Flare-up of patch test of trimethoprim–sulfamethoxazole (co-trimoxazole) during oral desensitization

Contact Dermatitis 2009: 61: 50–51

S. H. Kardaun[1,*], M. M. de Waard[1,*] and J. G. de Monchy[2]

[1]Department of Dermatology, and [2]Department of Allergology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Key words: AIDS; delayed hypersensitivity; flare-up reaction; HIV; oral desensitization; patch test; trimethoprim–sulfamethoxazole (co-trimoxazole).

We report a flare-up reaction on earlier patch test sites of trimethoprim–sulfamethoxazole (co-trimoxazole) during oral desensitization with this drug. Similar local flare-up reactions have been described in contact dermatitis, but to the best of our knowledge, they have not yet been reported for systemically administered drugs.

Case Report

A 36-year-old HIV-positive male developed an itchy maculopapular rash with fever (>39°C), 11 days after starting trimethoprim–sulfamethoxazole 960 mg daily for pneumocystis carinii pneumonia prophylaxis (CD4 lymphocyte count 74 × 10^9/l). At the time of the rash, and in the weeks before, he had not used any other medication. Trimethoprim–sulfamethoxazole was replaced by pentamidine inhalations, and the rash and fever disappeared within a week.

Two months later, highly active antiretroviral therapy (HAART) was started with good response and without complications. One year later, the patient was referred for evaluation of the reaction.

The patient had never used trimethoprim–sulfamethoxazole prior to the above. Two months before the rash started, he applied topical silver sulfadiazine without adverse effects. Patch testing with trimethoprim–sulfamethoxazole 10% (pure substance) and 30% (commercial preparation) in pet. resulted in a doubtful positive reaction; silver sulfadiazine cream 10 mg/ml and the European baseline series were negative.

One week later, retesting trimethoprim–sulfamethoxazole in duplicate on two different sites gave negative results. Subsequent in-patient oral desensitization with trimethoprim–sulfamethoxazole was attempted (Table 1). On D3, a few hours after the last desensitization step at a dose of 480 mg, he developed fever (38.3°C), a non-itchy flare-up of all six previous trimethoprim–sulfamethoxazole patch test sites, and a slightly increased CRP (18 mg/l, normal <5 mg/l) and eosinophilia (6.7%, normal <3%). On continuation of the therapeutic dose of trimethoprim–sulfamethoxazole (480 mg/day with a CD4 lymphocyte count between 100–200 × 10^9/l), the fever and the flare-up reactions disappeared within 1 week.

Discussion

Opportunistic infections, such as pneumocystis carinii pneumonia, constitute a major problem in patients with HIV/AIDS for which sulfonamides like trimethoprim–sulfamethoxazole are the first choice for treatment and prophylaxis. Unfortunately, HIV/AIDS patients also have an increased risk of cutaneous adverse drug reactions to trimethoprim–sulfamethoxazole (1, 2). These are often due to a type 4 delayed-type hypersensitivity reaction, presenting with a maculopapular rash and fever, 7–14 days after initiation of the drug, although severe cutaneous adverse drug reactions like Stevens–Johnson syndrome/toxic epidermal necrolysis or a drug-induced multi-organ syndrome (DRESS) may develop (3, 4).

In HIV and AIDS, a shift from Th1 to Th2 cytokine profile can be observed; during HAART, this shift may be partly reversed. Adverse drug reactions related to Th2 cytokines thus could be expected (e.g. urticaria and anaphylaxis). Somewhat unexpectedly, many HIV-infected patients also show delayed-type hypersensitivity reactions (e.g. maculopapular rash and DRESS). The relative preponderance of CD8 cells over CD4 cells in HIV and AIDS could be relevant because CD8 cells have been implied as effector cells in some drug reactions (5). In the abacavir hypersensitivity syndrome, a direct role for human leucocyte antigen-B*5701-restricted CD8+T cells was shown (6). Although delayed-type hypersensitivity

Table 1. Desensitization schedule

D1, suspension trimethoprim–sulfamethoxazole 48 mg/ml, diluted 1:10	
9.00 hours	1 ml
11.00 hours	2 ml
13.00 hours	5 ml
17.00 hours	10 ml
D2, suspension trimethoprim–sulfamethoxazole 48 mg/ml, undiluted	
9.00 hours	2 ml
15.00 hours	4 ml
21.00 hours	5 ml
D3, tablet trimethoprim–sulfamethoxazole 480 mg	
9.00 hours	1 tablet

*These two authors contributed equally to this work.

reactions are mainly Th1 driven, Th2 and regulatory cytokines are also involved in these reactions (7). We assume that the generally increased risk of adverse drug reactions in these patients could be related to changes in regulatory T cells and cytokines. Initial studies indeed showed functional deficiencies in spite of increased numbers of regulatory T cells with progressive disease; recent studies, however, have not confirmed these observations (8). Thus, the immunological basis of the increased rate of adverse drug reactions in HIV and AIDS is not yet fully understood. Moreover, (subclinical) viral infections and drug interactions may further complicate the analysis of such events.

Possible solutions when a reaction has occurred include continuation of treatment with antihistamines and steroids, a switch to an alternative drug or to stop and restart through desensitization or full dose. Although not yet fully proven, desensitization appears to result in fewer treatment discontinuations and adverse reactions compared with a stop and restart at full dose (1, 2). Generally, patch tests are regarded safe for determining the culprit in cutaneous adverse drug reactions, and they are positive in 32–50% (9).

In contact dermatitis, flare-up reactions of earlier patch test sites have been described for nickel and gold after systemic provocation (10, 11). To the best of our knowledge, these reactions have not been reported in cutaneous adverse drug reactions.

In allergic contact dermatitis, resident CD4+CCR10+ T cells can still be detected in clinically normal skin on patch test sites 3 weeks after testing (12). Persistent local CD4+CCR10+ T cells may possibly be triggered by later allergen ingestion, resulting in a flare-up. Moreover, in flare-ups of nickel patch tests, activation of local memory function seems to be inversely related to the period until reactivation (10).

In our case, all six sites earlier tested with trimethoprim–sulfamethoxazole showed a clear flare-up reaction at provocation, possibly reflecting the presence of local memory in the skin. Restriction of the clinical reaction to earlier tested skin could be explained by the long interval between the original reaction and desensitization, compared with the short interval between patch testing and desensitization.

Conclusion

We report a flare-up of previous patch test sites after oral desensitization with trimethoprim–sulfamethoxazole, suggesting persistent local memory after patch testing.

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Address:
Sylvia H. Kardaun MD
Department of Dermatology
University Medical Center Groningen
Hanzeplein 1
9713 GZ Groningen
The Netherlands
e-mail: s.h.kardaun@derm.umcg.nl