

Drug Allergies May Be More Frequent in Systemic Lupus Erythematosus Than in Rheumatoid Arthritis

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Objective: To measure the frequency of drug allergies in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and register the causal drug, the type, and severity of the reaction.

Material and Methods: Direct interview and chart review in patients with RA and SLE were conducted. We registered demographic data, drug allergies, the causal drug, how causality was assessed, and the type and severity of the allergic reaction. We include as drug allergies only those cases in which the result of exposure and re-exposure was known or in which a physician evaluating the original event established the causality link with the suspected drug. Differences between groups were assessed by χ^2 test.

Results: Two hundred ninety-three RA and 58 patients with SLE were included. Fifty-three of the patients with RA (18%) and 20 of the patients with SLE (34.3%, $P = 0.049$) reported drug allergies. Most of them presented skin rash as their clinical expression of allergy (73%); anaphylaxis was reported in 4 cases (5%). Allergy to sulfa drugs is found more frequently in SLE ($P = 0.0079$). No differences were found when comparing the frequency of other drug allergies, such as penicillin and metamizole.

Discussion: Drug allergies are more frequent in SLE than in RA. Sulfa drugs are still the most frequent cause of drug allergies in SLE. Allergies because of drugs forbidden in the United States but easily available in specific ethnic groups are frequent in patients with SLE and RA. Their specific consumption must be intentionally assessed in cases of suspected drug allergies.

Key Words: drug allergies, sulfa drugs, penicillin, metamizole, systemic lupus erythematosus, rheumatoid arthritis

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Adverse drug reactions affect almost 20% of hospitalized patients and more than 7% of nonhospitalized population. Almost one-third of adverse drug reactions are hypersensitivity reactions.¹ Their severity may vary from simple dis-

comfort and skin rash to life-threatening reactions such as anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. There are special populations with a higher risk of developing hypersensitivity reactions to drugs. Among these are women, HIV and herpes-infected patients, and systemic patients with lupus erythematosus (SLE).² As a general principle, patients with SLE seem to have higher frequencies of hypersensitivity reactions to antibiotics than healthy populations.³ In this study, we compared the frequency of drug allergies between 2 autoimmune diseases from the same urban population.

MATERIALS AND METHODS

We surveyed patients fulfilling the 1987 American Rheumatism Association revised criteria for the classification of RA⁴ and patients fulfilling the 1982 revised criteria for the classification of SLE⁵ in an outpatient rheumatology clinic in Mexico. The presence of a drug allergy was registered if the patient had presented any of the following conditions after the exposure and re-exposure to a specific drug: asthma, laryngeal edema, urticaria, skin rash or exanthem, cutaneous vasculitis, fever, or anaphylaxis. In those cases in which no re-exposure was documented, the presence of a drug allergy was registered when a physician witnessing and registering the clinical expression of the original event made the diagnosis and suspected the causal link. The specific drug was registered along with the kind and severity of the reaction suffered. Those events in which the recommended dosage of the causing drug was not respected were not included as drug allergies. We also excluded those cases with no re-exposure to the candidate drug in which drug allergy was suspected by the patient but not sustained by a physician.

We employed χ^2 test to define the significance of differences between groups.

RESULTS

We included 293 patients with RA and 58 patients with SLE. Fifty-three of the patients with RA presented drug allergies (18%) and 20 patients with SLE did (34.4%, $P = 0.049$). Of the 351 included patients, 311 were women. The mean age of patients with SLE was 43 years (range 22–56) and 38 years in RA patients (range 18–67).

As significant differences, more patients in the SLE group were previous users of azathioprine and were current users of corticosteroids in a dose higher than 7.5 mg of

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prednisone per day, and none of the patients with SLE included had ever used methotrexate.

All the patients included were regular users of antiinflammatory drugs, analgesics, and DMARDs. Approximately, a third of patients with SLE and RA were also regular users of antihypertensive drugs. There was no significant difference between the kind of antihypertensive drug used and the length of time of use between both diseases. Some patients in both groups were receiving regular treatment for other chronic conditions such as asthma, dyslipidaemia, and diabetes. These differences were not clinically significant. Patients with RA used an average of 5 drugs during the lapse of time evaluated in this presentation, whereas patients with SLE used an average of 6 drugs.

TABLE 1. Most Frequent Causes of Drug Allergies in the Conditions Surveyed

Drug	Rheumatoid Arthritis (n = 53) (% intragroup)	Systemic Lupus Erythematosus (n = 20) (% intragroup)	All the Reported Allergies (%) (n = 73)
Penicillin	15 (28.3)	5 (25)	27.3
Sulfa drugs	12 (22.6)	11 (55)	31.5
Diclofenac	2 (3.7)	0	2.7
Ciprofloxacin	1 (1.8)	1 (5)	2.7
Metamizole	2 (3.7)	2 (10)	5.4

Those drugs having just 1 case of reported allergy are not presented in the table.

