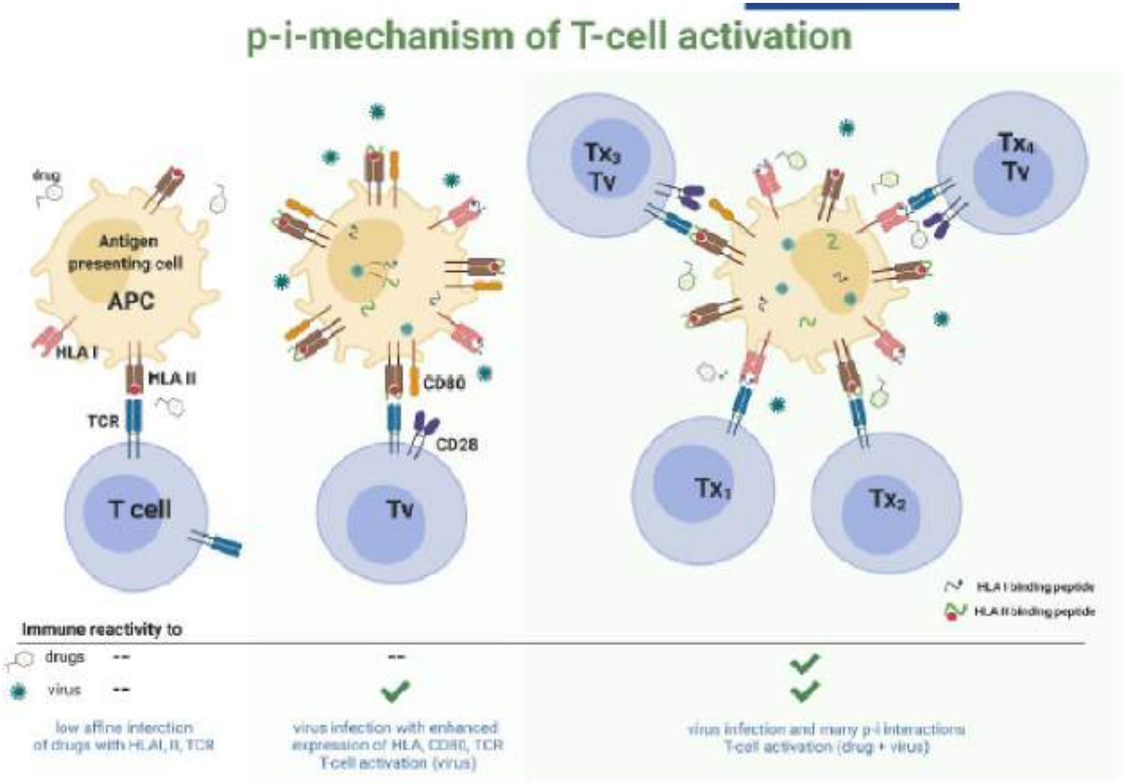
- Factores Genéticos:
  - Citrocromo p450
    - *CYP2C9*3- Fenitoína SCARs*
  - N-acetiltransferasa- Sulfonamida / Epoxidohidroxilasa- Carbamazepina
  - Polimorfismo HLA
    - HLA*58:01 DRESS-SSJ/TEN Allopurinol
    - HLA-A*31:01 DRESS-SSJ/TEN Carbamazepina
    - 3 modelos
      - Teoría hapteno/prohapteno
      - pi-concept
      - Repertorio peptídico alterado


A
Peptide A
Peptide B
MHC
APC membrane
Peptide A
MHC
APC membrane
T cell membrane
T cell receptor
Peptide A
MHC
APC membrane
B
T cell membrane
T cell receptor
Peptide A
MHC
APC membrane
Hapten/prohapten model
T cell membrane
T cell receptor
Peptide A
MHC
APC membrane
p-i model
T cell membrane
T cell receptor
Peptide B
MHC
APC membrane
Altered peptide repertoire model



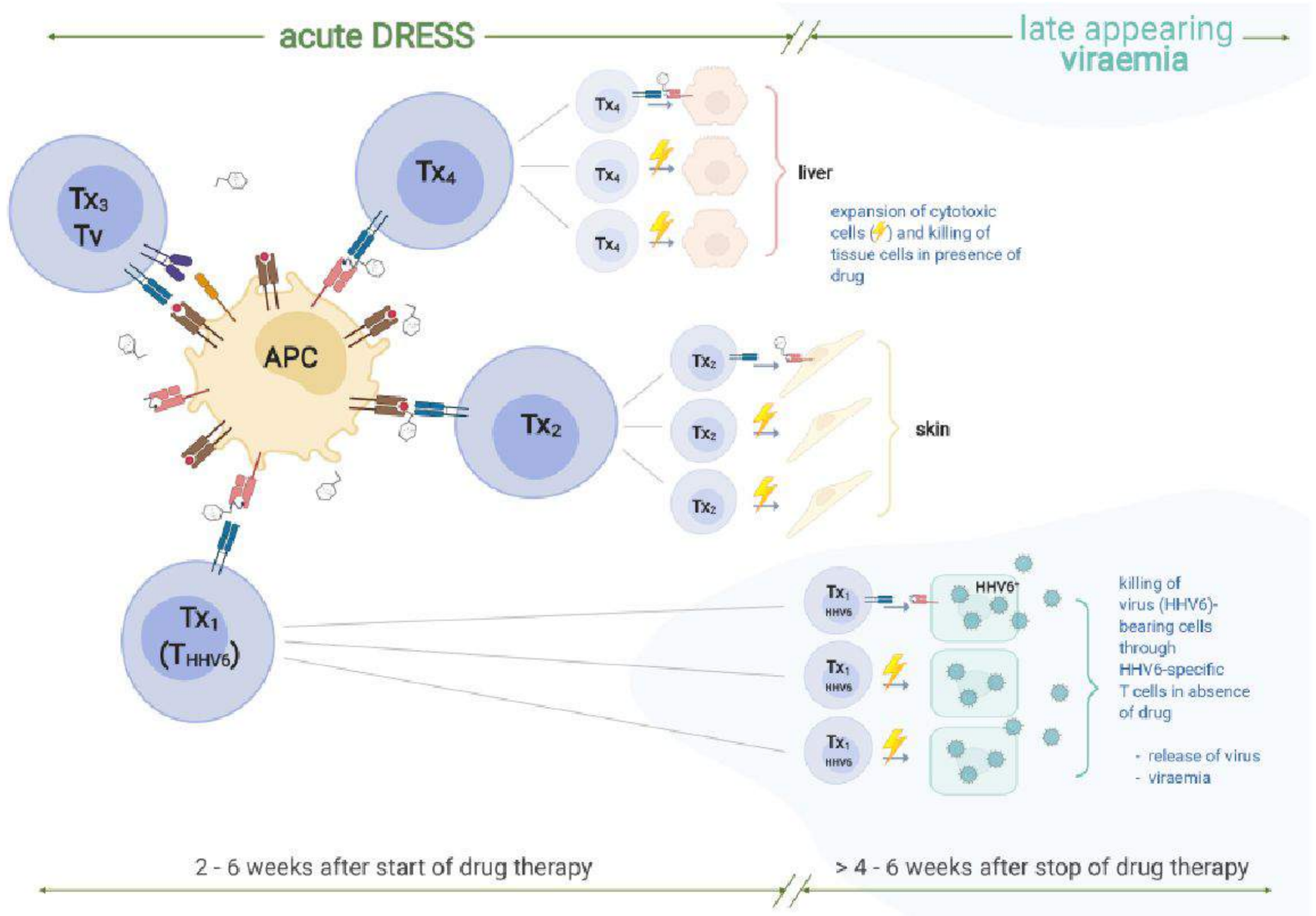
ALLERGY 2022;77:404





- Aumento expresión TCR, HLA, CD80-CD86 APC/Queratinocitos
- Mayor activación LT virus y LT AMX
- pi-concept activación mayor duración

Pichler, Allergy 2023



Pichler, Allergy 2023

Interacción Virus y Droga (Señales de Daño o Tormenta citoquinas)

