

Trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients: Long-term follow-up regarding efficacy and safety

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Trimethoprim-sulfamethoxazole (TMP-SMX or cotrimoxazole) is the best available therapeutic choice for prophylaxis of *Pneumocystis carinii* infection in HIV-infected patients,¹ but hypersensitivity reactions to TMP-SMX are 10 to 50 times more frequent² and usually necessitate drug discontinuation. Tolerance induction to TMP-SMX is often, but not always,³ carried out, and we recently published a rapid-onset protocol that was found to be safe and effective.⁴

Abbreviations used

SMX: Sulfamethoxazole
TMP: Trimethoprim

One of the problems with such tolerance induction protocols is that the long-term effect is very seldom reported. We have therefore performed a 1-year follow-up for patients who were submitted to a 6-hour protocol of TMP-SMX tolerance induction, as previously described.⁴ Forty-four consecutive HIV-infected patients with documented TMP-SMX hypersensitivity ingested 12 doses of increasing amounts of TMP-SMX at half-hour intervals. Thereafter, they took 80/400 mg TMP-SMX daily and were advised to "treat through" every nonbullous cutaneous adverse reaction with 10 mg of cetirizine daily and to immediately interrupt TMP-SMX if skin blistering or mucosal involvement would appear. All 44 patients tolerated the procedure without any

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TABLE I. Characteristics of the 44 patients with at least 1 year of follow-up after TMP-SMX tolerance induction

	No. of patients	Sex (M/F)	Age (y)	CDC stages							CD4 ⁺ lymphocyte count (per cubic millimeter)	Viral loads (copies per millimeter)	Anti-HIV treatments			
				A3	B1	B2	B3	C1	C2	C3			ART only	AP only	ART + AP	None
n	44	33/11		1	1	7	2	4	11	18			7	4	31	2
Median			36.5								171.0	19400				
25th percentile			34.5								101.5	1500				
75th percentile			43.5								308.0	117,492				

CDC, Centers for Disease Control and Prevention; AP, anti-HIV proteases; ART, anti-HIV reverse transcriptases.

adverse reactions during the day of challenge. Eleven of 44 experienced mild hypersensitivity reactions on days 1 to 2 (8 patients) and days 8 to 15 (3 patients), consisting mainly of a 1-day pruritic maculopapular eruption that was rarely associated with mild fever and conjunctivitis. Two patients stopped TMP-SMX at day 1 and two at day 10 and 15, giving an overall success rate at 1 month of 91% (40/44). Two were successfully rechallenged later on, giving an overall success rate of 95% (42/44). Although there are some case reports of life-threatening reactions during TMP-SMX graded challenge,⁵ in this study we did not observe any such reactions. From the literature, we cannot create a clear picture of the incidence of such life-threatening reactions during this procedure. In our 44-patient cohort, all individuals who tolerated TMP-SMX 1 month after tolerance induction still tolerate it, and all have undergone more than 1 year of follow-up (median, 21.0 months; 25th-75th percentiles, 18.0-25.5 months) without adverse drug reactions to TMP-SMX. Four patients stopped their *Pneumocystis carinii* prophylaxis without any particular reasons. No cases of *P carinii*-induced pneumonia have occurred so far. At the time of the tolerance induction, the patient population was heterogeneous in terms of CD4 counts, viral loads, Centers for Disease Control and Prevention stages, and associated treatments (Table I), which therefore do not seem to influence the outcome of a rapid-onset TMP-SMX tolerance-induction protocol.

Thus TMP-SMX tolerance induction in HIV-infected patients who cannot tolerate this drug is better than that for the other currently available drugs for *P carinii*-induced pneumonia prophylaxis regarding both

efficacy and safety. They include aerosolized pentamidine, dapsone, and atovaquone, which are often more expensive, difficult to use in some patients, less effective, and associated with other serious toxicity.¹ Indeed, in a recent, multicenter, randomized study comparing daily atovaquone with daily dapsone in 852 TMP-SMX-intolerant HIV-infected patients for a median follow-up period of 22 months (similar to ours), the authors were unsatisfied and asked for better options. This was because in both arms around one fourth of the patients had *P carinii*-induced pneumonia (none in this study), and one fourth experienced drug intolerance, leading to drug discontinuation.³ Tolerance induction is therefore a better option. Moreover, a 6-hour TMP-SMX tolerance-induction protocol allows close supervision, good compliance and education, and long-lasting efficacy.

REFERENCES

1. Ioannidis JPA, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of *Pneumocystis carinii* prophylactic regimens. Arch Intern Med 1996;156:177-88.
2. Coopman SA, Johnson RA, Platt R, Stem RS. Cutaneous disease and drug reactions in HIV infection. N Engl J Med 1993;328:1670-4.
3. Al-Sadr WM, Murphy RL, McCabe Yurik T, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. N Engl J Med 1998;339:1889-95.
4. Demoly P, Messaad D, Sahla H, et al. Six-hour trimethoprim-sulfamethoxazole graded challenge in HIV-infected patients. J Allergy Clin Immunol 1998;102:1033-6.
5. Caumes E, Guernonprez G, Katlama C, Bricaire F. A life-threatening adverse reaction during trimethoprim-sulfamethoxazole desensitization in a previously hypersensitive patient infected with human immunodeficiency virus. Clin Infect Dis 1996;23:1313-4.