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HOME INFUSION PROGRAM FOR FABRY DISEASE: EXPERIENCE WITH AGALSIDASE ALFA IN ARGENTINA

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Abstrac Fabry disease is an X-linked lysosomal storage disorder caused by inherited deficiency of the enzyme α-galactosidase A. Enzyme replacement treatment using agalsidase alfa significantly reduces pain, improves cardiac function and quality of life, and slows renal deterioration. Nevertheless, it is a life-long treatment which requires regular intravenous infusions and entails a great burden for patients. Our objective was to evaluate retrospectively the safety and tolerability of the home infusion of agalsidase alfa in patients with Fabry disease in Argentina. We evaluated all the patients with Fabry disease who received home infusion with agalsidase alfa 0.2 mg/kg between January 2005 and June 2011. The program included 87 patients; 51 males (mean age: 30 years) and 36 females (mean age: 34 years). A total of 5229 infusions (mean: 59 per patient; range: 1-150) were administered. A total of 5 adverse reactions were seen in 5 patients (5.7% of patients and 0.9% of the total number of infusions). All were mild in severity and resolved by reducing the rate of infusion and by using antihistaminics. All these 5 patients were positive for IgG antibodies, but none of them presented IgE antibodies and none suffered an anaphylactic shock. In our group 18 patients were switched from agalsidase beta to agalsidase alfa without complications. Home infusion with agalsidase alfa is safe, well tolerated and is associated to high compliance.

Key words: Fabry disease, home Infusion program, agalsidase alfa, enzyme replacement treatment

Resumen ***Programa de infusión domiciliaria para la enfermedad de Fabry: experiencia con agalsidasa alfa en la Argentina.*** La enfermedad de Fabry es un trastorno de almacenamiento lisosomal hereditario ligado al cromosoma X ocasionado por el déficit de la enzima alfa galactosidasa A. La terapia de reemplazo enzimático utilizando agalsidasa alfa reduce significativamente el dolor, mejora la función cardíaca y la calidad de vida y enlentece el deterioro renal. Sin embargo, es un tratamiento de por vida que requiere infusiones intravenosas regulares y supone una gran carga para los pacientes. Nuestro objetivo fue evaluar retrospectivamente la tolerabilidad y la seguridad del procedimiento de infusión domiciliaria de agalsidasa alfa en pacientes con enfermedad de Fabry en Argentina. Evaluamos a todos los pacientes con enfermedad de Fabry que recibieron infusiones domiciliarias de 0.2 mg/kg de agalsidasa alfa entre enero del 2005 y junio del 2011. El programa incluyó 87 pacientes; 51 hombres (edad media: 30 años) y 36 mujeres (edad media: 34 años). Se administraron un total de 5229 infusiones (media: 59 por paciente; rango: 1-50). Se observaron un total de 5 reacciones adversas en 5 pacientes (5.7% de los pacientes y 0.9% del número total de infusiones). Todas fueron de gravedad leve y se resolvieron reduciendo la velocidad de la infusión o usando antihistamínicos. Los 5 pacientes fueron positivos para anticuerpos IgG, pero ninguno presentó anticuerpos IgE o sufrió un *shock* anafiláctico. En nuestro grupo, 18 pacientes fueron cambiados de agalsidasa beta a agalsidasa alfa sin complicaciones. La infusión domiciliaria de agalsidasa alfa es segura, bien tolerada y logra una alta adherencia al tratamiento.

Palabras clave: enfermedad de Fabry, infusión domiciliaria, agalsidasa alfa, terapia de reemplazo enzimático

Fabry disease is a rare X-linked disorder of glycosphingolipid catabolism caused by inherited deficiency of the lysosomal enzyme α-galactosidase A[1, 2]. This deficiency leads to progressive lysosomal accumulation of undegradable glycosphingolipids, mainly globotriaosylceramide (Gb3), in different cell types, resulting in complications that can ultimately lead to death.

The positive experience of enzyme replacement therapy (ERT) in patients with other lysosomal storage disorders, such as Gaucher disease, has led to its development for patients with Fabry disease. Currently, two forms of α-galactosidase A developed by DNA technology are available for treatment of Fabry disease: agalsidase alfa (Replagal®, Shire Human Genetic Therapies) and agalsidase beta (Fabrazyme®, Genzyme Corporation) enzyme preparations produced in human fibroblasts, and

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in a CHO cell line; respectively[3-6]. ERT with agalsidase alfa significantly reduces pain[7], improves cardiac function and quality of life[8-10], and slows renal deterioration[10-12]. The enzyme is safe in children ($\geq$ 7 years of age)[13, 14].

