A Randomized, Pilot Trial Comparing Full Versus Escalating Dose Regimens for the Desensitization of AIDS Patients Allergic to Sulfonamides

Andrea Straatmann, Fabianna Bahia, Diana Pedral-Sampaio and Carlos Brites

Federal University of Bahia, Infectology Foundation of Bahia, Salvador, BA, Brazil

Sulfonamides are drugs extensively used in the management of AIDS patients. However, the use of sulfonamides is often associated with the development of allergic reactions, provoking the substitution of the drug (by another that may be less effective); alternatively attempts are made to desensitize the patient. Objective. Compare two drug regimens (full vs. escalating doses) for the oral desensitization of AIDS patients allergic to sulfonamides. Material and Methods. AIDS patients with previous allergic reactions to sulfonamides and requiring prophylaxis against *Pneumocistis carinii,* central nervous system toxoplasmosis and diarrhea caused by *Isospora belli* were randomly assigned to a group receiving a routine dose of cothrimoxazole, or another that received escalating doses of an oral suspension of the same drug, initiating with 75mg/day of sulfamethoxazole that was doubled every 48 hours till the full dose was reached, if no allergic reaction occurred. Patients were monitored for at least 6 months after enrollment in the trial. The major end-point was the ability to maintain prophylactic treatment after that period of time. Plasma viral load (PVL) and CD_4/CD_8 counts were measured at baseline. Liver enzymes and hematological parameters were measured at baseline and after 1, 3 and 6 months. Results. Eighteen patients were enrolled in the study (15 men and 3 women), with ages ranging from 30 to 57 years (mean 39.9). The mean CD_4 counts were slightly higher for patients receiving a full dose; there was also a trend towards higher baseline CD_8 counts among patients developing new reactions. The mean PVL was similar among the patients in both desensitization groups. The incidence of new allergic reactions was identical (40%) in the two groups. All adverse reactions were mild and no significant increase in liver enzymes were observed. Conclusion. Dose regimen is not a predictor of the development of new allergic reactions amongst patients challenged with sulfonamides after an initial allergic reaction.

Key Words: AIDS, allergy, sulfonamides, oral desensitization.

Trimethoprim- sulfametoxazole (TMP-SMX) is a combination of drugs extensively used in the management of ADS patients for the treatment of life-threatening opportunistic infections (OI), such as *Pneumocistis carinii* pneumonia, and diarrhea caused by some enteric pathogens [1,2]. In addition, these drugs are used for primary and secondary prophylaxis of these infections [3]. However, the use of sulfonamides is often associated with the development of diverse allergic reactions ranging from mild to severe, leading to the interruption of treatment or prophylaxis, and requiring the use of alternative drugs, usually less effective than the first-line approach [4-6].

Oral desensitization of AIDS patients allergic to sulfonamides has been attempted by using different doses or regimens, with a variable reported rate of success [6-11]. However, there are still answered questions about the impact of the type of desensitization

Received on 13 July 2002; revised 14 November 2002.

Address for correspondence: Dr. Carlos Brites. Hospital Universitário Prof. Edgard Santos, 6o. Andar. Rua João das Botas, s/n, Canela. Salvador, Bahia , Brazil . Zip code: 40.110-160. Phone: 55-71-235-4901. Fax: 55-71-2472756. E-mail: crbrites@ufba.br

This work was supported by a grant from Brazilian Ministry of Health, STD/AIDS Coordination. Partially presented as a poster at the 38th Annual Meeting of Infectious Diseases of America, New Orleans, LA, September 7-10, 2000. Poster 368.

The Brazilian Journal of Infectious Diseases 2002;6(6):276-280

1413-8670

regimen (full versus escalating doses) on the outcome of patients submitted to re-exposure to sulfonamides. A recent report showed a similar rate of new allergic reactions for patients submitted to a desensitization treatment compared to a second group rechallenged with TMP-SMX [12]. We designed a pilot trial to evaluate the efficacy of these two different regimens for the desensitization of AIDS patients allergic to sulfonamides.

Material and Methods

Patient population

All patients attending the AIDS clinic of Federal University of Bahia Hospital, who developed allergic reactions to sulfonamides from August, 1998, to October, 1999, were invited to participate in this experiment. The inclusion criteria required a recent diagnosis of allergic reaction to sulfametoxazole + thrimethoprim or sulfadiazine, age above 18 years, complete resolution of symptoms and signs associated with the allergic reaction, and absence of active opportunistic infections (OIs). All participants were enrolled only after a written informed consent was given. The Institutional Ethics Review Committee approved the protocol.

