

At-home compounding preparation of slow desensitization of elexacaftor/tezacaftor/ivacaftor for delayed hypersensitivity rash

Corinne Muirhead PharmD¹  | Deborah Verzasconi RPh¹ | Shyam Joshi MD²

¹Department of Pharmacy, Oregon Health and Sciences University, Portland, Oregon, USA

²Section of Allergy and Immunology, Oregon Health and Sciences University, Portland, Oregon, USA

Correspondence

Corinne Muirhead PharmD, Department of Pharmacy, Oregon Health and Sciences University, 3181 SW Sam Jackson Park Rd Cr9-4, Portland, OR 97239, USA.
Email: dustan@ohsu.edu

Abstract

As elexacaftor/tezacaftor/ivacaftor has proven to have robust clinical efficacy for eligible persons with cystic fibrosis, desensitization should be offered to those with maculopapular eruption hypersensitivity reactions to achieve tolerance. As presented in this case, if provided with tools for crushing and mixing the medication, a successful escalation protocol can be completed at home without coordinating the help of a compound pharmacy.

KEYWORDS

cystic fibrosis, desensitization, drug rash, maculopapular eruption, Trikafta

To the Editor,

A previous publication in *Pediatric Pulmonology* by Leonhardt, K, et al presented successful elexacaftor/tezacaftor/ivacaftor (ETI; Trikafta[®]) desensitization cases utilizing an independent pharmacy to compound ETI into cornstarch (powder) and three times per day escalating dosing.¹ We present a method of compounding ETI into suspension at home for desensitization. This protocol took 23 days with only one day required in the outpatient clinic setting while the remainder of the dose preparation and escalation was able to take place at home. Dose escalations took place once weekly after virtual visits with the allergist and once-daily administrations were taken the other days (Table 1).

1 | CASE

A 49-year-old female with cystic fibrosis (CF) (homozygous F508del), severe lung impairment (baseline FEV1 29%), chronic malnutrition (body mass index [BMI] 16.3 kg/m²) and modulator naïve, began ETI. She deferred treatment with lumacaftor/ivacaftor and tezacaftor/ivacaftor (ETI) to wait for longer-term safety data. Due to the efficacy noted with ETI, she opted to start therapy.

ETI (Trikafta[®] Vertex) increases expression and function of cystic fibrosis transmembrane conductance regulator (CFTR) protein. ETI is

a highly effective modulator, significantly increasing lung function and decreasing perceived respiratory symptoms in qualifying persons with CF, culminating in meaningful clinical outcomes.²

She had a positive response to ETI with sinus congestion and chronic cough resolution within days and two pound weight gain during the first month. No spirometry was performed. During the fifth week of therapy, she developed pruritic, erythematous papules bilaterally on her ankles that rapidly progressed to her trunk, hands, and feet. Within two days, she developed diffuse edema of her legs, arms, face, and ears but denied any mucosal involvement, blistering, or urticaria. Throughout this period, she had no other systemic complaints including fevers, respiratory distress, or arthralgias. ETI was discontinued. Symptoms improved within 24 h, and full rash resolution occurred at two weeks.

A delayed onset of a rash was reported in 10.9% of patients in the Phase 3 trials for ETI.² From our experience, this rash typically resolves within a week, even without disruption of medication, however, there have been cases of persistent allergic rashes that require discontinuation of therapy.^{1,3}

Six months later, she trialed the therapy again with a reduced starting dose of one orange tablet daily. Within six h, she developed flushing, jittery sensation, generalized erythema, and swelling of face, hands, and legs. The medication was immediately discontinued.

TABLE 1 Elexacaftor/tezacaftor/ivacaftor desensitization protocol.

Day(s)	Observation time after each dose	Setting	Administered dose ^a	Concentration	Daily cumulative dose (mg)
1	30 min	Allergy clinic	10 mcg, 20 mcg, 40 mcg, 100 mcg, 250 mcg	0.2 mg/ml	0.42
2–7	–	At home	500 mcg	1 mg/ml	0.5
8	60 min	At home	1 mg, 2 mg, 4 mg, 8 mg, 12 mg	1 mg/ml	27
9–14	–	At home	25 mg	1 mg/ml	25
15	60 min	At home	30 mg, 35 mg, 35 mg	1 mg/ml	100
16–21	–	At home	100 mg (1 orange tablet)	N/A	100
22	30 min/90 min	At home	100 mg, 100 mg	N/A	200
23		At home	200 mg (2 orange tablets)	N/A	200

^aBased on dose of elexacaftor. One tablet contains elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg.

TABLE 2 List of items dispensed to patient to prepare elexacaftor/tezacaftor/ivacaftor doses at home.

1. Glass mortar and pestle
2. Ora-Blend bottles (16 ounces) – 3 total
3. Amber bottles (4 ounces) – each marked with 100 ml fill volume line – 14 total
4. Oral syringes (various volumes) – 20 total
5. Written schedule of dosing

Our allergy specialist devised a desensitization plan and the pharmacy team a compounding plan (Table 1). Day one of desensitization was completed in the Allergy Clinic. The pharmacist compounded a concentration of 0.2 mg/ml suspension and all doses for first escalation were prepared in oral syringes. The patient continued on the highest completed dose once daily for a week. She met with the allergist virtually weekly before her next dose escalation, which she did at home.

