Rapid publication

Six-hour trimethoprim-sulfamethoxazole–graded challenge in HIV-infected patients

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Background: Hypersensitivity reactions to trimethoprim-sulfamethoxazole (TMP-SMX) are very common in HIV-infected patients, leading to drug discontinuation. However, it is the drug of choice as prophylaxis for *Pneumocystis carinii* pneumonia.
Objectives: We sought to determine the safety and long-term efficacy of a 6-hour TMP-SMX–graded challenge in a group of hypersensitive HIV-infected patients.
Methods: Forty-four consecutive HIV-infected patients with documented TMP-SMX hypersensitivity were seen in our outpatient allergy department. They 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.
Results: All 44 patients tolerated the procedure without any adverse reactions during the day of challenge. Eleven of the 44 patients experienced mild hypersensitivity reactions on days 1 to 2 (8 patients) and 8 to 10 (3 patients), consisting mainly on a 1-day pruritic maculopapular eruption. Two patients stopped TMP-SMX at day 1, and 2 stopped it at days 10 and 15, giving an overall success rate at 1 month of 91% (40 of 44). Two were successfully rechallenged late. After a median follow-up of 10 months, 42 patients were taking TMP-SMX without any adverse reaction, giving an overall success rate of 95%.
Conclusions: A 6-hour graded challenge with cautious "treating through" of mild reactions enables more patients to take TMP-SMX and is safe and effective. (J Allergy Clin Immunol 1998;102:1033-6.)

Key words: *Trimethoprim-sulfamethoxazole, cotrimoxazole, desensitization, graded challenge, HIV, tolerance, hypersensitivity*

Abbreviation used
TMP-SMX: Trimethoprim-sulfamethoxazole

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 frequent in these patients than in other patients[2] and usually necessitate drug discontinuation. The majority of these reactions, however, are moderate and limited to pruritic maculopapular eruptions and fever, although anaphylaxis, cytopenia (neutropenia, thrombocytopenia), transaminase elevations, Stevens-Johnson syndrome, and toxic epidermal necrolysis are rare occurrences.[2] The other currently available drugs for *Pneumocystis* pneumonia prophylaxis, including aerosolized pentamidine, dapsone, and atovaquone, are often more expensive, difficult to use in some patients, less effective, and may be associated with other serious toxicity.[1]

Given the advantages of TMP-SMX, protocols of graded challenge (or "desensitization") have been introduced to enable more patients to tolerate TMP-SMX (Table I),[3-14] and these protocols range in total duration time from 4 hours[7,12] to 26 days.[3] Tolerance can usually be induced safely, with an overall success rate varying from 33%[5] to 100%.[11] However, most of these protocols are either complex and require numerous doses or need a long-term induction phase.

In this report we prospectively studied the safety and efficacy of a 6-hour protocol in 44 TMP-SMX–hypersensitive HIV-infected patients.

METHODS

Patient selection

Forty-four consecutive TMP-SMX–hypersensitive HIV-infected patients were referred by the 2 AIDS Units of Montpellier University Hospital. They were 11 women and 33 men, with a median age of 36 years (25th to 75th percentiles, 34 to 43 years). They were treated with aerosolized pentamidine (32), dapsone (6), or atovaquone (4) for primary (34) or secondary (10) prevention of *Pneu-*

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TABLE I. Protocols of oral graded challenge for TMP-SMX–hypersensitive HIV-infected patients published in peer-reviewed journals and enrolling at least 10 patients

