Frequency of Adverse Drug Reactions in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** The literature suggests that patients with systemic lupus erythematosus (SLE) have a higher frequency of adverse drug reactions (ADR). We performed this case control study to compare the prevalence of ADR in patients with SLE and controls with inflammatory arthritis.

Methods. We surveyed 249 patients, 145 with SLE and 104 age and sex matched controls with other types of inflammatory arthritis, such as rheumatoid arthritis (RA), probable RA, and psoriatic arthritis. We asked about exposure and ADR to the following classes of drugs: (1) beta-lactam antibiotics, (2) sulfonamides, (3) other antibiotics, (4) disease modifying antirheumatic drugs (DMARD), and (5) nonsteroidal antiinflammatory drugs (NSAID). Personal and family atopic histories were obtained. The 2 groups were obtained from a single rheumatologic practice and had similar characteristics and drug exposures.

Results. The response rate was 63% in the SLE patients and 64% in the control group. The mean age was 47.8 ± 1.5 years in patients with SLE and 46.1 ± 1.7 years in controls ($p < 0.51$). Ninety-two percent of SLE patients and 88% of controls were female ($p < 0.42$). Both groups had been exposed similarly to all antibiotics, as there were no significant differences between groups (exposure to sulfa antibiotics 53% in SLE patients vs 46% in controls), and to NSAID (84% SLE group vs 93% controls). Few patients from the SLE group had DMARD exposure, with the exception of plaquenil (65% SLE group vs 30% controls; $p < 0.0001$) and azathioprine (18% SLE group vs 4% controls; $p < 0.006$). There were between-groups differences with respect to total number of ADR with sulfa antibiotics (exposed had 25/48 reactions in SLE group vs 6/31 in controls; $p < 0.003$), but not with other drugs. Most ADR to sulfa antibiotics were cutaneous (rash). Subjects with an allergic or atopic history had more ADR ($p < 0.0005$). There were no differences between SLE patients and controls in having an allergic history ($p < 0.88$). Subjects with a positive family history of allergies were more likely to have ADR ($p < 0.0043$). SLE patients and controls with a personal versus family history of environmental allergies did not differ in having ADR ($p < 0.16$ and $p < 0.83$, respectively).

Conclusion. Both intolerances and true allergic reactions were not dissimilar in patients with SLE compared to controls with inflammatory arthritis, with the exception of cutaneous reactions to sulfa antibiotics in SLE patients. This has not been the experience of other investigators (with increased ADR with several antibiotics in SLE groups) who used healthy, best friend, and relative controls with dissimilar frequencies of drug exposures. Perhaps differences observed in the past (where SLE patients have more ADR than healthy controls) are true of other inflammatory arthritis subjects (who have different drug exposures than healthy individuals) rather than just SLE. Differences could also exist in the pharmacogenetics, as our sample population was mostly Caucasian. (J Rheumatol 2003;30:480–4)

Key Indexing Terms:
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The literature suggests that patients with systemic lupus erythematosus (SLE) have a higher frequency of adverse drug reactions (ADR). Reports that examined this issue have been contradictory. Becker compared patients with SLE to controls who were hospitalized for pneumonia[1]. Von Maur, *et al* examined the frequency of penicillin hypersensitivity in patients with SLE compared to controls using skin testing[2]. Each of these studies concluded that no increased prevalence of ADR had been observed. Petri and Allbritton compared patients with lupus to their healthy friends and relatives and reported that the prevalence of ADR was increased[3]. More than 200 patients with SLE and relatives and friends used as controls were asked about drug allergies. Allergic reactions (rashes) were more common in the patients with SLE, including reactions to penicillins, sulfa

drugs, and erythromycin. Those with SLE may be exposed to more medications because they have a chronic disease, and several symptoms of SLE could potentially mimic allergic drug reactions or drug side effects. This could increase the chance of having more reactions (exposure bias) or calling a lupus problem (such as oral ulcers or rash) a drug reaction (misattribution). Thus, it is difficult to know if subjects with lupus truly have more ADR compared to others with the potential for equal exposure.

We wondered if the overall prevalence of side effects from drugs was increased in people with lupus and if so, if there was an increase in actual "allergic" drug reactions (such as angioedema or rash) compared to others with inflammatory arthritis who could have similar exposure rates. We speculated that certain classes of drugs were more likely to cause ADR in lupus.

