

A 5-day course of oral desensitization to trimethoprim/sulfamethoxazole (T/S) in patients with human immunodeficiency virus type-1 infection who were previously intolerant to T/S

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Background: Trimethoprim/sulfamethoxazole (T/S) is an essential drug in patients with human immunodeficiency virus type-1 (HIV-1) infection to prevent opportunistic infections. About 40% to 60% of them develop skin rash which leads to discontinue the medication. A precise mechanism of the reaction is not known.

Objective: To make the patients more tolerable to the medication and to make clear whether or not the reaction is caused by serum sulfamethoxazole-specific IgE.

Methods: We established a 5-day protocol, in which T/S was administered orally as a granular form in increasing doses beginning with 0.005 g (it contains trimethoprim 0.4 mg and sulfamethoxazole 2 mg) and doubled every 12 hours until the therapeutic dose was achieved. We tried to desensitize T/S in 17 patients with HIV-1 infection who were previously intolerant to T/S and measured the specific IgE in sera.

Results: Desensitization was successfully completed in 15 (88.2%) of the patients. In two patients who failed the desensitization, one was due to fever and the other was gastric irritation. During followup in a mean period of 16.6 months (range, 8 to 23 months) as of May, 1999, none has had *Pneumocystis carinii* pneumonia (PCP) while receiving T/S after desensitization. Sulfamethoxazole-specific IgE did not increase, indicating that it was not the major cause of skin rash due to T/S in our cases.

Conclusion: These preliminary results show that most patients who were thought to be intolerant to T/S and had no sulfamethoxazole-specific IgE can be safely desensitized and received the drug subsequently as an effective prophylaxis for PCP.

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INTRODUCTION

Pneumocystis carinii pneumonia (PCP) is one of the most common life-threatening opportunistic infections in patients with human immunodeficiency virus type-1 (HIV-1) infection.¹⁻⁴ In recent guidelines for the prevention of opportunistic infection,

prophylaxis with trimethoprim/sulfamethoxazole (T/S) for PCP is strongly recommended to the patients whose CD4 counts are below 200/ μ L because it is very effective in both clinically and costly.²⁻⁶ Furthermore, it also provides protection against toxoplasmic encephalitis, isosporiasis, and bacterial infections.⁴⁻⁷ A high incidence of adverse reactions including skin rash, fever, leukopenia, and gastrointestinal irritation is the relevant clinical problem especially in patients with HIV-1 infection.^{1,2,4} For example, the incidence of cutaneous reactions to T/S is 3.3% in non HIV-1-infected patients but 40% to 60% in HIV-1-infected patients.⁸⁻¹² Furthermore, the skin reac-

tion is very severe in some cases.¹³ An aerosolized or intravenous pentamidine has been, so far, used in Japan as an alternative for prophylaxis.

Although the mechanism of increased frequency of skin rash or allergy to T/S in HIV-1-infected patients is unknown, several reports have appeared demonstrating successful desensitization with incremental doses of T/S.⁸⁻¹² Each protocol has been different in each hospital, small numbers of patients have been studied, and long-term use of T/S for the prophylaxis has been limited. Thus, the standard protocol has not been confirmed yet.

Before starting this study, we decided that patients should be hospitalized during desensitization to avoid unexpected severe reactions such as toxic epidermal necrolysis we had experienced before,¹³ anaphylactic shock,^{14,15} delayed hematologic toxicity,¹⁶ and myocardial infarction.¹⁷ Then, we referred to several reported protocols including the fastest one (completed within 5 hours) and the longest (more than 10 days). Among them, we modified a 5-day course of protocol because of the higher success rate and the permitted period of hospitalization. In this paper, we report that our 5-day course of desensitization to T/S is both safe and successful, and allows subsequent use for the prophylaxis.

PATIENTS AND METHODS

Patients

A total of 17 Japanese patients with HIV-1 infection participated in this desensitization study. Informed consent was obtained from the patients. They

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were basically admitted and performed the desensitization under close observation. All of them had histories of one or more adverse reactions to T/S. There are about 400 HIV-1-infected-patients who were receiving comprehensive care at the AIDS Clinical Center, International Medical Center of Japan. Among them, 86 patients (about 22%) are receiving T/S for the prophylaxis of PCP. Participants in this study had histories of adverse reactions to T/S.

Protocol of Desensitization

A desensitization protocol is listed in Table 1. We used the granular form of T/S preparation (Shionogi & Co, Ltd, Osaka, Japan) in this study because the first dose of T/S in this protocol was as little as 0.005 g, which was equivalent to 1/200 T/S tablet. Uniformity of the granule was endorsed by the pharmaceutical company. An aliquot of T/S granule was prepared freshly in the morning at the each day. We administered 0.005 g (trimethoprim, 0.4 mg and sulfamethoxazole, 2 mg) of the aliquot as the first dose in the morning. Vital signs were monitored at the beginning, 30 minutes, 1 hour, and 2 hours later. If no adverse reactions appeared, we doubled the dose every 12 hours and reached the dose of one tablet (trimethoprim, 80 mg and sulfamethoxazole, 400 mg) at the morning of the day 5. If mild adverse reactions (including low grade fever and/or mild

cutaneous rash) appeared, we stayed the last dose until the reactions have gone and then restarted to double the dose. After completion of the desensitization, patients were put on the standard T/S oral prophylaxis for PCP. No patient had received an antihistamine or adrenal corticosteroids during the desensitization in this study.

