

Lymphocyte transformation test can be useful for the diagnosis of delayed adverse reactions to sulfonamides

To the Editor,

Sulfonamides consist of drugs with several pharmacological uses and can be grouped into antibiotic and nonantibiotic sulfonamides. Adverse sulfonamide reactions have been reported for both groups, and nonimmediate allergic reactions are more frequently observed in clinical practice. Diagnosis is difficult because skin testing shows low sensitivity and there is no reliable laboratory diagnostic test for allergy to sulfonamides.¹

We conducted an observational retrospective study of cases and controls in patients attended at a tertiary hospital (La Paz University Hospital, Madrid, Spain) between 2015 and 2019, including thirty-four patients diagnosed with allergy to sulfonamides. The allergy workup included compatible clinical history, the causality Naranjo algorithm to determining the likelihood of the adverse drug reaction,² skin testing (prick, intradermal, patch tests), and lymphocyte transformation test (LTT) with the sulfonamides involved in the adverse reactions.

Two possible and 1 probable DRESS syndrome (drug rash with eosinophilia and systemic symptoms) were assessed according to the European Registry of Severe Cutaneous Adverse Reactions Study Group (RegiSCAR).³ Agranulocytosis cases were identified by the Pharmacovigilance Program from Laboratory Signals at Hospital.⁴

The study was conducted according to the Declaration of Helsinki and approved by the local institutional ethical committee (PI-3829).

Thirty-four cases (20 women) with a median age of 52 years (interquartile range (IQR) = 36-68) were included in the study (Table 1). The median time interval between the reaction and the study was 5 months (IQR = 3-7), and the median interval between the drug administration and the onset of the reaction was 6 days (IQR = 4-11). As for clinical entities, 26 cases of benign delayed exanthema [15 maculopapular rash (MPR; 44.1%), 8 macular erythema (ME; 23.5%), 3 generalized erythema (GE; 8.8%)], 3 drug reaction with eosinophilia and systemic symptoms (DRESS; 8.8%), 2 agranulocytosis (5.8%), 1 fixed drug eruption (FDE; 2.9%), 1 acute generalized exanthematous pustulosis (AGEP; 2.9%), and 1 urticaria (2.9%) were observed. Drugs involved in adverse reactions were trimethoprim/sulfamethoxazole (TMP-SMX; $n = 18$), etoricoxib ($n = 6$), sulfasalazine (SFS; $n = 4$), cefecoxib ($n = 3$), furosemide ($n = 2$), sulfadiazine ($n = 1$), acetazolamide ($n = 1$), zonisamide ($n = 1$), and hydrochlorothiazide (HCT; $n = 1$).

The causality algorithm scored 3/34 (8.8%) patients with a definite reaction (score ≥ 9), 23/34 (67.6%) patients with a probable

reaction (score 5-8), and 8/34 (23.5%) patients with a possible reaction (score 1-4). In 16 cases, there were other drugs prescribed among which antibiotics were the most often used. Table 1 shows the concomitant drugs and the clinical condition for which they were prescribed.

The allergy workup included in vivo and in vitro testing (Methods_SupplInfo). Skin testing (prick, intradermal, and patch tests) allowed confirmation of the drugs involved in 3/20 cases showing a sensitivity of 15% in our study. Three cases of re-exposure to drugs were analyzed (Table S1). Clinical history and causality algorithm were considered as a reference to designate a true or false result to LTT.

Regarding the drugs involved in allergic reactions, LTT was able to identify the culprit agent and confirm sulfonamide allergy in 25/34 cases (Table 2).

Only 1 patient had HIV infection (patient 30), and this case was previously published.⁵ The median of the stimulation index (SI) in positive LTTs was 5.7 (IQR = 3.4-6.4). According to the symptoms most frequently reported, there were no significant differences between the SIs of MPR (median 6.1, IQR = 3.4-6.4) and ME (median 4.8, IQR = 2.9-7.4; $P = .48$). No significant association was found between SIs and time interval between the reaction and the study ($r = -.10$, $P = .54$) or interval between the drug administration and the onset of the reaction ($r = -.09$, $P = .60$). However, a moderate association was found between SIs and scores from the causality algorithm ($r = .38$, $P = .03$).

Lymphocyte transformation test was also performed in patients 16, 20, 25, 33, and 34 with the concomitant drugs, and negative results were obtained except in patient 33 with amiloride and ceftriaxone (Table 3). The positivity with chemically different drugs suggests that this patient is a case of multiple drug hypersensitivity.

