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CONCISE REPORT

Sulpha allergy in lupus patients: a clinical perspective

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Systemic lupus erythematosus is a chronic, relapsing autoimmune disease that can affect multiple organ systems. An increased prevalence of drug allergy has been reported in lupus patients compared with the general population. Using a cohort of 417 lupus patients, we found a history of sulpha allergy in 27.3% of patients. European-American lupus patients with sulpha allergy are about two times more likely to suffer from lymphopenia, two times more likely to have anti-Ro autoantibody, and four times less likely to have anti-nRNP antibodies compared with lupus patients without a reported sulpha allergy ($P = 0.0075$, 0.025 , and 0.032 , respectively). In African-American lupus patients, a history of sulpha allergy was associated with over three times increased odds of developing pericarditis ($P = 0.005$). *Lupus* (2008) 17, 202–205.

Keywords: lupus; sulpha allergy; lymphopenia; pericarditis; serology

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of a variety of autoantibodies targeted to nuclear components.¹ A conservative estimate of the burden of lupus in the United States has been reported to be 239,000 people; of these, 90% are women.² A number of factors are known to contribute to the pathogenesis of lupus. Evidence for a genetic role in part comes from familial aggregation of the disease and increased concordance among monozygotic twins. However, genetic contributions to the disease etiology are not straightforward, and the vast majority of lupus cases are sporadic without a relative known to be affected.

Drugs, especially antibiotics, have been reported both as predisposing factors and as exacerbating agents in SLE.^{3,4} In the 1970s, a report examining drug allergy in lupus patients showed no appreciable difference in the prevalence of allergy to sulpha drugs in lupus patients versus controls.⁵ This topic was revisited in 1992 with a larger cohort of 221 lupus patients studied at Johns Hopkins University. In this population, sulphonamide allergy was indeed more common in lupus patients compared with controls

(odds ratio = 2.4).⁶ In addition, there are many reports on sulpha drug-induced lupus in patients treated for inflammatory bowel disease and a variety of rheumatic diseases, including inflammatory arthritis, Sjögren's syndrome, and others.^{7–20}

In light of these reports, we evaluate whether a history of sulpha allergy in lupus patients is associated with changes in clinical and serological manifestations of the disease.

Materials and methods

Patients and clinical data

Our study group consisted of 417 unrelated lupus patients enrolled in the Lupus Family Registry and Repository at Oklahoma Medical Research Foundation (OMRF). All these patients met the American College of Rheumatology lupus classification criteria.^{21,22} Data used in this study were obtained from medical records, interviews, and participants' questionnaires. A history of sulpha allergy was self-reported by patients and documented in their medical records by the referring physicians. Of the 417 lupus patients, 114 had a history of sulpha allergy and 303 patients did not. Patients were from diverse racial backgrounds: 200 (48%) were European-Americans, 139 (33%) were African-Americans, 30 (7%) were His-

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panic, 31 (7%) were Gullah, 10 (2%) were American-Indians, and 7 (2%) were Asians. The Gullah is a group of individuals inhabiting in the southeastern United States who have retained nearly homogeneous West African bloodlines.

Serology

A single serum sample was obtained at the time of enrollment from each patient included in our study. All serological tests were performed in the clinical immunology lab at OMRF. Testing for autoantibodies against extractable nuclear antigens was performed using Ouchterlony immunodiffusion assays.²³ Antibodies against double-stranded DNA were detected by indirect immunofluorescence using *Crithidia luciliae* (Inova Diagnostics, San Diego, California, USA). Both immunoglobulin (Ig) M and IgG anticardiolipin antibodies were determined by enzyme-linked immunosorbent assay. Cardiolipin was purchased from Sigma-Aldrich (St Louis, Missouri, USA).

Statistical analysis

Logistic regression was used to identify association between sulpha allergy and various clinical manifestations and serological specificities in lupus. VassarStats online clinical research calculators²⁴ were used to perform statistical calculations, including the Pearson chi-square test and *P* values. The *P* values were considered statistically significant if <0.05 .

Results

Of 417 total lupus patients examined in this study, 114 (27.3%) reported allergy to sulpha medications. When segregated by race, 74 of 200 (37%) European-American lupus patients reported allergy to sulpha medications. In contrast, in the African-American subset, only 25 of 139 patients (18%) reported a history of sulpha allergy. Sulpha allergy was reported in 6 of 30 (20%) Hispanic, 3 of 31 (10%) Gullah, 5 of 10 (50%) American-Indian, and 1 of 7 (14%) Asian lupus patients. There was no difference in the age of onset, duration of the disease, or gender between lupus patients with and without sulpha allergy in all racial subgroups (Table 1).

