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THERAPEUTIC APPROACH TO PEDIATRIC PATIENTS WITH CLASSIC FABRY DISEASE: TOWARDS A NEW PARADIGM

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ABSTRACT **–** Fabry disease (FD) is an X-linked lysosomal disorder caused by pathogenic variants in the GLA gene encoding the enzyme α-galactosidase A (α-Gal A). Male patients with classic FD have severely reduced or absent α-Gal A activity, resulting in the accumulation of globotriaosylceramide in a variety of tissues. This causes early and progressive damage to the targeted organs, life-threatening complications, and an increased risk of premature death. The severity of the disease is more variable in females because of random X chromosome inactivation and its impact on α-Gal A activity. The definition of appropriate timing of treatment initiation is crucial in classic FD patients, notably in the pediatric population, as the clinically asymptomatic progression of renal, cardiac and cerebral manifestations spans many years.

Today, the key question is whether the state-of-the-art knowledge of Fabry, the available treatment options and the current physicians' experiences make it necessary to develop a new paradigm in the therapeutic management of patients with classic FD. To answer this question, the authors reviewed a selection of papers specifically reporting the results of enzyme replacement therapy in classic FD patients.

In the published literature, the authors highlight how the introduction of a new paradigm in the management of pediatric patients with classic FD is now possible through the definition of the appropriate treatment regimen and timing of treatment.

A Delphi panel on Early Treatment in pediatric classic Fabry Disease, under the aegis of the Italian Society for the Study of Inherited Metabolic Diseases and Newborn Screening (SIMMESN), is working on these novel approaches. The theoretical assumptions underlying the resulting consensus, that will be available in another publication, are reported here.

Keywords: Pediatric patients, Fabry disease, α-Gal A.

BACKGROUND

Fabry disease (FD, OMIM 301500) is an X-linked disorder caused by pathogenic variants in the *GLA* gene encoding the lysosomal glycohydrolase enzyme α-galactosidase A (α-Gal A)[1]. Absent or deficient α-Gal A activity results in the accumulation of glycosphingolipids, predominantly globotriaosylceramide (Gb3) and its deacylated derivative globotriaosylsphingosine (lyso-Gb3), in body fluids and a variety of tissues including the kidney, heart, and central and peripheral nervous systems. This causes progressive dam-

age to the targeted organs, life-threatening complications, and an increased risk of premature death. FD can be classified into classic or non-classic (later-onset) phenotypes. Male patients with classic FD have severely reduced or no residual α-Gal A activity and generally present signs and symptoms from childhood, such as neuropathic pain, cornea verticillata, gastrointestinal symptoms, hypohidrosis, and angiokeratoma[1]. Long-term disease manifestations include proteinuric chronic kidney disease leading to renal failure, hypertrophic cardiomyopathy, cardiac arrhythmia, and stroke[2]. Later-onset FD, a milder phenotype, is seen in male patients with residual α-Gal A activity due to missense and splicing GLA variants. Early clinical features are usually absent, and disease manifestations of key target organs may be absent or mild, occur later in life, and be limited to cardiac or renal involvement. Phenotypes are well characterized in males, whereas the severity of the disease is more variable in females because of X chromosome inactivation and its impact on residual α-Gal A activity in different organs[3]. FD was traditionally considered to be an adult disease, but it is now recognized that disease processes and symptoms start in infancy or early childhood. Early manifestations of classic FD in children do not include only functional symptoms, such as neuropathic pain, reduced sweating, fatigue or gastrointestinal discomfort, but it has been demonstrated that metabolic storage starts very early in life, as young patients with classic FD have severe globotriaosylceramide deposition in all kidney cellular types, long before overt clinical renal disease[4,5]. Consequently, the issue of timely initiation of treatment is an increasingly important debate.

The key question today is whether the current state of knowledge about Fabry, the available treatment options, and the current experience of clinicians necessitate the development of a new paradigm in the therapeutic management of patients with classic FD.