In 12 patients (2, 7, 11, 14, 15, 17, 18, 21, 24, 28, 29, and 33), LTT was performed with other drugs than those involved in adverse reactions or associated with episodes to test cross-reactivity (Table 3). A positive LTT was found in 4 (33%) cases whose involved drugs were nonantibiotic sulfonamides.

Lymphocyte transformation tests were performed in seven patients who had an adverse reaction with drugs other than sulfonamides and five subjects with no history of adverse drug reaction (Table S2), all results being negative.

Lymphocyte transformation test with antibiotic sulfonamides shows a sensitivity of 66.7%, a specificity of 100%, and negative and positive predictive values of 53.8% and 100%,

TABLE 1 Clinical and demographic data of patients

Patient	Age (y)	Sex	Reaction	Interval between reaction and study (m)	Interval between drug and reaction (d)	Episodes	Drug involved	Naranjo score	Concomitant drug (clinical condition)	Atopy
1	23	Female	MPR	3	7	2	TMP-SMX	10	No (cystitis)	No
2	74	Male	Macular erythema	2	10	1	TMP-SMX	2	Rituximab, tenofovir (non-Hodgkin's lymphoma)	No
3	70	Female	MPR	3	5	1	TMP-SMX	7	Ciprofloxacin (urinary tract infection)	No
4	43	Male	possible DRESS	2	15	1	Celecoxib	5	No (arthritis)	No
5	66	Female	MPR	56	3	1	Etoricoxib	7	No (arthritis)	No
6	51	Female	MPR + Eo	6	4	1	TMP-SMX	2	Metamizole (necrotizing fasciitis)	No
7	83	Female	Macular erythema + Urticaria	5	11	1	Celecoxib	7	No (arthritis)	No
8	19	Male	MPR	5	4	1	TMP-SMX	7	No (respiratory infection)	RC
9	21	Male	Fixed drug eruption	13	NK	8	TMP-SMX	7	No (respiratory infection)	No
10	79	Female	Urticaria	6	8	1	Etoricoxib	6	No (arthritis)	No
11	52	Male	MPR	5	30	1	Etoricoxib SFS	7	No (arthritis)	RC
12	64	Male	Macular erythema	1	21	1	TMP-SMX	1	Piperacillin-tazobactam, vancomycin (common variable immunodeficiency)	No
13	21	Female	Macular erythema	5	7	1	TMP-SMX	7	Ciprofloxacin (respiratory infection)	No
14	46	Female	MPR	5	>30	2	Etoricoxib	10	No (arthritis)	No
15	49	Female	possible DRESS	5	9	1	SFS	3	Mesalazine (ulcerative colitis)	No
16	44	Female	Macular erythema + fever	5	9	1	TMP-SMX	6	Aciclovir, allopurinol, ranitidine, rituximab, bendamustina (non-Hodgkin's lymphoma, hyperuricemia)	No
17	66	Male	AGEP	4	5	1	TMP-SMX	5	Streptokinase (renal colic)	No
18	66	Female	MPR	7	21	1	Acetazolamide	7	Miconazole (oral candidiasis)	No
19	48	Female	Generalized erythema + AE	276	<1	1	TMP-SMX	3	Meloxicam (fibromyalgia)	No
20	71	Male	Generalized erythema + fever + Eo	2	6	1	TMP-SMX	4	Omeprazole, folic acid, aciclovir, allopurinol (herpes zoster infection, hyperuricemia)	No

(Continues)

Patient	Age (y)	Sex	Reaction	Interval between reaction and study (m)	Interval between drug and reaction (d)	Episodes	Drug involved	Naranjo score	Concomitant drug (clinical condition)	Atopy
21	56	Male	MPR + fever	5	28	1	SFS	7	No (Crohn's disease)	No
22	29	Male	Generalized erythema	2	4	1	TMP-SMX	7	No (urinary tract infection)	No
23	54	Male	Probable DRESS	7	4	1	TMP-SMX	9	No (urinary tract infection)	No
24	77	Female	MPR	22	11	2	Celecoxib	8	No (arthritis)	No
25	83	Male	Agranulocytosis	2	NK	1	Furosemide	4	Amoxicillin-clavulanic acid, meropenem, piperacillin-tazobactam, teicoplanin (multiple comorbidity)	No
26	81	Male	MPR + AE	4	3	1	TMP-SMX	5	No (-)	No
27	36	Female	Macular erythema + Urticaria	2	28	1	Zonisamide	6	No (migraine)	RC
28	34	Female	Macular erythema + fever	5	4	1	SFS Etoricoxib	7	No (arthritis)	RC
29	36	Female	MPR + DIPH	12	4	1	Etoricoxib	6	No (arthritis)	No
30	48	Female	MPR	7	3	1	SDZ TMP-SMX	3	Levetiracetam, pyrimethamine (cerebral toxoplasmosis)	No
31	68	Female	Macular erythema	6	5	1	Furosemide	6	No (edema)	RC
32	4	Female	MPR	8	1	1	TMP-SMX	6	Clarithromycin (otitis media)	No
33	64	Female	MPR	4	1	2	HCT	7	Amiloride, ceftriaxone (hypertension, fever)	No
34	36	Male	Agranulocytosis	9	NK	1	TMP-SMX	6	Metamizole (fever)	No