Patient evaluation

All participants in the protocol were submitted to a complete clinical evaluation at baseline, weekly for the first 4 weeks, and monthly thereafter. After 6 months without a new allergic reaction, they were considered successfully desensitized. Laboratory evaluation included a $CD_{4/8}$ count, measured by flow cytometry, plasma RNA viral load (VL), determined by Nuclisens assay (Organon-Teknika, Boxtel, Netherlands), absolute and differential white blood cell counts, hemoglobin level, and platelet count. In the case of development of a new allergic reaction during the protocol period, liver enzymes were also measured, and the baseline evaluation was repeated.

Statistical analysis- Means were compared by variance analysis. The chi-square test was used for the comparison of proportions. All data were analyzed by using EPI-Info version 6.01 software.

Drug assignment

Patients were randomly assigned (according to a computer generated list) to receive a full dose of sulfamethoxazole + thrimethoprim (SMX/TMP, 800/160mg), three times per week, or escalating doses, using a pediatric solution of this combination of drugs. Patients assigned to the escalating group, received an initial daily dose equivalent to 75mg of SMX. The dose was doubled every 48h, until a full dose was reached, or a new allergic reaction developed. Patients presenting a new episode of allergy stopped using the drugs, and were treated with antihistaminic drugs, according to the severity of the reaction.

Results

Eighteen subjects were enrolled in the study (9 in each group). Mean age was 39.9 years (median 39 years). Table 1 summarizes the baseline characteristics of the patients.

The incidence of new allergic reactions was identical (40%) for individuals receiving full and escalating doses. All new reactions observed during the study developed within one week after restarting drugs. The new allergic episodes were of mild intensity, and were completely resolved, without any other serious consequences.

The mean CD_4 count was slightly higher for the 9 patients that were rechallenged (136 cells/mm^3, median 106 cells/mm^3) compared with the patients who used escalating doses (107 cells/mm^3, median 102 cells/mm^3). Patients who developed a new reaction had a higher CD_4 count (mean 138 cells/mm^3, median 141 cells/mm^3) than individuals who tolerated the re-exposure to sulfonamides (mean 109 cells/mm^3, median 96 cells/mm^3), but the difference was not significant ($p=0.7$, Kruskal-Wallis test). The same pattern was observed for the CD_8 count: mean 1,153 cells/mm^3 (median 851 cells/mm^3), for subjects who developed a new reaction, and a mean of 765 cells/mm^3 (median

Table 1. Characteristic features of AIDS patients sensitive to sulfonamides, at baseline

New	Sex	Age	CD_4	PVL*	AST	ALT	Hb	Group #	New reaction
AS	M	52	54	470,000	38	44	13.3	2	No
CAA	M	36	146	140	37	56	8.9	1	Yes
ECF	M	38	232	2,500	45	99	13.3	1	Yes
FSN	M	31	146	140	29	78	15.6	2	Yes
FTCL	M	48	90	1,054	48	52	10.1	1	No
JFS	M	40	106	310	56	105	12.6	1	No
JMP	F	57	176	180	73	36	12.2	2	Yes
JNM	M	54	137	120	26	31	12.4	2	Yes
JO	M	41	178	21,000	54	67	13.9	1	No
JSR	M	41	19	7,500	33	47	13.1	2	No
LBA	M	30	11	8,700	144	197	11.8	2	Yes
MAR	F	36	340	2,900	39	33	11.4	1	Yes
MJFC	M	41	19	7,500	33	47	13.1	2	No
MSR	M	42	11	29,000	21	16	9.9	1	Yes
PRRB	M	36	157	< 400	31	47	14.9	1	No
VLSL	F	30	102	46,000	28	41	6.7	2	No
VXJ	M	36	302	< 400	29	39	13.4	2	No
OS	M	28	68	58,000	44	42	11.8	1	No
Mean± SD		40.5±6.1	130±97.3	3.4±1.12	44.9±28.7	60.9±42.1	12.2±2.2		

Group 1 refers to patients assigned to receive escalating doses and group 2 includes patients rechallenged with full doses.
* PVL means plasma viral load (copies/ml).

337 cells/mm^3), for those who did not, (p=0.06, Kruskal-Wallis test). The mean VL was similar for patients at baseline, when considering the dose regimen groups (mean log 3.4 for the full-dose group and 2.4 for the escalating-dose group, median log 4.0 and 2.0, respectively). Also, patients that developed a new allergic reaction had a VL lower than those that were successfully desensitized (mean log 2.4, median log 2.0), versus a mean of log 3.4, median log 3.5 HIV RNA copies/ml of plasma, p=0.3, Kruskal-Wallis test).

Discussion

Sulfonamides are the first line drugs for the treatment of common OIs, in AIDS patients, but the frequent occurrence of allergic reactions in these patients can limit their use [4-6]. Oral desensitization to this class of drugs has been effective in most cases (50% to 80%), but the best regimen to accomplish this remains to be determined [7-12]. In a previous experience with oral desensitization, we were able to successfully reintroduce sulfonamides to almost 80% of the patients, by using escalating doses [13].

