Evaluation of Immune Parameters in HIV⁺ Subjects Reporting Adverse Reactions to Sulfamethoxazole

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Abstract

Trimethoprim-sulfamethoxazole (TMP-SMX) is frequently used in human immunodeficiency virus (HIV)-infected patients (HIV⁺) for treatment or prophylaxis of *Pneumocystis carinii* pneumonia (PCP). Up to 80% of those patients report adverse reactions to that drug combination. To test the hypothesis that these reactions are immunologically mediated, we quantitated specific IgG and IgE SMX-human serum albumin (HSA) antibodies and immune complexes (IC) in HIV⁺ patients and in HIV controls. Patients with mild HIV disease had elevated specific SMX-HSA IgG and IC levels compared with those having severe disease or with controls. Conversely, patients with severe HIV disease had statistically elevated levels of specific IgE when compared with patients having milder disease or with controls. There were no differences in either specific antibody or IC levels between patients reporting adverse reactions and those who did not. Results suggest that there are increased levels of SMX-HSA-specific antibodies in some HIV⁺ patients. The presence of these antibodies appears to be related to severity of disease, rather than clinically significant drug sensitivity.

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Trimethoprim-sulfamethoxazole (TMP-SMX) is frequently used in human immunodeficiency virus (HIV)-infected patients (HIV⁺) for the treatment or prophylaxis of *Pneumocystis carinii* pneumonia (PCP). In these individuals there is a high incidence (in some cases up to 80%) of adverse reactions to TMP-SMX [1]. Symptoms, time course of reaction, ability of some patients to be desensitized, and improvement of patients following corticosteroid treatment, suggest an antibody-mediated pathogenesis [2]. To investigate this hypothesis further, SMX-human serum albumin (HSA)-specific IgG and IgE antibodies, and immune complexes (IC) were quantitated in 40 HIV⁺ subjects and in 49 HIV⁻ controls.

Twenty-three of the HIV⁺ subjects (group 1) were recruited from ongoing AIDS Clinical Trials Group (ACTG) Protocol 081 – a randomized study of primary prophylaxis for PCP using oral TMP-SMX (n = 8), oral dapsone (Dap) (n = 6), or aerosolized pen-tamidine (A/P) (n = 9).

Eligibility for that study included a history of AIDS diagnosed by criteria other than PCP or toxoplasmosis, or late AIDS-related complex and the ability to tolerate zidovudine treatment. Blood samples from group 1 patients were obtained at entry into the protocol and serially every 2 weeks, for a period up to 24 weeks, after initiation of therapy. At the time baseline samples were obtained, patients were relatively well. The remaining 17 HIV⁺ patients (group 2) were inpatients receiving parenteral TMP-SMX for

treatment of PCP. These patients could be subdivided into those reporting (5/17, 29%) or not reporting (12/17, 67%) adverse reactions. Forty-nine control subjects (group 3) were recruited from Tulane Medical Center students and staff; their HIV⁺ status was confirmed serologically. All individuals signed an informed consent.

For in vitro studies, the classical diazotization procedure was used to prepare a stable drug-protein conjugate through covalent linkage of the aromatic amino function of SMX to HSA [3]. Use of 150 mg SMX and 500 mg HSA produced a maximally substituted product (13 M) which was used in these studies. Specific SMX-HSA IgG and IgE antibodies were quantitated by ELISA and RAST, respectively. For the ELISA, serum was diluted 1:40 and results are presented as a ratio to an HIV⁺ serum pool; RAST results are presented as percentage of total isotope added bound to the disc (% bound). Immune complexes were quantitated using a commercial Clq binding assay (Diamedix). Results are presented as microgram equivalents/milliliter ($\mu\text{g Eq/ml}$) of heat-aggregated IgG; a value greater than 20 is considered elevated. Evaluation of Immune Parameters in HIV⁺ Subjects Reporting Adverse Reactions to Sulfamethoxazole