In order to find an answer to this question, the authors reviewed a selection of papers reporting on the outcome of enzyme replacement therapy (ERT) in classic FD patients. They reported here the theoretical assumptions underlying a soon-to-be-published Consensus resulting from a Delphi panel on early treatment in pediatric classic Fabry disease under the aegis of the SIMMESN.

TREATMENT OF FABRY DISEASE: THE STATE-OF-THE-ART

Since 2001, ERT with exogenous recombinant α-galactosidase has been the mainstay of FD-specific treatment to stabilize, delay or prevent progressive organ damage and improve disease symptoms[6]. At present, there are three preparations of ERT available in most countries:

- Agalsidase alfa, approved in Europe as an intravenous infusion at the dose of 0.2 mg/kg every other week (eow) in patients with FD from the age of 7 years[7].
- Agalsidase beta, approved as an intravenous infusion at the dose of 1 mg/kg eow from the age of 8 years in Europe[8] and from the age of 2 years in the USA[9]. This extension of the pediatric indication in the USA has been based on the results of a trial that involved a cohort of young patients suffering from classic FD aged 2–8 years with elevated plasma GL-3 levels (i.e., >7.03 µg/mL) at baseline, who received agalsidase beta at the dose of 1 mg/kg over a 2-year period. Plasma GL-3 levels fell within the normal range (i.e., ≤7.03 µg/mL) in 91% (20/22), 95% (18/19), and 92% (12/13) of patients at 6, 12, and 24 months, respectively[9].
- Pegunigalsidase alfa, a novel PEGylated recombinant α-galactosidase for intravenous infusion, has been recently approved and for which, however, there is no pediatric indication yet[10].

In addition to enzyme replacement therapy, an alternative strategy for the treatment of FD is currently available, based on the enhancement of the residual α-Gal A activity by an oral chaperone therapy (migalastat; Galafold®, Amicus). Migalastat was approved for the treatment of a restricted cohort of FD patients with GLA amenable variants and the European Commission has recently expanded its use to children with specific amenable genetic variants starting from the age of 12 years[11].

Although there is a lack of head-to-head studies between different therapies, there are several switches and comparative studies that show relevant real-world data valuable for clinical practice precisely because they are conducted in real-world clinical settings.

Concerning the long-term outcome of Fabry patients treated by ERT, the accumulation of clinical trials and real-world evidence over the last 20 years has shown that ERT via the lifelong intravenous infusions of recombinant agalsidase alfa[12] or recombinant agalsidase beta[13] every other week is safe and clinically and biologically effective in patients with FD[14-18].

Indeed, with regard to enzyme replacement therapies, the data available to date have demonstrated dose-dependent efficacy in both pediatric and adult patients.

In pediatric patients, the correlation of clinical dose response in pediatric patients was demonstrated at the renal level in a prospective open-label study with consecutive enrollment of 12 classic Fabry pediatric patients who started ERT. These patients were given renal biopsies at baseline and after 5 years of ERT and additional biopsies at 1 and 3 years. The study showed that only patients treated with the highest cumulative dose (1 mg/kg) achieved complete clearance of podocyte storage material, which was not achieved in patients treated with the lowest cumulative dose (0.2–0.4 mg/kg)[19]. Dose-dependent effects of ERT have been further investigated in another study that evaluated the impact of different ERT regimens in serial kidney biopsies from patients treated for up to 14 years. In this study, 20 patients with classic Fabry disease started ERT at a median age of 21 (range: 7–62) years old. Agalsidase-alfa or agalsidase-beta was prescribed for a median of 9.4 years. The lower fixed dose group received agalsidase 0.2 mg/kg every other week (eow) throughout the follow-up period. The higher dose group received a range of agalsidase doses (0.2–1.0 mg/kg every other week). Kidney biopsies showed that podocyte Gb3 reduction correlated with cumulative agalsidase dose (r=0.69; p=0.001), and also arterial/arteriolar intima Gb3 cleared significantly in the higher dose group. Residual plasma lyso-Gb3 levels remained higher in the lower fixed dose group (20.1 nmol/L [SD=11.9]) compared with the higher dose group (10.4 nmol/L [SD=8.4]) and correlated with cumulative agalsidase dose in men (r=0.71; p=0.01)[20].