References	No of patients	Starting dose TMP-SMX	Increments (time/dose)	No of doses	Total duration
Absar (1994)[4]	28	0.4/2 mg	24 hrs	10	10 days
Bachmeyer (1995)[5]	12	0.2/1 mg	3 hrs	?	2 days
Bissuel (1995)[6]	20	9 cHx2/day,			10 days,
		15 cHx2/day	—	40	10 days
Gluckstein (1995)[7]	22	4/20 μg	1 hr/10×	6	4 hrs
Nguyen (1995)[8]	45	10 ng	15 min	40	36 hrs
			at start		
Picketty (1995)[9]	21	0.4/2 mg	24 hrs/2×	5	5 days
Belchi-Hernandez (1996)[10]	33	0.2/1 mg	12 hrs/2×	10	10 days
Kalanadhabhatta (1996)[11]	13	4/20 ng	15-120 min/2×	37	24 hrs
Rich (1997)[13]	22	44/220 ng	24 hrs/10×	8	8 days
Caumes (1997)[14]	48	0.8 mg/4 mg	2-4 hrs	7	2 days
Our protocol (1998)	44	0.2/1 μg	30 min/3×	12	5 hrs 30 min

*An *early event* is defined as a hypersensitivity reaction during the challenge procedure. It is defined as severe when the protocol was stopped because of this event.
cH, Centesimal Hahnemannian; *×2*, twice daily

TABLE II. One-day TMP-SMX–graded challenge*

Dose	TMP-SMX (μg)	Dose	TMP-SMX (mg)
1	1/0.2	7	1/0.2
2	3/0.6	8	3/0.6
3	9/1.8	9	9/1.8
4	30/6	10	30/6
5	90/18	11	90/18
6	300/60	12	300/60

*Twelve doses were prepared from the pediatric solution and given orally at half-hour intervals.

mocystis pneumonia. They had a clear history of hypersensitivity with pruritus (11), maculopapular eruption (39), and fever (13) a few days after starting TMP-SMX. These reactions were severe enough to necessitate discontinuation of TMP-SMX. None of them had a history of anaphylaxis or of skin blistering or mucosal involvement. Rechallenge procedures with the full dose of TMP-SMX were performed in every patient. They were also treated with conventional triple combination therapy, including HIV reverse transcriptase inhibitors (40) and HIV protease inhibitors (33).

Oral graded challenge

Protocol was started at least 1 month after the original TMP-SMX hypersensitivity reaction, without any premedication. Twelve doses of the drug were prepared the day of the challenge from the pediatric solution (containing 8/40 mg/mL TMP-SMX) and given orally at half-hour intervals (Table II). These were followed from day 2 by TMP-SMX 80/400 mg once daily. Patients were advised in great detail to "treat through" nonbullous cutaneous adverse reactions with cetirizine 10 mg daily and to interrupt immediately TMP-SMX if skin blistering or mucosal involvement appeared. They were then followed up by phone twice a week for the first month and then monthly thereafter. In addition, they were seen at bimonthly intervals at the AIDS Units of Montpellier University Hospital.

RESULTS

Median time interval from the original TMP-SMX reaction was 22 months (25th to 75th percentiles, 7 to 36 months). All 44 patients tolerated the procedure without any adverse reactions during the day of challenge. Eleven of the 44 patients experienced mild hypersensitivity reactions on days 1 to 2 (8 patients) and 8 to 10 (3 patients), consisting mainly of pruritic maculopapular eruptions. One patient had urticaria, and 2 patients had conjunctivitis also. Two patients stopped TMP-SMX at day 1, and 2 stopped it at days 10 and 15, giving an overall success rate at 1 month of 91%. Among those 4 failures, 2 patients fully complied with instructions to take cetirizine, without stopping TMP-SMX, in the event of developing a rash. They had to stop TMP-SMX because of the persistence of the symptomatology more than 8 days after a trial of cetirizine 10 mg daily to which they rapidly added prednisolone 40 mg daily. Ten and 15 months later, respectively, they were rechallenged with a 10-day protocol adapted from Belchi-Hernandez et al,[10] with one success (now receiving TMP-SMX for 5 months) and 1 failure at day 9 (now receiving aerosolized pentamidine). Two other patients refused to "treat through" the mild maculopapular eruption with fever that they experienced at day 10. One agreed to be rechallenged 7 months later, with a successful trial and 9 months of follow-up, and 1 refused. Thus only 2 patients could not tolerate TMP-SMX, and after a median follow-up of 10 months (25th to 75th percentiles, 7 to 16 months), 42 patients were taking TMP-SMX (at least 80/400 mg daily) without any adverse reaction, giving an overall success rate of 95%. Five patients doubled the amount of TMP-SMX (at 160/800 mg) later.