However; ERT with agalsidase alfa is a life-long treatment and patients require regular intravenous infusions every 2 weeks; which entails a great burden for patients. Home-based therapy has been developed for conditions requiring prolonged intravenous infusion therapy. Among the main advantages of home treatment is the possibility for patients to maintain a relatively normal lifestyle, to receive their treatment in a comfortable and familiar environment, and to schedule the infusions at a time of their convenience.

Experience with home-based therapy for lysosomal storage disorders date back to the early 1990s when ERT was administered at home to Gaucher patients[15]. The successful implementation of home-based ERT for Gaucher disease with excellent results; together with the good safety profile and low incidence of infusion-related reactions of ERT with agalsidase alfa[16 17], has prompted studies investigating the applicability of home-based therapy for Fabry disease. Several studies from Europe have now demonstrated the feasibility and safety of ERT in the home setting for Fabry disease[16, 18]. Furthermore, North America and some European countries have implemented guidelines to establish which patients are eligible for home-based therapy[18]. In addition, home infusion therapy may be associated with considerable financial savings to the healthcare centers[19]. Nevertheless, countries like Italy have been so far unable to implement this system due to technical and economic reasons. Moreover, there are no reports from Latin American countries where large distances, distribution of patients in rural areas and limited resources from the Public Health system pose difficult challenges regarding feasibility.

Newborn screening revealed the surprisingly high incidence of Fabry disease of ~ 1 in 37 000 males for the classical phenotype compared with ~ 1 in 3 373 males, for the later onset form[20]. In Argentina, 210 patients were diagnosed by AADELFA between 2003 and 2012 (Dra P Rozenfeld. *LISIN-Diagnóstico de enfermedades lisosomales. Universidad Nacional de LA Plata* personal communication). Many of these patients are distributed in rural areas and they have to travel long distances every other week for treatment, which makes the infusion of agalsidase alfa in the hospital setting very inconvenient, stressful and time consuming.

ERT with agalsidase alfa has a very good tolerance[16], relatively short infusion time[9] and infrequent adverse events[8, 17], and in view of the previous positive international experience with home-based therapy for Gaucher and Fabry diseases[15, 16, 18]; we implemented a Home Infusion Program with agalsidase alfa for the treatment of Fabry disease in 2005 and we evaluated retrospectively the safety and tolerability of the procedure.

Materials and Methods

The Home Infusion Program involves a professional team consisting of a coordinating physician, a local primary physician for each patient, a specialized nurse in charge of the infusion, a social worker, and a logistic manager of the Home Infusion Program. The coordinating physician is in direct and permanent contact with the local primary physician and the nurse to monitor any complication during the infusions. The entire team is part of the Argentinean association for the evaluation and treatment of patients with Fabry disease (AADELFA)[21].

To enter the Home Infusion Program, each patient first receives an average of 3 infusions at his local hospital or infusion center. If no adverse events occur he is invited to participate in the Home Infusion Program and for this purpose he has to sign an informed consent before starting the program and before each infusion. He then receives the number of vials necessary for 2-4 infusions through a logistic system trained to preserve the storage conditions of the drug. Patients are responsible for keeping the drug refrigerated until infusion. The nurse visits the patient every 2 weeks to perform the infusions of agalsidase alfa 0.2 mg/kg, in 40 minutes with no premedication, checks vials condition before administration, records details of the vials administered, and controls for vital signs and adverse reactions. In case of any adverse reaction, the primary physician is immediately notified.

Each patient is monitored with routine lab tests every 3 months; cardiac, neurological and ophthalmological examinations every 6 months, and an audiometry every 12 months.

Results

Between January 2005 and June 2011, 121 patients received agalsidase alfa in Argentina (Dr Camilo Lis Medical Director Shire HGT Argentina, personal communication) and within this group 87 patients (72%) were included in the Home Infusion Program. The patients included in the program comprised 51 males (59%; mean age: 30 years; range 8-62 years) and 36 females (41%, mean age: 34 years; range 12-77 years). Nine patients started their treatment before the age of 18 years (range 8-13 years). Among home treated patients there were 2 pregnant women. One female patient had undergone renal and pancreatic transplantation and one male patient had undergone kidney transplant. A total of 5229 infusions (mean: 59 per patient; range: 1-150) were administered. The program extended over 5 provinces (Buenos Aires,

Santa Fe, Corrientes, Chaco and Catamarca) and the autonomous city of Buenos Aires.

