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CASE REPORT

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Successful Modulator Treatment Desensitization in a Patient with Cystic Fibrosis

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ABSTRACT

Cystic fibrosis is a life-shortening disease characterized by the mutation of the salt transporter cystic fibrosis transmembrane conductance regulator (CFTR) protein. Elexacaftor/tezacaftor/ivacaftor treatment, which has been used since 2019, has had effects such as improving the quality of life, improving respiratory functions, and reducing the rate of pulmonary exacerbations. The real-life side effects of the drug are still emerging due to the new use of modulator therapies and their new spread around the world. There are no proven protocols regarding these side effects yet. Strategies for managing adverse drug reactions to these drugs are important to ensure that as many patients as possible benefit from them.

Keywords: Pediatric, desensitization, cystic fibrosis, pulmonology, slow oral desensitization

INTRODUCTION

Cystic fibrosis (CF) is a multisystem disease caused by a mutation in the gene that encodes the protein cystic fibrosis transmembrane conductance regulator (CFTR). Although various treatments have been administered to reduce mortality and morbidity in patients with CF, complete recovery is not achieved in these patients. The use of modulator therapies—recently used to improve CFTR protein synthesis and function—has improved quality of life and respiratory function in patients with CF and reduced the incidence of pulmonary exacerbations (1). These therapies are aimed at enhancing CFTR synthesis and functions. During the administration of these treatments, some side effects, such as serum sickness-like reactions and maculopapular rash, have been reported. Real-world data indicate that the frequencies of treatment discontinuations and adverse events may be higher than those observed in clinical trials (2). Rash has been observed as an adverse reaction to ivacaftor monotherapy, lumacaftor/ivacaftor, and tezacaftor/ivacaftor in ≤5% of all patients in phase-3 clinical trials, and it has not been reported to be severe or life-threatening (3). As modulator therapies have only recently been introduced and have begun to spread worldwide, real-world hypersensitivity reactions to the drugs remain unclear. In this treatment model, which affects the patient's prognosis, there is no proven protocol that can be used in specific cases of hypersensitivity reactions. Strategies to manage the side effects of these drugs are important to ensure the management of as many cases as possible. This case study presents our treatment approach for a patient who developed a diffuse pruritic maculopapular rash associated with modulator therapy.

CASE PRESENTATION

A 15-year-old female patient suffered from recurrent pneumonia, which was first diagnosed at the age of 6 months. The sweat test, which was performed due to the presence of fecal fat in the patient, revealed a chloride level of 108 meq/lt. Her genetic analysis revealed a G85E/1677 delTA heterozygous mutation, and she was diagnosed with CF. The patient's and her parents' consent was obtained for the study and the use of images. In August 2021, elexacaftor, tezecaftor, and ivacaftor (elx/tez/iva) therapy was initiated for the patient with a history of frequent hospitalizations,

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for pancreatic insufficiency, inability to gain weight, chronic lung infection, and recurrent pneumothorax. In the first week of the treatment, diffuse maculopapular rashes were observed on her face, neck, arms, and trunk; these rashes were pruritic with no mucosal involvement (Figure 1). Subsequently, the elx/tez/iva therapy was discontinued. Thereafter, levocetirizine 1 mg/kg, famotidine 1 mg/kg, and oral methylprednisolone 1 mg/kg were administered for 5 days, and the rashes regressed within 1 week. The patient was considered to have type-4 hypersensitivity reaction as the rash was noticed within 1 week of treatment initiation. Her complete blood count and biochemical test results revealed no abnormalities. Although the patient presented with rashes, desensitization was scheduled with no further delay of the modulator therapy because the patient's respiratory test results had improved and her cough- and sputum-associated symptoms had already regressed after 1 week of treatment. Therefore, slow oral desensitization using elx/tez/iva therapy was performed without skin testing. As the modulator therapy desensitization protocol was unknown, the patient was desensitized at the lowest divisible doses (4,5). Elx/tez/iva therapy consists of a 2-tablet formulation in which elx 100 mg, tez 50 mg, and iva 75 mg are administered as morning tablets and iva 150 mg is administered as the evening tablet. The target dose was 2 elx/tez/iva tablets in the morning and 1 iva tablet of 150 mg in the evening.

The patient reached the full dose in 31 days with the escalation of drug doses. As the rash had recurred on day 9, the dose was not increased and the same dose was continued for another 10 days (till day 19) (Table I). The patient continued to use antihistamines during desensitization, and we believe that their use facilitated tolerance. No abnormality was observed in the complete blood count and biochemical test results. The patient has been using the modulator therapy for 1 year with no complications, and the patient's rash did not recur even after the antihistamine treatment was discontinued.

DISCUSSION

As modulator therapies have just lately been implemented and begun to spread worldwide, real-world hypersensitivity reactions to medications have only recently begun to be reported. Regarding these side effects, there are no proven management methods. Therefore, methods must be modified based on patient history, comorbidities, hypersensitivity classification, and drug pharmacokinetics. In the present case, as our patient benefited from the elx/tez/iva therapy and as there was no alternative treatment, she accepted that the rash might recur and approved the desensitization protocol. To ensure that as many patients as possible benefit from these medications, strategies for managing adverse effects are crucial. Because cutaneous adverse reactions to CFTR modulators are uncommon, many facilities will need to pool their data in order to develop strategies for managing these patients.

