Rapid intravenous infusion of velaglucerase-alfa in adults with type 1 Gaucher disease

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Gaucher disease (GD) is a lysosomal storage disorder for which safe and effective intravenous enzyme replacement therapy (ERT) has been available for more than 25 years [1]. The safety of the several ERTs for GD has also afforded the possibility of home infusions, reported by patients to be less stressful than those received in the hospital setting [2]. ERT is usually a life-long commitment to infusions, and many patients find the every-other-week (EOW) hourly infusions onerous, impacting aspects of their quality of life, including time taken off school/ work. Over the past two decades, we became aware of several anecdotal reports from patients who while responsible for their infusions at home, decreased the infusion duration from the standard 60 minutes to as little as 2 to 5 minutes without apparent untoward effect.

Previous experience with a rapid intravenous infusion of biological materials, in particular, monoclonal antibodies, have defined a variable potential for reactions. Ranging from mild local irritations at the access site, various inflammatory and immunological responses to life-threatening hypersensitivities and anaphylactoid reactions. These reactions could conceivably occur too quickly for an effective response by a medical team, particularly in the home environment. Even in patients previously exposed to a particular drug without a reaction when infused at a standard rate, such concern is never trivial. Thus, in designing a study protocol to

assess the safety of reduction of infusion duration of an ERT, the decision was taken to employ velaglucerase alfa (Shire, Zug Switzerland); an agent with good safety and tolerability profiles established during clinical trials and in post-marketing surveillance [3, 4]. This investigator-initiated study aimed to ascertain the safety of decreased infusion time of velaglucerase alfa from 60 to 10 minutes using a step-wise reduction in time and allowing for home infusions in the final phase.

Methods

Figure 1 shows the timeline of the study design. The volume for each infusion in the study was set at 100 ml, controlled with an infusion pump. This study was a prospective study. The protocol guaranteed the safety of the patient by measuring blood pressure, heart rate and temperature at four time points during the hospital clinic setting (i.e., 10 minutes prior, at the start, at the end of infusion and 1 hour after the start of the infusion) and at the home setting (i.e., blood pressure was measured before and after the infusion).

Inclusion criteria for the study were: age ≥18 years, non-splenectomized, ≥ three months exposure to velaglucerase alfa at a stable dose with no infusion-related or drug-related adverse events (AEs) and no clinically significant comorbidities. Safety was the primary end-point as determined by AEs during or directly after infusions as monitored by an experienced nurse. Efficacy parameters included hemoglobin concentration and platelet counts, spleen and liver volume estimation by ultrasound and determination of the biomarker glucosylsphingosine (lyso-

Gb1) (Centogene, Rostock, Germany) [5]. Drug concentration was assessed in plasma samples taken at time 0 to 90 minutes post-transfusion at study baseline, i.e. 60-minute transfusion, and at EOS, i.e. 10-minute transfusion. Non-validated questionnaire of seven visual analog scales in Hebrew was used to assess disease impact. These were continua of 0-10 points, worst case to best case scenarios regarding: [1] dependence, [2] constant fatigue [3] unremitting bone pain, [4] depression related to GD; [5] dissatisfaction with treatment, [6] family severely impacted by GD and [7] pessimistic about future -. Local institutional review board approval was granted for the study, and all participating patients provided written informed consent before commencing study procedures.

Descriptive statistics were employed. Baseline and nine months hematologic parameters, spleen, and liver volume estimation and lyso-Gb1 levels were compared using the paired t-test for normally distributed data. Statistical analysis was performed with SPSS statistical package (version 22 for Windows). A P value < 0.05 was considered significant.

Results

Fifteen patients, mean age 32 (range 22-44) years, genotype N370S homozygous (n=7) or heterozygous, were recruited (Table 1, supplement). No patient had AEs while receiving velaglucerase alfa infusions for a mean of 9.6 (range: 2.5-17) years. All patients were maintained on pre-study dosages (15-60 units/kg body weight)/infusion EOW.

There were no severe AEs associated with the 10-minute infusions, in the clinic or at home; the

only mild AE was a single female patient who experienced discomfort (feeling cold) in the infused arm during two 10-minute infusions. This patient subsequently became pregnant and was withdrawn from the trial. A second patient withdrew for personal reasons.

