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Commentary

Fabry disease during the COVID-19 pandemic. Why and how treatment should be continued

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ABSTRACT

Fabry disease is an X-linked disease due to a deficiency of the lysosomal enzyme alpha-galactosidase A. Clinical symptoms in classically affected males include acroparesthesia, anhydrosis and angiokeratoma, which may present during childhood followed by cardiac, cerebral and renal complications. Even though pulmonary involvement is not widely appreciated by clinicians, an obstructive lung disease is another recognized component of Fabry disease. Coronavirus Disease-19 (COVID-19), caused by the SARS-CoV-2 virus was labeled as a global pandemic and patients with Fabry disease can be considered at high risk of developing severe complications. The impact of COVID-19 on patients with Fabry disease receiving enzyme replacement therapy is still unknown. Many patients who receive treatment in the hospital experienced infusion disruptions due to fear of infection. Effects of temporary treatment interruption was described in more detail in other lysosomal storage diseases, but the recommencement of therapy does not fully reverse clinical decline due to the temporary discontinuation. When possible, home-therapy seems to be the most efficient way to maintain enzyme replacement therapy access during pandemic.

Sentence take-home message: Home-therapy, when possible, seems to be the most efficient way to maintain enzyme replacement therapy access during pandemic in patients with Fabry disease.

Fabry disease (FD) is a progressive, X-linked inherited lysosomal storage disorder caused by mutations in the α-Galactosidase A gene (*GLA*). Partial or complete deficiency of the enzyme α-Galactosidase A (α-Gal A) results in a progressive accumulation of lipids, primarily globotriaosylceramide (Gb3) and its deacylated derivative globotriaosylsphingosine (lyso-Gb3) [1].

Typical signs and symptoms in the early phase of the classic phenotype are acroparesthesia, episodes of diarrhea and abdominal pain, cornea verticillata, dyshidrosis, tinnitus, angiokeratomas, and microalbuminuria [1]. Severe organ manifestations become evident during the third decade of life in males and approximately the fourth decade of life in females [2,3]. Cardiac hypertrophy, renal dysfunction, and stroke are the most severe complications [4].

Two preparations of enzyme replacement therapy (ERT) -agalsidase alfa and agalsidase beta- with recombinant α-galactosidase was approved in Europe in 2001 [5]. Agalsidase beta is the only ERT approved by the US Food and Drug Administration since 2003 [6]. Migalastat (Galafold®) was approved in Europe in May 2016, in Canada in September 2017, in Japan in March 2017 and in the USA in August 2018 for long-term treatment of FD in adults with an amenable mutation [7].

Even though pulmonary involvement is not widely appreciated by clinicians, an obstructive lung disease (specifically of the small airways) is another recognized component of Fabry disease. The original patient described by Fabry in 1898 had “asthma” and frequent respiratory tract infections [8] and died at age 43 of lung disease [9]. Several reports describe signs and symptoms of pulmonary involvement such as dyspnea, wheezing, and dry cough in Fabry disease [10–13]. Many of these signs and symptoms were described without simultaneous cardiac compromise. Less frequent signs like haemoptysis, pneumothorax and pulmonary thromboembolism have been described.

Rosenberg et al. [11] reported on light and electron microscopic evaluation of cells recovered from alveolar lavage fluid and from brushing the airway epithelium in 3 patients. In all of them, cytoplasmic inclusion bodies in ciliated epithelial cells and goblet cells were revealed. Sputum induced exam showed lamellar inclusion bodies within all ciliated bronchial epithelial cells examined in one patient. The same report examined sputum from five subjects without Fabry disease and were unable to find similar inclusions [14].

A histochemical study of a lung biopsy specimen from one patient revealed a marked increase of Gb3 that accounted for 10.7% of total lipids, and histopathologic examination revealed laminated inclusions in the capillary endothelium and type II pneumocytes [15]. Smith et al.

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[16] reported the histopathology and electron microscopy autopsy findings of the pulmonary vasculature in a 52 year-old man with Fabry disease. Zebra bodies inclusions were found within the endothelial cells of capillaries, arterioles and veins and in the smooth muscle cells of small pulmonary arteries. Zebra bodies with much thinner, delicate dense bands were also found in the lung parenchyma, either in the alveolar interstitium or within capillary endothelial cells.

The proposed mechanisms for the development of airway obstruction in Fabry disease include loss of lung elastic recoil, hyperreactivity (bronchospasm), airway inflammation and airway narrowing related to accumulation of glycosphingolipid and hyperplasia in airway epithelial and smooth muscle cells [11–13]. However, a putative mechanism involving airway hyperreactivity and bronchospasm was not supported in one study. None of the patients subjected to methacholine challenge testing exhibited a positive response [11].

Brown et al. [10] studied pulmonary manifestations and pulmonary function test in 25 affected Fabry men. Shortness of breath on mild to moderate exertion was reported by 36% of the subjects and cough and wheezing were present in 24%. Nine patients (36%) had reduced FEV1/FVC ratio consistent with obstructive ventilatory impairment; four of the nine were nonsmokers. Forced expiratory time to deliver the middle half of the FVC ($FEF_{25–75}$) was elevated in eight of these patients. The prevalence of obstructive impairment was strongly age-dependent, in parallel with the relationship found for extra-pulmonary symptoms [11].

