Challenges in the treatment of cystic fibrosis in the era of CFTR modulators

Caroline Jacoby Schmidt[1], Laura Silveira de Moura[1], Paulo de Tarso Roth Dalcin[1,2], Bruna Ziegler[1,3]

The paper entitled "Use of elexacaftor+tezacaftor+ivacaftor in individuals with cystic fibrosis and at least one F508del allele: a systematic review and meta-analysis," published in the Brazilian Journal of Pulmonology, highlighted the effects of triple combination therapy targeting the cystic fibrosis transmembrane conductance regulator (CFTR) protein—elexacaftor+tezacaftor+ivacaftor (ETI). However, we believe that it is important to emphasize some challenges emerging regarding the maintenance of symptom treatment for the disease.

The maintenance of airway clearance techniques (ACTs) after the use of ETI is a challenge for professionals, families, and individuals with cystic fibrosis (CF). In addition to improving lung function and quality of life, as well as reducing the number of exacerbations, patients report a decrease in lung secretions with this therapy, leading to anxiety about the reduction of inhaled therapies (ITs) and ACTs.[1,2]

To date, no literature data supports the long-term reduction of ITs and ACTs. A randomized clinical trial with adults using ETI evaluated the suspension of ITs with hypertonic saline solution (SSH) or dornase alfa for six weeks. The authors observed non-inferiority in lung function with the suspension of one of the nebulization during the study follow-up. However, the group that suspended one of the ITs (SSH or dornase alfa) experienced a higher number of adverse effects when compared with the group maintaining ITs.[3]

A study conducted in the United Kingdom demonstrated that ITs and ACTs are considered the most demanding parts of the treatment. Professional guidance to patients who experienced a reduction in respiratory symptoms was to reduce routines but never to suspend them. Even with the increased flexibility and individualization of routines, the assisting team is often resistant to changes in treatment routines due to the fear that patients will not implement them again in case of an exacerbation.[2]

It is important to note that, in both studies, the included population had preserved lung function, not being representative of most of the Brazilian population with CF. These findings still hinder the extrapolation of these data to our referral centers in terms of reducing ITs and ACTs in the long term.[2,3]

Physical exercise has become increasingly important in the daily lives of patients, representing a significant area of intervention for physiotherapists and physical education professionals. With the reduction of ACT routines, the encouragement of routine exercise, both aerobic and anaerobic, is important for maintaining physical conditioning and preventing excessive weight gain, which may become a reality for patients using ETI.

For the first time, patients are optimistic about their future due to a reduction in symptoms and the possibility of reducing the burden imposed by treatment. It is up to the teams to customize the treatment carefully for each patient according to their new reality. The positive effects of reducing ITs and ACTs are associated with improvements in well-being, mental health, and social life. However, their effects on long-term lung function are yet to be described. It is necessary to act with caution and rigorously monitor routine changes until more evidence can guide future treatment guidelines for patients undergoing ETI.

REFERENCES

1. Silva Filho LVRFD, Athanazio RA, Tonon CR, Ferreira JC, Tanni SE. Use of elexacaftor+tezacaftor+ivacaftor in individuals with cystic fibrosis and at least one F508del allele: a systematic review and meta-analysis. J Bras Pneumol. 2024;49(6):e20230187. https://doi.org/10.36416/1806-3756/e20230187
2. Almulhem M, Harnett N, Graham S, Haq I, Visram S, Ward C, et al. Exploring the impact of elexacaftor-tezacaftor-ivacaftor treatment on opinions regarding airway clearance techniques and nebulisers: TEMPO a qualitative study in children with cystic fibrosis, their families and healthcare professionals. BMJ Open Respir Res. 2022;9(1):e001420. https://doi.org/10.1136/bmjresp-2022-001420
3. Mayer-Hamblett N, Ratjen F, Russell R, Donaldson SH, Riekert KA, Sawicki GS, et al. Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials. Lancet Respir Med. 2023;11(4):329-340. https://doi.org/10.1016/S2213-2600(22)00434-9

1. Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
2. Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre – HCPA – Porto Alegre (RS) Brasil.
3. Serviço de Fisioterapia, Hospital de Clínicas de Porto Alegre – HCPA – Porto Alegre (RS) Brasil.