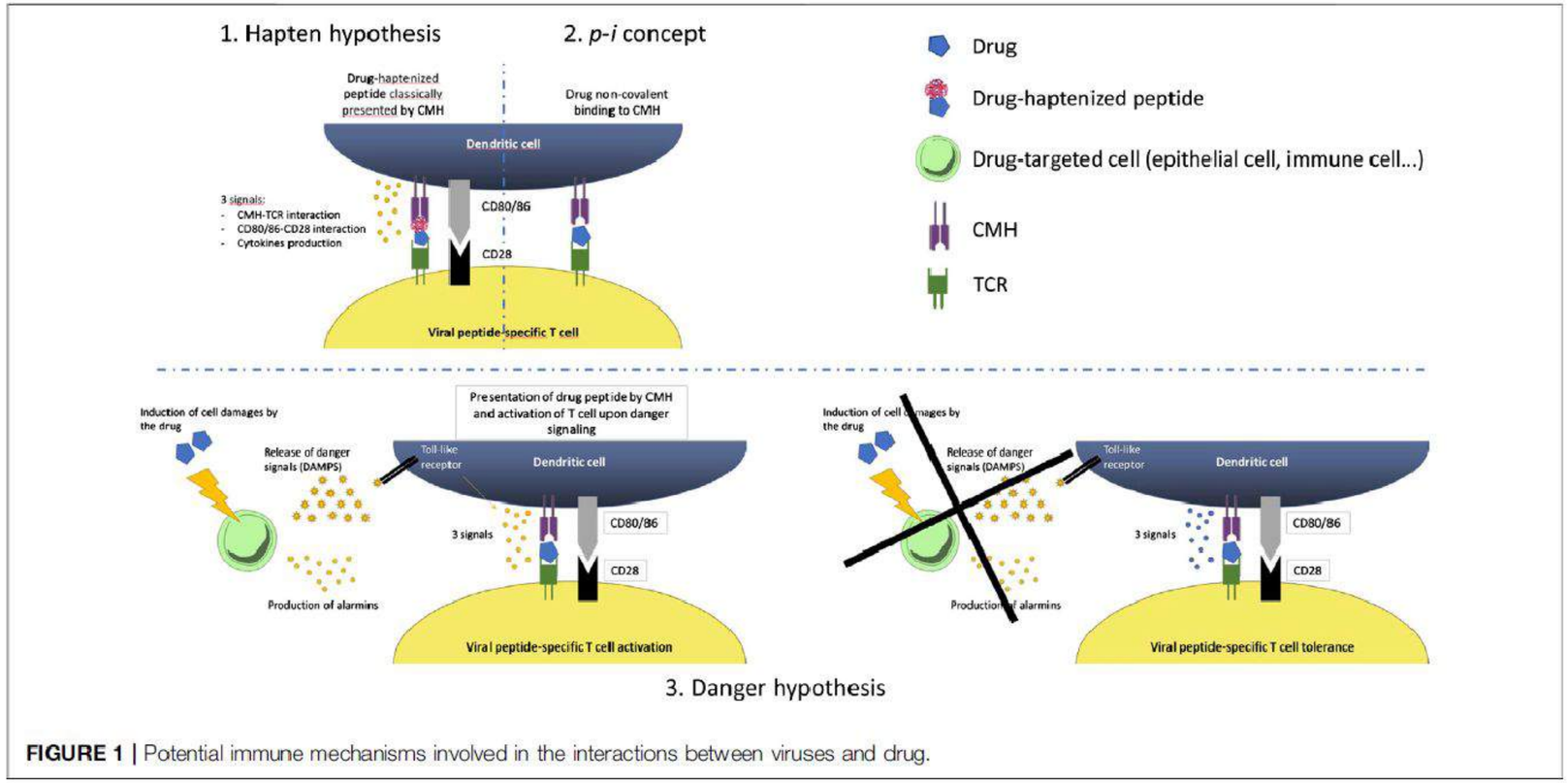


FIGURE 1 | Potential immune mechanisms involved in the interactions between viruses and drug.

Anci, Frontiers in Pharmacology 2021

Diferentes patrones citoquinas

Overexpression of Cytokines in the Skin of 36 DIEs and in 30 VBIEs

Cytokines	DIEs, n (%)	VBIEs, n (%)
FAS-L	16 (44.4)	13 (43.3)
GrB	18 (50.0)	12 (40.0)
IL-2	6 (16.7)	7 (23.3)
IL-4	11 (30.6)	9 (30.0)
IL-5	19 (52.8)*	7 (23.3)
IL-10	15 (41.7)	12 (40.0)
IL-13	10 (27.8)	8 (26.7)
INF-γ	14 (38.9)	12 (40.0)
Perforin	21 (58.3)	12 (40.0)
TNF-α	8 (26.7)	6 (16.7)

*$P < 0.05$.

The Trend of Associations Among IL-5, Perforin, and GrB Expression

Cytokines	DIEs, n (%)	VBIEs, n (%)
IL-5+ Perforin+ GrB+	10 (27.8)*	2 (6.7)
IL-5− Perforin− GrB−	7 (19.4)	11 (36.7)
IL-5+ Perforin+ GrB−	5 (13.9)	2 (6.7)
IL-5− Perforin+ GrB−	5 (13.9)	4 (13.3)
IL-5− Perforin− GrB+	4 (11.1)	4 (13.3)
IL-5+ Perforin− GrB+	3 (8.3)	2 (6.7)
IL-5+ Perforin− GrB−	1 (2.8)	1 (3.3)
IL-5− Perforin+ GrB+	1 (2.8)	4 (13.3)

*$P < 0.05$.

Hansel, 2017

Cutaneous Expression of Cytokines in 36 Exanthemas Induced by Amoxicillin in 11 Patients, Allopurinol in 5, and Other Drugs in 20

	DIEs		
Cytokines	Amoxicillin, n (%)	Allopurinol, n (%)	Other Drugs, n (%)
FAS-L	9 (81.8%)*	0*	7 (35.0)*
GrB	6 (54.5)	4 (80.0)	8 (40.0)
IL-2	2 (18.2)	1 (20.0)	3 (15.0)
IL-4	5 (45.5)	1 (20.0)	5 (25.0)
IL-5	8 (72.7)	1 (20.0)	10 (50.0)
IL-10	6 (54.5)	3 (60.0)	6 (30.0)
IL-13	5 (45.5)	1 (20.0)	4 (20.0)
INF-γ	7 (63.6)	3 (60.0)	4 (20.0)
Perforin	8 (72.7)	3 (60.0)	10 (50.0)
TNF-α	5 (45.5)†	1 (20.0)	2 (10.0)†

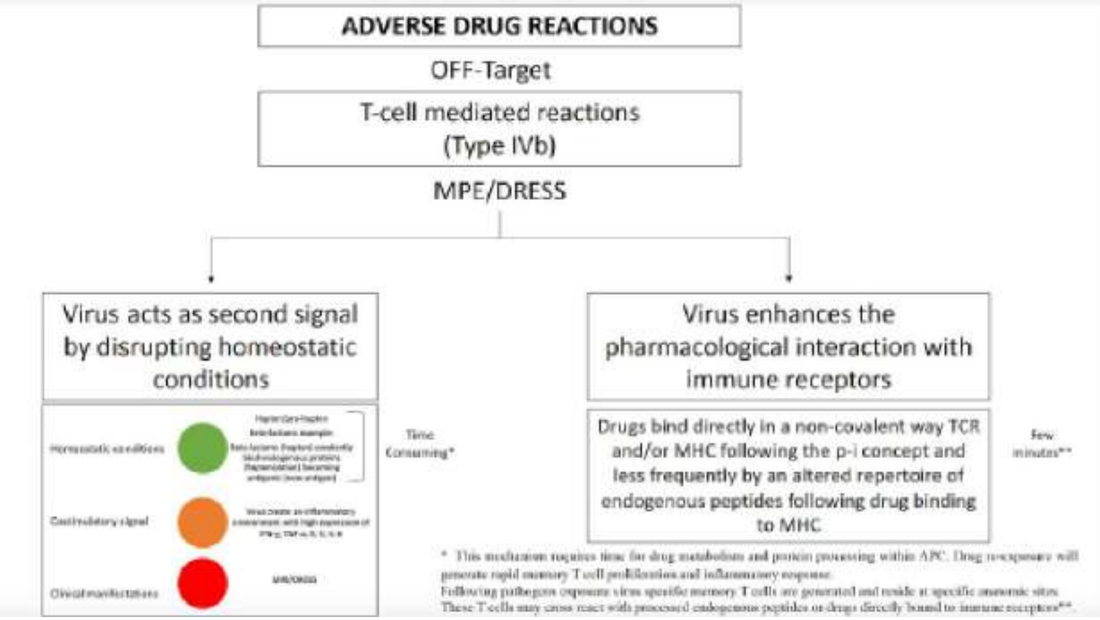
**FAS-L expression in DIEs: amoxicillin versus allopurinol, $P < 0.05$; versus other drugs, $P < 0.05$.*

†TNF-α expression in DIEs: amoxicillin versus other drugs, $P < 0.05$.

Mecanismos de cómo infección virus favorece una alergia drogas

1	Activation **of the immune system by viruses (uptake processing, presentation, development of CD4 and CD8 mediated immunity, NK cell activation, antibody generation)**
2	**Release of cytokines** (IFNγ, TNFα, IL-5, GranzymeB, perforin, granulysin, others), in severe cases **cytokine storm**
3	**Enhanced expression of HLA and/or adhesion molecules** on tissue cells like keratinocytes etc.; higher number of TCR/cell during virus activation
4	DHR appear as a result of a. **hapten** (e.g., β-lactams) binding and presentation by already activated APC, thus providing 1st and 2nd signal for drug specific T-cell activation; or b. **enhanced p-i** binding (*TCR-drug-HLA*), which per se can be sufficient for T-cell stimulation/cytotoxicity: The activated T cells secrete cytokines like IL-5 and kill tissue cells, leading to variable clinical pictures.