Dose-dependent efficacy of the ERT has also been confirmed in other FD adult series. In a prospective observational study, end-organ damage and clinical symptoms have been assessed in 112 patients who had received agalsidase-beta (1.0 mg/kg) for >1 year, who were (i) non-randomly assigned to continue this treatment regimen (regular-dose group, n = 37); (ii) received a reduced dose of agalsidase-beta and subsequent switch to agalsidase-alfa (0.2 mg/kg) or a direct switch to 0.2 mg/kg agalsidase-alfa (switch group, n=38); or (iii) were re-switched to agalsidase-beta after receiving agalsidase-alfa for at least 12 months (re-switch group, n=37) with a median follow-up of 53 months. eGFR of patients in the regular-dose group remained stable. Patients in the switch group showed an annual eGFR loss of - 4.6 ± 9.1 mL/min/1.73 m^2 (p<0.05). Patients in the re-switch group also had an eGFR loss of - 2.2 ± 4.4 mL/min/1.73 m^2 after re-switch to agalsidase-beta, but to a lower degree compared with the switch group (p<0.05). Lyso-Gb3 remained stable in the switch (p=0.97) and the regular-dose (p=0.48) groups but decreased in the re-switch group after change of the therapy regimen (p<0.05). After a switch to agalsidase-alfa, Fabry patients experienced a continuous decline in eGFR, while this decline was attenuated in patients who were re-switched to agalsidase-beta. Decreasing lyso-Gb3 levels may indicate a better treatment response in the latter group[21]. These results are consistent with 10-year follow-up data from the Canadian Fabry Disease Initiative Registry[22] and with the results of a recent prospective observational study including 14 consecutive patients with classic FD originally treated with a 0.2 mg/kg eow ERT regimen, in which dried blood spot Lyso-Gb3 levels decreased from 27.2 ± 17.9 ng/mL to 16.8 ± 10.5 ng/mL over a 1-year period following the switch to the 1 mg/kg eow ERT regimen[23].

TIMING OF TREATMENT INITIATION IN CLASSIC FABRY PATIENTS

In addition to the choice of an appropriate therapy, also the definition of an appropriate timing of treatment initiation turns out to be crucial in patients with classic FD, as the clinically asymptomatic progression of renal, cardiac and cerebral disease manifestations spans many years.

The findings of a recent study attempt to shed light on this subject. In this cross-sectional retrospective study[24], 7 males aged 5–16 years with complete α-galactosidase A deficiency, without symptoms of major organ damage, were enrolled to receive agalsidase-beta intravenous infusion at different dosing regimens. One group was treated with 0.5 mg/kg biweekly (3 patients), the other with 1.0 mg/kg once a month (4 patients). All patients were evaluated after 10 years of treatment (age range at evaluation: 14–26 years) and no differences in outcome were found between the 2 groups of treated patients. Notably, cardiac imaging (echocardiography and MRI) data and renal biomarkers of the 7 treated patients were compared to those of 23 untreated males with classic FD (age range at evaluation: 13–27 years). Results showed that albuminuria was less common and less severe in treated patients (albumin to creatinine ratio, ACR 0-8.8 mg/mmol, median 0.4) compared to untreated patients (ACR 0–248 mg/mmol, median 3.7, p=0.02). The treated group had a lower left ventricular mass, measured using echocardiography (median 80 g/m^2 *vs.* 94 g/m^2, p=0.02) and MRI (median 53 g/m^2 *vs.*