We next determined the frequency of the various American College of Rheumatology clinical manifestations, as well as autoantibody specificities in lupus patients with a reported sulpha allergy compared with lupus patients who did not report an allergy to sulpha in both the European-American and African-American subsets (Table 2). European-American lupus patients who reported sulpha allergy were about

Table 1 Demographic characteristics of the lupus patients enrolled in our studies stratified by ethnicity

	Sulpha allergic (n = 114)	Sulpha non-allergic (n = 303)	P value
European-American	74	126	
Female	68 (92%)	106 (84%)	NS
Male	6 (8%)	20 (16%)	NS
Age of onset (years)	40.31	37.07	NS
Disease duration (years)	6.14	5.87	NS
African-American	25	114	
Female	25 (100%)	109 (96%)	NS
Male	0 (0%)	5 (4%)	NS
Age of onset (years)	37.64	34.56	NS
Disease duration (years)	6.20	6.17	NS
Hispanic	6	24	
Female	5 (83%)	23 (96%)	NS
Male	1 (17%)	1 (4%)	NS
Age of onset (years)	39.67	33.54	NS
Disease duration (years)	6.83	6.79	NS
Gullah	3	28	
Female	3 (100%)	23 (92%)	NS
Male	0 (0%)	5 (8%)	NS
Age of onset (years)	38.00	37.21	NS
Disease duration (years)	4.00	4.54	NS
American-Indian	5	5	
Female	5 (100%)	5 (100%)	NS
Male	0 (0%)	0 (0%)	NS
Age of onset (years)	29.20	33.00	NS
Disease duration (years)	1.20	9.80	NS
Asian	1	6	
Female	1 (100%)	6 (100%)	NS
Male	0 (0%)	0 (0%)	NS
Age of onset (years)	44.00	38.60	NS
Disease duration (years)	9.00	8.75	NS

NS, Not Significant

two times more likely to have lymphopenia compared with race-matched lupus patients without a reported history of sulpha allergy (45% vs 26%, OR = 2.27, $P = 0.0075$). Furthermore, European-American lupus patients who are allergic to sulpha were about two times more likely to have anti-Ro precipitating antibody (23% vs 11%, OR = 2.39, $P = 0.025$) and about four times less likely to have anti-nRNP antibodies (4% vs 13%, OR = 0.27, $P = 0.032$). However, African-American lupus patients who have a history of sulpha allergy were over three times more likely to suffer from pericarditis as part of their disease (48% vs 21%, OR = 3.46, $P = 0.005$) (Table 2).

Discussion

One of the most common adverse drug reactions is hypersensitivity to sulpha drugs, reported to have about 3% prevalence in the general population.²⁵ Often misunderstood and misdiagnosed as an allergy to any sulphur-containing compound, the chemical moiety involved in true sulpha hypersensitivity is

Table 2 Clinical and serological manifestations in European-American and African-American lupus patients with and without a reported history of allergy to sulpha medications