Pichler, Allergy 2023



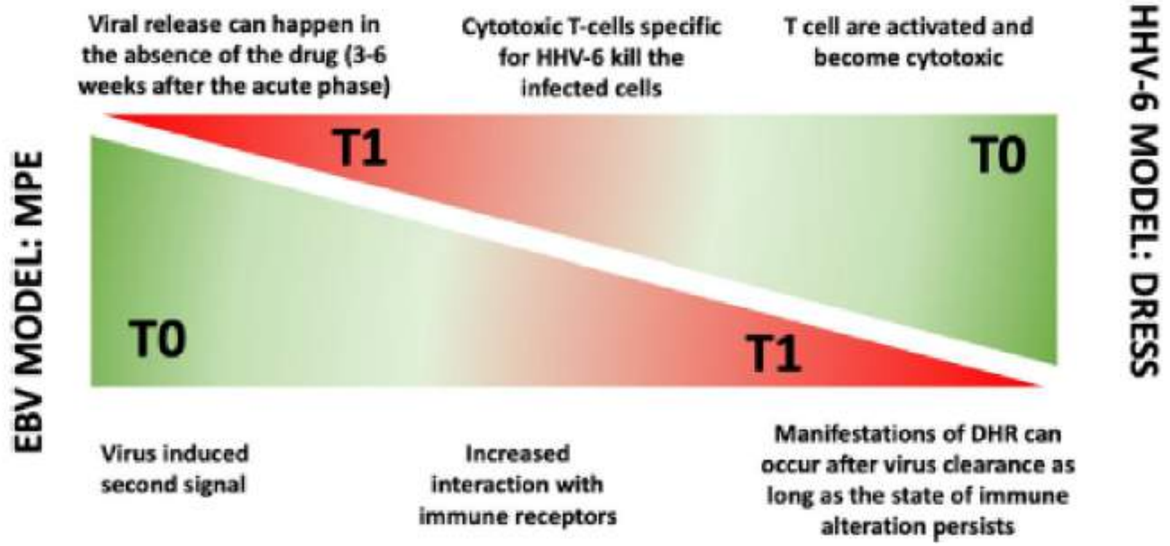
Mori, WAOJ 2024

Reactivación Viral

- Activación secundaria misma droga
  - AMP/ AMX- EBV
  - Ac Valproico- HHV6/CMV

- Tormenta citoquinas
  - ↑ IL-10 por aumento Treg y ↓ LB e Hipogamaglobulinemia: (+) viral
  - ↓ IP-10 disminuye CDp que generan INF-1

LISIS CÉLULAS INFECTADAS



INFECCIÓN VIRAL ACTIVA

Mori, WAOJ, 2024

Clinical examples of viral infection preceding DHR

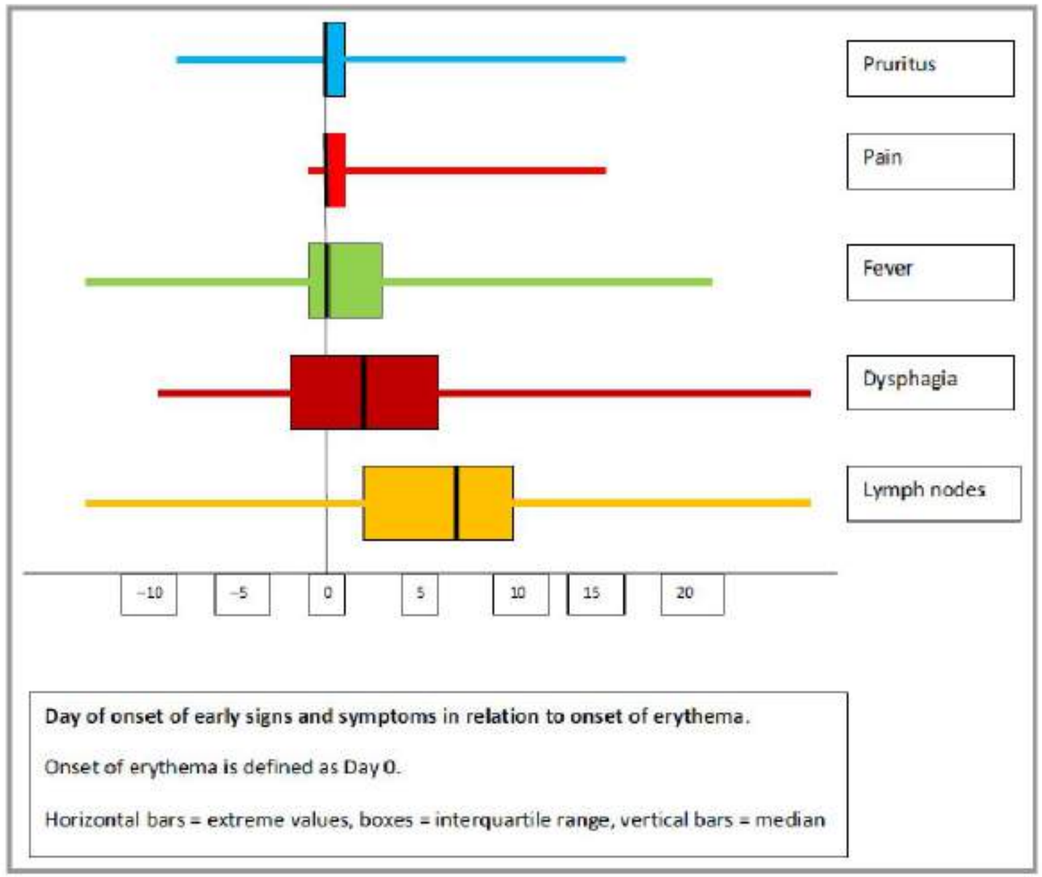
1	**Acute primary viral infections in childhood with mostly mild and transient exanthema**
2	Herpes virus (mostly EBV) infection and high incidence of exanthemas during aminopenicillin therapy
3	SARS-CoV2 infection enhancing DHR
4	HIV infection and "Sulfa-Allergy"
5	HIV infection and SJS/TEN

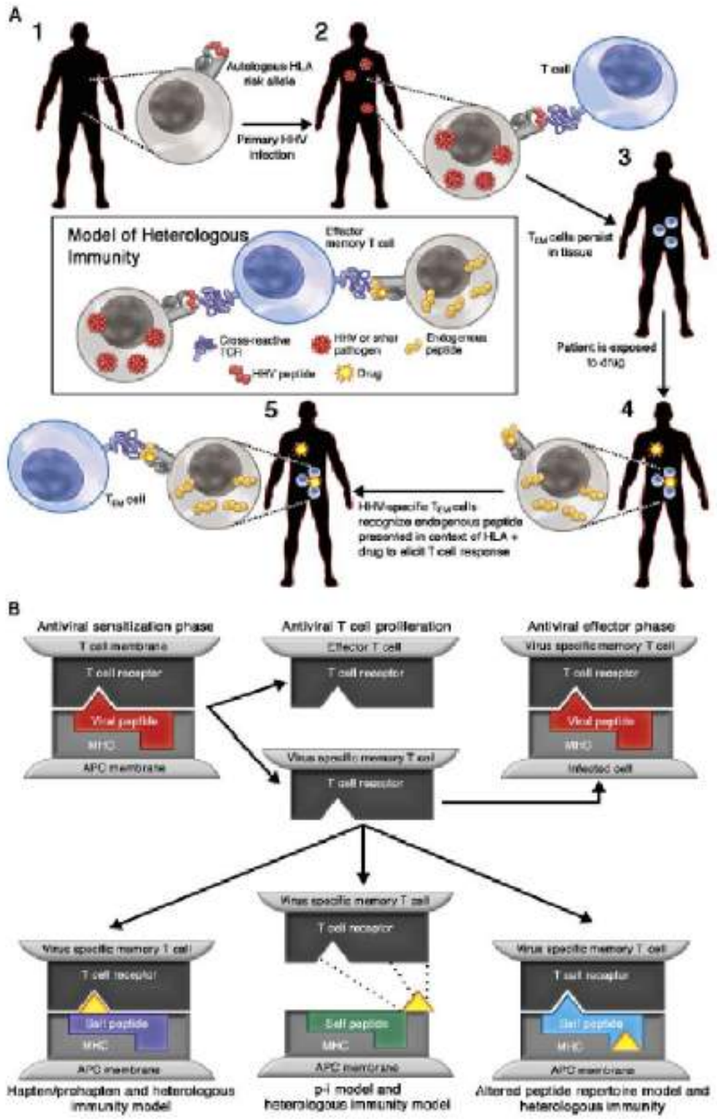
Delayed DHRs	Virus induced exanthemas
Activated $CD4^+CD8^+$ T cells HLA predisposition/hapten; pro-hapten nature Time of appearance >3 days from the first drug intake More severe exanthemas Eosinophilia IL-5; granzyme B; perforin	Only activated $CD4^+$ T cells No HLA predisposition (p-I concept) Time of appearance <3 days from the first drug intake Mild exanthemas No Eosinophilia IFN-gamma
Long Duration of skin manifestations	Short Duration of skin manifestations
Persistent nature (Memory T cells)	Transient nature (No memory T cells)
Allergy Work up (IDTs; PTs; LTT)	Allergy work up not required or not complete

Síndrome DRESS

- Incidencia 1: 1000-10000 exposiciones a fármacos

Exposure	Cases	Median	Interquartile range
At least one drug	115 (98%)		
Total number of drugs used	634	4	2–7
Causality	**Cases**	**Drugs**	
Very probable	39 (33%)	39	
Probable	54 (46%)	57*	
Possible	10 (9%)		
Undetermined	5 (4%)		
Unlikely	7 (6%)		
No drug use	2 (2%)		
Associated very probable drugs		**Median latency**	**Interquartile range**
AED	41 (35%)*		
Carbamazepine	23	29	20–36
Phenytoin	8	29	27–37
Lamotrigine	8	27	20–34
Oxcarbazepine	2	n.a.	n.a.
Phenobarbital	2	n.a.	n.a.
Allopurinol	21 (18%)	20	12–30
Sulfonamides	14 (12%)		
Sulfasalazine	8	20	18–25
Dapsone	3	n.a.	n.a
Sulfamethoxazole–trimethoprim	2	n.a.	n.a
Sulfadiazine	1	n.a.	n.a.
Antibiotics	13 (11%)		
Vancomycin	7	17	13–21
Minocyclin	4	20	17–26
Amoxicillin	1	n.a.	n.a.
Ampicillin/sulbactam	1	n.a.	n.a.
Other drugs[c]	5 (4%)	26	25–28

