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Successful Desensitization With ELX/TEZ/IVA

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Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was given US Food and Drug Administration approval based on its therapeutic benefits to treat patients with cystic fibrosis (CF) who had at least 1 allele of the CF transmembrane conductance regulator (CFTR) with phenylalanine deleted at position 508 (F508del). The increase in genotyping studies has increased the frequency of use of CFTR modulators; however, severe allergic reactions to CFTR modulators have also been described. It is critical to avoid the offending medication and select alternative treatments while dealing with drug allergies. Drug desensitization may be taken into consideration in situations where there is no other option. This article describes home desensitization treatment for a patient with CF who developed a maculopapular rash following CFTR modulator medication. There are currently no alternative drugs for CFTR modulators, which are crucial for patients with CF, and limited experience is available with allergic reactions to these drugs. It is important to establish desensitization protocols in order to control drug reactions to CFTR modulators, which are vital for individuals with CF.

ABBREVIATIONS CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA, elexacaftor/tezacaftor/ivacaftor

KEYWORDS CFTR modulator; cystic fibrosis; desensitization; ELX/TEZ/IVA; Trikafta

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Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the gene encoding the cystic fibrosis transmembrane regulatory protein, leading to a chloride channel defect that causes multiorgan involvement, including the lung. The aim of treatment is to minimize organ damage and prevent infection [1]. CF transmembrane conductance regulator (CFTR) modulators offer therapeutic improvement by restoring the function of defective channels. Studies have demonstrated that in patients with CF who had at least 1 allele of the CFTR with phenylalanine deleted at position 508 (F508del), a combination of the CFTR modulators elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), known by the trade name Trikafta (Vertex Pharmaceuticals, Boston, MA), dramatically decreased the incidence of pulmonary exacerbations while also improving pulmonary function tests[2,3]. Nevertheless, rash was seen in 4% to 10% of patients, resulting in 1% to 2% discontinuation[4–6]. When allergies associated to ELX/TEZ/IVA emerge, there is typically no recognized standard treatment, and management approaches vary widely. Allergic reactions brought on by CFTR modulators might be T-cell–mediated delayed reactions. T-cell clones were obtained from a patient with CF who had an adverse reaction after starting lumacaftor/ivacaftor, and it was revealed that only the clones obtained after lumacaftor were sensitive to the drug, while those taken after ivacaftor and tezacaftor were not[7]. Additionally, it was noted that these T-cell clones did not exhibit cross-reactivity between lumacaftor and tezacaftor. According to the report, MHC (Major Histocompatibility Complex) class II molecules directly connect to lumacaftor-responsive CD4+ T-cell clones, activating them.

In the development of allergies to essential medicines in cases of chronic usage, desensitization protocols such as the use of a fraction of tablets or compounded aliquots gain importance. In this report, we describe a home desensitization procedure for a patient with CF who had a maculopapular rash after using a CFTR modulator.

Search Strategy

The search was performed through PubMed/MEDLINE, using the following keywords: *cystic fibrosis*, *CFTR modulators*, *ELX/TEZ/IVA*, *Trikafta*, *Elexacaftor*, *Tezacaftor*, *Ivacaftor*, *allergic reaction*, *hypersensitivity*, *drug reaction*, and *drug desensitization*, filtered for articles published. The systematic review was performed according to the PRISMA checklist[8]. We included all articles related to patients with CF who experienced an allergic reaction to CFTR modulators. The titles, abstracts, and entire contents of the relevant articles were examined separately by 2 researchers.

We obtained informed consent from the patient and his family. It was approved by the ethics board (KAEK-157) at the University of Akdeniz, Turkey.

Case

A 16-year-old male patient with widespread maculopapular rash and intense body itching presented to our clinic. Apart from the rash, no mucosal wounds, angioedema, or any systemic involvement were seen. Because the patient was using pancrelipase, budesonide/formoterol, vitamins, and dornase alfa for years, the rash was attributed to an allergic reaction related to ELX/TEZ/IVA that started 10 days prior due to the delta F508/G85E mutation. CFTR modulators were not previously prescribed to the patient.