	European-Americans					African-Americans				
	<i>Sulpha allergic</i> (n = 74)	<i>Non-sulpha allergic</i> (n = 126)	<i>Odds ratio</i>	χ^2	<i>P value</i>	<i>Sulpha allergic</i> (n = 25)	<i>Non-sulpha allergic</i> (n = 114)	<i>Odds ratio</i>	χ^2	<i>P value</i>
Clinical features										
Malar rash	34 (46%)	57 (45%)	1.03	1.00	0.92	9 (36%)	31 (27%)	1.51	0.78	0.38
Discoid rash	6 (8%)	12 (10%)	0.83	0.11	0.74	9 (36%)	25 (22%)	2.00	2.20	0.14
Photosensitivity	31 (42%)	64 (51%)	0.70	1.48	0.22	6 (24%)	32 (28%)	0.81	0.17	0.68
Oral ulcers	27 (36%)	46 (37%)	1.00	0.00	1.00	8 (32%)	37 (32%)	0.98	0.00	1.0
Arthritis	53 (72%)	79 (63%)	1.14	1.65	0.20	19 (76%)	80 (70%)	1.35	0.34	0.56
Pericarditis	16 (22%)	14 (11%)	0.80	0.48	0.49	12 (48%)	24 (21%)	3.46	7.76	0.005 ^a
Pleuritis	26 (35%)	33 (26%)	1.34	1.79	0.18	4 (16%)	29 (25%)	0.56	1.01	0.31
Proteinuria	20 (27%)	38 (30%)	0.86	0.22	0.64	13 (52%)	60 (53%)	0.98	0.00	1.0
Cellular castes	6 (8%)	13 (10%)	0.77	0.26	0.61	4 (16%)	23 (20%)	0.75	n/a	0.78
Seizures	7 (9%)	7 (6%)	1.78	1.09	0.30	4 (16%)	18 (16%)	1.02	n/a	1.0
Psychosis	2 (3%)	0 (%)	n/a	n/a	1.0	4 (16%)	9 (8%)	2.22	n/a	0.25
Hemolytic anemia	1 (1%)	5 (4%)	0.33	n/a	0.42	1 (4%)	6 (5%)	0.75	n/a	1.0
Leukopenia	14 (19%)	29 (23%)	0.82	0.46	0.50	11 (44%)	41 (36%)	1.40	0.57	0.45
Lymphopenia	33 (45%)	33 (26%)	2.27	7.14	0.0075 ^b	12 (48%)	34 (30%)	2.17	3.05	0.080
Thrombocytopenia	12 (16%)	31 (25%)	0.59	1.94	0.16	2 (8%)	19 (17%)	0.43	n/a	0.37
Autoantibodies										
anti-ANA	67 (91%)	118 (94%)	0.65	0.65	0.42	23 (92%)	108 (95%)	0.64	n/a	0.63
anti-dsDNA	14 (19%)	33 (26%)	0.66	1.37	0.24	9 (36%)	47 (41%)	0.80	0.23	0.63
anti-Sm	1 (1%)	5 (4%)	0.33	n/a	0.42	4 (16%)	15 (13%)	1.26	n/a	1.0
anti-nRNP	3 (4%)	17 (13%)	0.27	4.61	0.032 ^c	9 (36%)	42 (37%)	0.96	0.01	0.92
anti-Ro	17 (23%)	14 (11%)	2.39	5.01	0.025 ^d	3 (12%)	29 (25%)	0.40	2.09	0.15
anti-La	5 (7%)	5 (4%)	1.75	n/a	0.50	2 (8%)	4 (4%)	2.39	n/a	0.59
anti-P	0 (%)	1 (1%)	n/a	n/a	1.0	1 (4%)	0 (0%)	n/a	n/a	0.17
aPL IgG (>10)	20 (27%)	48 (38%)	0.60	2.55	0.11	10 (40%)	44 (39%)	1.06	0.02	0.89
aPL IgM (>10)	5 (7%)	17 (13%)	0.46	2.16	0.14	3 (12%)	7 (6%)	2.08	n/a	0.39

95% Confidence interval for odds ratios: ^a1.40–8.55, ^b1.24–4.16, ^c0.077–0.96, ^d1.10–5.18.

n/a, not applicable

sulphonamide, a chemical entity characterized by nitrogen and sulphur dioxide bonded to an aromatic ring.²⁶ Sulphonamide antibiotics have this arylamine group (benzene + amine) bonded along the benzene ring at the N⁴ location.²⁶ It is this positioning that is believed to be crucial in the reactions seen in patients with sulpha hypersensitivity as it allows for complex metabolic processes whose endpoints lead to immunogenicity. Because a hyperactive immune system is a hallmark of SLE, an assumption could be made that hypersensitivity to sulpha drugs should be more prevalent in this population. The prevalence of reported sulpha allergy in our lupus cohort is close to a report by Petri and Allbritton,⁶ who reported a frequency of sulpha allergy of 32% in lupus patients compared with 12% in unrelated controls. In a report by Pope et al.,²⁷ 25 of 48 (52%) lupus patients exposed to sulpha reported a sulpha skin rash compared with 6 of 31 (19%) controls with inflammatory arthritis (rheumatoid or psoriatic arthritis).

We report that European-American lupus patients are about two times more likely to suffer from lymphopenia when they also report a history of sulpha allergy. A mechanistic explanation for this association

is lacking; however, it is possible that the immune mechanism(s) mediating both lymphopenia and sulpha allergy overlap. Further, both sulpha allergy and lymphopenia could share common susceptibility genes. African-American lupus patients with sulpha allergy also show a trend for increased lymphopenia, although this does not reach statistical significance in our cohort. However, about half the African-American lupus patients, who give a history of sulpha allergy, develop pericarditis compared with only about a fifth of patients without a reported sulpha allergy. Curiously, European-American lupus patients who are allergic to sulpha are also more likely to have anti-Ro antibody but are less likely to have anti-nRNP antibodies at the time of enrollment in our study. However, it should be noted that the *P* values presented here were not corrected for multiple testing.

In summary, we confirm a higher prevalence of reported sulpha allergy in lupus patients than the general population. Moreover, we report for the first time on the clinical and serological manifestations in lupus patients who also report an allergy to sulpha compared with lupus patients without a reported sulpha allergy.