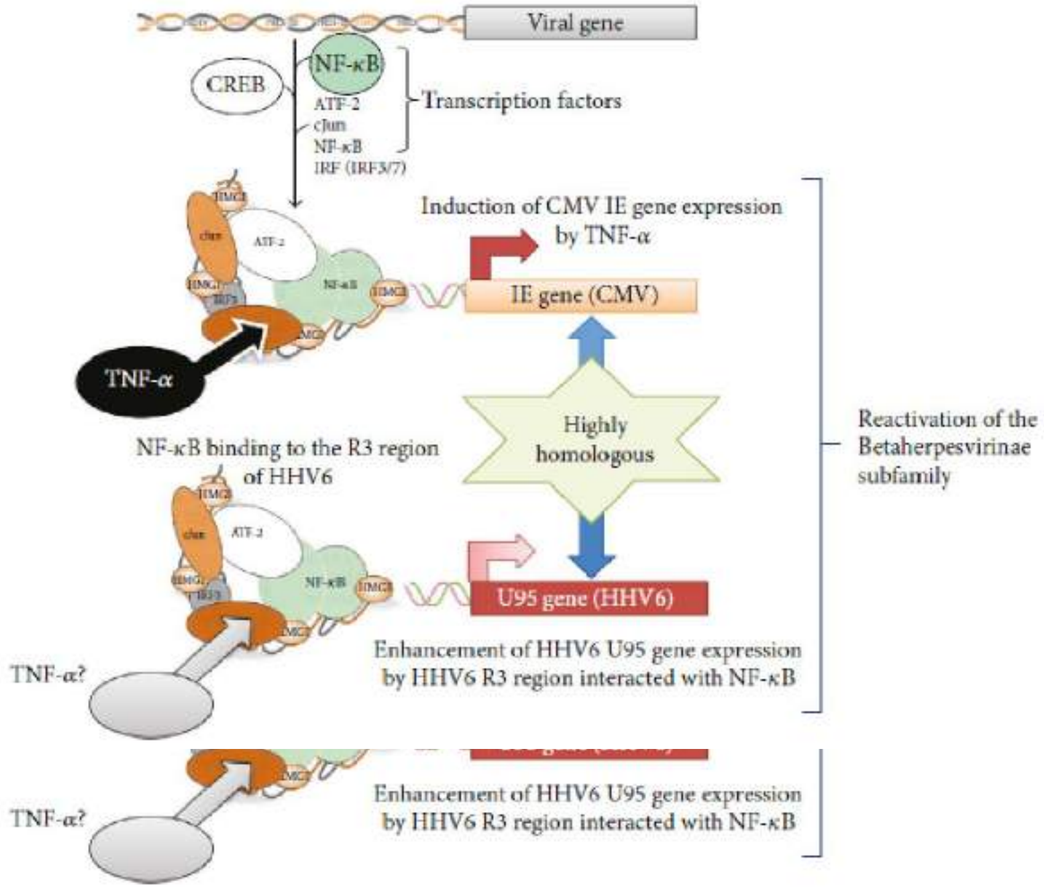




2% población EEUU, UK, Europa
tiene G-HHV6 integrado
1% RN transmisión vertical

White et al, 2015

HHV6/CMV Y TOXICODERMIAS



- Criterio?
- Consecuencia?
- Curso prolongado

Anci, 2021
Watanabe, 2018

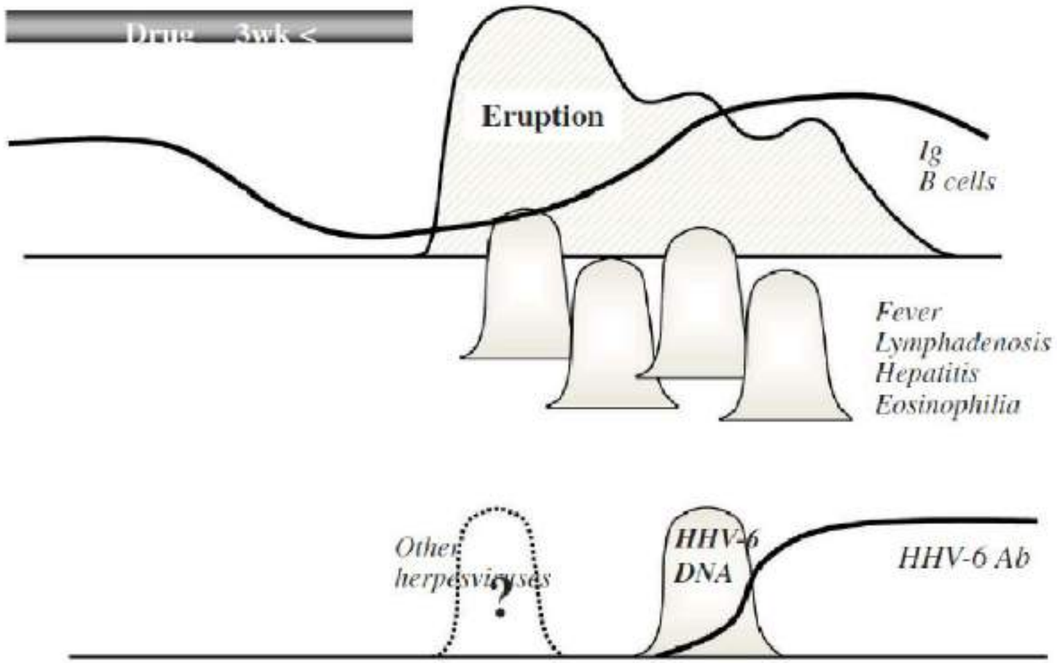


Figure 1. Clinical course of DiHS/DRESS [3]. This syndrome usually begins with a fever shortly followed by a maculopapular rash >3 weeks after starting therapy with a limited number of drugs, such as anticonvulsants. Patients usually develop two or three features of symptoms followed by a step-wise development of other symptoms. These symptoms continue to deteriorate or several flare-ups can be seen even for weeks or months after stopping the offending drug. Serum Ig levels continue to decrease for a weak after withdrawal of the drug. Despite such a wide variety of clinical symptoms, HHV-6 reactivation occurs 2–3 weeks after onset.

Shiohara, 2017

Infección HHV6 y DRESS

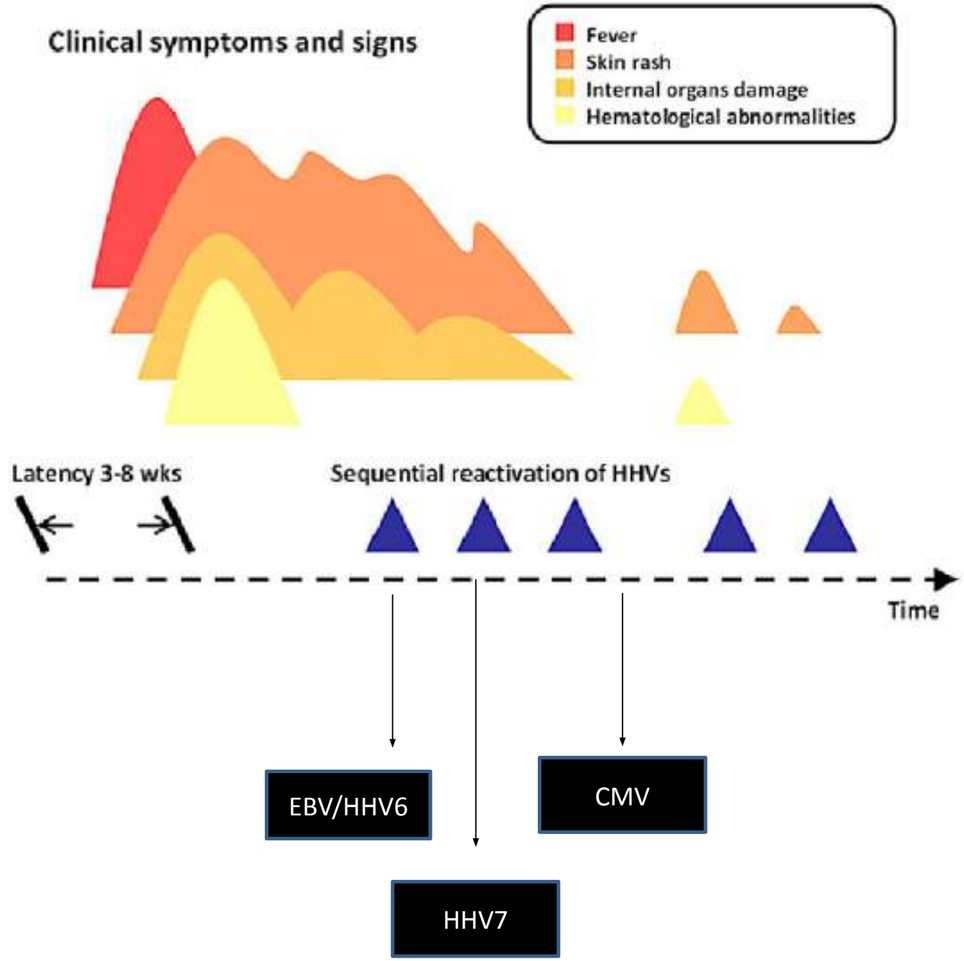
	Increase of HHV-6 IgG titres (n = 62)	No increase of HHV-6 IgG titres (n = 38)	P-value
Symptoms and signs, n (%)			
Fever	61 (98)	29 (76)	< 0·001
Duration of fever (days)	12·4 ± 7·1	4·8 ± 2·9	< 0·001
Lymphadenopathy	44 (71)	10 (26)	< 0·001
Leucocytosis[a]	38 (61)	8 (21)	< 0·001
Eosinophilia[b]	38 (61)	19 (50)	0·27
Appearance of atypical lymphocytes	55 (89)	20 (53)	< 0·001
Flaring, n (%)	32 (52)	7 (18)	< 0·001
Fever	22 (35)	2 (5)	< 0·001
Hepatitis[c]	32 (52)	2 (5)	< 0·001
Skin rash	12 (19)	5 (13)	0·42
Use of systemic corticosteroid, n (%)	50 (81)	27 (71)	0·17
Prognosis			
Duration of illness (weeks)	5·3 ± 2·6	2·8 ± 1·5	< 0·001
Death, n (%)	5 (8)	0 (0)	0·07

[a]Leucocytosis was evaluated based on white blood count (WBC), i.e. leucocytosis-positive patients were defined as those who had more than $1{\cdot}1 \times 10^{10}$ leucocytes L^{-1} if they had not received corticosteroids, or more than 5×10^{10} leucocytes L^{-1} if they had been treated with systemic corticosteroids. [b]Eosinophilia was scored as positive when the peripheral blood eosinophil count was higher than $1{\cdot}5 \times 10^{9}$ L^{-1} or more than 10% of the WBC. [c]Hepatitis was evaluated by measuring alanine aminotransferase (ALT) levels. Severe hepatitis indicated that ALT levels revealed more than 10 times the normal value.