These drugs significantly improve patient management, but they are hardly accessible worldwide; therefore, the supply of these medicines is also difficult in Turkey. The improvement observed in the present case, even during the first week of treatment, forced the patient and us to act quickly and practically. We implemented this approach

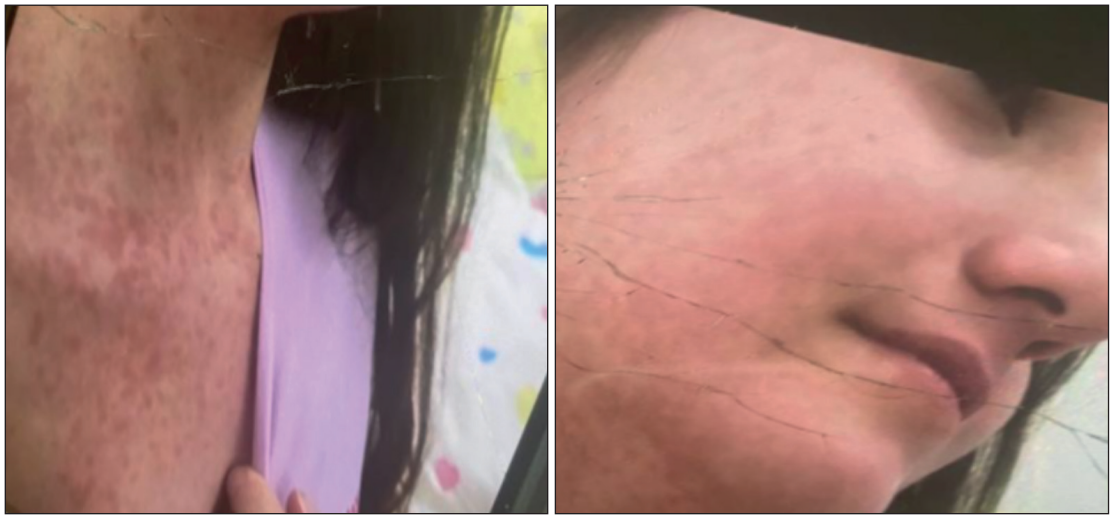

Figure 1.
Maculopapular rash.

Table I: Desensitization protocol.

Day		Morning dose	Evening dose
1	Elexacaftor/tezacaftor/ivacaftor tablet 225 mg (orange tablet)	0.25 mg	0.25 mg
2		0.5 mg	0.5 mg
3		1 mg	1 mg
4		2 mg	2 mg
5		4 mg	4 mg
6		8 mg	8 mg
7		16 mg	16 mg
8		32 mg	32 mg
9		64 mg	64 mg
Because of recurrent rash, this dose was continued for another 10 days.			
20, 21, and 22		112.5 mg (half a tablet)	112.5 mg (half a tablet)
23, 24, and 25		225 mg (one tablet)	225 mg (one tablet)
26, 27, and 28	Elexacaftor/tezacaftor/ivacaftor tablet 225 mg (orange tablet) + ivacaftor	2 tablets in the morning	Evening 75 mg ivacaftor tablet
29, 30, and 31	Elexacaftor/tezacaftor/ivacaftor tablet 225 mg (orange tablet) + ivacaftor	2 tablets in the morning	Evening 150 mg ivacaftor tablet (target dose)

only using the resources at our disposal, and we believe that this approach will be valuable for further studies.

CONCLUSION

CFTR modulators have revolutionized the treatment of CF. Patients with CF are waiting for these drugs to become available, hoping that they will bring long-term improvement and reduce the incidence of pulmonary exacerbations. Therefore, it is extremely important to develop strategies to alleviate drug hypersensitivity reactions, including delayed-type hypersensitivity reactions.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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None.

Conflict of Interest

There are no conflicts of interest.

Authorship Contributions

Concept: **Ozge Kangalli Boyacioglu,** Design: **Suna Asilsoy,** Data collection or processing: **Ozge Kangalli Boyacioglu,** Analysis or Interpretation: **Nevin Uzuner,** Literature search: **Ozge Atay,** Writing: **Ozge Kangalli Boyacioglu,** Approval: **Suna Asilsoy.**

REFERENCES

1. Southern KW, Patel S, Sinha IP, Nevitt SJ. Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis. Cochrane Database Syst Rev 2018;8(8):CD010966.
2. Dagenais RVE, Su VCH, Quon BS. Real-world safety of CFTR modulators in the treatment of cystic fibrosis: A systematic review. J Clin Med 2020;10(1):23. Erratum in: J Clin Med. 2022 Jan 10;11(2).
3. Patterson A, Autry E, Kuhn R, Wurth M. Ivacaftor drug desensitization. Pediatr Pulmonol 2019;54(6):672-4.
4. Yıldız E, Çölkesen F, Aykan FS, Evcen R, Kılınç M, Aytekın, G, et al. Successful oral desensitization to rabeprazole: A case report of a patient with duodenal ulcer. Asthma Allergy Immunol 2022;20:120-3.
5. Kan A, Akgül M, Bakırtaş A. Successful rapid desensitization protocol for delayed type drug eruption in a patient using temozolamide. Asthma Allergy Immunol 2018;16:175-8.