MATERIALS AND METHODS

We performed a case control study using our patients with SLE as cases. All cases met the American College of Rheumatology criteria for SLE[4]. Age and sex matched controls with inflammatory arthritis (but no evidence of mixed connective tissue disease as assessed by chart review) were randomly selected from the same rheumatologist's practice (JEP). Controls had rheumatoid arthritis (RA), psoriatic arthritis, or probable RA. All cases and controls were mailed a detailed survey asking about medication history and side effects including intolerances and actual perceived allergic reactions. The questions specifically asked about history of rash, hives, swelling of the mouth, breathing problems, asthma, stomach upset, nausea, vomiting, diarrhea, and meningitis. Stomach upset, nausea, and diarrhea were considered to be intolerances. The allergic reactions were categorized by systems: Gastrointestinal, Respiratory, Cutaneous, Others. Detailed responses about exposures to antibiotics (beta-lactam and sulfa antibiotics and other), antirheumatic drugs, nonsteroidal antiinflammatory drugs (NSAID), and other drugs were elicited. For sulfa antibiotics, an example of sulfamethoxazole-trimethoprim (SMX-TMP) was provided using Septra or Bactrim as drug names. Antirheumatic drugs were listed individually using generic and trade names. Nonresponders were remailed a questionnaire twice. The results were entered for all subjects, including diagnosis and current age. Chi-square tests and t tests were performed where appropriate, comparing lupus cases to the controls with inflammatory arthritis. Results were adjusted for past exposure by excluding those with no exposure. Relationships between drug allergies and atopy (personal and family history) were explored. Allergic history was defined by self-report as having food or environmental allergies and family history of allergies and atopy including asthma, eczema, nasal polyps, and drug allergies.

RESULTS

Two-hundred forty-nine patients were surveyed, of whom 145 had SLE (cases) and 104 were controls with inflammatory arthritis. The response rate was 63% in the SLE group and 64% in the control group. Ninety-one subjects with SLE (92%) and 67 controls (88%) were female ($p < 0.4$). The mean age for subjects with lupus was 47.8 ± 1.5 versus 46.1 ± 1.7 years for controls ($p < 0.5$). The mean disease duration in the SLE group was 12 years. Forty percent had a history of allergies in the SLE group and 42% in controls ($p < 0.2$). Drug exposure histories for penicillin and sulfa antibiotics (specifically Septra and Bactrim) were not statistically significantly different. NSAID exposure was high in both groups. As expected, disease modifying antirheumatic drug (DMARD) exposure was more frequent in controls, except for hydroxychloroquine and azathioprine. Methotrexate use was more frequent in the controls ($p < 0.0008$), whereas in patients with SLE hydroxychloroquine ($p < 0.0001$), azathioprine ($p < 0.006$), and prednisone ($p < 0.10$) exposures were more common. Sulfasalazine was rarely used in the SLE group ($p < 0.0005$). Table 1 displays baseline characteristics and drug exposure rates.

A history of ADR was slightly (but not significantly) higher in patients with SLE (cases) (62% vs 54%; $p < 0.4$). Skin reactions were the most common ADR. There were no reported cases of anaphylaxis. For most drugs there were no significant differences for true allergic reactions having occurred in SLE patients versus controls. However, we did observe that with respect to ADR, SLE patients had reported that they were significantly more likely to have skin reactions (rash) to sulfa antibiotics (Septra, Bactrim). Twenty-five of 48 SLE patients reported a sulfa rash versus 6 of 31 inflammatory arthritis controls (OR 4.5, $p < 0.003$). The other intolerances and allergic reactions were not different between the 2 groups. No subject in either group reported aseptic meningitis with NSAID use. Results are shown in Tables 2 and 3. Table 4 lists less commonly used drugs, for which there were no obvious differences in ADR.

Seventy-seven percent of allergic subjects had ADR, whereas only half of nonallergic subjects had ADR ($p < 0.0005$). Not surprisingly, allergic subjects had more ADR. This trend was consistent in both those with SLE and with inflammatory arthritis. Participants with a family history of allergies or atopy had a higher likelihood of reporting allergies ($p < 0.0001$, OR 6.7) and of having had ADR ($p < 0.0043$, OR 3.6). SLE patients with a positive family history of allergies had a higher likelihood of having been allergic themselves ($p < 0.0012$, OR 9.4). Furthermore this association was found for controls ($p < 0.0099$, OR 6.4). Patients with SLE and controls with a history of allergies and those with a family history of allergies did not differ in having ADR [82% SLE group vs 66% controls ($p < 0.16$) and 65% SLE group vs 63% controls ($p < 0.83$), respectively] (Table 5).

DISCUSSION

Due to the small sample size in this study, we were unable to characterize rare drug ADR, such as aseptic meningitis precipitated by NSAID in patients with SLE. However, even more common associations (such as a 1% to 3% prevalence in SLE) could have been missed in a study of this size. It is also very difficult to discern true allergies from drug intolerances when using the patient self-report method of data collection.

Multiple comparisons were performed with no statistical correction of the p value. However, we had *a priori* hypotheses that were our primary outcome measurements. Recall bias should not be different between the 2 groups as

Table 1. Baseline characteristics in patients with SLE and controls with inflammatory arthritis and frequency of drug exposure ever.

