Rapid drug desensitization protocol in delayed hypersensitivity reactions to CFTR modulator drugs: When everyday counts

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Small molecule cystic fibrosis transmembrane regulator (CFTR) modulator drugs have revolutionized the care of cystic fibrosis (CF) patients targeting the underlying cause, with the aim of slowing disease progression. [1] Currently, there are two types of approved CFTR modulators (CFTRm) known as potentiators (ivacaftor) and correctors (lumacaftor, tezacaftor, elexacaftor). The elexacaftor/tezacaftor/ivacaftor triple combination, which has been recently approved by the FDA and EMA in 2019 and 2020 respectively, is now available for almost 90% of CF patients (75% in Spain). [1,2] They have radically changed the course of the disease with lung function and body mass index improvement, and pulmonary exacerbations reduction. [3] Safety data have shown good tolerance to triple combination, nevertheless skin rash is frequent in 4-10% of patients, especially in women and under hormonal contraceptive treatment. [3] Notwithstanding, the risk of allergy to these drugs remains unknown. [4]

We report the case of a 9-year-old boy with CF (F508del homozygote), pancreatic insufficiency and mild lung impairment (baseline FEV1 75%). One week after starting therapy with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA); 200/100/150 mg in the morning and ivacaftor (IVA); 150 mg at night, he presented pruritic, erythematous papules all over his body and face. Within 24 hours, he also developed lip angioedema. (Fig. 1) There wasn't any mucosal involvement, skin blistering and he had no other symptoms including fever,

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respiratory distress, arthralgias, nor gastrointestinal complaints. Nor liver involvement or eosinophilia in the peripheral blood were evidenced. All viral serologies were negative, including parvovirus, measles, cytomegalovirus and Eipsten-Barr virus. PCRs of respiratory samples for coronavirus, influenza and respiratory syncytial virus, as well as mycoplasma pneumoniae were negative. The skin biopsy showed a spongiotic epidermis without detachment or necrotic keratinocytes. The dermis was slightly edematous with a mild perivascular lymphohistocytic inflammatory infiltrate with punctate neutrophils, along with an interstitial component containing abundant neutrophils, punctual eosinophils, and isolated mast cells. There was no leukocytoclasia nor fibrinoid necrosis. Therefore, exudative erythema multiforme (EEM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) were excluded. Skin lesions improved within 72 hours after high-dose systemic corticosteroids, antihistamines and CFTRm discontinuation. Full rash resolution occurred at three weeks. In order to determine whether this therapy could be restarted, an allergy study was performed. Since it was not possible to obtain each drug separately, patch tests were performed with IVA, TEZ/IVA, and ELX/TEZ/IVA at 5%, 10% in vaseline. Patch testing with ELX/TEZ/IVA at 10% was 2+ positive after 48 hours and negative in control subjects. In order to assess the patient´s in vitro specific T-cell response to these drugs we performed lymphocyte transformation tests (LTTs) with all three presentations. [4,5] Whereas IVA did not activate the patient´s T cells, TEZ/IVA LTT resulted in a weakly positive (stimulation index = 2.43 at a concentration of the 50 µM), ELX/TEZ/IVA LTT was clearly positive (stimulation index = 4.89 at a concentration of the 50 µM, stimulation index = 5.12 at a concentration of the 20 µM). Whereas a SI between 2 and 3 was considered a weakly positive proliferation response, a SI≥3 was considered positive as it follows. [6] These results suggested that TEZ or ELX or both of them activated specific effector T cells. We decided to perform an oral challenge with TEZ/IVA due to its questionable LTT outcome. After 9 hours, he developed a less severe

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pruritic rash over his thighs and trunk which subsided after oral corticosteroids and antihistamine administration. Blood tests were normal. Considering the possibilities, a slow desensitization protocol with ELX/TEZ/IVA was performed due to the limited experience with delayed hypersensitivity reactions with these therapies. [1] Unfortunately, on the fifth day of desensitization, four hours after the intake of 8 mg, a similar rash appeared again on the thighs and spread outwards. Skin lesions improved within 24 hours after oral corticosteroid and antihistamine. Finally, following our experience in desensitization to chemotherapy and biological drugs, we designed a rapid drug desensitization (RDD) protocol with ELX/TEZ/IVA with premedication (Supplementary material; table 1), which was successful and CFTRm therapy has been maintained to the present day with. Moreover, one month after desensitization he exhibited a new best FEV1 of 94% predicted and reported a clear improvement in his quality of life. Premedication was maintained for the two subsequent days at home. Except on two occasions, he presented a discrete rash that subsided after a few hours with the administration of oral antihistamines. At no time during these drugs introductions were eosinophilia or abdominal transaminases elevation, fever or systemic symptoms. Particularly in this case, due to the history of severe skin lesions, we performed a half dose desensitization to ELX/TEZ/IVA (100/50/75 mg) on a single day to assess tolerance and then the remaining dose was introduced on another day with the same protocol until 200/100/150 mg were reached. We also propose to reach therapeutic doses in one day for less severe cases. Dilutions were prepared using crushed tablets mixed with ORA-Plus® as an aqueous-based suspending vehicle and ORA-Sweet® as a syrup vehicle (1:2 mixture). [7] One month after desensitization we obtained a negative LTT with ELX/TEZ/IVA. (Supplementary material; figure 2) Taking into account the genetic predisposition, we investigated HLA-A 31:0, a known allele associated with susceptibility to drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome (SJS) in diverse populations. Nevertheless, the