Two tablets containing VX-445 (elexacaftor–100 mg)/VX-661 (tezacaftor–50 mg)/VX-770 (ivacaftor–75 mg) were prescribed for the patient in the morning, and 1 tablet of ivacaftor (150 mg) in the evening. It was decided to discontinue the ELX/TEZ/IVA treatment owing to the rash. Improvement was shown 4 days after starting therapy with lansoprazole, methylprednisolone, and desloratadine at doses of 30 mg/day, 1 mg/kg/day, and 5 mg/day, respectively. The patient's viral markers all tested normal. No patch test or skin prick test was carried out. Six weeks after the improvement of symptoms, similar complaints developed after re-exposure to the drug, which was thought to be a drug eruption (Figures 1 and 2). Naranjo Adverse Drug Reaction Probability Scale score of 9 for the patient indicated the presence of a drug-related rash[9]. It was decided to continue the ELX/TEZ/IVA treatment after drug desensitization because the expected reductions in pulmonary exacerbations with ELX/TEZ/IVA had great importance for our patient. The desensitization protocol is shown in Table 1. The yellow tablet was crushed, and the resulting suspension was diluted with 100 mL of water to create the required liquid at a concentration of 1 mg/mL. We then took 1 mL of this liquid and diluted it once again with 100 mL of water. The prepared 10 mcg/1 mL solution was used in the desensitization process; because of stability problems, the preparation was remade every 24 hours. This desensitization protocol began with the premedication of desloratadine, and the premedication was stopped after the full dose was reached. No reaction was observed.

Discussion

The currently approved CFTR modulators act via 2 different mechanisms: potentiators (ivacaftor) and correctors (lumacaftor, tezacaftor, and elexacaftor). These medications are used in various combinations. Skin rash was observed in 4% to 10% of patients receiving ELX/TEZ/IVA and fewer than 5% of those taking ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor in phase 3 clinical trials [4–6]. Discontinuation of the drug has been

Figure 1. Maculopapular rash.

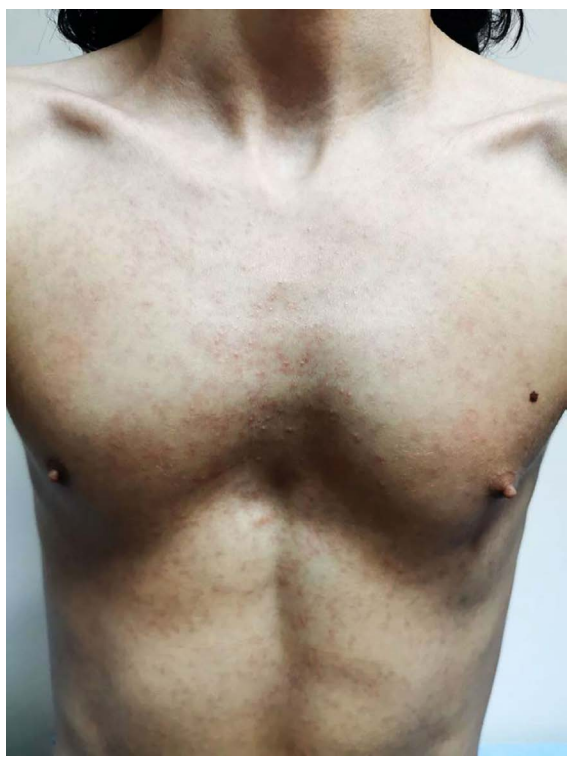

Figure 2. Maculopapular rash.

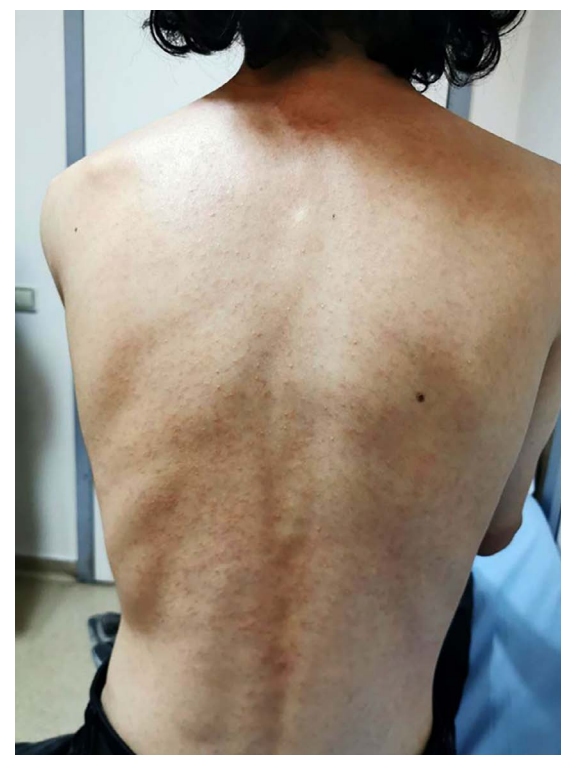

Table 1. Trikafta Desensitization Protocol (Adapted From Muirhead[15])