All the patients maintained stability in the key disease features including the hematological parameters, organ volumes and lyso-Gb1 levels (Table 1; $p > 0.1$). The drug concentration/time curves differed in peak levels (higher for 10-minute infusion) and width (longer for the 60-minute infusion) (Figure 2, supplement). Of the 13 patients who completed the questionnaire at baseline and at EOS, , scores across scales remained stable over time with only the pregnant patient mean scores are decreasing from 9.2 to 3.5. The remaining mean scores ranged from 5.3-9.4 at baseline and 7.6-9.7 at EOS. Similarly, mean responses to the specific questions were not significantly altered over the study period, remaining in the 6.2-9.7 range. No patient developed antibodies. Twelve patients have continued into a 15-month extension phase of the study which is ongoing (MOH_2017-10-19_001865).

Discussion

With this study protocol, we established that step-wise shortening of infusion duration, from one hour to 10 minutes in three stages over 6 months and as home infusions, did not compromise the safety or efficacy of treatment in adult patients with type 1 GD receiving velaglucerase alfa EOW at dosages ranging from 15-60 units/kg body weight. Return to the home setting was uneventful and was assisted by the known safety profile of this ERT [3]. The pharmacodynamics

differences seen when shortening infusion duration to 10 minutes are expected, however future studies, such as our pending trial in naïve patients are required to explore the potential ramification with regard to efficacy.

Regarding the impact on some features of disease-related psychosocial issues, all but one patient indicated no change over time when asked to complete scales of some basic health-related quality of life queries. Disease-specific clinical parameters and the biomarker lyso-Gb1 were maintained over the course of the study among all patients. Anecdotal reports and willingness of most patients to continue in an extension phase confirm the value of convenience, specifically decreased infusion duration, to patients for whom ERT infusions are currently envisioned to be a life-long commitment. Thus, as the impetus for reducing infusion times for ERT was also initially driven by patients (some with decades-long exposure to intravenous ERT), it is not unlikely that patients with comparable medical profiles might be encouraged to attempt this "change in practice" protocol.

Moreover, this approach may also have broader implications for healthcare providers and payers because of the possibility of reducing the considerable costs engendered by both prolonged intravenous administrations and the reliance on a hospital setting [6]. For many patients, the safety of velaglucerase alfa allows for shorter home infusion durations.

We conclude that this study provides evidence to consider more rapid infusion of velaglucerase alfa in patients with type 1 GD stable on infusion therapy without prior infusion-related toxicities and is equally applicable in the clinic setting and for home therapy.

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Authorship Contributions

AZ conceived the study and helped design the protocol, analyzed the results, and reviewed all versions of the manuscript; he is the Director of the Gaucher Clinic, and all the patients are under his medical care. SRV is a physician in the Gaucher Clinic; she was involved in data analysis, manuscript writing and reviewed all versions of the manuscript. MBC assisted in the various technical and logistic aspects of the trial and reviewed all versions of the manuscript. NA was the Study Nurse Coordinator for all patients in the trial and reviewed all versions of the manuscript. GC was the Study Coordinator for the trial and reviewed all versions of the manuscript. AR was in charge of the lyso-Gb1 analyses and reviewed all versions of the manuscript. JS was a visiting physician at the Gaucher Clinic during part of the study, saw the patients and reviewed all versions of the manuscript.

Disclosure of Conflicts of Interest

This investigator investigator-initiated study was supported by a grant from Shire (Zug, Switzerland). AZ receives honoraria from Shire, Pfizer and Sanofi/Genzyme. SRV receives speakers fees and travel support from Shire, Pfizer and Sanofi/Genzyme. The SZMC Gaucher Clinic receives support from Sanofi/Genzyme for participation in the ICGG Registry, from Shire for the GOS Registry, and from Pfizer for TALIAS. The Clinic also receives research grants from Shire and from Pfizer. NA is an employee of Medison Pharma (Petach Tikva, Israel), whose home infusion service for patients with Gaucher disease receiving velaglucerase alfa is supported in part by Shire. AR is founder and CEO of Centogene AG, the company that has done the lysoGb1 analysis. He has received honoraria and speakers fees from Shire. JS has received honoraria and speakers fees from Shire, Pfizer and Sanofi/Genzyme.

