Protocol for Successful Desensitization to Ivacaftor and Elexacaftor/Tezacaftor/Ivacaftor in a Delayed Hypersensitivity Reaction Confirmed by the Lymphocyte Transformation Test

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The development of cystic fibrosis transmembrane conductance regulator (CFTRs) modulators has transformed the care of patients with cystic fibrosis (CF) by reducing pulmonary exacerbations and improving lung function. These drugs improve CFTR function by preventing protein misfolding and degradation [1]. In phase 3 clinical trials, 11% of patients had skin rash compared with 6.5% in the placebo group, consistent with real-life data for elexacaftor/tezacaftor/ivacaftor (ETI) since its launch [2].

We report the case of a 40-year-old man with CF (Phe508del mutation), severe lung disease (forced expiratory volume in the first second [FEV_1], 27%), and multiple infectious respiratory exacerbations in the previous 6 months who was a candidate for lung transplantation. In February 2022, he started CFTR modulators: 2 tablets of the compound ETI 100 mg/50 mg/75 mg every morning and 1 tablet of ivacaftor 150 mg every night. On day 7 of treatment, he presented with a maculopapular rash and eosinophilia (1020/µL, no fever), edema, enlarged lymph nodes, and desquamation. Liver enzymes and acute-phase reactants were within the normal range. ETI was withdrawn, and prednisone (tapering doses), topical corticosteroids, and antihistamines were started. The rash resolved 8 days after discontinuation of ETI.

The patient was referred to our allergy unit. We performed patch tests with ETI and ivacaftor in 30% petrolatum, with negative readings at 48, 72, and 96 hours. We also performed a lymphocyte transformation test (LTT) with commercial tablets

Table. Desensitization Protocol for Ivacaftor Followed by Cumulative Desensitization for ETI.

Phase 1: Desensitization to ivacaftor					Phase 2: Desensitization to ETI					
Day	Eos/µL		Administration of IVA	Dose, mg	Week	Eos/µL	ETI 100 mg/ 50 mg/75 mg	Dose of IVA, mg	Dose of ELX, mg	Dose of TEZ, mg
1	300	[a]	0.15 mg → 0.30 mg → 0.60 mg[c]	1.05	1	720[d]	¼ tablet[f]	168.75	25	12.5
2	ND	[a]	1.2 mg → 2.4 mg → 4.8 mg[c]	8.4	2	ND	½ tablet[f]	187.5	50	25
3	ND	[a]	10 mg	10	3	610[e]	¾ tablet[f]	206.25	75	37.5
4	ND	[a]	15 mg	15	4	520[e]	1 tablet[f]	225	100	50
5	ND	[b]	⅛ tablet[d]	18.75	5	ND	1 ¼ tablets[f]	243.75	125	62.5
8	360	[b]	¼ tablet[f]	37.5	6	160	1 ½ tablets[f]	262.5	150	75
15	ND	[b]	½ tablet[f]	75	7	ND	1 ¾ tablets[f]	281.25	175	87.5
22	360	[b]	¾ tablet[f]	112.5	8	ND	2 tablets[f]	300	200	100
29	ND	[b]	1 tablet[f]	150						

Abbreviations: ELX, elexacaftor; Eos, eosinophils; ETI, elexacaftor/tezacaftor/ivacaftor (Kaftrio); IVA, ivacaftor; ND, not detemined; TEZ, tezacaftor.
[a]Solution of 2 mg/mL by crushing tablet of ivacaftor 150 mg diluted in 75 mL of sterile water. A fresh suspension was made each day.
[b]Ivacaftor 150 mg tablet (Kalydeco).
[c]Interval of 90 min.
[d]Maintain at home 1/8 tablet for 3 d.
[e]Value over the normal rage (limit 500 cells/µL).
[f]Maintain 1 wk.

of ETI 100 µg (equivalent to ETI 33 µg/22 µg/44 µg) and ivacaftor. The tablets were dissolved in dimethyl sulfoxide. We incubated fresh peripheral blood mononuclear cells previously separated over a density gradient (Histopaque-1077, Sigma-Aldrich) for 6 days in flat-bottom wells of microtiter plates at 2×10^5 cells/well. The test was performed in triplicate with ETI and ivacaftor at 1 µg/mL, 10 µg/mL, and 100 µg/mL. We used phytohemagglutinin (5 µg/mL) as a positive control. Proliferation was determined by adding 3H-thymidine (0.5 µCi/well) for the final 18 hours of the incubation period. We determined proliferative responses using the stimulation index (SI), ie, the ratio of mean counts per minute with drugs to those without drugs. Based on previous studies, the LTT result was considered positive at an SI >2 [3]. The LTT performed with ETI and ivacaftor in 2 healthy controls yielded an SI <2. We obtained a positive SI of 3.2 for ETI at 1 µg/mL and 2.5 at 10 µg/mL. Ivacaftor was positive with an SI of 2.6 at 10 µg/mL. With these results, we can confirm sensitization to ivacaftor, although sensitization to the other 2 components cannot be excluded. The patient gave his written informed consent for his data to be reported.