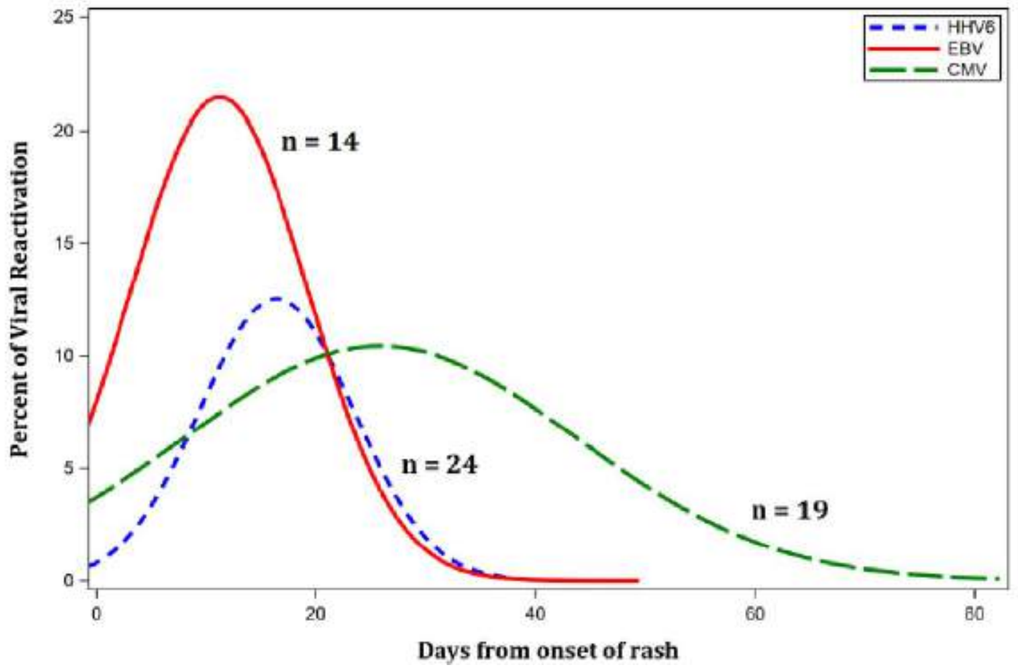
- CURSO MÁS PROLONGADO
- MAYOR COMPROMISO SISTÉMICO

Tohyama, Clinical and Laboratory Investigations

Secuencia Reactivaciones Virales



- SSJ/TEN
- HHV6 CASI EXCLUSIVAMENTE DRESS



Science Reports, (2024) 14: 28492

	Inpatient mortality, n (%)	Mortality in 1 year, n (%)	ICU, n (%)	Dialysis, n (%)	Length of hospital stay**, Mean (SD)	Flares in 1 year, n (%)	Readmission in 1 year, n (%)
Viral reactivation							
No (N = 54)	5 (9.3)	5 (9.3)	6 (11.1)	5 (9.3)	14.4 (16.5)	9 (16.7)	13 (24.1)
Yes (N = 39)	9 (23.1)	11 (28.2)	9 (23.1)	10 (25.6)	31.3 (47.5)	15 (38.5)	19 (48.7)
Total (N = 93)	14 (15.1)	16 (17.2)	15 (16.1)	15 (16.1)	21.5 (34.0)	24 (25.8)	32 (34.4)
Unadjusted OR/IRR (95% CI)*	2.9 (0.9–9.6)	3.9 (1.2–12.2)	2.4 (0.8–7.4)	3.4 (1.1–10.9)	2.2 (1.4, 3.3)	3.1 (1.2–8.2)	1.3 (0.7–2.3)
p-value	0.07	**0.02**	0.13	**0.04**	< 0.01	**0.02**	0.41
HHV6 Reactivation							
No (N = 61)	7 (11.5)	8 (13.1)	9 (14.8)	8 (13.1)	11.0 (15.0)	14 (23.0)	22 (36.1)
Yes (N = 24)	6 (25.0)	7 (29.2)	6 (25.0)	6 (25.0)	18.0 (22.5)	10 (41.7)	10 (41.7)
Total (N = 85)	13 (15.3)	15 (17.6)	15 (17.6)	14 (16.5)	12.0 (14.0)	24 (28.2)	32 (37.6)
Unadjusted OR/IRR (95% CI)*	2.6 (0.8–8.7)	2.7 (0.9–8.6)	1.9 (0.6–6.2)	2.2 (0.7–7.2)	1.1 (0.7, 1.8)	2.4 (0.9–6.6)	1.2 (0.5–3.1)
p-value	0.13	0.09	0.27	0.19	0.68	0.09	0.74
CMV Reactivation							
No (N = 70)	7 (10.0)	8 (11.4)	8 (11.4)	8 (11.4)	10.5 (12.0)	18 (25.7)	23 (32.9)
Yes (N = 19)	6 (13.6)	7 (36.8)	6 (31.6)	6 (31.6)	24.0 (30.0)	6 (31.6)	9 (47.4)
Total (N = 89)	13 (14.6)	15 (16.9)	14 (15.7)	14 (15.7)	13.0 (14.0)	24 (27.0)	32 (36.0)
Unadjusted OR/IRR (95% CI)*	4.2 (1.2–14.4)	4.5 (1.4–14.8)	3.6 (1.1–12.1)	3.6 (1.1–12.1)	2.6 (1.8, 4.0)	1.3 (0.4–4.0)	1.7 (0.6–4.8)
p-value	**0.03**	**0.01**	**0.04**	**0.04**	**< 0.01**	0.61	0.30
EBV Reactivation							
No (N = 73)	8 (11.0)	8 (11.0)	10 (13.7)	9 (12.3)	11.0 (12.0)	20 (27.4)	23 (31.5)
Yes (N = 14)	4 (28.6)	6 (42.9)	3 (21.4)	4 (28.6)	22.0 (22.0)	4 (28.6)	9 (64.3)
Total (N = 87)	12 (13.8)	14 (16.1)	13 (14.9)	13 (14.9)	12.0 (13.0)	24 (27.6)	32 (36.8)
Unadjusted OR/IRR (95% CI)*	3.3 (0.8–12.8)	6.1 (1.7–22.1)	1.7 (0.4–7.3)	2.8 (0.7–11.0)	1.2 (0.7, 2.1)	1.1 (0.3–3.8)	3.7 (1.1–12.2)
p-value	0.09	**< 0.01**	0.46	0.13	0.53	0.93	**0.03**
Number of Herpesvirus reactivations							
< 2 (N = 78)	8 (10.3)	8 (10.3)	10 (12.8)	10 (12.8)	20.0 (36.0)	19 (24.4)	25 (32.1)
≥ 2 (N = 15)	6 (40.0)	8 (53.3)	5 (33.3)	5 (33.3)	29.1 (19.0)	5 (33.3)	8 (53.3)
Total (N = 93)	14 (15.1)	16 (17.2)	15 (16.1)	15 (16.1)	21.5 (34.0)	24 (25.8)	33 (35.5)
Unadjusted OR/IRR (95% CI)*	5.8 (1.7–20.7)	10.0 (2.9–34.9)	3.4 (1.0–12.0)	3.4 (1.0–12.0)	1.5 (0.9, 2.5)	1.6 (0.5–5.1)	2.4 (0.8–7.4)
p-value	**< 0.01**	**< 0.01**	0.06	0.06	0.16	0.47	0.12

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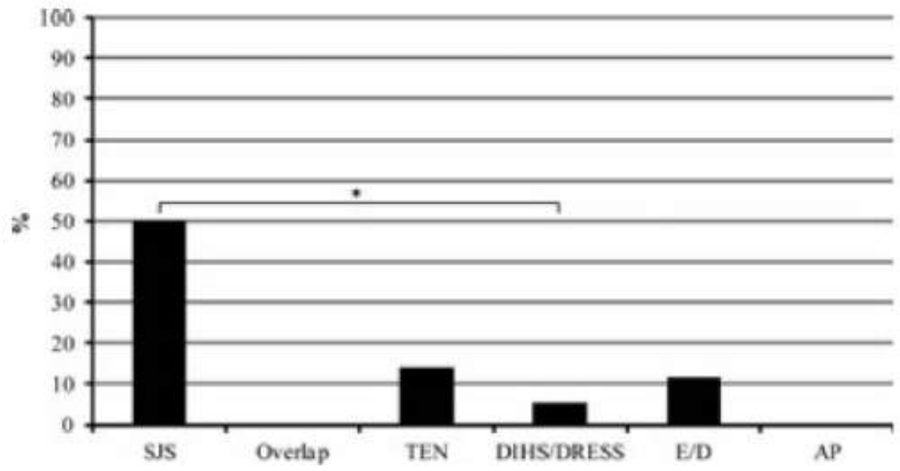
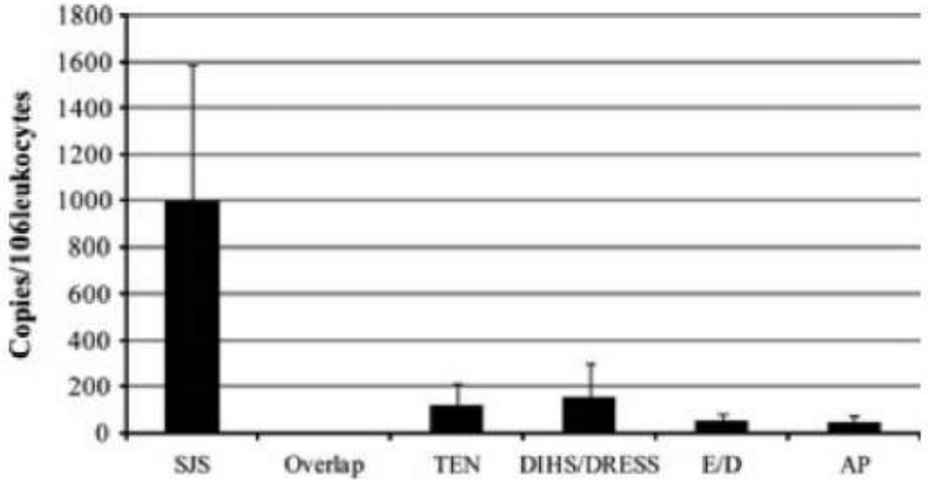
Importancia tipo virus según toxicodermia





