

SUPPLEMENTARY MATERIAL

Table S1. Clinical and demographic data of patients. LTT results (expressed as Stimulation Index), drug reexposure and LTT final interpretation.

N°	Age	Sex	Reported reaction	Interval between drug and reaction (days)	NSAIDs involved (causality score) §	Other drugs involved (causality score) §	NSAIDs involved (Stimulation index)*	Other drugs (Stimulation index)*	NSAID involved tolerated in reexposure	LTT interpretation**
1	47	F	Pruritic exanthema	10	Ibuprofen (+5)	No	Ibuprofen (1.1)	No	Yes	TN
2	6	M	AGEP	7	Ibuprofen (+5)	Guaifenesin (+5), Pseudoephedrine (+5)	Ibuprofen (0.5)	Guaifenesin (0.5), Pseudoephedrine (0.5)	Yes	TN
3	35	M	AGEP	2	Ibuprofen (+5) Metamizole(+5)	Metronidazole (+5)	Ibuprofen (1.8) Metamizole (3.3)	Metronidazole (4.5)	Only ibuprofen	TN TP
4	28	F	Maculopapular Exanthema	3	Ibuprofen (+4)	Codeine (+4)	Ibuprofen (1.1)	Codeine (3.3)	Yes	TN
5	55	F	Erythema multiforme major	7	Ibuprofen (+4) Naproxen (+4)	Codeine (+4)	Ibuprofen (1.5) Naproxen (1.9)	Codeine (4.5)	Unknown	TN TN
6	78	F	Maculopapular Exanthema	28	Metamizole (+6)	Daptomycin (+5) Cefepime (+5)	Metamizole (1.1)	Daptomycin (1.1) Cefepime (0.9)	Unknown	FN
7	9	M	Generalized Exanthema	10	Metamizole (+4)	Cefotaxime (+5) AMX (+5)	Metamizole (1.9)	Cefotaxime (15.9) AMX (4.0)	Unknown	TN
8	55	M	Maculopapular Exanthema	21	Metamizole (+4)	No	Metamizole (1.3)	No	Yes	TN
9	53	M	Generalized Exanthema	6	Metamizole (+3)	Enoxaparin (+5) Amoxicillin (+5)	Metamizole (1.2)	Enoxaparin (0.8)	Yes	TN
10	37	M	Exacerbation of eosinophilic gastroenteritis	3	Ibuprofen (+3)	No	Ibuprofen (0.5)	No	Unknown	TN
11	86	F	Maculopapular Exanthema	3	Ibuprofen (+6)	Clindamycin (+7), AMX (+6)	Ibuprofen (0.8)	Clindamycin (1.3), AMX (1.1)	Yes	TN
12	61	F	Maculopapular Exanthema	1	Ibuprofen (+7)	AMX (+6)	Ibuprofen (2.5)	AMX (3.5)	Unknown	TP
13	50	M	Maculopapular Exanthema	1	Ibuprofen (+6)	Lidocaine (+6) Acetaminophen (+6)	Ibuprofen (8.8)	Lidocaine (3.7) Acetaminophen (1.9)	Unknown	TP

14	46	F	Maculopapular Exanthema	1	Ibuprofen (+3)	AMX/CLV (+3)	Ibuprofen (0.8)	No	Yes	TN
15	39	F	Erythema multiforme major	1	Ibuprofen (+3)	Sulfamethoxazole (+4)	Ibuprofen (2.1)	Sulfamethoxazole (2.7)	Unknown	FP
16	39	F	Agranulocytosis	15	Ibuprofen (+5)	Diazepam (+5)	Ibuprofen (1.3)	Diazepam (0.9)	Yes	TN
17	29	F	Interstitial nephritis	6	Ibuprofen (+3)	Moxifloxacin (+7), penicillin (+6)	Ibuprofen (1.2)	Moxifloxacin (11.0), penicillin (3.3)	Yes	TN
18	50	F	Interstitial nephritis	1	Ibuprofen (+7)	No	Ibuprofen (3.1)	No	Unknown	TP
19	61	M	Immune Thrombocytopenic Purpura	Unknown	Metamizole (+6)	No	Metamizole (2.3)	No	Unknown	TP
20	39	M	Agranulocytosis	7	Ibuprofen (+3) Metamizole (+2)	AMX/CLV (+6)	Ibuprofen (1.6) Metamizole (1.0)	AMX/CLV (2.2)	Yes	TN TN
21	26	F	Neutropenia	2	Ibuprofen (+7), naproxen (+5)	No	Ibuprofen (2.5) Naproxen (1.1)	No	Only naproxen	TP TN
22	44	F	Maculopapular Exanthema	3	Ibuprofen (+4)	AMX/CLV (+4)	Ibuprofen (0.9)	AMX/CLV (0.8)	Yes	TN
23	2	M	Exanthema, Hepatitis	5	Ibuprofen (+6)	No	Ibuprofen (2.0)	No	Unknown	TP
24	31	F	Exanthema, eosinophilia	6	Ibuprofen (+7)	Lamotrigine (+7)	Ibuprofen (2.4)	Lamotrigine (12.9)	Unknown	TP
25	66	M	Neutropenia	15	Ibuprofen (+3)	No	Ibuprofen (0.6)	No	Yes	TN
26	20	M	SJS	8	Ibuprofen (+3)	Azithromycin (+4)	Ibuprofen (1.8)	Azithromycin (2.8)	Yes	TN
27	24	M	Morbiliform exanthema	7	Ibuprofen (+5)	AMX/CLV (+5)	Ibuprofen (1.2)	AMX/CLV (1.0)	Unknown	FN
28	36	F	Possible DRESS	7	Ibuprofen (+5)	Azithromycin (+5), Omeprazole (+5)	Ibuprofen (16.5)	Azithromycin (1.5)	Unknown	TP
29	62	M	Maculopapular Exanthema	3	Ibuprofen (+4)	No	Ibuprofen (0.9)	No	Yes	TN
30	4	F	Maculopapular Exanthema	30	Metamizole (+4)	TMP/SMX (+5)	Metamizole (0.7)	SMX (0.3) TMP (0.3)	Unknown	TN
31	46	F	Maculopapular Exanthema	5	Metamizole (+5)	Enoxaparin (+7)	Metamizole (0.7)	Enoxaparin (0.8)	Yes	TN
32	70	M	Delayed urticarial	2	Metamizole (+5)	No	Metamizole (1.4)	No	Unknown	FN
33	66	F	Erythema exudative multiforme	4	Metamizole (+3)	No	Metamizole (1.4)	No	Unknown	TN
34	80	F	Generalized Exanthema	2	Metamizole (+5), Naproxen (+3)	No	Metamizole (2.6) Naproxen (1.9)	No	Only naproxen	TP TN
35	37	F	Exanthema	3	Metamizole (+6)	No	Metamizole (2.6)	No	Unknown	TP
36	53	F	Maculopapular Exanthema	3	Metamizole (+4)	Ceftriaxone (+4), Scopolamine (+4)	Metamizole (1.4)	No	Unknown	TN
37	54	F	Hepatitis	3	Metamizole (+6)	AMX (+7),	Metamizole (6.8)	AMX (4.9), Diclofenac	Unknown	TP