Based on the in vitro test result and the patient's comorbidities (severely compromised pulmonary function, poor quality of life, and absence of effective alternative therapies), treatment was reintroduced with a desensitization protocol, which was designed based on our experience, previous literature [4,5], and research (Table). Desensitization started with ivacaftor 0.15 mg (a thousandth of the therapeutic dose). For this purpose, the hospital pharmacy prepared an oral suspension by crushing 1 tablet of ivacaftor 150 mg and diluting it in 75 mL of sterile water for the first doses, obtaining a concentration of 2 mg/mL. Given the unknown stability of ivacaftor when diluted, we made a fresh suspension each day. We doubled the amount to 1/8 tablet daily over 5 days, subsequently increasing by a quarter tablet weekly, reaching 150 mg of ivacaftor. Elexacaftor and tezacaftor were not available as independent drugs. We then added a quarter tablet of ETI weekly until the patient reached the therapeutic dose (2 tablets of ETI + 1 tablet of ivacaftor, daily). Ebastine 10 mg was used as premedication throughout the protocol owing to the patient's dermographism. We monitored eosinophilia (patient's baseline, 300 µL) and liver function with periodic blood tests. Elevated values (720/µL) without organ involvement were observed in only 1 analytical control after introducing a quarter tablet of ETI, and the dose increase was maintained as planned (Table). At the one-and-a-half tablet dose of ETI in the second phase of the protocol, the patient developed a mild COVID-19 respiratory infection, which did not require hospital admission, modification of the desensitization protocol, or lowering of the ETI dose tolerated up to that point. He has been receiving full-dose treatment for 10 months with no adverse reactions, significant improvement in his pulmonary function (baseline FEV_1, 1.10 L, 27%; FEV_1 at 10 months of treatment/current, 1.84 L, 46%), and weight gain (+6 kg).

Delayed hypersensitivity reactions have been reported since the introduction of CFTR modulators in 2019 [2]. Few clinical cases involved an allergy study using lymphocyte clone cultures to demonstrate T cell–mediated hypersensitivity [6]. In the present case, we obtained a positive result in the LTT with ivacaftor and ETI (3 components). Positivity was even more marked with the latter, although we were unable to rule out the involvement of the other 2 active ingredients.

As described in the literature, therapeutic doses can be safety reintroduced in some patients with cutaneous reactions

to CFTR modulators [7]. After introduction of the compound ETI, the patient experienced peak eosinophilia with no further issues. Other groups have reported the loss of tolerance in ivacaftor-desensitized patients switching to compounds containing elexacaftor, thus emphasizing the need for close surveillance when reintroducing this drug/component [8]. In the present case, we proposed desensitization as the safest and most effective method of restarting and continuing treatment, given the positive diagnostic test result, the patient's poor baseline condition (low FEV_1), and the risk of provoking a new reaction. Clinically, desensitization protocols have successfully induced temporary tolerance after mild type IV hypersensitivity reactions [9]. The effectiveness of desensitization in this type of reaction is supported by evidence of immunomodulation at the humoral and cellular levels during the protocol [10].

Based on 2 previously published cases of desensitization to ivacaftor [4] and another to ETI [5] and adaptation to our available resources, the protocol we used was designed to start with higher doses of ivacaftor than the previously mentioned protocols (Table). By undergoing the desensitization process, the patient was able to tolerate his first-line treatment, resulting in a significant improvement in lung function (FEV_1, +19%), weight gain, no hospitalizations or antibiotic treatment for respiratory infections (including SARS-CoV-2), and avoidance of lung transplantation, which is a key objective of the treatment.

We present a safe and effective protocol for desensitization to CFTR modulators in a case of delayed hypersensitivity to ivacaftor confirmed by a positive LTT result without being able to rule out hypersensitivity to elexacaftor and/or tezacaftor.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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ERRATUM:

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In Figure 1, the right arm corresponds to the patients included (N=39 555).