Abbreviations: AE, angioedema; AGEP, acute generalized exanthematous pustulosis; DIPH, drug-induced photosensitivity; DRESS, drug reaction with eosinophilia and systemic symptoms; Eo, eosinophilia; HCT, hydrochlorothiazide; MPR, maculopapular rash; NK, not known; RC, rhinoconjunctivitis; SDZ, sulfadiazine; SFS, sulfasalazine; TMP-SMX, trimethoprim-sulfamethoxazole.

TABLE 2 Results of in vitro testing with culprit drugs

Patient	Drugs tested	LTT(SI)	Interpretation
1	Trimethoprim-sulfamethoxazole	6.1	TP
2	Trimethoprim-sulfamethoxazole	0.9	FN
3	Trimethoprim-sulfamethoxazole	3.4	TP
4	Celecoxib	5.8	TP
5	Etoricoxib	6.4	TP
6	Trimethoprim-sulfamethoxazole	1.7	TN
7	Celecoxib	9.1	TP
8	Trimethoprim-sulfamethoxazole	2.9	TP
9	Trimethoprim-sulfamethoxazole	1.3	FN
10	Etoricoxib	7.5	TP
11	Etoricoxib	6.3	TP
	Sulfasalazine	6.4	TP
12	Trimethoprim-sulfamethoxazole	1.4	TN
13	Trimethoprim-sulfamethoxazole	2.2	TP
14	Etoricoxib	6.2	TP
15	Sulfasalazine	1	FN
16	Trimethoprim-sulfamethoxazole	3.8	TP
17	Trimethoprim-sulfamethoxazole	1.5	FN
18	Acetazolamide	3.5	TP
19	Trimethoprim-sulfamethoxazole	2.2	TP
20	Trimethoprim-sulfamethoxazole	5.7	TP
21	Sulfasalazine	4	TP
22	Trimethoprim-sulfamethoxazole	7.2	TP
23	Trimethoprim-sulfamethoxazole	4.7	TP
24	Celecoxib	1.4	FN
25	Furosemide	5.7	TP
26	Trimethoprim-sulfamethoxazole	5.6	TP
27	Zonisamide	1	FN
28	Sulfasalazine	3.8	TP
	Etoricoxib	6.9	TP
29	Etoricoxib	3.4	TP
30	Sulfadiazine	5.7	TP
	Trimethoprim-sulfamethoxazole	1.3	TN
31	Furosemide	3.1	TP
32	Trimethoprim-sulfamethoxazole	0.3	FN
33	Hydrochlorothiazide	6.4	TP
34	Trimethoprim-sulfamethoxazole	2.2	TP

Note: SI in bold denotes the positive LTT with involved drugs ($SI \geq 2$).

Abbreviations: FN, false negative; TN, true negative; TP, true positive.

respectively. LTT with nonantibiotic sulfonamides shows a sensitivity of 83.3%, a specificity of 100%, and negative and positive predictive values of 85% and 100%, respectively. Finally, considering all cases, LTT showed a sensitivity of 75%, a specificity of 100%, and negative and positive predictive values of 72.7% and 100%, respectively.