Day(s)	Observation Place and Duration	Dose*	Concentration, mg/mL	Cumulative dose, mg/day	Reaction
Premedication drug: desloratadine 5 mg/day					
1	Pediatric Allergy Clinic (each dose was increased at 30-min intervals) (yellow tablet)	10 mcg	0.2	0.42	None
		20 mcg			None
		40 mcg			None
		100 mcg			None
		250 mcg			None
2–7	Home (yellow tablet)	500 mcg	1	0.5	None
8	Home (each dose was increased at 60-min intervals) (yellow tablet)	1 mg, 2 mg, 4 mg, 8 mg, 12 mg	1	27	None
9–14	Home (yellow tablet)	25 mg	1	25	None
15	Home (each dose was increased at 60-min intervals) (yellow tablet)	30 mg, 35 mg, 35 mg	1	100	None
16–21	Home (yellow tablet)	100 mg (1 yellow tablet)	N/A	100	None
22	Home (each dose was increased at 60-min intervals) (yellow tablet)	100 mg, 100 mg	N/A	200	None
23	Home (yellow and blue tablets)	200 mg (2 yellow tablets) and 1 blue tablet)	N/A	200	None

N/A: not applicable

* Based on dose of elexacaftor. One yellow tablet contains 100-mg elexacaftor/50-mg tezacaftor/75-mg ivacaftor. One blue tablet contains 150-mg ivacaftor.

reported to be sufficient in cases with mild drug reactions, while steroid support has also been required in more severe cases. Stashower et al[10] reported the case of a 24-year-old female patient who developed erythema multiforme 2 weeks after starting ELX/TEZ/IVA, and Loyd et al.[11] described a widespread erythematous macula in a 7-year-old child on the third day, both of whom had clinical improvement upon discontinuation of the drug. However, a 39-year-old male patient described by Mederos-Luis et al.[2] required critical care follow-up and needed 20 days of high-dose systemic steroids after developing toxic epidermal necrolysis on the 10th day of therapy. Brennan et al.[12] documented the case of a child who required systemic steroid treatment after developing symptoms resembling serum sickness. Adult patients were effectively treated by using desensitization methods, as reported in the studies by Leonhardt et al.[13] Patterson et al.,[14] and Muirhead et al.[15] (Table 2).

Approaches in desensitization protocols should be chosen according to the concentration of the drug, the dose range, and the route of administration (oral, intravenous, intramuscular, or subcutaneous). Immunologic tolerance can be maintained with continuous administration of the drug. During the desensitization process, mild reactions or severe reactions ranging up to anaphylaxis may occur. Because the protocol of Muirhead and colleagues[15] was designed to be adopted more slowly, it provided the basis for our desensitization protocol. The protocol used by Loyd et al.[11] started with half of the required dose and continued with the full dose on the third day. In the protocol of Leonhardt et al.[13], the first dose was started at home. However, in that of Muirhead et al.[15] which we have also used

Table 2. Clinical Features, CFTR Modulator Reactions, and Treatment Strategies of Patients With Cystic Fibrosis

First Author (Reference number)	Country	Number of Patients	Age, yr	Mutation	Sex	Reaction Time After Drug Intake	Symptom	Treatment
Stashower[10]	USA	1	24	Not specified	F	2 wk	Pruritic rash	Stop medication
Leonhardt[13]	USA	2	20, 47	Phe508del/Phe508del, Phe508del/3849+10kbC-T	2F	7 days/ 9 days	Maculopapular rash/red pruritic spot	For case 1 stop medication, methylprednisolone, topical triamcinolone, desensitization; for case 2 stop medication, prednisone, loratadine, desensitization
Muirhead[15]	USA	1	49	Homozygous F508del	F	5 wk	Erythematous, pruritic papules and diffuse edema	Desensitization at home
Loyd I[11]	USA	1	7	Not specified	M	3 days	Diffuse erythematous macules	Stop medication, systemic steroid, acetaminophen and diphenhydramine
Mederos-Luis[2]	Spain	1	39	F508del/G542X	M	10 days	Toxic epidermal necrolysis TEN	Stop medication High-dose systemic steroid
Brennan[12]	USA	1	12	Phe508del/Arg347Pro	M	5 days	Serum sickness–like reaction	Stop medication Systemic steroid

CFTR, cystic fibrosis transmembrane conductance regulator; TEN, toxic epidermal necrolysis

as a reference, the first dose is given in the hospital environment and continued by increasing the dose in 3 weeks, which makes it safer. The desensitization protocol was successfully applied to our patient, and we were able to continue the ELX/TEZ/IVA treatment. Unlike that of Muirhead and colleagues,[15] the preparation of the drug consisted only of dilution with distilled water to a certain concentration.

Because patients with CF lack alternatives in their treatment, drug desensitization may be required in such cases owing to allergic reactions to CFTR modulators. For our patient, we showed that it is important to establish desensitization protocols for drug reactions to CFTR modulators, which are vital for individuals with CF.

Article Information

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