						Diclofenac (+6)		(3.4)		
38	42	F	Exanthema	1	Metamizol (+4)	Bemiparin (+4), Cefazolin (+4)	Metamizole (1.4)	Bemiparin (8.8), Cefazolin (7.3)	Unknown	TN
39	87	F	Hepatitis	5	Metamizol (+7)	Omeprazole (+7) acetaminophen (+7)	Metamizole (4.8)	Omeprazole (2.7) acetaminophen (1.9)	Unknown	TP
40	23	F	Agranulocytosis	3	Metamizol (+7), Dexketoprofen (+7)	Esomeprazole (+7)	Metamizole (3.1) Dexketoprofen (6.1)	Esomeprazole (9.1)	Unknown	TP TP

Abbreviations: SJS: Stevens-Johnson Syndrome; DRESS: Drug Rash with Eosinophilia and Systemic Symptoms; AGEP: Acute Generalized Exanthematous Pustulosis; AMX: amoxicillin, CLV: clavulanic acid; TMP/ SMX: trimethoprim-sulfamethoxazole

§ Drugs causality for hepatitis cases were assessed with the RUCAM algorithm, for the rest of entities Naranjo algorithm was used.

*LTT was considered as positive when a stimulation index ≥ 1.95 was obtained.

**LTT interpretation was based on post-episode re-exposure to the suspected NSAID or otherwise algorithm causality score ≥ 5 in cases where re-exposure was not performed.

TN (True Negative), FN (False Negative), TP (True Positive), FP (False Positive)

Table S2. Positive skin testing results in the study (two cases with metamizole and six cases with concomitant drugs).

N°	Symptoms	Drugs involved	SPT, IDT or epicutaneous test
6	Maculopapular Exanthema	Metamizole, daptomycin, cefepime	Metamizol: positive IDT
7	Generalized Exanthema	Metamizole, cefotaxime, amoxicillin/clavulanic acid (AMX/CLV)	Cefotaxime: positive IDT
9	Generalized Exanthema	Metamizole, enoxaparin	Enoxaparin: positive IDT
11	Maculopapular Exanthema	Ibuprofen, clindamycin, amoxicillin	Clindamycin: positive IDT and epicutaneous test
22	Maculopapular Exanthema	Ibuprofen, AMX/CLV	AMX/CLV and penicillin G: positive IDT
28	Possible DRESS	Ibuprofen, Azithromycin, omeprazole	Azithromycin: positive epicutaneous test.
30	Maculopapular Exanthema	Metamizole, sulfamethoxazole/trimethoprim	Sulfamethoxazole: positive IDT
32	Delayed urticarial	Metamizole	Metamizol: IDT positive

Table S3. Receiver operating characteristic curves for LTT for ibuprofen and metamizol hypersensitivity

Algorithm score	Stimulation index	Sensitivity	1-Specificity	AUC	95% Confidence interval	Asymptotic significance
≥ 4	1.95	0.737	0.074	0.853	0.737-0.968	0.001
≥ 5	1.95	0.923	0.121	0.883	0.768-0.999	0.001
≥ 6	2.35	1.000	0.275	0.854	0.748-0.960	0.006