There are two studies analyzing the utility of LTT for the diagnosis of adverse sulfonamide reactions. One study analyzed nine

patients with skin eruptions associated with TMP-SMX treatment and 9 controls without a history of drug allergy. LTT sensitivity and specificity were 60% and 100%, respectively.⁶ In the other study, 17 patients showing drug eruptions with sulfonamides and 8 controls were assessed with LTT. LTT showed sensitivity of 29% and specificity of 62%.⁷ Our results showed a higher specificity and sensitivity than the previous studies. These differences in diagnostic accuracy are a limiting factor for LTT to be considered as a diagnostic test

TABLE 3 Results of in vitro testing with other drugs

Patient	Drugs tested	LTT(SI)
2	Furosemide	0.8
	Acetazolamide	1
7	Etoricoxib	1.9
11	Celecoxib	4.4
14	Celecoxib	2.2
	Trimethoprim-sulfamethoxazole	4.1
15	Trimethoprim-sulfamethoxazole	0.9
16	Concomitant drugs	<2
17	Furosemide	1.7
18	Etoricoxib	1.7
	Trimethoprim-sulfamethoxazole	1.3
	Sulfasalazine	1.2
	Furosemide	1.5
20	Concomitant drugs	<2
21	Trimethoprim-sulfamethoxazole	1.7
24	Etoricoxib	1.4
25	Amoxicillin-Clavulanic	<2
28	Trimethoprim-sulfamethoxazole	2.3
	Celecoxib	3.2
29	Celecoxib	1.3
33	Furosemide	14.2
	Concomitant drugs	>2
34	Metamizole	<2

Note: Drugs tested include concomitant drugs (in bold) and drugs with possible cross-reactivity.

in clinical practice. The reasons for the variability are probably the same as those that have been reported to influence LTT results for other drugs, such as timing of the test with respect to the initial reaction, the clinical picture of the reactions, and the type of drug involved among others.⁸

Drug provocation test (DPT) is the gold standard for the diagnosis of drug hypersensitivity, but it is a procedure that consumes time and resources and can pose a risk for the patient.

Sulfonamides are cost-effective drugs for first- and second-line treatments in various infections. Our results show that LTT is a useful tool in the allergy workup for adverse reactions to sulfonamides. Interestingly, the association between the Naranjo scores and SI values further supports that LTT can contribute to the assessment of the causality of hypersensitivity drug reactions. These results are in line with recently published data on the sensitivity and specificity of LTT in SJS/TEN using the ALDEN algorithm as the standard.⁹ A limitation of this study is that DPT has not been performed in all patients. Therefore, our results have to be confirmed in a prospective future study including DPT. Nevertheless, the sensitivity, specificity, and predictive values indicate that LTT can help to reduce the need for medication change or provocation testing.

CONFLICTS OF INTEREST

The authors declare that they have no relevant conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Table 1 SuppInfo. Results of *in vivo* testing

Patient	Drugs tested	Prick test	IDT	Patch test	DPT
1	Trimethoprim-Sulfamethoxazole	ND	+	ND	+*
2	Trimethoprim-Sulfamethoxazole	ND	ND	-	ND
3	Trimethoprim-Sulfamethoxazole	-	-	ND	ND
4	Celecoxib	ND	ND	-	ND
5	ND	ND	ND	ND	ND
6	Trimethoprim-Sulfamethoxazole Metamizole	ND ND	ND ND	ND ND	ND +*
7	Celecoxib	ND	ND	-	ND
8	Trimethoprim-Sulfamethoxazole	ND	ND	-	ND
9	Trimethoprim-Sulfamethoxazole	ND	ND	-	ND
10	ND	ND	ND	ND	ND
11	Etoricoxib Sulfasalazine	- -	ND ND	- -	ND ND
12	Trimethoprim-Sulfamethoxazole	-	-	ND	-
13	Trimethoprim-Sulfamethoxazole	-	-	ND	ND
14	ND	ND	ND	ND	ND
15	Sulfasalazine	ND	ND	-	ND
16	ND	ND	ND	ND	ND
17	Trimethoprim-Sulfamethoxazole Furosemide	ND ND	ND ND	- -	ND ND
18	Acetazolamide Trimethoprim-Sulfamethoxazole Furosemide	ND ND ND	ND ND ND	- - -	ND ND ND
19	ND	ND	ND	ND	ND
20	ND	ND	ND	ND	ND
21	ND	ND	ND	ND	ND
22	Trimethoprim-Sulfamethoxazole	ND	ND	-	ND
23	ND	ND	ND	ND	ND
24	ND	ND	ND	ND	ND
25	ND	ND	ND	ND	ND
26	Trimethoprim-Sulfamethoxazole	-	-	-	ND
27	Zonisamide	ND	ND	-	ND

28	Sulfasalazine Etoricoxib	ND ND	- ND	- +	ND
29	Etoricoxib Celecoxib	ND ND	ND ND	- -	ND ND
30	Sulfadiazine Trimethoprim-Sulfamethoxazole Trimethoprim	- - -	ND - ND	- - ND	ND - ND
31	Furosemide	ND	ND	-	ND
32	Trimethoprim-Sulfamethoxazole Trimethoprim	- -	+ ND	- -	ND ND
33	ND	ND	ND	ND	ND
34	ND	ND	ND	ND	ND

