

Induction of tolerance in a patient with a history of exfoliative dermatitis to trimethoprim-sulfamethoxazole

Induction of drug tolerance can be considered in patients with immunoglobulin E (IgE)-mediated drug hypersensitivity when there are no acceptable alternative drugs. Induction of tolerance can also be considered in select non-IgE-mediated reactions. Protocols for induction of tolerance have been successful in human immunodeficiency virus (HIV)-positive patients with non-IgE-mediated mild cutaneous reactions to trimethoprim-sulfamethoxazole (TMP-SMX).^{1,2} In patients who are not HIV positive, the standard of care for drug-induced erythroderma is avoidance of the offending agent. Additionally, serious non-IgE mediated reactions such as exfoliative dermatitis or toxic epidermal necrolysis are considered a contraindication to graded drug challenge or induction of tolerance.³ We describe successful induction of tolerance in an HIV-negative patient with a history of exfoliative dermatitis to TMP-SMX.

A 53-year-old woman with a history of psoriatic arthritis presented for worsening left wrist pain. She had a history of severe steroid-induced osteoporosis, bilateral total knee arthroplasty, right total hip arthroplasty, cervical spine fusions, lumbar spine fusions, and recurrent methicillin-resistant staphylococcus aureus (MRSA) infections. One month before presentation, she was diagnosed with MRSA septic arthritis of the native left wrist and prosthetic right knee and underwent debridement and resection of the prosthetic knee, with temporary antibiotic spacer placement. Cultures grew MRSA that was susceptible to vancomycin, linezolid, and TMP-SMX. She was started on 6 weeks of vancomycin intravenously. Given the patient's history of recurrent septic arthritis, the patient was subsequently started on TMP-SMX for chronic suppressive therapy. On day 2 of TMP-SMX, the patient developed an erythematous and pruritic rash that peeled. The face, arms, and trunk were involved. The patient also reported a fever. There were no vesicles, bullae, or mucosal lesions. She was diagnosed with exfoliative dermatitis.

Three weeks after the adverse reaction to TMP-SMX, a 10-day induction of tolerance to 160 mg TMP–800 mg SMX was attempted with the patient's informed consent, given the limited oral antibiotic treatment options and the need for chronic suppressive therapy. The 10-day protocol reported by Absar et al¹ in HIV patients was used. The patient developed pruritus on day 10 followed by generalized erythema and increase in absolute eosinophil count from 64 cells/ μ L to 341 cells/ μ L on day 13 (Fig 1). The protocol was stopped, and prednisone 60 mg was given for 5 days. Relative eosinophilia resolved, and the patient's skin returned to baseline.

One month after the initial attempt at induction of tolerance, the patient was admitted for worsening back pain. The patient underwent arthrodesis, pedicle subtraction osteotomy, laminectomy,

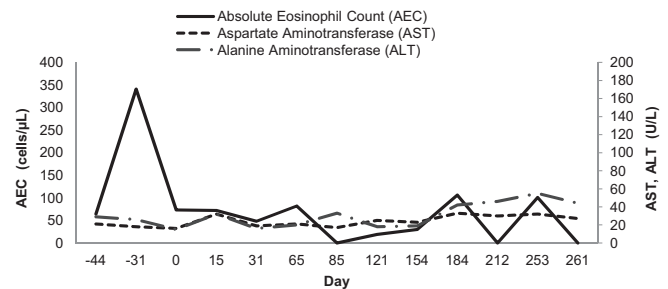


Fig. 1. Absolute eosinophil count (AEC) and liver enzymes over time. Day –44 marks the initial 10-day induction of tolerance that was attempted but failed. Note the rise in eosinophil count with the failed induction of tolerance. Day 0 marks the beginning of the successful prolonged induction of tolerance.

and extension of lumbar fusion. Lumbar spine cultures grew MRSA susceptible to vancomycin, linezolid, and TMP-SMX. Infectious disease service recommended acute therapy with vancomycin followed by chronic suppressive antibiotic therapy. Chronic therapy with linezolid was not preferred, given its cost and unfavorable side effect profile, including thrombocytopenia. Chronic therapy with vancomycin was not preferred, given its parenteral administration and cost.

Because of limited treatment options, induction of tolerance to 160 mg TMP–800 mg SMX was attempted again with the patient's informed consent, starting at 1/10th the previous starting dose and increasing at half the rate (Table 1). The protocol was slowed to advance by 2 mg TMP–10 mg SMX every other day once the 80 mg TMP–400 mg SMX was achieved, because this was the highest dose the patient tolerated in the previous protocol. The induction of tolerance took 266 days. Weekly laboratory tests showed no eosinophilia, cytopenias, altered renal function, or altered liver function. The patient's skin examination results were unchanged.

At the time of this publication, the patient has remained on 160 mg TMP–800 mg SMX for 9 months. Since the induction of tolerance, she has had no invasive MRSA infections. She underwent bilateral total hip arthroplasty without incident. After starting TMP-SMX prophylaxis, she has developed recurrent *Candida* vaginitis necessitating monthly prophylaxis with fluconazole.

In previous reports, HIV-positive patients with mild non-IgE-mediated cutaneous reactions to TMP-SMX tolerated drug challenges or induction of tolerance. We report the first case of successful induction of tolerance in an HIV-negative patient with a history of exfoliative dermatitis to TMP-SMX. Such a procedure is not currently the standard of care. However, given the limited choices for oral antibiotics, the procedure was attempted. Further study is needed to determine whether induction of tolerance can be consid-

Table 1
Protocol for prolonged induction of tolerance to TMP-SMX

Day	Dose (TMP-SMX)
1, 2	0.04–0.2 mg
3, 4	0.08–0.4 mg
5, 6	0.16–0.8 mg
7, 8	0.32–1.6 mg
9, 10	0.64–3.2 mg
11, 12	1.28–6.4 mg
13, 14	2.56–12.8 mg
15, 16	5.12–25.6 mg
17, 18	10–50 mg
19, 20	20–100 mg
21, 22	40–200 mg
23, 24	80–400 mg
25–104	Increase by 2–10 mg every other day toward goal of 160–800 mg in the morning
105–266 (introduce evening dose)	Increase by 2 mg–10 mg every other day toward goal of 160 mg–800 mg at night

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole.

ered in HIV-negative patients with non-IgE-mediated severe reactions to TMP-SMX.

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