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The effectiveness of desensitization versus rechallenge treatment in HIV-positive patients with previous hypersensitivity to TMP-SMX: a randomized multicentric study

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Summary – Our study was undertaken to evaluate if desensitization treatment is more effective than rechallenge in preventing hypersensitivity reactions in HIV-positive patients with previous allergic reactions to TMP-SMX; the secondary aim was to evaluate the frequency of reactions to TMP alone.

This was a randomized, multicentre open study. Patients with previous documented hypersensitivity to TMP-SMX who required primary or secondary PCP prophylaxis were enrolled; subjects who had previously had serious adverse reactions to TMP-SMX were excluded. All eligible patients assumed 200 mg TMP for 14 days and in case of no reactions were randomized for desensitization or rechallenge with TMP-SMX. The patients were then followed up by periodical visits for six months. Seventy-three patients were enrolled; 14 subjects (19%) presented reactions on TMP alone during the pre-enrollment phase. The remaining 59 subjects were randomly assigned to the two treatment groups: 34 carried out desensitization (group 1) and 25 rechallenge (group 2) with TMP-SMX.

Seven patients in group 1 (20.5%) and seven in group 2 (28%) showed hypersensitivity reactions during treatment; this difference was not statistically significant. No serious reaction occurred in either group.

This study showed the comparable effectiveness of the desensitization procedure and rechallenge in patients with a previous, not serious, allergic reaction to TMP-SMX. © 2000 Éditions scientifiques et médicales Elsevier SAS

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Compared to the general population, HIV-infected patients more frequently present hypersensitivity to sulpha drugs, causing remarkable treatment problems in the primary and secondary prophylaxis of infection from *Pneumocystis carinii* and neurotoxoplasmosis.

In order to make the treatment of allergic subjects with TMP-SMX possible, various desensitization procedures have been experimented.

The first experiences go back to 1985–86; however, these were with very limited numbers of subjects, where there was also concomitant therapy with antihistamines or steroids [1, 2]. More recent studies present surveys with larger numbers of subjects who, having carried out desensitization with TMP-SMX, tolerated low-dose treatment with the same drug; the success percentage rate varies from 55 to 75% [3-5].

However, there does not seem to be any rationale concerning desensitization when the reaction is due to mechanisms other than those of type I, according to the Gell and Coombs classification, such as hypersensitive reactions to sulpha drugs in HIV-positive patients for whom a toxic pathogenesis has been hypothesized [6-8].

Along this line Carr et al. studied 31 patients with HIV infection and hypersensitivity to TMP-SMX, submitting them to rechallenge first with only trimethoprim and subsequently, if it was tolerated, with TMP-SMX, achieving success in 42% of cases [9]. At the end of another study in which 60% success was reported after desensitization, Nguyen et al. asked themselves whether such a treatment could produce results significantly superior to simple rechallenge [3].

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The present study, carried out by the CISAI Group, was undertaken to evaluate whether desensitization treatment is more effective than rechallenge in preventing hypersensitivity reactions in HIV-positive patients with a previous allergic reaction to TMP-SMX. The secondary aim of the study was to evaluate the frequency of hypersensitivity reactions to trimethoprim alone.

MATERIALS AND METHODS

This was a randomized, multicentre open study, comparing a desensitization scheme with another rechallenge scheme to TMP-SMX in patients with previous hypersensitivity to the drug. Fifteen Infectious Disease Divisons in northern Italy participated in the study.

Patients

Adult HIV seropositive subjects with a previous hypersensitivity reaction to TMP-SMX and a life expectancy of at least one year observed consecutively at the participating centres were eligible for the study. In order to avoid inclusion of patients with previous reactions which could not be definitely attributed to TMP-SMX, the clinical manifestations diagnosed as hypersensitivity had to have been observed and certified by a physician; patients were evaluated where the reaction was shown by rash and/or fever. In agreement with the guidelines of the CDC in Atlanta, serious reactions such as exfoliative dermatitis, asthma and anaphylactic shock were reasons for exclusion [10].

Because previous studies had shown metabolic variations of the drug in the case of acute infection, the patients had to be asymptomatic at the time of enrollment [11]. As far as concomitant treatment was concerned, all antiretroviral drugs and other prophylaxes already in course were allowed; however, drugs able to mask hypersensitivity reactions, such as antihistamines and/or steroids, were excluded.

The protocol was approved by the Ethical Committees of each participating centre; each patient gave written, informed consent.

Study design

The study took place in three phases:

1) Pre-enrollment phase: the patients had to take 200 mg of trimethoprim for 14 days in order to evaluate whether there was possible hypersensitivity towards this drug. The choice of dosage was made considering the quantity of trimethoprim generally used together with sulphametoxazole in prophylactic treatment. The length of time during which the patients had to take TMP before passing onto the subsequent phase was chosen considering that the average time for hypersensitivity to appear in HIV-positive patients is seven to ten days.

