

Anderson-Fabry disease: No histological signs of pathological accumulation in arterial and venous endothelium during pegunigalsidase alfa therapy

Gabriela Dostálová¹, Helena Hulková^{2,3}, Ales Linhart¹

¹2nd Department of Internal Cardiovascular Medicine, ^{1st} Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic

²Department of Pediatrics and Adolescent Medicine, ^{1st} Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic

³Department of Pathology, ^{1st} Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic

Correspondence to:

Gabriela Dostálová, MD, PhD,
2nd Department of Internal
Cardiovascular Medicine,
1st Faculty of Medicine,
Charles University and General
University Hospital,
U Nemocnice 2, 128 08 Prague,
Czech Republic,
phone: +42 073 123 93 97,
e-mail: gabriela.dostalova@vfn.cz

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A 43-year-old male patient with Anderson-Fabry disease (AFD) diagnosed in adulthood during a family screening (mutation c.734DEL61) [1] was qualified for surgical removal (phlebectomy) of varicosities. This enzymatic defect results in pathological accumulation of glycolipids in lysosomes of the vascular endothelium and several cell types [2].

Since 2003, the patient has received an intravenous biweekly enzyme replacement therapy (ERT) for the classic form of AFD, with skin involvement, hypertrophic cardiomyopathy, severe gastrointestinal symptoms, arthralgias, and peripheral neuropathy. The indications for starting ERT in different countries are covered by national guidelines, e.g. a position statement in Poland [3]. Between 2003 and 2006, the patient was treated by agalsidase beta (Sanofi/Genzyme, Cambridge, MA, USA), followed by agalsidase alfa (Shire/Takeda, Lexington, MA, USA). In 2017, he was successfully enrolled in the “Bridge” study (Protalix BioTherapeutics) fulfilling inclusion criteria such as persistent symptoms and disease progression. The “Bridge” study (PB-102-F30 NCT03018730) is an ongoing phase III, open-label, switch-over study, assessing the safety and efficacy of pegunigalsidase alfa in AFD patients previously treated with agalsidase alfa for at least 2 years [4].

The patient’s treatment was started in November 2017 according to the study protocol by biweekly infusions of the enzyme pegunigalsidase alfa (1 mg/kg). This enzyme

is a chemically modified pegylated plant cell culture-expressed version of the recombinant α -galactosidase A enzyme. In comparison to currently available enzymes, its half-life is substantially longer. In a pivotal trial, the enzyme was shown to reduce globotriaosylceramide deposits within the kidney [5]. Notably, our patient’s kidney function stabilized during more than 2 years of the study medication administration, and gastrointestinal symptoms, arthralgias, and peripheral pain improved.

In December 2019, the patient underwent surgical removal of varices of the great saphenous vein of the right leg due to clinical worsening. Tissue samples were taken and referred for an electron microscopic examination. The lysosomal storage characterized by typical lamellar inclusions was not demonstrated either in venous or arterial endothelial cells. In contrast, inclusions were detectable in arterial and venous smooth muscle cells (Figure 1A–D) and, massively, in the perineurial cells of the small peripheral nerves (Figure 1F, G). More discrete accumulation was demonstrated in fibroblasts and Schwann cells.

These results suggest the potential benefits of applying pegunigalsidase alfa on endothelial storage of AFD patients currently being treated with the available ERT.