Due to the unknown stability of ETI when diluted, the patient was instructed to discard each suspension after 24 h. She made a new suspension every other day, taking the second dose within 24 h after preparation. The pharmacist and patient discussed proper compounding procedure on Day one in the clinic and then over the telephone during the patient's first home compound attempt on Day two. A list of items dispensed to the patient is outlined in Table 2. One orange ETI tablet was crushed with a glass mortar and pestle. Due to poor dissolution in water, 10 ml of ORA-Blend[®] (Perrigo) syrup was added to form a paste. More ORA-Blend[®] was added to make a uniform suspension, which was transferred into an amber plastic bottle. ORA-Blend[®] was added to a final volume of 100 ml and concentration of 1 mg/ml elexacaftor component. The total cost was approximately \$100 for the supplies. This does not include the cost of the medication, which was covered by the patient's insurance.

Dose escalation proceeded as planned without issue. She began to appreciate meaningful benefit when she reached one full orange

ETI tablet during the desensitization protocol. At the start of full morning dose of two orange ETI tablets daily, she reported some mild insomnia, which improved after a few days. She added the second daily dose of one blue ivacaftor tablet, two weeks after completion of dose escalation to full morning dose. Preceding this desensitization, her FEV1 percent predicted (FEV1pp) was 21%. After two months of full-dose ETI, her spirometry showed an improvement of FEV1pp to 29% and her weight increased from 38.6 kg (BMI 16.1 kg/m²) to 42.3 kg (BMI 17.6 kg/m²).

Our patient's history of a delayed cutaneous-only reaction to ETI is concerning for a non-IgE-mediated maculopapular eruption (MPE). Other forms of non-IgE-mediated drug reactions were unlikely including Severe Cutaneous Adverse Reactions (SCARs). Which component of this three-drug combination medication caused this allergic response is unknown, and excipients and coloring agents cannot be excluded as the culprit.

As expected with MPEs to a specific drug, subsequent exposure to the culprit medication for this patient led to a more rapid reaction. Since the medication is critical for the long-term management of the patient's CF and not available in other forms, a desensitization protocol was developed in an attempt to induce a state of tolerance through gradual dose escalation.

The role of desensitization for IgE-mediated reactions is well established but is not nearly as well-defined for non-IgE-mediated reactions. However, "slow" desensitization protocols have been used for mild to moderate MPEs. The underlying mechanism of this process is unknown and studies of efficacy have shown mixed results. Most of the published data on desensitization of MPEs is from the human immunodeficiency virus (HIV) literature for sulfonamide antibiotics. Over 20 protocols have been developed and proven efficacious, and a relatively large long-term study reported a significantly higher percentage of patients with a history of MPE able to remain on trimethoprim-sulfamethoxazole (TMP-SMX) that underwent desensitization (80%) compared to those directly restarted on the full-dose (62.8%).^{4,5}

2 | CONCLUSION

As ETI has proven to have robust clinical efficacy for eligible persons with CF, desensitization should be offered to those with MPE hypersensitivity reactions to achieve tolerance. As presented with this case, if provided with tools for crushing and mixing the medication, a successful escalation protocol can be completed at home without coordinating the help of a compound pharmacy.

AUTHOR CONTRIBUTIONS

Corinne Muirhead: Conceptualization (equal); methodology (equal); writing — original (lead); writing — review & editing (equal). **Deborah Verzasconi:** Methodology (equal); writing—original draft (supporting). **Shyam Joshi:** Conceptualization (equal); methodology (equal); writing —original draft (equal); writing—review & editing (equal).

ACKNOWLEDGMENT

NA.

CONFLICT OF INTEREST

Corinne Muirhead served on an Advisory Board for Vertex in 2021-2022.

DATA AVAILABILITY STATEMENT

Not applicable.

ORCID

Corinne Muirhead  <http://orcid.org/0000-0002-6269-6459>

REFERENCES

1. Leonhardt K, Autry EB, Kuhn RJ, Wurth MA. CFTR modulator drug desensitization: Preserving the hope of long term improvement. *Pediatr Pulmonol*. 2021;56(8):2546-2552.
2. Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med*. 2019;381(19):1809-1819.
3. Stashower J, Carr P, Miller V, Zlotoff B. Novel reaction to new cystic fibrosis medication Trikafta. *Clin Case Rep*. 2021;9(5):e04116.
4. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for *Pneumocystis Carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. 2001;184(8):992-997.
5. Khan DA, Knowles SR, Shear NH. Sulfonamide hypersensitivity: fact and fiction. *J Allergy Clin Immunol Pract*. 2019;7(7):2116-2123.

How to cite this article: Muirhead C, Verzasconi D, Joshi S. At-home compounding preparation of slow desensitization of elexacaftor/tezacaftor/ivacaftor for delayed hypersensitivity rash. *Pediatric Pulmonology*. 2022;57:1779-1781. doi:10.1002/ppul.25938