Authors' reply

Luiz Vicente Ribeiro Ferreira da Silva Filho[1], Rodrigo Abensur Athanazio[2], Carolina Rodrigues Tonon[3], Juliana Carvalho Ferreira[2], Suzana Erico Tanni[3]

We received the correspondence entitled "Challenges in the treatment of cystic fibrosis in the era of CFTR modulators" and would like to thank the authors for bringing up such an important issue. As more evidence accumulates, CFTR modulators such as elexacaftor-tezacaftor-ivacaftor (ETI) stand for as a revolutionary therapeutic option for people with cystic fibrosis (CF). The magnitude of improvement in many key health outcomes of the disease is quite impressive[1] and will certainly transform the scenario of CF care in the next few years.

We do agree with the authors of the correspondence that many uncertainties about standard CF care will emerge, including management of respiratory infections, use of mucolytics, and airway clearance therapies (ACTs). As stated in the correspondence, nebulized therapies and ACTs are indeed responsible for most of the treatment burden in CF, and towards that, the SIMPLIFY study[2] aimed to investigate the safety of withdrawing hypertonic saline or dornase alfa use in people with CF treated with ETI. Although the study confirmed the non-inferiority outcome, it enrolled patients with well-maintained lung function and assessed the impact on lung function over a relatively brief period of six weeks.[2]. A recently published data from the SIMPLIFY substudy, however, focusing on individuals with CF and impaired lung function, demonstrated comparable results after discontinuation of hypertonic saline among those with FEV_1 levels ranging from 40% to 69%.[3] Consequently, we acknowledge that CF healthcare providers, while potentially making such decisions, should remain aware of associated risks and ensure vigilant and thorough monitoring of individuals when implementing these practices.

While we also believe that ACTs represent one of the main-stem aspects of CF care, a revision of the role of each professional composing the multidisciplinary team involved in CF care is anticipated. Doctors themselves should be observant to changes in life expectancy and possible complications related to aging. Psychologists should focus on behavior adjustments in the face of a new lifestyle and life expectancy. Physiotherapists may need to focus on muscular conditioning and rehabilitation of individuals who may have spent most of their lives with severe physical limitations.

Finally, we believe that we are witnessing a very exciting new era in CF. This is a much more optimistic scenario, although there is still plenty of uncertainties that must be adequately evaluated and investigated in the coming years in order to provide the best treatment options for individuals with CF.

REFERENCES

1. Silva Filho LVRFD, Athanazio RA, Tonon CR, Ferreira JC, Tanni SE. Use of elexacaftor+tezacaftor+ivacaftor in individuals with cystic fibrosis and at least one F508del allele: a systematic review and meta-analysis. J Bras Pneumol. 2024;49(6):e20230187. https://doi.org/10.36416/1806-3756/e20230187
2. Mayer-Hamblett N, Ratjen F, Russell R, Donaldson SH, Riekert KA, Sawicki GS, et al. Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials. Lancet Respir Med. 2023;11(4):329-340. https://doi.org/10.1016/S2213-2600(22)00434-9
3. Nichols D, Gifford A, Russell R, Odem-Davis K, Young J, Amaro-Galvez R, et al. Assessing Safety of Discontinuing Hypertonic Saline in Those with Lower Forced Expiratory Volume in 1 Second after Elexacaftor/Tezacaftor/Ivacaftor. Ann Am Thorac Soc. 2024;21(2):360-362. https://doi.org/10.1513/AnnalsATS.202308-735RL

1. Unidade de Pneumologia Pediátrica, Instituto da Criança e do Adolescente, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Botucatu, (SP) Brasil.