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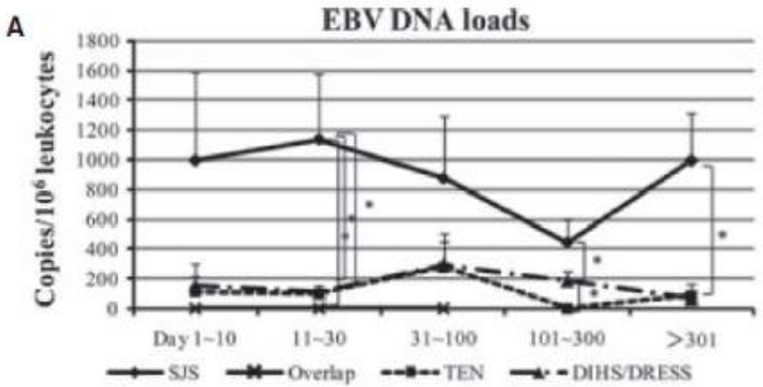

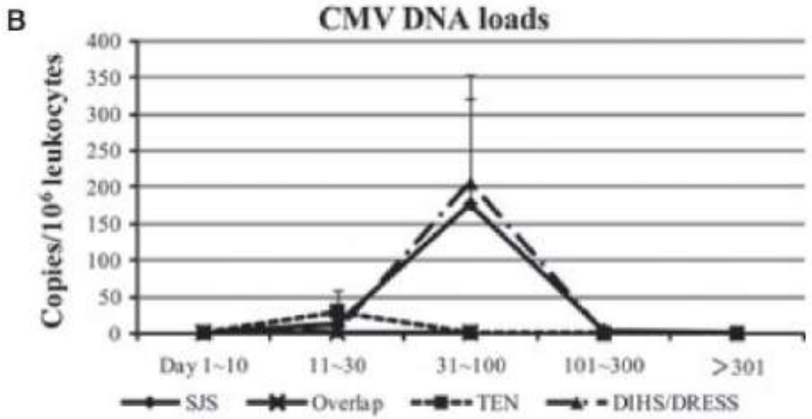

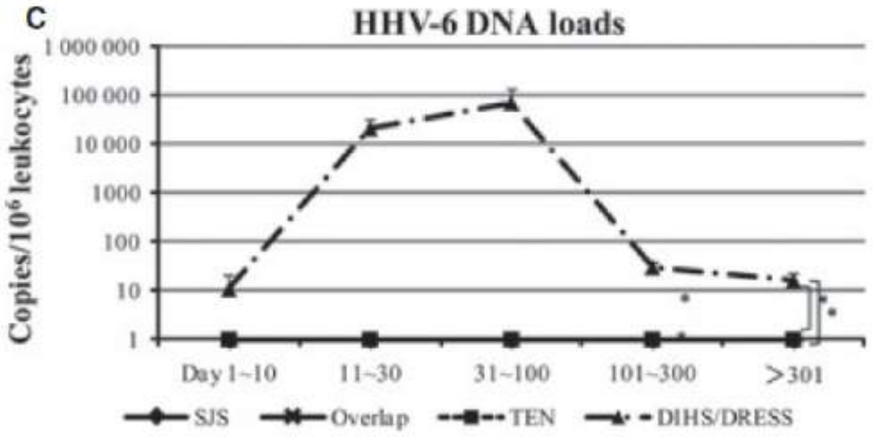

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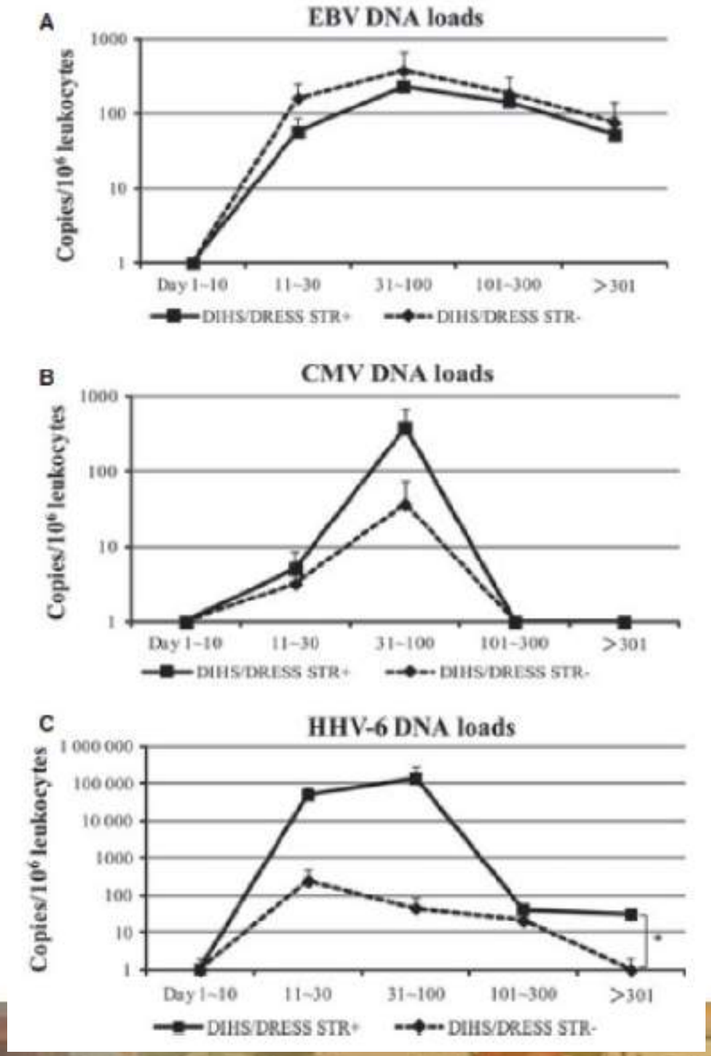
Efecto corticoides en reactivación viral

- CON Y SIN TTO CS
- CV (-) INICIO



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Efecto uso corticoides

Group	Case no.	Age/ sex	Culprit drug	Duration between starting of drug and develop of skin eruption	Body temperature (°C)	Lymphadenopathy	Peripheral blood† WBC (/μL)	Eosinophils (/μL)	Atypical lymphocytes (%)	ALT† (U/L)	CRP† (mg/dL)	Systemic corticosteroid Initiation day	Dose of prednisolone‡ (mg/kg per day)	Duration (days)	Detection of viral DNA in blood (days from onset to initial detection) HHV-6	EBV	CMV	Relapsing symptoms or complications over 1 month after the onset
A	1	64/F	Mexiletine	30 days	>38	+	11 800	1530	3	447	1.79	–	–	–	+ (28)	–	–	Hepatitis
	2	46/F	Phenytoin	2 years	>39	+	15 900	7350	0	146	2.96	–	–	–	+ (19)	+ (33)	–	Fever, skin rash
	3	88/F	Carbamazepine	50 days	>38	–	10 100	0	0	139	4.04	–	–	–	+ (14)	+ (14)	+ (33)	No
	4	30/M	Carbamazepine	39 days	>37	+	10 600	2900	8	729	3.43	–	–	–	+ (21)	–	+ (33)	No
	5	64/M	Carbamazepine	28 days	>37	–	10 800	430	3	5521	1.3	–	–	–	+ (21)	+ (35)	–	No
	6	76/F	Carbamazepine	25 days	>39	–	10 400	5529	8	158	5.25	–	–	–	+ (18)	–	–	Neurogenic bladder dysfunction, mild impairment
	7	32/F	DDS	21 days	>39	+	16 000	400	44	272	1.24	–	–	–	–	–	–	No
	Average ± SED						12 229 ± 850	1606 ± 634	9.8 ± 5.1	487 ± 165	3.11 ± 0.54							
B	8	38/F	Zonisamide/ Phenobarbital	31/6 days	>39	+	28 300	1300	29	1202	4.68	4	1.1	42	+ (14)	–	–	Alopecia areata
	9	24/F	Phenobarbital	30 days	>40	+	15 900	742	3	275	3.38	3	1.0	20	–	+ (13)	–	No
	10	42/F	Carbamazepine	48 days	>38	+	14 800	2550	2.5	350	0.92	5	1.1	25	–	–	–	No
	11	47/M	Vancomycin	22 days	>39	+	56 800	2976	0.8	628	3.22	2	1.0	30	–	+ (14)	+ (23)	Fever, urticaria
	12	54/M	Sulfamethoxazole/ trimethoprim	35 days	>38	+	11 800	236	24	1389	6.31	4	1.3	22	–	+ (8[1])	+ (14)	Urticaria
	13	69/M	Carbamazepine	34 days	>39	+	17 500	835	9.5	162	8.08	2	0.9 → 1.1 (day 8)	38	+ (15)	+ (39)	+ (43)	Pneumocystis pneumonia, skin rash
	Average ± SED						24 017 ± 5713	1697 ± 494	11.0 ± 3.8	651 ± 178	4.43 ± 0.87			29 ± 7				
C	14	48/F	Carbamazepine	2 year	>39	+	21 800	5777	1	70	7.44	13	1.1	120	+ (20)	+ (38)	+ (58)	CMV gastroenteritis, skin rash
	15	44/M	Carbamazepine	29 days	>39	+	22 400	5710	10	282	6.21	9	0.4 → 0.8 (day 12)	50	+ (17)	–	–	Fever, skin rash
	16	75/M	Phenytoin	34 days	>39	+	15 000	264	3	22	2.69	4	0.5	66	+ (15)	+ (28)	+ (30)	Pneumocystis pneumonia, skin rash
	17	69/M	Zonisamide	5 months	>39	+	13 000	1430	15	1655	7.88	2	0.2 → 1.8 (day 15)	82	+ (23)	+(19[2])	+(19[2])	Skin rash
	18	75/F	Moxifloxacin	23 days	>39	+	29 500	2011	0	114	5.85	6	0.6 → 1.0 (day 13)	35	+ (13)	+ (9)	+ (23)	Skin rash
	19	30/M	Carbamazepine	30 days	>39	+	13 200	0	1	427	9.67	11	0.8	43	–	+ (36)	–	Skin rash
	20	40/F	Carbamazepine	40 days	>40	+	15 600	2960	11	213	2.9	7	0.5	27	+ (13[2])	–	+(13[2])	Skin rash
	Average ± SED						18 663 ± 2008	2383 ± 777	5.9 ± 2.0	397 ± 187	6.09 ± 0.84			65 ± 31				

