

## Successful Desensitization Protocol to Ivacaftor and a Compound of Elexacaftor/Tezacaftor/Ivacaftor in a Delayed Hypersensitivity Reaction Confirmed by Lymphocyte Transformation Test

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**Palabras clave:** Fibrosis quística. Moduladores del regulador de conductancia transmembrana de la fibrosis quística. Desensibilización. Hipersensibilidad retardada. Test de transformación linfocitaria.

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

We report a case of a 40-year-old male with CF (Phe508del mutation), severe lung disease (forced expiratory volume in the first second (FEV1): 27%), and multiple infectious respiratory exacerbations in the last six months, who was a candidate for lung transplantation. In February 2022, he started CFTR modulators: two tablets of the combination of Elexacaftor 100mg/Tezacaftor 50mg/Ivacaftor 75mg every morning and one tablet of Ivacaftor (IVA) 150mg every night. On day 7 of treatment, he presented with a maculopapular rash and eosinophilia (1020/ $\mu$ L) without fever, edemas, adenomegaly, or desquamation. Liver enzymes and acute-phase reactants were within normal range. ETI was withdrawn, and prednisone in tapering doses, topical corticosteroids, and antihistamines were started. Finally, the rash resolved eight days after ETI discontinuation.

He was referred to our allergy unit. We performed epicutaneous patch tests with ETI and IVA in 30% vaseline, with negative readings at 48, 72, and 96 hours. In addition, we performed a lymphocyte transformation test (LTT) with commercial tablets of ETI 100 ug (equivalent to Ivacaftor 33 ug, Tezacaftor 22 ug and Elexacaftor 44 ug) and IVA. The tablets were dissolved in dimethyl sulfoxide (DMSO). We incubated fresh peripheral-blood mononuclear cells from our patient previously separated over a density gradient (Histopaque-1077, Sigma-Aldrich) for six days in flat bottom wells of microtitre plates at  $2 \times 10^5$  cells/well. The test was performed in triplicates with ETI and IVA 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), the ratio of mean counts per minute with drugs to those without drugs. Based on previous studies, LTT was considered positive at a SI >2[3]. The LTT performed with ETI and IVA in two healthy subjects yielded SI < 2. We obtained a positive SI of 3.2 for ETI at 1 µg/mL and 2.5 at 10 µg/mL concentrations. IVA was positive with an SI of 2.6 at 10 µg/mL. With these results, we can confirm sensitization to IVA, but sensitization to the other two components cannot be excluded.

Based on the *in vitro* test result and the patient's comorbidities (severely compromised pulmonary function, poor quality of life, and the lack of effective alternative therapies), the treatment was reintroduced with a desensitization protocol, which was designed based on our experience, previous literature[4,5], and research (Table 1). Desensitization started with 0.15mg IVA (a thousandth of the therapeutic). For this purpose, the hospital pharmacy prepared an oral suspension crushing one tablet of IVA 150mg diluted in 75mL of sterile water for the first doses, obtaining a 2mg/mL concentration. We made a fresh suspension each day due to the unknown stability of IVA when diluted. We doubled the

amount to 1/8 tablet daily over five days, subsequently increasing by a quarter tablet weekly, reaching 150mg of IVA. 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 IVA, daily). Ebastine 10mg was used as premedication throughout the protocol due to the patient's dermographism. We monitored eosinophilia (patient's baseline 300  $\mu$ L) and liver function with periodic blood tests. Only in one analytical control, when introducing a quarter tablet of ETI, we observed eosinophilia of 720 cells/ $\mu$ L without organ involvement, keeping the dose increase planned (Table 1). At the one-and-a-half tablet dose of ETI in the second phase of the protocol, our patient developed a mild COVID-19 respiratory infection, which did not require hospital admission, modification of the desensitization protocol, or lowering the ETI dose tolerated up to that point. He has been on full-dose treatment for ten months with no adverse reactions and significant improvement in his pulmonary function (baseline FEV1: 1.10 liters, 27%; FEV1 at ten months of treatment/current: 1.84 liters, 46%) and weight gain (+6kg).

Delayed hypersensitivity reactions have been reported since the introduction of CFTR modulators in 2019[2]. Few clinical cases had an allergy study using lymphocyte clone cultures to demonstrate T cell-mediated hypersensitivity[6]. In our case, we obtained a positive result in the LTT with IVA and the three components ETI, being even more positive with the latter and, therefore, without being able to rule out the involvement of the other two active ingredients.