Measurement of Sulfamethoxazole-Specific IgE in Sera

Serum sulfamethoxazole-specific IgE level was measured by a fluorometric enzyme-linked immunosorbent assay. Briefly, sulfamethoxazole (Shionogi & Co, Ltd) was conjugated with serum albumin of guinea pigs (Sigma Chemical Co, St. Louis, MO, USA) with glutaraldehyde and purified by gel filtration. A 96-well microplate (Black Clini-Plate; Labsystems, Helsinki, Finland) was coated with sulfamethoxazole conjugate, then blocked with skim milk (Block Ace; Snow brand, Hokkaido, Japan) and kept at 4°C until use. Patients' sera were diluted from 1:5 to 1:125 and incubated in each well of the plate at 4°C for over night. After washing the plate, rabbit anti-human IgE antibodies conjugated with β -D-galactosidase (Pharmacia & Upjohn, Sweden) was added and incubated at room temperature for 3 hours. The plate was washed again and stayed for 20 to 60 minutes at room temperature after adding the substrate, 4-methylumbelliferyl- β -D-galactoside (Sigma, USA). The fluorescence unit was measured by a fluorometric microplate reader (Wallac1420 Arvo-Sx, Pharmacia, Sweden) at Ex 355 nm/Em 460 nm. Serum specimen obtained from an HIV-1-infected patient who has had toxic epidermal necrolysis (TEN) by pyrimethamine-sulfadoxin was also assayed as a reference sample.

RESULTS

Baseline demographics of 17 study subjects are noted in Table 2. Mean CD4 counts at desensitization to T/S were 152/ μ L (range; 2 to 590/ μ L). Fourteen patients (82.3%) received the combination therapy with two or three antiviral drugs. Although CD4 counts

of the two patients at the desensitization were over 200/ μ L because of the effective antiretroviral therapy, CD4 counts at nadir were below 200/ μ L in all patients. All patients except two were desensitized as an inpatient but the remaining two were desensitized as an outpatient due to their personal reason.

Allergic reactions to T/S appeared at varying intervals and were not predictable. The most common reaction reported by their histories was the generalized skin rash (Table 3). Some patients had the rash accompanied with fever. Four patients developed reactions during the treatment for PCP and 13 developed during the prophylaxis. Seven patients have experienced allergic reactions to other kind of drugs as well as T/S. A mean period from the first reaction to the desensitization was 21 months (range, 0 to 60 months) (Table 2). Table 3 shows immediate and long-term outcomes of the desensitization. Fourteen patients were successfully desensitized within 5 days. Among them, nine patients had no adverse reaction during and after the desensitization. Patient no. 16 developed fever during and after the desensitization; however, it was subsided by continuing the prophylaxis. Although patient no. 17 developed mild cutaneous rash on the second day, it was disappeared naturally and the desensitization was completed within 5 days. Two patients underwent the re-desensitization. Patient nos. 3 and 10 developed cutaneous reaction, the former was 4 days and the latter was 2 days after the desensitization while on the prophylaxis. The former was performed the re-desensitization 13 days after the reaction. She developed mild cutaneous eruption on the second day; however, it was successfully completed within 5 days. She is on the prophylaxis for 13 months until now. The latter had continued the prophylaxis, because the eruption has gone. The same reaction developed 10 months later. Re-desensitization was successfully completed within 5 days without any problems. Two patients no. 4 and 15, had skin rash during the desensitization. The

Table 1. Protocol for a 5-Day Course of Oral Desensitization to Trimethoprim/Sulfamethoxazole (T/S)

Day	Dose of T/S (g)	
	Morning	Evening
1	0.005	0.01
2	0.02	0.04
3	0.1	0.2
4	0.4	0.8
5	1	1

A granular form of T/S was used in this study. One gram of the granule contains 80 mg of trimethoprim and 400 mg of sulfamethoxazole, which is equivalent to one tablet of T/S. A starting dose (0.005 g) would contain 0.4 mg of trimethoprim and 2 mg of sulfamethoxazole.

Table 2. Baseline Characteristics of 17 Subjects Participating in this Study

Characteristics	No. of Patients (n = 17)
Age (y)	33 (range; 18–63)
Sex	
Male	15 (88%)
Female	2 (12%)
Risk factor	
Homosexual	5 (29%)
Heterosexual	5 (29%)
Hemophiliac	7 (42%)
CD4 counts (/μL)	152 (range; 2–590)
HIV status at desensitization	
AC	5 (29%)
AIDS	12 (71%)
Allergy to other medication	7 (41%)
Period from the skin rash to desensitization (month)	21 (range; 0–60)

HIV: human immunodeficiency virus, AC: asymptomatic carrier, and AIDS: acquired immunodeficiency syndrome.

former was on the third day and the latter was on the first day. They were successfully desensitized with the modified prolonged doses.