68 g/m^2, p=0.02), whilst cerebral manifestation did not differ. These data have confirmed that the start of treatment with ERT in childhood in male patients with classic FD is associated with reduced occurrence of renal and cardiac manifestations in line with the pivotal study addressing the beneficial impact on renal prognosis following a very early initiation of ERT in children with classic FD[19]. Confirmation that this approach delays or even prevents renal failure and cardiac events certainly requires further follow-up. However, the ability of specific therapy to alter the natural history of classic FD and the importance of the choice of appropriate timing of treatment initiation create the preconditions for thinking differently about treatment strategies. It is no coincidence that more and more questions are being asked today, e.g., in a recent document addressing the management of Fabry disease in pediatric patients[25], as to whether the concept of disease-stabilizing therapy in the symptomatic/paucisymptomatic phase should not be replaced by a concept of 'preventive treatment' suitable for young classic Fabry patients still in an asymptomatic phase of the disease, before the appearance of the first signs and symptoms of organ damage.

TOWARDS A NEW PARADIGM IN THE MANAGEMENT OF CLASSIC FABRY PATIENTS

But today it is correct to deal with the concept of 'preventive treatment' in a genetic condition such as classic Fabry disease, in which male patients have a complete lack of key enzyme activity and in which the deposition of toxic glycosphingolipids starts since the fetal and the neonatal period[26-29], rapidly progresses in the first years of life asymptomatically or with minor functional symptoms[4,30] and then results in irreversible organ damage within the age of 40 years[1]?

Analyzing the semantic domain of the term 'preventive', it connotes an action taken to prevent an undesirable problem or condition from occurring. 'Preventive treatment' thus indicates in medicine a measure suitable to prevent the occurrence of a disease. In the specific case of classic FD, because of the congenital nature and of the early accumulation of toxic metabolites since the antenatal period that characterizes this condition, the intimate pathogenetic mechanism of FD cannot be prevented *stricto sensu*, whereas its progression can be halted or at least slowed down at an early stage.

The action of instituting specific treatment in FD is not preventive but it represents a strategy for the risk management of the occurrence of organ damage. In light of this, the question arises as to whether it is not more appropriate to deal with the concept of 'pre-emptive treatment'. The semantic domain of these two syntagms, 'pre-emptive treatment' and 'preventive treatment' differs precisely in relation to the strategy of risk management. The semantic domain of 'pre-emptive' connotes an action undertaken to neutralize or prevent an intended or potential action by another entity. In the military context, a pre-emptive action is an action taken to neutralize a perceived threat before the threat can attack. Translating this to the medical field, a pre-emptive treatment is an action aimed at interrupting the development of specific signs and, in the case of FD, neutralizing the development of potentially irreversible renal, cardiac or cerebral damage.

In our opinion, therefore, a 'pre-emptive treatment' in classic FD, i.e., a therapeutic strategy aimed at neutralizing the development of symptoms in advance by acting on the specific target and/or mitigating or interrupting the pathogenic process, represents more than an option in the context of the management of this inherited lysosomal disorder, based on the choice of an effective therapy and of an appropriate timing of treatment initiation.

Does the state of the art of Fabry knowledge, the available treatment options and the current clinicians' experiences make the present time ready for introducing a new paradigm in the management of patients suffering from classic FD? This is one of the key questions on which the E-TREAT (Early Treatment in pediatric classic Fabry Disease) study group, under the aegis of SIMMESN, is working in the context of a Delphi Panel specifically focused on the treatment strategy of classic FD patient, mindful of the epistemological lesson of Thomas Kuhn, who, in his *"Structure of scientific revolution"*[31] pointed out that revolutions do not follow a linear and cumulative pattern of progress and what an important role new paradigms play. A new paradigm offers a new worldview that resolves the anomalies of the old paradigm and sets new standards for research. Accepting a new paradigm is not only a question of data and evidence but also cultural and social change within a scientific community. Several elements point to the need for 'pre-emptive treatment' as a new paradigm in the management of pediatric patients with classic FD.

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