Article information

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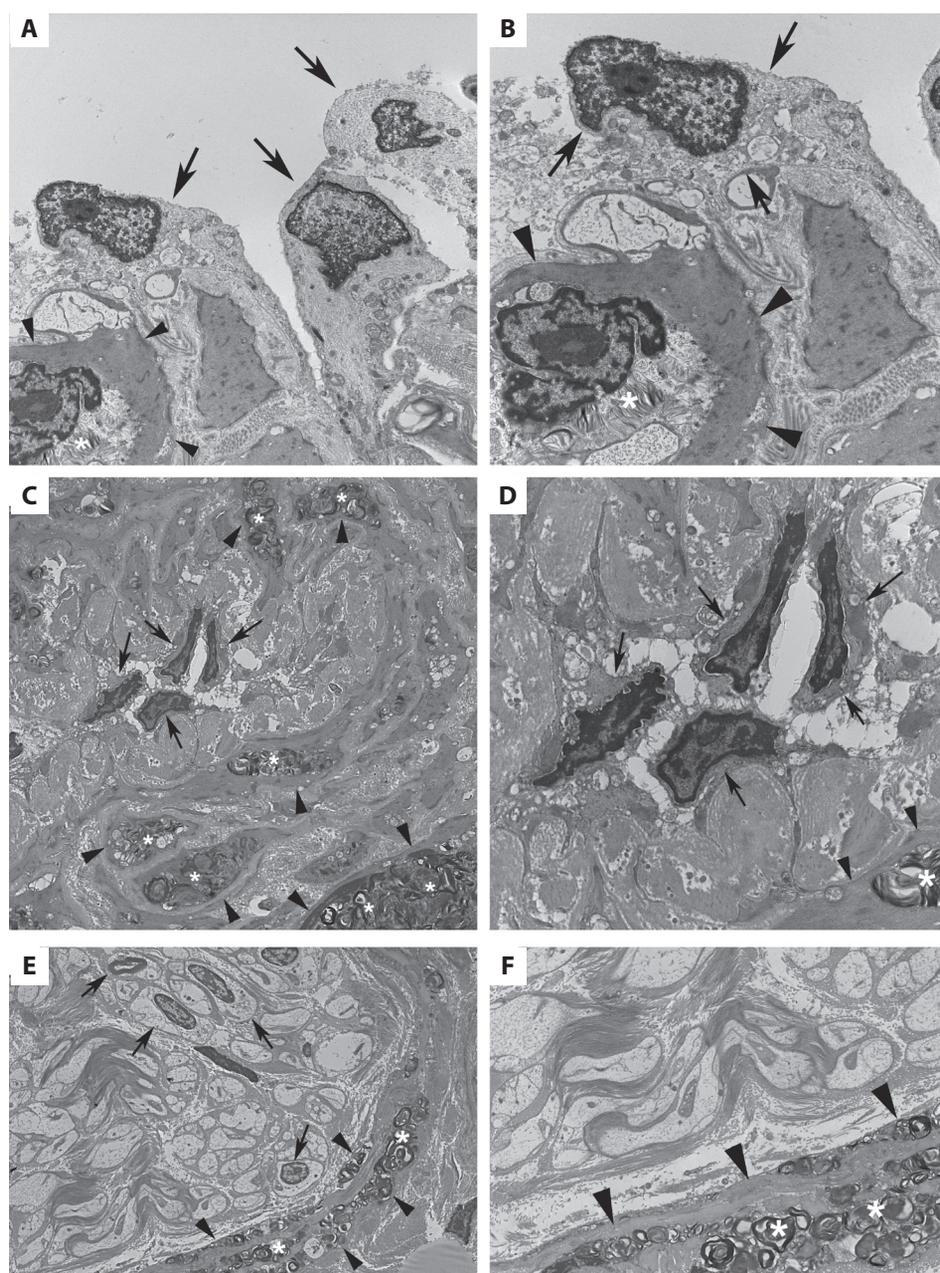


Figure 1. Ultrastructural analysis of lysosomal storage in the vena saphena magna, small artery and peripheral nerves.

A, B. Vena saphena magna. Absence of lysosomal storage in endothelial cells together with clearly detectable lysosomal storage of membranous parallel structures (zebra-like) in a vascular smooth muscle cell.

A. Magnification $\times 8000$.

B. Magnification $\times 12000$. Endothelial cells are marked by arrows, smooth muscle cells by arrowheads.

C, D. Small artery. Absence of lysosomal storage in endothelial cells. Vascular smooth muscle cells reveal lysosomal storage of membranous concentric or parallel structures. **C.** Magnification $\times 5000$. **D.** Magnification $\times 12000$. Endothelial cells are marked by arrows, smooth muscle cells by arrowheads.

E, F. Peripheral nerve. Conspicuous lysosomal storage of osmiophilic membranous material typical of Fabry disease in a perineurial cell. The cytoplasm of demonstrated Schwann cells is without detectable lysosomal storage. **E.** Magnification $\times 3000$. **F.** Magnification $\times 6000$. Schwann cells are marked by arrows, the perineurial cell by arrowheads. Storage material is marked by asterisks in all the photos

Genzyme, and Takeda/Shire HGT. AL received honoraria and consulting fees from Amicus Therapeutics, Sanofi Genzyme, and Takeda/Shire HGT; Fabry Registry Board member. HH declares no conflict of interest.

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