Desensitization failed in two. Patient no. 1 developed fever of 37.6°C on the second day of the desensitization and it lasted for 17 days. Re-desensitization was performed 2 months later, which failed due to the relapse of fever. Patient no. 2 was successful with this protocol, but discontinued T/S because of gastric irritation 1 month after the desensitization. A total of 15 patients completed the procedure and continued taking T/S (Table 3). Up to now, a mean followup period was 16.6 months (range, 8 to 23 months).

So far, some investigators have suggested that sulfamethoxazole-specific IgE antibodies are possibly involved in the hypersensitive reaction to T/S.^{18–20} We, therefore, measured the specific IgE levels in HIV-1-infected patients' sera. There was no significant difference between the levels in patients who developed the hypersensitive reaction and those who did not. In this assay, a reference serum from an HIV patient with TEN by sulfa complex showed a higher level of the specific IgE, although it is unclear whether TEN is IgE-mediated. Furthermore, there was also no significant difference in the specific IgE between those who failed the desensitization and those who succeeded. And finally, in the pa-

tients who were successful with desensitization, no significant changes in the IgE level were observed during the desensitization (data not shown).

DISCUSSION

Despite advantages offered by T/S, there is the high incidence of adverse reactions, particularly in patients with HIV-1 infection. The mechanism of hypersensitivity to T/S is poorly understood. Positive skin tests for a diluted T/S solution were reported by White et al¹⁸ suggesting involvement of IgE.

Gruchalla and Sullivan have recently developed a skin test which detects IgE antibodies to a sulfonamide determinant.¹⁹ Some reactions to sulfonamides may be mediated by IgE directed to the 5-methyl-3 isoxzoyl group of the sulfamethoxazole molecule.²⁰ Those patients with detectable levels of the IgE often have urticaria or anaphylactic reactions. Adverse reactions in our cases initially occurred several days after starting T/S without the classic presentations of such IgE-mediated reactions. Our experiments might also support that the sulfamethoxazole-specific IgE is not, at least, the major cause of the hypersensitive reaction in our cases. It is possible that the generation of toxic intermediate hydroxylamine metabolites causing cell toxicity and liberating cytokines (such as IL-1, IL-6 and histamine) might explain the patients' symptoms.²⁰

In addition, the reason why the desensitization can be done is not well explained. Hughes and colleagues have shown that the success rate decreased if the desensitization process was started with a higher dose.²¹ Juan et al reported that increasing doses of T/S can alter a regulating mechanism of the immune system.⁸ Furthermore, another author hypothesized that oral

Table 3. Immediate and Long-Term Outcomes of the Desensitization

Pt #	Prior Reaction Other than Rash	Duration (day) of Desensitization	Reaction at Desensitization	Followup Period (month)
1	fever	17	fever	discontinued
2	—	5	gastric irritation	discontinued
3*	—	5*/5	rash*/none	14
4	—	17	rash	21
5	—	5	none	17
6	—	5	none	23
7	—	5	none	18
8	—	5	none	21
9	fever	5	none	18
10	leukopenia†	5/5	rash/none	8
11	—	5	none	19
12	—	5	none	19
13	—	5	none	18
14	fever	5	none	13
15	fever	10	rash	16
16	—	5	fever	13
17	—	5	rash	11

* The first attempt was discontinued due to skin rash.

† The nadir number was 1,380 cells/μL.

tolerance could also be induced by differential production of TGF- β and IL-4.²² We tried the re-desensitization in two patients and it was successful. The success of re-desensitization may give us the further opinion.

Successful oral desensitization of T/S has been reported in the past.^{8-12,18,20-27} Gluckstein et al performed a 5-hour desensitization in 22 patients and 15 patients successfully completed it with a mean followup period of 14 months.²⁴ A 10-day protocol by Juan et al succeeded in 21 out of 34 patients with up to 9 months' observation.⁸ Gilquin et al reported the best result with a 5-day desensitization that had a success rate of 95% (20 out of 21 patients) and 7 months' followup.²⁵ We compared several protocols and have chosen some to modify. Although there are some reports that described severe adverse reactions such as anaphylactic shock,¹³⁻¹⁵ delayed hematologic toxicity,¹⁶ and myocardial infarction,¹⁷ such life threatening reactions did not occur in our cases. Finally, 15 out of 17 patients were successfully desensitized with no evidence of *Pneumocystis carinii* pneumonia during the followup period. This study also revealed that T/S desensitization is safe and effective, and allows sustained administration of T/S to patients needing the agent. In addition, when desensitization fails, re-desensitization might be effective. In conclusion, our 5-day course of desensitization was successful, at least, in patients with HIV-1 infection who were previously intolerant to T/S but had no sulfamethoxazole-specific IgE.

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