Final dose TMP-SMX	Premedication	Early events (severe)*	Late reaction (time)	Overall success	
				Rate (%)	Follow-up
160/800 mg	None	1 (1)	9 (3-33 wks)	12/28 (43)	2-81 wks
80/400 mg	None	4 (0)	4 (1st mo)	4/12 (33)	5.8-12.5 mos
80/400 mg	None	6 (0)	1 (3 mos)	13/20 (65)	2-10 mos
160/800 mg	None	3 (3)	3 (2 wks)	15/22 (68)	2-41 mos
160/800 mg	None	0	—	27/45 (60)	4-16 mos
80/400 mg	None	0	1 (13 days)	20/21 (95)	1-14 mos
160/800 mg	None	22 (3)	0	25/33 (76)	3 mos
160/800 mg	None	0	0	13/13 (100)	4-84 wks
160/800 mg	None	8 (3)	0	12/15 (80)	16.5 mos
80/400 mg	Dexchlorpheniramine	8 (1)	3 (9, 11, 90 days)	37/48 (77)	16 mos
80/400 mg	None	0	11 (before day 10)	42/44 (95)	1-21 mos

DISCUSSION

The results of this study confirm the safety and efficacy of TMP-SMX–graded challenge in hypersensitive HIV-infected patients. The success rate of 95% compares favorably with the literature (Table I).[9,11] Considering the superiority of TMP-SMX in the prophylaxis of *Pneumocystis carinii* infection,[2] HIV-infected patients hypersensitive to this drug should cautiously be challenged gradually. A 6-hour protocol should allow close supervision, good compliance, and education to overcome the frequent (25% in our case) but mild (milder and of shorter duration that the original reactions) hypersensitive reactions these patients experienced after challenge.

The desensitization procedure consists of the incremental administration of TMP-SMX. Neither the exact mechanism of TMP-SMX hypersensitivity nor the effect of desensitization are understood. Desensitization implies an IgE mechanism, which is not established for sulfonamide hypersensitivity, and *graded challenge*, *test dosing*, or *tolerance induction* are preferable terms rather than *desensitization*, despite the fact that this term is widely used.[3-14]

The high success rate (95%) of our 6-hour graded challenge protocol in a large cohort of 44 HIV-infected patients is among the best success rates recorded (Table I).[9,11] Only 1 of these studies was carried out over a 24-hour period, but with a complicated buildup phase of 3 steps and 37 doses.[11] Two other protocols achieved cumulative maintenance dose within 4 hours[7,12] with lower success rates (40%[12] to 68%[7]) than ours. Protocols with success rates of less than 60% are not dramatically different from the former protocols (Table I).[4,5,8,12] However, the handling of the mild hypersensitivity reactions that may occur thereafter is different. Indeed, in all 4 papers TMP-SMX was stopped as soon as even very mild hypersensitivity reactions occurred, with no "treating through" trial. We and others[13] have demonstrated that cautious "treating through" is not only feasible but also allows more patients to tolerate TMP-SMX. Although there are reports of life-threatening reactions during TMP-SMX graded challenge,[15] in this study we did not observe any, but a larger number of patients may be needed to definitively rule out such severe reactions.

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Correction

The following correction applies to the article by Ledford et al entitled “Osteoporosis in the corticosteroid-treated patient with asthma,” which appeared in volume 102, number 6, pp 353-362 of The Journal.

The first sentence of the legend for Fig 2, A, mistakenly identifies the biopsy specimen as being “. . . from a normal 1-year-old boy.” The sentence should read that the specimen is “. . . from a normal 44-year-old man.”