As described in the literature, some patients with cutaneous reactions to CFTR modulators can be safely reintroduced to therapeutic doses[7]. After introducing the compound with ETI, our patient had a pick of eosinophilia without further issues. Other groups have reported the loss of tolerance in ivacaftor-desensitized patients switching to

compounds containing elexacaftor, emphasizing the need to close surveillance when reintroducing this drug/component [8]. We proposed desensitization to our patient 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 FEV1) and the risk of provoking a new reaction. Clinically, desensitization protocols have successfully induced temporary tolerance after mild type IV hypersensitivity reactions[9]. Recently, evidence of immunomodulation at the humoral and cellular levels during desensitization explains its effectiveness in this type of reaction[10].

Based on two previously published cases of desensitization to IVA[4] and another to ETI[5] and adapting them to our available resources, the protocol used in our patient was designed, starting with higher doses of IVA than the previously mentioned protocols (See Table 1). By undergoing the desensitization process, the patient was able to tolerate his first-line treatment, resulting in a significant improvement in lung function (FEV1 + 19%), weight gain, no hospitalizations or antibiotic treatment for respiratory infections (including SARS-CoV2), and avoidance of lung transplants, which is one of the most relevant objectives of the treatment.

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

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## ABBREVIATIONS

cystic fibrosis transmembrane conductance modulators (CFTR); cystic fibrosis (CF); forced expiratory volume in the first second (FEV1); elexacaftor/tezacaftor/ivacaftor (ETI); Ivacaftor (IVA); lymphocyte transformation test (LTT); stimulation index (SI)

## PATIENT'S CONSENT

Written patient consent has been obtained for publication.

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## DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interests to disclose.

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Table 1. Desensitization protocol for ivacaftor and then in an additive way to the compound elexacaftor/tezacaftor/ivacaftor (ETI).

Phase I: IVACAFTOR DESENSITIZATION				Phase II: ETI DESENSITIZATION						
Day	Eosinophilia / $\mu$ L	IVA administration	Dose (mg)	Week	Eosinophilia / $\mu$ L	ETI 100mg/50mg/75mg	Dose IVA (mg)	Dose ELX (mg)	Dose TEZ (mg)	
1 <sup>o</sup>	300	a	0.15mg→0.30mg→0.60mg <sup>c</sup>	1.05	1 <sup>o</sup>	720 <sup>d</sup>	$\frac{1}{4}$ tablet <sup>f</sup>	168.75	25	12.5
2 <sup>o</sup>	ND		1.2mg→2.4mg→4.8mg <sup>c</sup>	8.4	2 <sup>o</sup>	ND	$\frac{1}{2}$ tablet <sup>f</sup>	187.5	50	25
3 <sup>o</sup>	ND		10mg	10	3 <sup>o</sup>	610 <sup>d</sup>	$\frac{3}{4}$ tablet <sup>f</sup>	206.25	75	37.5
4 <sup>o</sup>	ND		15mg	15	4 <sup>o</sup>	520 <sup>d</sup>	1 tablet <sup>f</sup>	225	100	50
5 <sup>o</sup>	ND		$\frac{1}{8}$ tablet <sup>e</sup>	18.75	5 <sup>o</sup>	ND	$1\frac{1}{4}$ tablets <sup>f</sup>	243.75	125	62.5
8 <sup>o</sup>	360	b	$\frac{1}{4}$ tablet <sup>f</sup>	37.5	6 <sup>o</sup>	160	$1\frac{1}{2}$ tablets <sup>f</sup>	262.5	150	75
15 <sup>o</sup>	ND		$\frac{1}{2}$ tablet <sup>f</sup>	75	7 <sup>o</sup>	ND	$1\frac{3}{4}$ tablets <sup>f</sup>	281.25	175	87.5
22 <sup>o</sup>	360		$\frac{3}{4}$ tablet <sup>f</sup>	112.5	8 <sup>o</sup>	ND	2 tablets <sup>f</sup>	300	200	100
29 <sup>o</sup>	ND		1 tablet <sup>f</sup>	150						

Abbreviations: IVA: Ivacaftor. ELX: Elexacaftor. TEZ: Tezacaftor. ETI: elexacaftor/tezacaftor/ivacaftor (*Kaftrio*®). ND: not done.

<sup>a</sup>Solution of 2mg/mL= crushing tablet of IVACAFTOR 150mg diluted in 75mL of sterile water. A fresh suspension was made each day.

<sup>b</sup>Tablet 150mg Ivacaftor (*Kalydeco*®).

<sup>c</sup>Interval of 90 minutes.

<sup>d</sup>Value over the normal range (limit 500 cells/mcl).

<sup>e</sup>Maintain at home  $\frac{1}{8}$  tablet for three days.

<sup>f</sup>Maintain one week.