- A: SIN CS
- B: ALTAS CS MENOS 1 SMN
- C: ALTAS CS MAYOR 1 SMN
  BAJAS CS INICIO

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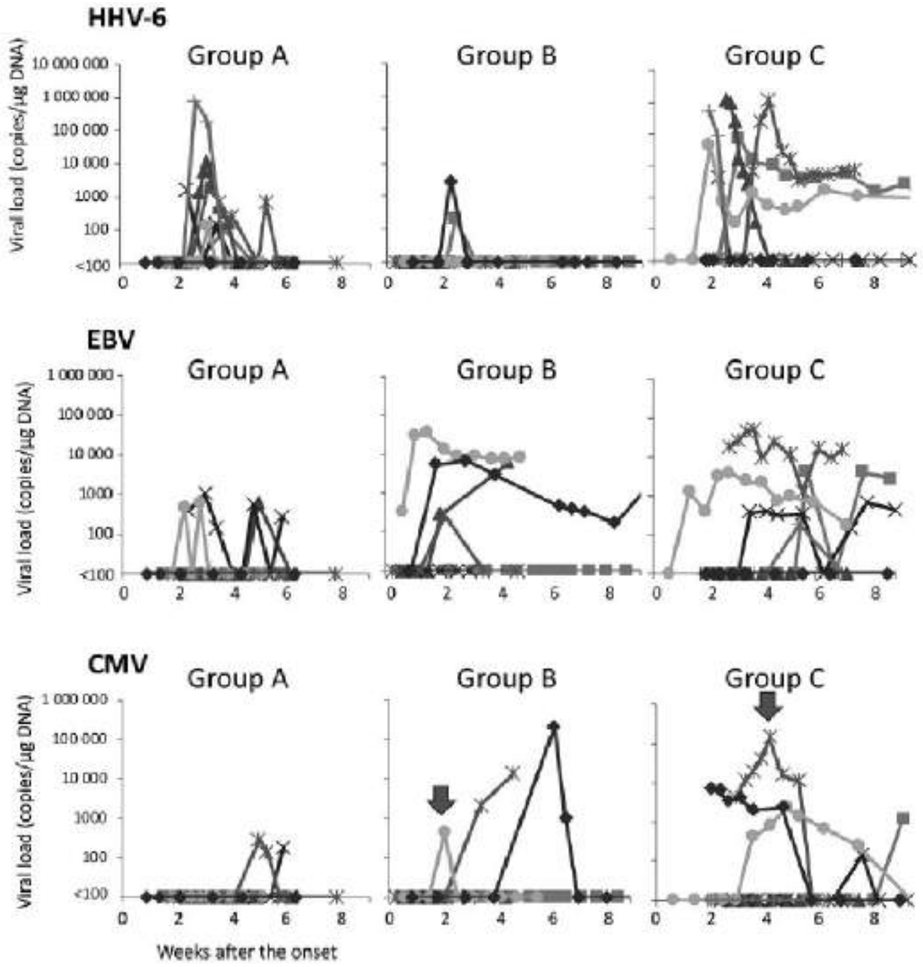
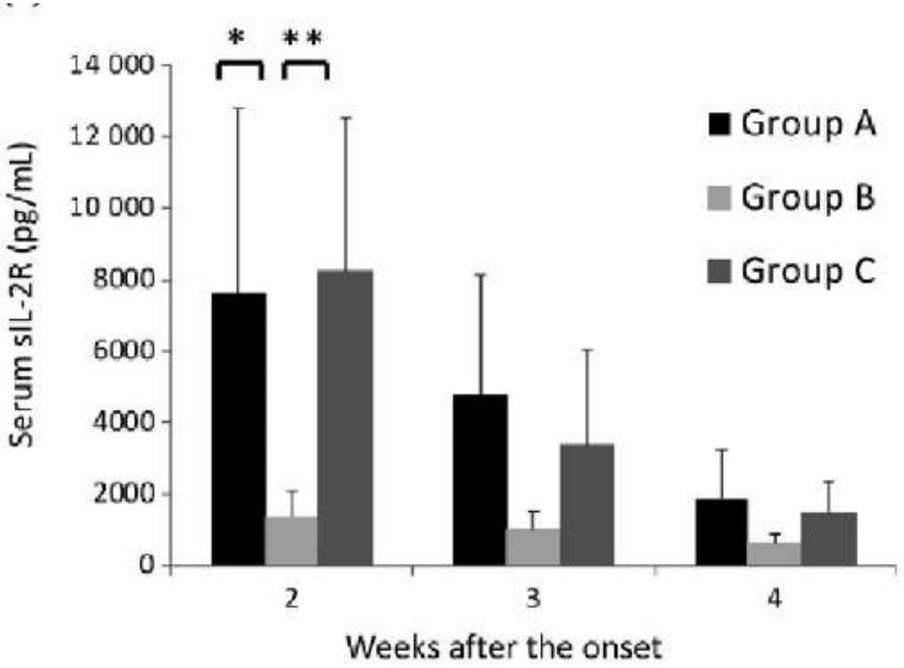
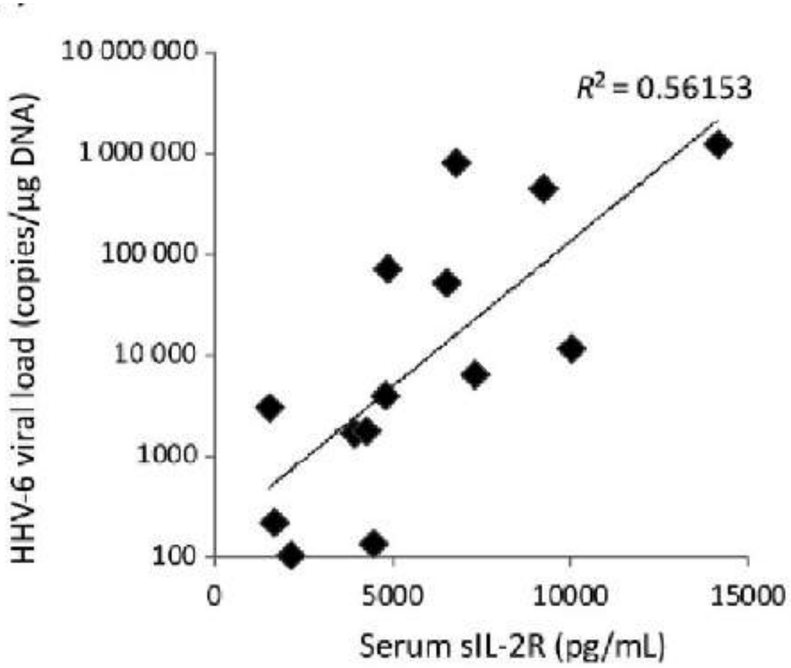


Interestingly, when a high-dose corticosteroid was started within 1 week after disease onset, HHV-6 reactivation tended to be suppressed. Although it remains unclear how HHV-6 is reactivated from monocytes, reactivated HHV-6 infects CD4 T cells through CD134,[16] a receptor for HHV-6, and multiplies, resulting in viremia. CD134 is expressed only in activated T cells, and Miyagawa *et al.*[17] clearly demonstrated that the number of T cells expressing CD134 increased in the acute phase of DIHS/DRESS. Our findings revealed that a high-dose corticosteroid started within 1 week after onset effectively suppressed T-cell activation. Under these conditions, reactivated HHV-6 eventually loses its ability to proliferate after being reactivated from monocytes.