Before beginning treatment with TMP all patients were aerosolized with Pentamidine.

The first dose of TMP was given in hospital with an observation period afterwards of at least eight hours, in order to monitor the appearance of serious reactions.

2) Randomization phase: all patients who had tolerated TMP for 14 days were randomized for either densensitization or rechallenge treatment. Randomization was effected centrally with separate lists for each centre.

The treatment scheme proposed by Nguyen et al. was used for desensitization, which took place in hospital [3].

Rechallenge was carried out by administering a tablet of TMP-SMZ at the dosage commonly used for the prophylaxis dose. Treated patients were kept under observation in hospital for at least eight hours.

3) Follow-up phase: at the end of desensitization or rechallenge treatment, patients who had not shown hypersensitivity reactions began home treatment at the standard dose of 160 mg trimethoprim and 800 mg sulphametoxazole per day.

Control visits were carried out after two, 15 and 30 days, and then once per month for a further five months from the beginning of treatment.

Evaluation parameters

The main evaluation parameter for the effectiveness was the appearance of hypersensitivity reactions in the two groups. Skin symptoms such as exanthema, erythema and urticaria were considered to be hypersensitive reactions as well as fever (if absent before the introduction of the drug and disappearing after its suspension), exfoliative dermatitis and anaphylactic manifestations.

Itching without skin lesions was not considered a reason to suspend the therapy.

Hypersensitivity reactions to trimethoprim were shown in the pre-enrollment phase.

Statistical analysis

The statistical significance of the difference in the frequency of the appearance of hypersensitivity reactions in the two treatment groups was evaluated by means of the chi square test; the eventual imbalance in the general or clinical characteristics of the two groups treated was considered using the Mantel and Haenszel method. The analyses were carried out on the intention-to-treat basis.

Table I. Patients' characteristics at baseline.

	Desensitization (n = *34*)	*Rechallenge* (n = *25*)	*Hypersensitivity to TMP* (n = *14*)
Male/female	22 (65%)/12 (35%)	18 (72%)/7 (28%)	10 (71%)/4 (29%)
Mean age (SD)	35.18 (5.44)	34.84 (5.65)	34.07 (5.73)
Mean CD4 count (cell/μL) (SD)	102 (70)	137 (128)	140 (92)
Risk factors			
– Drug abusers	21 (62%)	13 (52%)	6 (43%)
– Heterosexual	11 (32%)	8 (32%)	6 (43%)
– Homosexual	2 (6%)	3 (12%)	1 (7%)
– Other	–	1 (4%)	1 (7%)
AIDS status			
– AIDS	19 (56%)	14 (56%)	5 (36%)
– Not AIDS	15 (44%)	11 (44%)	9 (64%)
Previous reaction			
– Rash	23 (68%)	16 (64%)	12 (86%)
– Urticaria	6 (17%)	7 (28%)	1 (7%)
– Fever	5 (15%)	2 (8%)	1 (7%)
Interval between previous reaction and treatment (months) (SD)	17.8 months (25.4)	12.6 months (10.6)	7.6 months (8.4)

RESULTS

Enrollment and patient characteristics

Enrollment of patients took place between 1 January and 31 December 1997, and the follow-up period ended on 30 June 1998.

A total of 73 patients entered the study, of whom 14 presented reactions taking only TMP during the pre-enrollment phase. The remaining 59 subjects were randomly assigned to the two treatment groups: 34 carried out desensitization and 25 rechallenge with TMP-SMZ. Patients' characteristics when entering the study are shown in *table I.*

With regard to baseline characteristics, the treatment groups were largely comparable. All selected patients needed primary or secondary prophylaxis for PCP.

In 25 (34.2%) cases, the previous allergic reactions had appeared during treatment for an attack of pneumonia from *Pneumocystis carinii.*

Hypersensitivity reactions

All patients had carried out therapy with 200 mg TMP per day for 15 days; hypersensitivity reactions appeared in 14 cases (19.1%), which in 12 patients presented characteristics which clinically overlapped those seen previously. The median time for reaction appearance was five days (range 1–14). No patients had serious reactions, and hospitalization was not necessary in any case.

In the group of patients randomly assigned to desensitization treatment, seven subjects (20.5%) showed hypersensitivity reactions and had, therefore, already interrupted the treatment; the remaining 27 patients all concluded the follow-up period of six months without presenting events *(figure 1).*

The reactions observed were diffused erythema in five cases, three of them associated with fever; exanthema occurred in two cases and was associated with arthralgia/myalgia in one of them. The median time for the appearance of reactions was one day (range 1–7), but in four cases they were observed in hospital during the desensitization procedure.