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findings in this specific case were negative. The patient's HLA typing revealed A:03 A:03. Traditionally, the management of delayed drug reactions has involved employing slow desensitization protocols that extend over several days or even weeks [8] The underlying mechanism of this process remains unknown. [2] RDD protocols in delayed reactions can efficiently attain the target dose within a brief timeframe, which can be a crucial aspect in many pathologies. It has been demonstrated to be a safe procedure when conducted by allergists with expertise. [8] There is a lack of conclusive evidence regarding the utilization of premedication either before or after RDD [8, 9] Based on the experience so far with these patients, it is likely that sensitization to a CFTRm will develop if there is a previous history of sensitization to another one. [1] It is imperative to establish an adequate multidisciplinary management in these cases, always contemplating individualization.

RDD could be an effective and safe method for patients with delayed hypersensitivity reactions to CFTRm. This approach enables them to resume therapy swiftly, minimizing periods without treatment, hospital visits, or potential errors at home associated with slower desensitization protocols.

Conflict of interests

This paper has been read and approved by all authors.

Informed patient consent for publication was obtained.

Data and material were obtained from all the authors Departments who participated in this paper.

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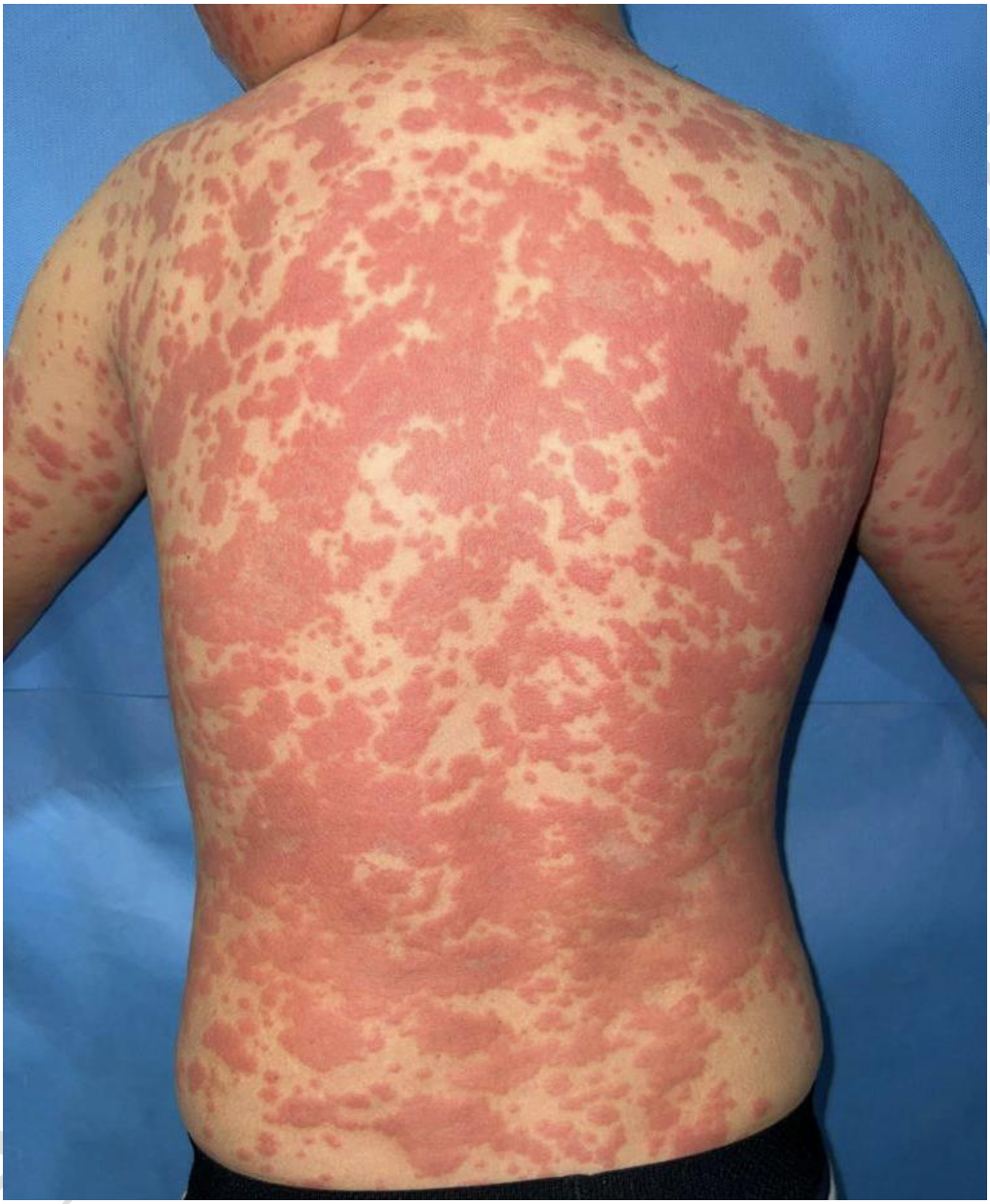
Figure 1. Erythematous plaques and papules with a tendency to confluence distributed on the back, blanching under pressure. No epidermal involvement.



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