In this pilot, randomized trial, we used 2 different dosage regimens of sulfonamides, in order to determine if the rate of successful desensitization is dose-dependent or not. The proportion of patients tolerating reintroduction of oral sulfonamides after a previous allergic reaction was similar for those receiving escalating doses, and for those to whom the drugs were given in a full, usual dose. Oral desensitization was effective in 60% of the patients submitted to a new exposure to sulfonamides, regardless of the dose regimen they used.

The time till onset of a new allergic episode was quite short: all patients presenting new episodes of allergy did so within one week after re-exposure to the drugs. All reactions were mild, and needed only a few days of oral antihistaminic drugs for complete recovery. Mean age, and VL were not predictive of new reactions. To date, many questions remain unanswered about the mediators of TMP-SMX intolerance, and the mechanisms of desensitization in patients with HIV infection. A previous report showed evidence of a high susceptibility of CD_8^+ cells to the toxic effects of TMP-SMX, through enhanced cell death by apoptosis [14]. In addition, individuals with history of a previous allergic reaction to TMP-SMX presented detectable IgE specific to SMX, even 3 years after the allergy developed [15]. In our experiment, the development of new reaction was associated with higher mean CD_4/CD_8 counts, although the difference was not significant, probably due to the small number of patients enrolled in the trial. The higher CD_8^+ cells counts found in the group with new allergic reactions reinforces the hypothesis that T cells play a role in the genesis of allergic reactions among AIDS patients. However, the study design was not appropriate to answer this question, and the small number of patients limits the power of this association.

In conclusion, in this preliminary trial, desensitization with TMP-SMX was safe, and made it possible to use these drugs again in the prevention of opportunistic infections in AIDS patients requiring primary or secondary prophylaxis. The rechallenge with a full dose of TMP-SMX is faster and more practical, and does not seem to increase the risk or the severity of a new allergic reaction.

References

1. Masur H. Prevention and treatment of Pneumocystis pneumonia. N Eng J Med **1992**;327:1853-60.
2. Fischl M.A., Dickinson G.M., La Voie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocistis carinii* pneumonia in AIDS. JAMA **1988**;259:1185-9.
3. Kovacs J.A., Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. N Eng J Med **2000**;342:1416-28.
4. Jaffe H.S., Abrams D.I., Ammann A.J., et al. Complications of co-trimoxazole in treatment of AIDS-associated *Pneumocystis Carinii* pneumonia in homosexual men. The Lancet **1983**;nov:1109-11.
5. Coopman S.A., Johnson R.A., Platt R., Stern R.S. Cutaneous Disease and Drug Reactions in HIV Infection. The New England Journal of Medicine **1993**;June:1670-993.
6. Van der Ven A.J.A.M., Koopmans P.P., Vree T.B., Van der Meer J.W.M. Adverse reactions to co-trimoxazole in HIV infection. The Lancet **1991**;338(Aug):431-3.

7. Gluckstein D., Ruskin J. Rapid oral desensitization to Trimethoprim-Sulfamethoxazole (TMP-SMZ): Use in Prophylaxis for *Pneumocystis carinii* Pneumonia in Patients with AIDS Who Were Previously Intolerant to TMP-SMZ. Clinical Infectious Disease **1995**;20:849-53.
8. Finegold I. Oral desensitization to trimethoprim-sulfamethoxazole in a patient with acquired immunodeficiency syndrome. J Allergy Clin Immunol **1996**;nov: 905-8.
9. Absar N., Daneshvar H., Beall G. Desensitization to trimethoprim e /sulfamethoxazole in HIV-infected patients. J Allergy Clin Immunol. **1994**;93(6):1001-5.
10. Cortese L.M., Soucy D.M., Endy T.P. Trimethoprim/ sulfametoxazole desensitization. Ann Pharmacother **1996**;30:184-6.
11. Demonly P., Messaad D., Sahla H., et al. Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. J Allergy Clin Immunol **1998**:1033-6.
12. Bonfanti P., Pusterla L., Parazzini F., et al. The effectiveness of desensitization versus rechallenge treatment in HIV-positive patients with previous hypersensitivity to TMP-SMX: a randomized multicenter study. Biomed Pharmacother **2000**,54:45-9.
13. Brites C., Silva N., Sampaio M.S., et al. Oral desensitization to Sulfonamides in AIDS patients. 31st. Infectious Disease Society of America. Meeting. October, **1993**, New Orleans, LO, USA.
14. Hess D.A., Sisson M.E., Suria H., et al. Cytotoxicity of sulfonamide reactive metabolites: apoptosis and selective toxicity of CD_8^+ cells by the hydroxylamine of sulfamethoxazole. FASEB J **1999**;13(13):1688-98.
15. Gruchalla R.S., Sullivan T.J. Detection of human IgE to sulfamethoxazole by skin testing with sulfamethoxazoyl-poly-L-tyrosine. J Allergy Clin Immunol **1991**;88(5):784-92.