In the rechallenge group, events appeared in seven cases (28%), whereas 18 patients (72%) continued the treatment for the six months foreseen by the protocol *(figure 1).* Reactions observed were exanthema in four cases and diffused erythema in three; five patients also had fever. The median time for the appearance of reactions was two days (range 1–90); however, in three subjects the reaction appeared in the first 24 hours.

No serious reaction occurred in either group. In only one patient, treated with desensitization, was hospitalization necessary for 48 hours for erythema accompanied by high fever.

The difference between the frequency of the events in the two groups treated with desensitization and rechallenge was not statistically significant.

There was also no significant difference between patients in the two groups (as regards sex, age, risk factors, modality of previous reaction and CD4+ cells

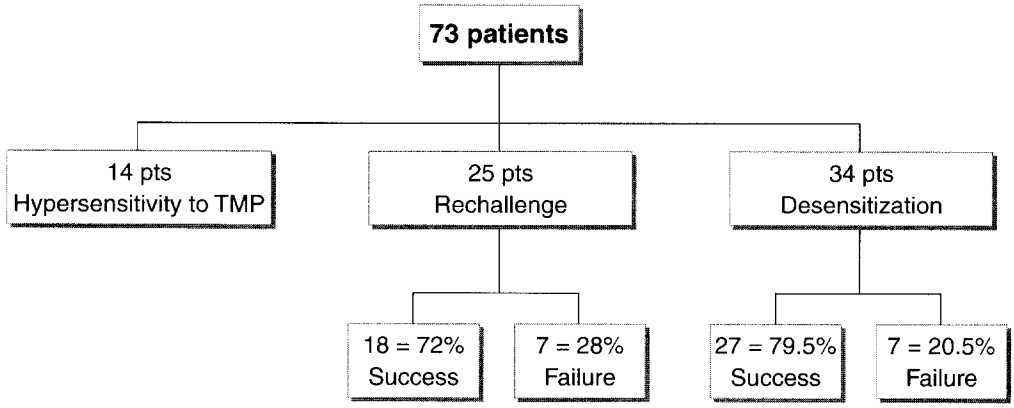

Figure 1. Results.

mean) as to those who tolerated the treatment and those in whom hypersensitivity reappeared (data not shown). No correlation at all was found between the daily dose of the first treatment and rechallenge or desensitization success. The interval of time between the previous reaction and the treatment did not predict the final result.

DISCUSSION

This study showed the comparable effectiveness of the desensitization procedure and rechallenge in patients with a previous, not serious, allergic reaction to TMP-SMX; in fact, desensitization was carried out successfully six months after treatment in approximately 80% of the cases and rechallenge in 68%, and this difference is not statistically significant. A further fact to emerge from this experience was the high frequency of reactions to TMP alone (19%), confirming that already described by Carr, who encountered this phenomenon in 16% of cases. This is relevant in that it allows us to identify patients with hypersensitivity only to TMP, in whom it will still be possible to use sulpha drugs alone. This class of drugs covers an important role in the therapy and prophylaxis of *Toxoplama gondi* infections.

Systemic reactions were not found in any patient and in the majority of cases the clinical manifestation overlapped the previous one. The median time before the reaction appeared in the two groups was similar.

Concerning the possible epidemiologic, biological and clinical factors associated with the success or failure of the two techniques, no difference was observed in the two groups regarding age, sex, risk factors, mean of CD4+ lymphocytes and previous reaction characteristics.

It remains to evaluate the reason why the two treatments have an overlapping possibility of success. One explanation could be found in the pathogenesis of these reactions; this remains unknown, though the toxic-allergic hypothesis gains more and more ground in explaining this phenomenon with the modification of the normal metabolism of the drugs; the increased frequency of the slow acetylator phenotype in these subjects would be proof. It has also been demonstrated in certain studies that the acetylator phenotype may vary in relation to the presence of infection [11-13].

Therefore, it seems possible to hypothesize that it is not the desensitization procedure per se which induces a state of tolerance in the patient, but more the assumption of the drug in clinically and metabolically different conditions to those when the reaction appeared. The success of simple rechallenge confirms this hypothesis, or at least is an indirect demonstration of the absence of an IgE mechanism in which the reaction is repeatable by definition.

Taking into account the results of this study, of the greater simplicity in carrying out rechallenge and the absence of an adequate rationale for the use of desensitization, the authors advise carrying out rechallenge on patients with a previous delayed light-moderate reaction to TMP-SMX who need the prophylaxis.

Bearing in mind the high frequency of reactions to TMP, provocation tests with this drug should be carried out for diagnostic reasons on all patients with previous light-moderate reactions to TMP-SMX.

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