	SLE	Controls	p	OR (95% CI)
N	91	67		
Age (SE)	47.8 (1.5)	46.1 (1.7)	0.5	
Sex F:M (% F)	84:7 (92)	58:8 (88)	0.4	
History of allergies, n (%)	37 (40)	28 (42)	0.2	0.95 (0.5, 1.8)
History of ADR, n (%)	56 (62)	36 (54)	0.4	1.36 (0.7, 2.6)
History of exposure to, n (%)				
Penicillin	72 (79)	59 (88)	0.6	0.8 (0.3, 2.1)
Sulfa antibiotics	48 (53)	30 (46)	0.2	1.6 (0.8, 3.1)
Prednisone	59 (65)	39 (58)	0.1	1.8 (0.9, 3.5)
D-penicillamine	2 (2)	5 (8)	0.1	0.3* (0.06, 1.6)
MTX	5 (5)	17 (26)	0.0008	0.83 (0.07, 0.5)
Plaquenil	59 (65)	19 (30)	0.0001	5.1 (2.5, 10.2)
Gold	4 (4)	7 (10)	0.2	0.4* (0.1, 1.5)
Azathioprine	16 (18)	3 (4)	0.006	4.9* (1.3, 17.5)
Cyclophosphamide	5 (5)	3 (4)	0.7	1.3* (0.3, 5.7)
Cyclosporin A	2 (2)	4 (6)	0.2	0.4* (0.07, 2.1)
Sulfasalazine	1 (1)	10 (15)	0.0005	0.07* (0.01, 0.5)
NSAID	76 (84)	62 (93)	0.7	0.7 (0.2, 3.2)

*Unstable estimates due to small numbers. Not all of the questions were answered by each participant.

Table 2. Commonly exposed drugs and adverse drug reactions in patients with SLE and controls with inflammatory arthritis.

	SLE				Controls			
	Number of Exposed	Skin Reaction, n	GI Upset, n	Swelling of Mouth, Breathing Difficulties, n	Number of Exposed	Skin Reaction, n	GI Upset, n	Swelling of Mouth, Breathing Difficulties, n
Penicillin	72	17	7	4	59	9	2	3
Sulfa antibiotics	48	25	9	8	31	6	3	3
Prednisone	59	5	5	1	39	1	1	0
NSAID	76	5	15	4	62	3	16	4

Table 3. Adverse drug reactions in commonly exposed drugs reported as number of reactions in patients with SLE and controls with inflammatory arthritis.

	Skin Reaction, n	p	OR	GI Upset, n	SLE/Controls p	OR	Swelling of Mouth, Breathing Difficulties, n	p	OR
Penicillin	17/9	0.23	1.7	7/2	0.14	—	4/3	0.90	—
Sulfa antibiotics	25/6	0.003	4.5	9/3	0.26	2.15	8/3	0.37	1.9*
Prednisone	5/1	0.20	—	5/1	0.20	—	1/0	0.78	—
NSAID	5/3	0.66	—	15/16	0.40	0.7	4/4	0.77	—

*Unstable estimate due to small numbers. Missing OR not calculated due to very small numbers, rarity of reports.

the exposure rates to antibiotics and NSAID were similar in both SLE patients and controls, as was the reporting of most ADR. The exposure to most DMARD was higher in the control group who had inflammatory arthritis, and there were no observable differences between the groups with respect to total number of ADR and intolerances. However, skin reactions were more frequent in SLE patients who had taken sulfa antibiotics and this was statistically significant. This was not found for sulfasalazine use, but exposure in the patients with SLE was minimal. Our findings are with sulfa antibiotics (a sulfonamide antibiotic with an aromatic amine combined with trimethoprim, SMX-TMP). Our response rate was fair. Due to inadequate information from chart review, we could not include the nonresponders in our analyses.

Petri and Allbritton studied antibiotic sensitivities in

Table 4. Less commonly exposed DMARD/immunosuppresives. Numbers were too small to analyze.

	SLE				Controls			
	Number of Exposed	Skin Reaction, n	GI Upset, n	Swelling of Mouth, Breathing difficulties, n	Number of Exposed	Skin Reaction, n	GI Upset, n	Swelling of Mouth, Breathing Difficulties, n
D-penicillamine	2	2	0	0	5	1	1	0
Methotrexate	5	1	3	1	17	2	3	1
Plaquenil	59	3	4	1	19	3	3	1
Gold	4	1	1	2	7	0	0	0
Azathioprine	16	2	3	1	3	0	0	0
Cyclosporin A	2	0	0	0	4	0	0	0
Cyclophosphamide	5	0	2	1	3	0	1	0
Sulfasalazine	1	0	0	0	10	1	0	0

Table 5. Comparison of allergic history and family history of allergies with the likelihood of having ADR in patients with SLE compared to controls.