A total of 5 adverse reactions were seen in 5 patients (5.7% of patients and 0.9% of the total number of infusions). They occurred between the first and third home infusions, they were all mild in severity and consisted of skin rash, shivering, nausea and vomiting which subsided in all patients when the infusion rate was slowed by half or when antihistaminics were administered (diphenhydramine 50 mg IV). All the patients that developed adverse reactions were positive for IgG antibodies, but none of them presented IgE antibodies. No anaphylactic shock was observed. None of the adverse reactions was life-threatening or required admission to the hospital. Patients developing adverse reactions were examined at the local physician's practice and they were able to restart home infusion after 2 consecutive infusions at the physician's practice without any adverse reaction.

Compliance reached 90% in patients in Home Infusion Program. In our group 18 patients (12 males, mean age: 39 years; and 6 females, mean age: 37 years) were previously switched from agalsidase beta to agalsidase alfa without complications. Only 2 of these patients received premedication with oral antihistaminics 1h pre-infusion due to previous allergic reaction to agalsidase beta.

Discussion

The Home Infusion Program included 87 patients on agalsidase alfa in Argentina. The remaining 34 patients did not enter the Home Infusion Program for several reasons; including refusal of patients to admit nurses at their homes, or refusal of physicians to register their patients in the program. Further diffusion of the program and its benefits could overcome these barriers.

The few infusion-related reactions observed resolved by slowing the infusion rate by half or by administering antihistaminics (diphenhydramine 50 mg IV). Safety of home treatment in Argentina was consistent with previous reports[16, 18]. None of the patients was neither withdrawn from the program due to adverse reactions nor developed IgE which has been reported with the use of agalsidase beta, but not with agalsidase alfa[10, 16].

In line with the experience in other countries, compliance to therapy was very high with the Home Infusion Program.

A survey conducted in the UK involving 20 patients with Fabry disease revealed that 95% of patients were in favor of home therapy and reported that it was less stressful in comparison with hospital visits for treatment[24]. In addition; home therapy was reported to be more effective than hospital-based therapy by 90% of patients[24]. A recent study in Norway underlines the value of Home Infusion Program in the more efficient allocation of national medical resources[25]. Moreover, good results have also been reported with the use of agalsidase Beta and Home Infusion Program[26].

In contrast, according to a survey carried out in Italy in patients with lysosomal disorders, only 60% of patients were in favor of home therapy, and 23% were actually against it[27]. In the latter study, 93% of patients received treatment at the hospital and perceived it safer and better monitored by healthcare professionals. The authors explain that hospital pharmacies as well as physicians and nurses are reluctant to implement the Home Infusion Program in Italy where home nursing services are not provided by the National Medical System. Therefore; for the few patients who were on home treatment the infusions were performed by a friend or relative who was a doctor or nurse. In our program, home infusion of agalsidase alfa was accompanied by a logistical and medical team to ensure safe administration of the drug by a specially trained nurse, thorough monitoring and close contact with local primary physicians and specialized centers. Patients in the Home Infusion Program established a strong relationship with nurses providing their home therapy, which contributes to patient satisfaction and confidence; which in turn, reflects on patient compliance.

Argentina is the first country in Latin America to implement this system for Fabry disease. Our experience has shown that home infusion of agalsidase alfa was safe both in adults as well as in children, during pregnancy and after kidney transplant. Moreover it has excellent tolerability and its use was associated with a very high compliance.

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Mis ojos no vieron a los hombres de antaño;
Y ahora ha pasado su época.
Lloro (pensando que no veré
A los héroes de la posterioridad):

Eso dice el poeta chino; pero es rara esta imparcialidad en la atmósfera más belicosa de Occidente, donde los campeones del pasado y del futuro libran una batalla interminable, en lugar de ponerse de acuerdo para descubrir los méritos de ambos.

Bertrand Russell (1872-1970)

Misticismo y lógica. Barcelona: Romanyà/Valls S.A., 2001, p 74-5