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References

- 1 Sawalha, AH, Harley, JB. Antinuclear autoantibodies in systemic lupus erythematosus. *Curr Opin Rheumatol* 2004; **16**: 534–540.
- 2 Lawrence, RC, Helmick, CG, Arnett, FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998; **41**: 778–799.
- 3 Domz, CA, McNamara, DH, Holzapfel, HF. Tetracycline provocation in lupus erythematosus. *Ann Intern Med* 1959; **50**: 1217–1226.
- 4 Honey, M. Systemic lupus erythematosus presenting with sulphonamide hypersensitivity reaction. *Br Med J* 1956; **1**: 1272–1275.
- 5 Becker, LC. Allergy in systemic lupus erythematosus. *Johns Hopkins Med J* 1973; **133**: 38–44.
- 6 Petri, M, Allbritton, J. Antibiotic allergy in systemic lupus erythematosus: a case-control study. *J Rheumatol* 1992; **19**: 265–269.
- 7 Borg, AA. Sulphasalazine-induced autoimmune abnormalities in patients with rheumatic disease. *Br J Rheumatol* 1995; **34**: 1097–1098.
- 8 Carr-Locke, DL. Sulphasalazine-induced lupus syndrome in a patient with Crohn's disease. *Am J Gastroenterol* 1982; **77**: 614–616.
- 9 Crisp, AJ, Hoffbrand, BI. Sulphasalazine-induced systemic lupus erythematosus in a patient with Sjogren's syndrome. *J R Soc Med* 1980; **73**: 60–61.
- 10 Griffiths, ID, Kane, SP. Sulphasalazine-induced lupus syndrome in ulcerative colitis. *Br Med J* 1977; **2**: 1188–1189.
- 11 Gunnarsson, I, Kanerud, L, Pettersson, E, Lundberg, I, Lindblad, S, Ringertz, B. Predisposing factors in sulphasalazine-induced systemic lupus erythematosus. *Br J Rheumatol* 1997; **36**: 1089–1094.
- 12 Gunnarsson, I, Nordmark, B, Hassan Bakri, A, et al. Development of lupus-related side-effects in patients with early RA during sulphasalazine treatment-the role of IL-10 and HLA. *Rheumatology* 2000; **39**: 886–893.
- 13 Khattak, FH, Morris, IM, Mattingly, PC. Sulphasalazine-induced systemic lupus erythematosus in a patient with rheumatoid arthritis. *Br J Rheumatol* 1996; **35**: 104.
- 14 Laversuch, CJ, Collins, DA, Charles, PJ, Bourke, BE. Sulphasalazine-induced autoimmune abnormalities in patients with rheumatic disease. *Br J Rheumatol* 1995; **34**: 435–439.
- 15 Mongey, AB, Hess, EV. Sulphasalazine-induced systemic lupus erythematosus. *Br J Rheumatol* 1994; **33**: 789–790.
- 16 Rafferty, P, Young, AC, Haeney, MR. Sulphasalazine-induced cerebral lupus erythematosus. *Postgrad Med J* 1982; **58**: 98–99.
- 17 Tsai, WC, Chen, CJ, Yen, JH, Liu, HW. Sulphasalazine-induced systemic lupus erythematosus in a patient with ankylosing spondylitis. *Clin Rheumatol* 2002; **21**: 339–340.
- 18 Vanheule, BA, Carswell, F. Sulphasalazine-induced systemic lupus erythematosus in a child. *Eur J Pediatr* 1983; **140**: 66–68.
- 19 Veale, DJ, Ho, M, Morley, KD. Sulphasalazine-induced lupus in psoriatic arthritis. *Br J Rheumatol* 1995; **34**: 383–384.
- 20 Walker, EM, Carty, JE. Sulphasalazine-induced systemic lupus erythematosus in a patient with erosive arthritis. *Br J Rheumatol* 1994; **33**: 175–176.
- 21 Tan, EM, Cohen, AS, Fries, JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271–1277.
- 22 Hochberg, MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; **40**: 1725.
- 23 Clark, G, Reichlin, M, Tomasi, TB. Characterization of a soluble cytoplasmic antigen reactive with sera from patients with systemic lupus erythematosus. *J Immunol* 1969; **102**: 117–122.
- 24 Lowry, R. VassarStats: Web Site for Statistical Computation. <http://faculty.vassar.edu/lowry/VassarStats.html> 1998–2007.
- 25 Tilles, SA. Practical issues in the management of hypersensitivity reactions: sulphonamides. *South Med J* 2001; **94**: 817–824.
- 26 Hemstreet, BA, Page, RL. Sulphonamide allergies and outcomes related to use of potentially cross-reactive drugs in hospitalized patients. *Pharmacotherapy* 2006; **26**: 551–557.
- 27 Pope, J, Jerome, D, Fenlon, D, Krizova, A, Ouimet, J. Frequency of adverse drug reactions in patients with systemic lupus erythematosus. *J Rheumatol* 2003; **30**: 480–484.