Characterisitic	SLE	Controls	p	OR
Subjects with allergic history				
No.	37	28		
ADR, %	82	66	0.16	2.30
Subjects with family history of allergies				
No.	33	17		
ADR, %	65	63	0.83	1.15

patients with SLE and found increased sensitivities to sulfonamides, penicillin/cephalosporin, and erythromycin in the patients compared to controls (relatives and friends)[3]. We only found drug reactions to sulfa antibiotics to be increased in SLE patients compared to controls (those with inflammatory arthritis). The differences could be due to (1) pharmacogenetics — we had only a few non-Caucasian subjects in our population whereas the Baltimore cohort had a large number of black subjects; (2) differences in controls — our controls were taking DMARD and thus had many drug exposures and the potential for drug interactions or idiosyncratic reactions (the rates of drug exposures overall were similar in the 2 groups for most drugs); (3) other reasons including selection bias of the comparison group or response bias; and (4) a small sample size. Some of our control group could evolve into SLE over time, but most met diagnostic criteria for RA[5] or had psoriatic arthritis. Very few had probable RA and none had obvious features of other connective tissue disease.

Years ago aseptic meningitis and fever, headache, and hypotension were reported in patients with SLE receiving ibuprofen. Other NSAID have subsequently also been implicated[6]. We did not find this in our cohort of patients with SLE; genetic differences and the rarity of this idiosyncratic reaction may account for our negative finding of NSAID causing aseptic meningitis.

There have been reports of thrombosis among patients with connective tissue diseases treated with cyclooxygenase-2 inhibitors[7]. Celecoxib was also reported to be associated with Sweet's syndrome in one patient[8]. Our subjects reported no thrombotic events with the coxibs. We did not find more cutaneous reactions with sulfonamides (i.e., certain diuretics). This could be due to low exposure rates and because these sulfonamides do not have an aromatic amine as do the sulfa antibiotics; the cutaneous hypersensitivity reaction could be due to the aromatic amine as opposed to the SO_2NH_2 moiety that they all have in common.

Patients with SLE commonly experience flare during an infection, thus SLE manifestations can be misattributed to side effects from antibiotics used to treat infections[9]. This was not found in our subjects — only rash associated with sulfa antibiotics was found to be increased.

It has been thought that genetic slow acetylators are more likely to have ADR to several drugs that are associated with drug induced lupus such as procainamide, hydralazine, and isoniazid[10]. There was debate in the past that spontaneous SLE was more common in slow acetylators, but in case control studies acetylator phenotype was found not to be associated with idiopathic SLE[11-13].

We found that sulfa antibiotics cause more ADR (rashes) among patients with SLE. Our questionnaire specifically asked about the exposure to sulfa and we used an example of SMX-TMP combination. SMX is thought to be the most important cause of ADR, although TMP has been found to be a causative agent of fever, malaise, head and backache, hypotension, confusion, and meningitis among individuals with SLE and others with Sjögren's syndrome or no rheumatic disease[14-18]. Antonen, *et al* suggested that interleukin 6 might be the key mediator in TMP induced ADR[16]. To what extent the reactions to sulfa antibiotics are due to SMX or TMP cannot be determined using our data, although this investigation would be interesting. Sulfa allergies are known to be increased in individuals with human immunodeficiency virus (HIV) infection, with a hypersensitivity reaction (rash, fever, and myalgia)[19]. It is more likely to occur in advanced disease. Obviously the HLA associations and exposures of SLE and HIV are not common, but genetic

polymorphism for sulfa metabolism could be similar as an explanation to high incidences of sulfa reactions in the 2 groups.

Studying a family heterozygous to C2 deficiency, McCarty *et al* found the index case had SLE, but a family member had joint pains while taking sulfa drugs and a positive LE preparation[20]. She did not have SLE. C2 deficiency could be associated with increased problems with sulfa drugs, but from the evidence of one case report we can only speculate. Our subjects did not complain of arthralgias as ADR, but had reasons for their joint pains related to their SLE or inflammatory arthritis.

We conclude that most adverse drug reactions were not increased in patients with SLE, except rashes from sulfa antibiotics or sulfamethoxazole-trimethoprim, which were increased by 4-fold compared to other subjects with inflammatory arthritis. The reason for this is not clear, and could be due to an SLE phenotype or other pharmacogenetic differences between individuals with SLE and those with inflammatory arthritis. In addition, subjects with a personal or family history of atopy and/or environmental allergies were more likely to have ADR than those without. Physicians should take a detailed personal and family history of allergies while treating patients with SLE and inflammatory arthritis. When prescribing sulfa antibiotics to patients with SLE, there should be an index of suspicion for cutaneous reactions.

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