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Table 1. Mean SMX-HSA-specific IgG (ratio to an HIV⁺ serum pool), IgE (% bound), and IC ($\mu\text{g Eq/ml}$) levels in two groups of HIV-infected individuals and in controls

Table 2. Mean values of SMX-HSA-specific IgG (ratio of HIV⁻ serum pool), IgE (% bound), and IC ($\mu\text{g Eq/ml}$) levels for patients reporting or not reporting adverse reactions to TMP-SMX

React	n	IgG $\pm$ SEM	IgE $\pm$ SEM	IC $\pm$ SEM
Group 1				
No	17	3.40 $\pm$ 0.34	0.62 $\pm$ 0.73	14.12 $\pm$ 1.94
Yes	6	3.62 $\pm$ 0.69	0.92 $\pm$ 0.57	9.50 $\pm$ 3.01
Group 2				
No	12	1.83 $\pm$ 0.55	1.33 $\pm$ 0.25	5.00 $\pm$ 1.04
Yes	5	0.82 $\pm$ 0.23	1.19 $\pm$ 0.33	6.00 $\pm$ 1.30

elevated. Prior to statistical analysis, data were log transformed. Data for all three groups were compared using analysis of variance. Values for reactors versus nonreactors in groups 1 or 2 were compared using a Student's t test.

Initial mean SMX-HSA-specific IgG levels were elevated in group 1 patients when compared with groups 2 and 3 ($p < 0.05$). IC levels also followed this pattern ($p < 0.05$); however, mean values were not elevated in any patient group. Mean RAST values were elevated in group 2 as compared with groups 1 and 3 ($p < 0.05$). These data are summarized in table 1. For group 1 patients receiving TMP-SMX, there were no changes in specific antibody levels over time; nor were antibody levels in these subjects different from those receiving Dap or A/P (data not presented).

Of the group 1 patients receiving TMP-SMX, 6/8 (75%) reported morbilliform rash, with or without fever. For these patients, drug therapy was generally 2 weeks or less in duration. Comparison of specific antibody and IC levels in serum samples from these patients obtained at the time of reaction with the remainder of group 1 patients demonstrated no differences (table 2). Comparison of these immune parameters in patients receiving parenteral TMP-SMX also failed to show differences between reactors and nonreactors (table 2).

These studies demonstrate that statistically elevated specific SMX-HSA antibody or IC levels could be detected in some HIV-infected individuals, when compared with controls. The IgG antibodies were of low affinity. Further, the antigenic stimulus for these antibodies is not clear, but does not appear to be related to therapy. The level and isotype of these antibodies appears to be related to the stage of HIV disease, rather than reported adverse drug reactions. In general, patients with less severe HIV disease (group 1) had elevated specific IgG levels and patients with more severe disease (group 2) had higher specific IgE levels. This pattern is also consistent with reported levels of total immunoglobulins in HIV+ patients [4]. Although these data do not rule out the possibility that an immune pathogenesis is responsible for product-ing adverse symptoms to TMP-SMX, they do suggest that there is not a clinically significant antibody response to this conjugate in HIV+ subjects.

Acknowledgements

This work was supported by NIH-NIAID AI 24930 and NIH-NIAID 5-U01 AI 27674. The authors thank Arlene Lefebre and Nicholas DiPiazza for their excellent technical assistance.

References

- Gordin FM, Simon GL, Wofsy CB, Mills J: Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1985; 100: 495–499.
- Finegold I: Oral desensitization to trimethoprim-sulfamethoxazole in a patient with acquired immunodeficiency syndrome. *J Allergy Clin Immunol* 1986;78:905–908.
- Erlanger BF: Principles and methods for the preparation of drug protein conjugates for immunological studies. *Pharmacol Rev* 1973;25:271–280.
- Wright DN, Nelson RP Jr, Ledford DK, Fernandez-Caldas E, Trudeau WL, Lockey RF: Serum IgE and human immunodeficiency syndrome virus (HIV) infection. *J Allergy Clin Immunol* 1990;85:445–452.