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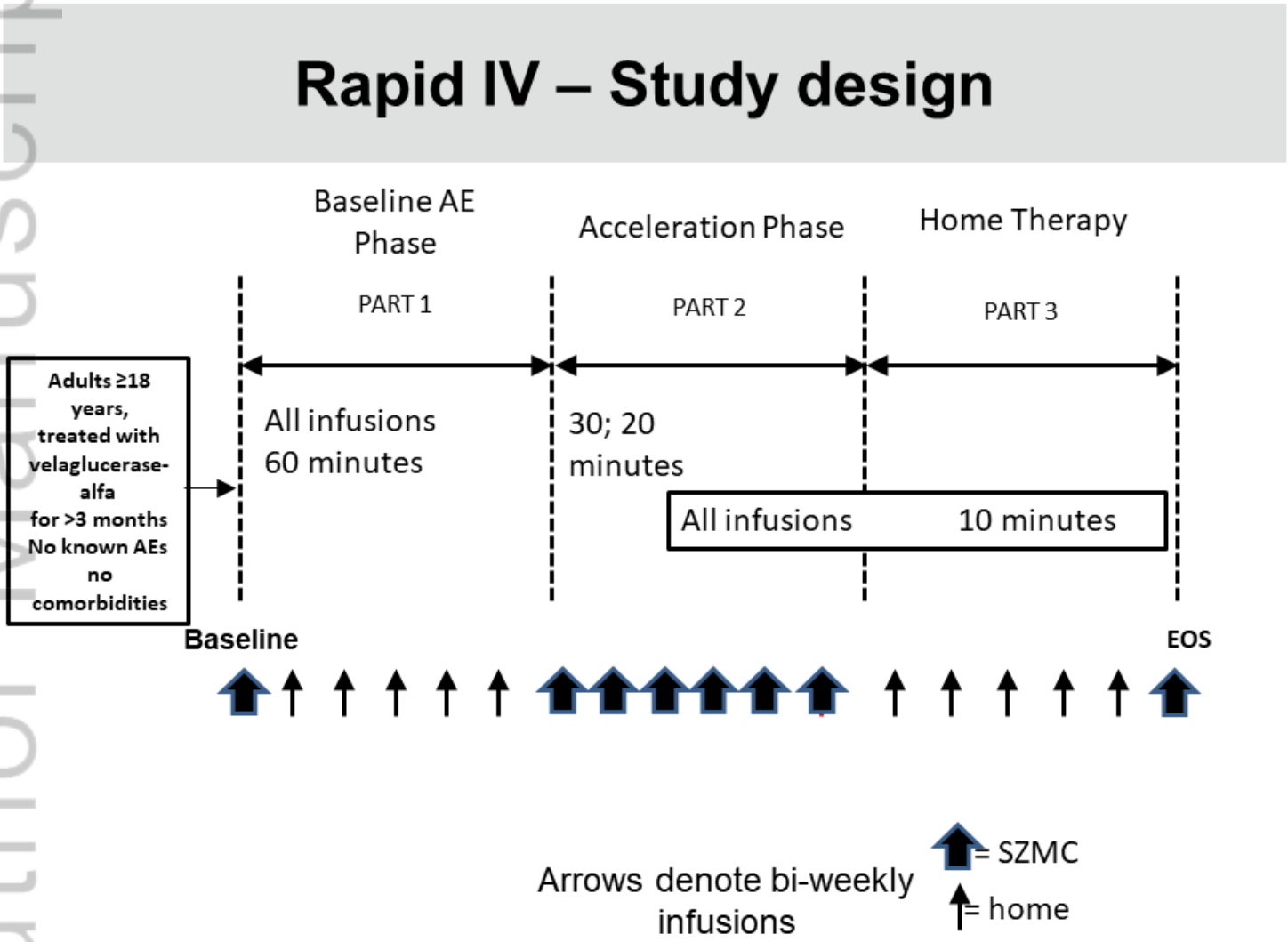
Legends:

Figure 1: The timeline of the study consisted of three parts , starting with three months at the standard infusion time of 60 minutes EOW in the home setting. Next was an accelerated infusion rate phase of three months with one infusion at 30 minutes, one infusion at 20 minutes, and then four infusions over 10 minutes, all in the hospital clinic setting. The final stage of three months duration was five infusions over 10 minutes at home and an end-of-study (EOS) infusion plus study evaluations in the clinic. Arrows denote bi-weekly infusions. The wide arrow show infusions given in the hospital setting (SZMC) and the thin arrows show infusions given in the home setting. AE, adverse event; EOS, end of study clinic evaluation.

Figure 2a: Plot of drug concentration (ng/mL) versus time profile at pre-specified time points (pre-dose, 10, 20, 40, 60, 75 and 90 minutes) at baseline.

Figure 2b: Plot of drug concentration (ng/mL) versus time profile at pre-specified time points (pre-dose, 10, 20, 40, 60, 75 and 90 minutes) at end of study.



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