Efecto uso corticoides





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Activación CMV

Table II. Demographic and clinical characteristics of patients with CMV$^+$ and CMV$^-$ drug-induced hypersensitivity syndrome and drug reaction with eosinophilia and systemic symptoms

	CMV$^+$ (n = 11)	CMV$^-$ (n = 44)
Age, y, mean ± SEM	73.3 ± 3.4*	49.8 ± 2.9
Gender, M:F	7:4	16:28
Underlying disease (n)	Arrhythmia (1), brain tumor (2), bullous disease (1), cerebrovascular disease (1), dementia (1), epilepsy (2), Guillain–Barre syndrome (1), and hyperuricemia (3)	Brain tumor (1), cerebrovascular disease (2), epilepsy (12), fibromyalgia (1), hyperuricemia (7), neuralgia (3), psychological illness (17), and restless legs syndrome (1)
Causative drug (n)	Allopurinol (2), carbamazepine (5), dapsone (1), mexiletine (1), phenytoin (1), and trimethoprim/sulfamethoxazole (1)	Allopurinol (5), carbamazepine (27), lamotrigine (9), and phenytoin (3)
Early score, median (IQR)	6 (4-7)*	2 (1-4)
Late score, median (IQR)	3 (1-5)*	−1 (−2 to 0)
Duration of causative drug exposure before onset, mean ± SEM	42.9 ± 8.1 days	44.3 ± 8.1 days
Hospitalization period, mean ± SEM (range)	56.9 ± 6.1 days* (28-81 days)	25.3 ± 1.9 days (6-54 days)
Total doses of systemic corticosteroids before initial presentation, mean ± SEM (range) [n]†‖	673.3 ± 600.8 mg (75-1875 mg) [3]	120.3 ± 64.5 mg (7.5-690 mg) [10]
Starting doses of systemic corticosteroids after initial presentation, mean ± SEM (range) [n]†	54.3 ± 4.8 mg (40-80 mg) [9]*	45.5 ± 5.1 mg (10-70 mg) [11]
Total doses of systemic corticosteroids until 8 weeks after initial presentation, mean ± SEM (range) [n]†‖	1928.9 ± 127.0 mg (1290-2470 mg) [9]*	1729.1 ± 232.1 mg (260-3200 mg) [11]
No. of cases with CMV disease/complications‡	5*	0
Mortality rate (no. of deaths)‡	27.3% (3)*	0% (0)

Table IV. Risk stratification of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms cases based on the early score

	Mild (1>) (n = 5)	Moderate (1-3) (n = 23)	Severe (4≤) (n = 27)
No. of CMV$^+$ cases‡	0	1*	10*
Late score, median (IQR)	−2 (−2 to −1.5)	−1 (−1 to 0)	1 (0-5)†
No. of cases with CMV disease/complications‡	0	0	5†
Mortality rate (no. of dead patients)‡	0% (0)	0% (0)	11.5% (3)
Hospitalization period, days, mean ± SEM (range)	16.2 ± 3.7 (9-27)	23.2 ± 2.4 (6-65)	41.7 ± 3.8† (14-81)
Total doses of systemic corticosteroids until 8 weeks after initial presentation, mean ± SEM (range) [no. of cases]‖	0 mg (0 mg) [0]	1459.2 ± 247.8 mg* (260-2170 mg) [6]	1973.2 ± 154.6 mg* (620-3200 mg) [14]
WBC (cells/μL), mean ± SEM	5740.0 ± 1059.1	8708.7 ± 1521.8	10,388.9 ± 972.0
Plt (μL), mean ± SEM	21.8 ± 2.0	19.9 ± 1.6	29.8 ± 7.8
ALT (IU/L), mean ± SEM	115.0 ± 32.2	201.9 ± 48.9	80.4 ± 15.2
CRP (mg/dL), mean ± SEM	0.8 ± 0.2	2.9 ± 0.5	7.4 ± 1.1*
Early NLR, mean ± SEM	1.6 ± 0.6	4.3 ± 0.6	6.5 ± 1.3
Late NLR, mean ± SEM	1.4 ± 0.2	2.1 ± 0.3	3.2 ± 0.4

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	Inpatient mortality, n (%)	Mortality in 1 year, n (%)	ICU, n (%)	Dialysis, n (%)	Length of hospital stay**, Mean (SD)	Flares in 1 year, n (%)	Readmission in 1 year, n (%)
Viral reactivation							
No (N = 54)	5 (9.3)	5 (9.3)	6 (11.1)	5 (9.3)	14.4 (16.3)	9 (16.7)	13 (24.1)
Yes (N = 39)	9 (23.1)	11 (28.2)	9 (23.1)	10 (25.6)	31.3 (47.5)	15 (38.5)	19 (48.7)
Total (N = 93)	14 (15.1)	16 (17.2)	15 (16.1)	15 (16.1)	21.5 (34.0)	24 (25.8)	32 (34.4)
Unadjusted OR/IRR (95% CI)*	2.9 (0.9–9.6)	3.9 (1.2–12.2)	2.4 (0.8–7.4)	3.4 (1.1–10.9)	2.2 (1.4, 3.3)	3.1 (1.2–8.2)	1.3 (0.7–2.3)
p-value	0.07	**0.02**	0.13	**0.04**	< 0.01	**0.02**	0.41
HHV6 Reactivation							
No (N = 61)	7 (11.5)	8 (13.1)	9 (14.8)	8 (13.1)	11.0 (15.0)	14 (23.0)	22 (36.1)
Yes (N = 24)	6 (25.0)	7 (29.2)	6 (25.0)	6 (25.0)	18.0 (22.5)	10 (41.7)	10 (41.7)
Total (N = 85)	13 (15.3)	15 (17.6)	15 (17.6)	14 (16.5)	12.0 (14.0)	24 (28.2)	32 (37.6)
Unadjusted OR/IRR (95% CI)*	2.6 (0.8–8.7)	2.7 (0.9–8.6)	1.9 (0.6–6.2)	2.2 (0.7–7.2)	1.1 (0.7, 1.8)	2.4 (0.9–6.6)	1.2 (0.5–3.1)
p-value	0.13	0.09	0.27	0.19	0.68	0.09	0.74
CMV Reactivation							
No (N = 70)	7 (10.0)	8 (11.4)	8 (11.4)	8 (11.4)	10.5 (12.0)	18 (25.7)	23 (32.9)
Yes (N = 19)	6 (13.6)	7 (36.8)	6 (31.6)	6 (31.6)	24.0 (30.0)	6 (31.6)	9 (47.4)
Total (N = 89)	13 (14.6)	15 (16.9)	14 (15.7)	14 (15.7)	13.0 (14.0)	24 (27.0)	32 (36.0)
Unadjusted OR/IRR (95% CI)*	4.2 (1.2–14.4)	4.5 (1.4–14.8)	3.6 (1.1–12.1)	3.6 (1.1–12.1)	2.6 (1.8, 4.0)	1.3 (0.4–4.0)	1.7 (0.6–4.8)
p-value	**0.03**	**0.01**	**0.04**	**0.04**	**< 0.01**	0.61	0.30
EBV Reactivation							
No (N = 73)	8 (11.0)	8 (11.0)	10 (13.7)	9 (12.3)	11.0 (12.0)	20 (27.4)	23 (31.5)
Yes (N = 14)	4 (28.6)	6 (42.9)	3 (21.4)	4 (28.6)	22.0 (22.0)	4 (28.6)	9 (64.3)
Total (N = 87)	12 (13.8)	14 (16.1)	13 (14.9)	13 (14.9)	12.0 (13.0)	24 (27.6)	32 (36.8)
Unadjusted OR/IRR (95% CI)*	3.3 (0.8–12.8)	6.1 (1.7–22.1)	1.7 (0.4–7.3)	2.8 (0.7–11.0)	1.2 (0.7, 2.1)	1.1 (0.3–3.8)	3.7 (1.1–12.2)
p-value	0.09	**< 0.01**	0.46	0.13	0.53	0.93	**0.03**
Number of Herpesvirus reactivations							
< 2 (N = 78)	8 (10.3)	8 (10.3)	10 (12.8)	10 (12.8)	20.0 (36.0)	19 (24.4)	25 (32.1)
≥ 2 (N = 15)	6 (40.0)	8 (53.3)	5 (33.3)	5 (33.3)	29.1 (19.0)	5 (33.3)	8 (53.3)
Total (N = 93)	14 (15.1)	16 (17.2)	15 (16.1)	15 (16.1)	21.5 (34.0)	24 (25.8)	33 (35.5)
Unadjusted OR/IRR (95% CI)*	5.8 (1.7–20.7)	10.0 (2.9–34.9)	3.4 (1.0–12.0)	3.4 (1.0–12.0)	1.5 (0.9, 2.5)	1.6 (0.5–5.1)	2.4 (0.8–7.4)
p-value	**< 0.01**	**< 0.01**	0.06	0.06	0.16	0.47	0.12

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CONCLUSIONES

- TOXICODERMIAS SON CUADROS POCA FRECUENCIA, PERO SEVERIDAD, ESPECIALMENTE SI SE PRESENTAN REACTIVACIONES VIRALES DURANTE SU EVOLUCIÓN
- EL TIPO DE VIRUS ACTIVO PUEDE SER DIFERENTE SEGÚN LA TOXICODERMIA QUE SE TRATE
- LA PRESENCIA DE AGENTES VIRALES SE RELACIONA: CON MAYOR MORTALIDAD, POR SU MAYOR COMPROMISO SISTÉMICO, HOSPITALIZACIONES MÁS PROLONGADAS Y EXACERBACIONES MÁS FRECUENTES, ESPECIALMENTE DURANTE EL PRIMER AÑO DE EVOLUCIÓN
- EL INICIO DE CORTICOIDES EN DOSIS BAJAS O DE INICIO TARDÍO SON UN FACTOR ASOCIADO A ESTAS REACTIVACIONES
- FALTAN ESTUDIOS PARA DILUCIDAR SI ESTAS ACTIVACIONES PUEDEN SER UTILIZADAS COMO VERDADEROS CRITERIOS DIAGNÓSTICOS.

GRACIAS

Exantema virales

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