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Elexacaftor/Tezacaftor/Ivacaftor Outpatient Desensitization

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Delayed hypersensitivity reactions characterized by rashes occur in patients taking elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA, Trikafta), a cystic fibrosis transmembrane conductance regulator (CFTR) modulator. ELX/TEZ/IVA was approved

in 2019 for cystic fibrosis (CF) patients ≥ 12 years who carry the Phe508del mutation on at least one allele¹. ELX and TEZ increase expression of the CFTR protein¹ whereas IVA enhances CFTR channel gating¹.

Approximately 90% of CF patients in the U.S. possess the Phe508del mutation¹. In a phase III clinical trial, ELX/TEZ/IVA, compared to placebo, improved the percentage of predicted FEV1 at 4 and 24 weeks, lowered the rate of pulmonary exacerbations, and reduced sweat chloride concentration¹. Rash, defined as generalized, macular, and/or pruritic, occurred in 10.9% of patients in the treatment group and more commonly in females on hormonal contraceptives compared to those not¹. The combination drug tezacaftor/ivacaftor (TEZ/IVA, Symdeko) without ELX was associated with rash in 9% of participants without necessitating discontinuation². IVA desensitization has been reported after a TEZ/IVA associated drug eruption³.

We describe here two patients with ELX/TEZ/IVA-induced delayed hypersensitivity rashes who successfully resumed this drug after slow outpatient oral desensitization.

Patient A is a 48-year-old female heterozygous for the Phe508del mutation. She had no history of CFTR modulator therapy. One month after stopping a hormonal contraceptive, she started ELX/TEZ/IVA. About two weeks later, she noted intermittent fevers to 100.9 F. One week later, she noted scalp pruritus, then developed a rash on her arms, torso, and legs. The rash was pruritic, follicular, interspersed with uninvolved skin, and without wheals, blisters, or mucosal involvement. Her pulmonologist instructed her to stop

ELX/TEZ/IVA and start diphenhydramine and famotidine. Within four days, the pruritus resolved; within 10 days, the rash subsided.

Patient B is a 37-year-old female homozygous for the Phe508del mutation. After three years on TEZ/IVA, she was switched to ELX/TEZ/IVA without stopping her hormonal contraceptive. Six days later, she developed a macular, pruritic rash on her chest without wheals or blisters. By the following morning, the rash spread to her entire body and face. Her pulmonologist instructed her to stop ELX/TEZ/IVA and present to her local ED. She received dexamethasone, diphenhydramine, and famotidine. The rash resolved in a few days. Her pulmonologist recommended stopping her hormonal contraceptive and starting ELX/TEZ/IVA one week later. Eight hours after taking the first tablet, she noted a fever to 101 F and recurrence of the rash. She discontinued ELX/TEZ/IVA with resolution of the rash.

Both patients were referred to our clinic. Neither had labs or a biopsy during the rash. Based on the delayed onset of both rashes and their macular or follicular appearance, we diagnosed both patients with type IV hypersensitivity reactions to ELX/TEZ/IVA. Neither patient experienced respiratory symptoms, urticaria, blisters, or mucosal lesions. Drug reaction with eosinophilia and systemic symptoms was thought to be unlikely given the rapid resolution of rash, limited skin involvement, and absence of lymphadenopathy and desquamation. Skin testing to ELX/TEZ/IVA was not done. Slow oral desensitization was offered.

ELX/TEZ/IVA consists of two tablet formulations packaged together, with ELX 100 mg, TEZ 50 mg, and IVA 75 mg in the morning tablet and IVA 150 mg in the evening tablet. Goal dosing is two ELX/TEZ/IVA tablets in the morning and one IVA 150 mg tablet in the evening. TEZ/IVA consists of two separate tablets packaged together, with TEZ 100 mg and IVA 150 mg in the morning tablet and IVA 150 mg in the evening tablet.

For patient A, we could not determine which component of ELX/TEZ/IVA caused her rash without prior exposure to TEZ/IVA. Therefore, her desensitization schedule involved escalation of both the ELX/TEZ/IVA and the IVA tablets (Table 1). Since patient B had previously tolerated TEZ/IVA, we surmised that ELX caused her reaction. Her protocol provided increasing doses of ELX/TEZ/IVA similar to patient A's protocol, concurrent with decreasing morning doses of TEZ/IVA and stable evening doses of IVA to maintain full doses of TEZ and IVA throughout desensitization for CF control. Both patients were instructed to remain off hormonal contraceptives during desensitization.

Dose escalations were planned to occur weekly based on the pharmacokinetics of the components. Neither patient had hepatic dysfunction. Intervals stretched to 1-3 weeks partly due to challenges with monitoring early in the COVID-19 pandemic. Patient A completed desensitization, but after two weeks on full dose ELX/TEZ/IVA, she noticed a burning sensation on her head and neck without rash. No other medications, including antihistamines or steroids, were started. We reduced her dose to one tablet ELX/TEZ/IVA in the morning and one tablet IVA in the evening, and her symptoms resolved. After two weeks, she tolerated increasing to 1.5 tablets ELX/TEZ/IVA in the

morning and one tablet IVA in the evening. Further escalation resulted in rash recurrence. Since then, she has tolerated this dose with good effect on her CF symptoms. Patient B achieved full dose ELX/TEZ/IVA.

Desensitization induces a temporary state of tolerance in some patients through dose escalation. In addition to rapid desensitization for immediate, IgE-mediated hypersensitivity reactions, “slow” desensitization has been employed for some delayed hypersensitivity reactions with variable success⁴. Protocols should be tailored based on drug pharmacokinetics, hypersensitivity classification, patient history, and comorbidities. As a general rule, neither rapid nor slow desensitization should be employed after severe, cutaneous reactions. Because our patients benefited from ELX/TEZ/IVA and did not have effective alternatives, they accepted the risk of rash recurrence.

As an estimated 90% of CF patients carry the Phe508del mutation on at least one allele, ELX/TEZ/IVA may become standard of care and allergists may be called upon to handle related rashes. These cases describe two successful slow outpatient desensitization protocols for patients with benign, delayed rashes to ELX/TEZ/IVA.

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Table 1: Desensitization Schedule for Patient A

	ELX/TEZ/IVA, AM	IVA, PM
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Week 1	0.25 tab	0.25 tab
Week 2	0.5 tab	0.5 tab
Week 3	0.75 tab	0.75 tab
Week 4	1 tab	1 tab
Week 5	1.25 tab	1 tab
Week 6	1.5 tab	1 tab
Week 7	1.75 tab	1 tab
Week 8	2 tab	1 tab

The above table shows the desensitization protocol for Patient A.