Odler et al. [17] published the evaluation of 7 Fabry patients (40.2 ± 5.6 years) before and after ERT. At baseline, all patients had respiratory symptoms; however, these symptoms were usually mild. The most prominent lung function changes were registered in parameters reflecting small airway involvement, including significant decrease in $FEF_{25–75}$, increase in residual volume (RV) and RV/ total lung capacity ratio. Furthermore, a review by Franzen et al. [18] found that obstructive lung disease was up to 10 times more frequent in patients with Fabry disease compared to the general population. The same author later reported the long-term follow-up of pulmonary function in 95 patients (41% males). The overall prevalence of bronchial obstruction was 46%, and FEV1 decreased 29 ml per year [19].

In two small retrospective studies, ERT has been reported to stabilize or even ameliorate the burden of pulmonary involvement in Fabry disease, mainly bronchial obstruction and/or sleep apnea [20,21]. An interventional study of six patients receiving either ERT or placebo showed an increased exercise tolerance in patients receiving ERT [22]. Lung function parameter in five patients (2 males) on ERT were followed longitudinally for an average of five years [17]. In three patients, FVC and FEV1 increased during the treatment period, in one patient slight decrease of FVC and FEV1 were registered and in one patient a slight decrease in FVC, with an increase in FEV1. Recently, Franzen et al. [23] reported the change in z-scores of FEV1 and FEV1/FVC over time in 53 patients. In the same study, they investigated whether factors related to age, sex, tobacco, phenotype, residual α-gal activity, age at ERT initiation, Mainz Severity Score Index (MSSI) and lyso-Gb3 levels in plasma may affect change in FEV1 and FEV1/FVC over time. Median spirometric follow-up time was 7.7 years. When considering z-scores, 27 patients (51%) developed airflow limitation over time. Factors including male sex, active tobacco or past history of smoking, cardiac involvement and increased patient age at ERT initiation were associated with faster FEV1 decline in the univariate analysis. These results suggest that earlier ERT initiation may help to stabilize FEV1 decline and preserve pulmonary function.

Coronavirus Disease-19 (COVID-19), caused by the SARS-CoV-2 virus was characterized as a global pandemic by the World Health Organization in March 2020. Rare diseases, like inborn errors of metabolism, were included in the group of conditions considered to have an extremely high risk of severe illness [24]. There are no reports describing Fabry patients affected with COVID-19 or practical recommendations related to ERT during this period. Due to lack of data analogy to other inherited diseases is used for recommendations for Fabry disease.

Sechi et al. [25] recently reported their experience with 102 patients affected by the following diseases: Gaucher, Pompe, Fabry, mucopolysaccharidosis, Niemann Pick type C and cystinosis. At the beginning of the pandemic, 71 pt. (69.6%) were receiving ERT and 26 (25.5%) were on oral treatments. No interruption or modification occurred for patients receiving only oral therapy. All patients who were already on home-therapy continued their ERT infusions regularly, but 49% of patients receiving ERT in the hospital experienced treatment disruptions.

There is limited evidence regarding temporary discontinuation of ERT in Fabry disease. Cabrera and Politei [26] reported one male who started agalsidase beta. After two years of favorable response to ERT, the patient decided to suspend treatment. Patient presented two years later with increasing pain, fatigue, progression of cardiac involvement and new white matter lesions in brain MRI. Treatment discontinuation resulted in a fast deterioration of impaired organs and the appearance of new Fabry manifestations.

Effects of temporary ERT interruption were described in more detail in other lysosomal storage diseases like Gaucher disease type I and mucopolysaccharidoses (MPS). Drelichman et al. [27] reported a group of Gaucher type I patients, that after 1 to 7 years of ERT, none had skeletal manifestations, organomegaly had decreased or disappeared and hematologic features had improved. However, after 15 to 36 months of ERT interruption, splenomegaly recurred or worsened in all children, hepatomegaly and hematologic features recurred or worsened, serious bone manifestations developed in 4 children, and 3 children experienced growth retardation. They concluded that skeletal manifestations did not resolve after treatment reinstatement. In MPS, ERT interruption can lead to the loss of the beneficial effects and, in some circumstances, the abrupt withdrawal of ERT significantly worsened the clinical evolution of the patient, especially if the interruptions were for more than two months [28–31].

1. Conclusions

ERT has a beneficial clinical impact in Fabry disease, as it can relieve neuropathic pain and gastrointestinal symptoms, improve quality of life, reduce plasma lyso-Gb3 levels and clear Gb3 inclusions from renal cells, with a dose-dependent mechanism in podocytes. Evidence, mainly derived from male studies, shows that patients may benefit from early treatment initiation, before major clinical organ damage has developed.

After ERT interruption, a recommencement of therapy does not fully reverse clinical decline resulting from the discontinuation. Home-therapy seems to be the most efficient way to maintain therapy access during the COVID-19 pandemic when possible and correct use of personal protective equipment should be guaranteed. If home-therapy is not available, safe locations and plans that separate COVID-19 and non-COVID-19 patients should be carefully prepared in hospitals and infusion centers.

Individual author contributions

Juan Politei is the only contributor to the concept/design of the manuscript, data acquisition, data analysis/interpretation and critically revising the manuscript.

Declaration of Competing Interest

Juan Politei has no conflicts of interest to declare related to this manuscript

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