* Accidental re-exposure. ND: not determined

Table 2 SuppInfo. Results of LTT in controls

Control	Drug involved/symptoms	Drug tested	LTT (SI)
Type 1			
1	Amoxicillin-clavulanic/pustulosis	Celecoxib Etoricoxib Sulfasalazine	1.1 1.0 1.2
2	Piperacillin-tazobactam/neutropenia	Etoricoxib Celecoxib Hydrochlorothiazide	0.8 1.1 1.2
3	Leflunomide/unknown	Sulfamethoxazole Furosemide	1.2 0.9
4	Amoxicillin/maculopapular rash	Sulfamethoxazole Furosemide	0.8 0.7
5	Metformina, Empagliflozina/macular erythema	Sulfamethoxazole	0.8
6	Ibuprofen/angioedema	Etoricoxib	1.3
7	Amoxicillin/Fixed drug eruption	Sulfamethoxazole Furosemide	0.8 0.6
Type 2			
8	–	Sulfamethoxazole Celecoxib	1.2 0.7
9	–	Sulfamethoxazole Sulfasalazine	0.8 1.1
10	–	Hydrochlorothiazide Acetazolamide	1.4 1.0
11	–	Acetazolamide Furosemide	0.8 0.8
12	–	Sulfamethoxazole Celecoxib	1.3 0.9

Type 1 controls: patients that were not exposed previously to sulfonamides but had an adverse drug reaction with another drug. Type 2 controls: patients with no history of adverse drug reaction. SI: stimulation index

Methods_SupplInfo

Skin testing

Skin tests were carried out at least 4 weeks after the adverse reaction. Every patient had a study designed by their clinician. It could include a prick test, followed by an intradermal test (IDT) if no reaction was elicited by the prick. In many cases, patch tests were also performed. A prick test result was considered positive if, within 15 to 20 minutes of injecting the drug solution on the forearm, a wheal with a diameter >3 mm appeared. An immediate- or delayed-reading IDT result was considered positive if a wheal with a diameter equal to at least double the injection bleb appeared and was surrounded by a flare.

The drugs used in the skin tests were: celecoxib (patch test: 5%, 10% Vaseline), furosemide (IDT: 1 mg/ml; patch test: 1% Vaseline), sulfadiazine (patch test: 5% Vaseline), SMX (IDT: 10–20 mg/ml or 0.03 mg/ml; patch test: 10% Vaseline), sulfasalazine (SFS; patch test: 10% Vaseline), TMP (IDT: 0.001 mg/ml; patch test: 10% alcohol or Vaseline).

For patch tests of reactions to zonisamide and etoricoxib, the coating of the tablet was removed and it was then pulverized into fine powder and incorporated into Vaseline at 30% (in relation to the weight of the powder obtained) and diluted in water, also at 30%. Both preparations were patched. When the patient presented a severe cutaneous reaction, the study was started with lower concentrations, starting at 0.1% (in water and Vaseline), and, if these were negative, the concentration was progressively increased to 1% and 10%.

Lymphocyte transformation test

The LTT was performed using different concentrations of the drug/drugs involved.

Mononuclear cells were separated over a density gradient (Histopaque-1077, Sigma-Aldrich) from fresh peripheral blood and were incubated for 6 days at 10^6 cells/ml with various drug concentrations in triplicate. Drugs were assayed at four concentrations from 1 to 200 µg/ml, except celecoxib and etoricoxib, whose concentration range was 0.1–50 µg/ml.

Phytohemagglutinin (5 µg/ml) was used as a positive control. For the final 18 hours of the

incubation period, proliferation was determined by the addition of [³H] thymidine (0.5 μ Ci/well). Proliferative responses were calculated as stimulation indices (SIs), defined as the ratio between the mean values of counts per minute in cultures with drug and those obtained without drug. A positive response was defined as an SI ≥ 2 in at least 1 concentration of the drug.

Drug provocation test

DPT was performed with increasing doses of TMP-SMX over 3 days until 1 tablet of TMP-SMX (160 mg/800 mg) was tolerated. Laboratory values were monitored and temperature was controlled. Subsequently, patients continued to take the treatment at home at a dose of 1 tablet every 24 hours for 5 days, thus confirming good tolerance.