TABLE 2. Clinical Expression of Drug Allergy Distributed by Disease

	Rheumatoid Arthritis (%)	Systemic Lupus Erythematosus (%)
Anaphylaxis	3 (6)	1 (5)
Rash	38 (71)	15 (75)
Asthma	1 (2)	0
Urticaria	2 (4)	0
Hypotension	1 (2)	0
Angio-oedema	1 (2)	1 (5)
Other	7 (13)	3 (15)
Total	53 (100)	20 (100)

Fifty-three of the patients with RA (18%) and 20 of the patients with SLE (34.3%, $P = 0.049$) reported drug allergies. The 3 most frequent causes of drug allergies in both diseases surveyed were penicillin, sulfa drugs, and metamizole (Table 1). Allergies to sulfa drugs were seen more frequently in the SLE group (55% of drug allergies in patients with SLE) than in the RA group (22%) ($P = 0.0079$). No differences were found between penicillin and metamizole, the 2 other groups of drugs registered as frequent causes of allergies in both diseases.

Most clinical manifestations of drug allergies registered were mild in their final reported intensity. The most frequent clinical manifestation of drug allergy was skin rash in 53 cases (73% of all cases). Four cases of anaphylaxis were found (5%). No differences in the frequencies of the diverse clinical manifestations of drug allergy were found between both diseases. (Tables 2 and 3).

DISCUSSION

Drug allergies were more frequent in patients with SLE than in patients with RA. Among the drugs responsible for these reactions, sulfa drugs are notoriously more frequent in SLE than in RA.

SLE is a disease with indications of a T_H2 -deviated immune activation. On the contrary, RA is a disease with indications of a T_H1 -deviated immune activation. Based on this scheme, atopic conditions and predisposition to allergies should be more frequent in SLE than in RA. Although theoretically attractive, this hypothesis is not sustained by published evidence.^{6–9} Some authors even show that some allergic disorders are less frequent in SLE than in non-SLE population.¹⁰

Among allergies, those provoked by drugs are known to be more frequent in patients with SLE than in healthy populations. Allergies in general, and among them allergies to sulfa drugs, have been proposed as an important risk factor to develop SLE.^{11,12} Interesting as it is, this finding has not been sustained in Mexican patients with SLE.¹³

We did find a higher frequency of allergic reactions to sulfa drugs in patients with SLE as compared with patients with RA from the same population. Sulfa drugs are not the most frequent cause of allergy to antibiotics. In open population and in hospitalized patients, penicillin-related antibiot-

TABLE 3. Frequency of Clinical Expression of Allergy by Specific Drugs

	Anaphylaxis	Rash	Asthma	Urticaria	Hypotension	Angio-oedema
Penicillin	0	18	0	0	0	0
Sulfa drugs	2	17	0	0	0	1
Azathioprine	0	1	0	0	0	0
Diclofenac	1	0	0	0	0	1
Ciprofloxacin	0	1	0	0	0	0
Ranitidine	0	2	0	0	0	0
Tetracycline	1	0	0	0	0	0
Metamizole	0	2	0	0	1	0
Methotrexate	0	1	0	0	0	0
Other	0	1	1	2	0	0

ics are the most frequent causes.¹⁴ This higher frequency of allergy to sulfa drugs seems to be a common clinical finding in SLE.

Metamizole, a pirazolone derivate also known as dipirone, is frequently used in Latin American countries. This product was banned in the United States in 1979 because of a higher risk of agranulocytosis associated with its use. Despite this, it is frequently employed for diverse common ailments such as fever and pain in various ethnic groups in the United States, and possibly in other countries where its sale is forbidden. It is an over-the-counter drug in diverse countries in Latin America and patients and their families commonly bring this and other forbidden medications to the countries where they have their regular residency. Recognizing this drug as a frequent cause of drug allergy may uncover cases in those places where it is officially banned. Thus, the ethnic origin of the patient should be taken into account when trying to assign causality in a suspected allergic reaction to drugs, because of the potential use of drugs currently unavailable in the geographic setting where the reaction occurs.

The method to assign causality in the diverse allergies reported was carefully selected. Based on this, some considerations are pertinent. We did not re-expose the patient to the possible causal drug to confirm the reported drug allergy. All our information is based on the information given by the patient and that registered in the patient's chart. Because this bias was present in both groups of patients included, it possibly did not influence the results obtained. Obviously, the allergies registered are those that did not result in death. Severe drug allergies that may have caused the death of patients are a potential confounder because we included patients attending the clinic. If several deaths as the result of drug allergies had occurred in previous years, the natural exclusion of these patients from the group presented could underestimate the real frequencies of severe drug allergies in our presentation. Because there is no published evidence that RA has more frequent or severe drug allergies than other conditions, the potential underestimation of severe drug al-

lergies could be expected, if existent, in the SLE group, not in the RA group, so that the difference we report could be wider than the numbers shown.

Despite the ample use of new groups of drugs in SLE and RA, the pattern of drug allergies has not changed from the one known in them in the last years.

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