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Safety of a protocol for reduction of agalsidase beta infusion time in Fabry disease: An Italian multi-centre study

Agalsidase beta is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) [1]. The European Summary of Product Characteristics (SmPC) states that the initial infusion rate should be no more than 0.25 mg/min (15 mg/h) and that after patient tolerance is established, the infusion rate may be increased gradually with subsequent infusions [1].

However practical guidance regarding reducing agalsidase beta infusion time is not provided in the SmPC. Sanchez and coworkers (2021) have recently suggested a protocol to reduce infusion times [2]. In their study, the main endpoint was clinical tolerance to a rapid and progressive reduction of agalsidase beta infusion [2]. This work, however, does leave unanswered when to start reducing infusion times, how to monitor efficacy of agalsidase beta and the impact of infusion rate on the development of anti-drug antibodies. The latter is of particular importance as there are reports that the development of anti-drug antibodies is influenced by infusion protocols [3]. Furthermore Riccio et al. published in 2021 their retrospective experience with a stepwise infusion rate escalation protocol in a cohort of 53 Fabry patients infused mainly at home after the first four hospital infusions and explored the infusion rate tolerability without evaluating the immune-response in all patients (Ab measurement was implemented only in 18 patients); they conclude that their infusion rate escalation protocol is safe and could improve patient compliance, satisfaction and quality of life [4].

In January 2021 to address these knowledge gaps, we started a multicentre Italian prospective study with the aim of testing a new agalsidase beta infusion time reduction protocol. The primary endpoints of the study are tolerance (evaluated by the incidence of infusion associated reactions (IARs)) and the frequency of seroconversion by the onset of anti-drug antibodies. The secondary endpoint is focused on evaluating the efficacy of agalsidase beta using the FAbry STabilization indEX (FASTEX) as a measure of clinical stability [5].

As the literature suggests that in the early months of initiating agalsidase beta is most critical for anti-drug antibody development, our protocol (see Table 1) stipulates a stable infusion dosage of 15 mg/h for the first four months (eight infusions). This is without premedication treatment. During the following four infusions, the infusion rate is increased progressively from 15 to 35 mg/h so that at the end of the sixth month, the patient reaches their shortest infusion time for agalsidase beta. In case of IARs during the rate escalation, the patient will stop the infusion and/or decrease the infusion rate together with the administration of premedication (non-steroidal anti-inflammatory medicinal products, antihistamines and/or corticosteroids). For the following infusions, the patient will continue to receive the premedication while keeping constant the maximum tolerated infusion rate. Anti-drug antibodies are evaluated in all patients at baseline and thereafter monthly for the following 12 months. Both treatment naive and patients previously treated with agalsidase alfa (seronegative at baseline) have been enrolled in our multicentre study. According to the SmPC, if eligibility criteria for home infusion are satisfied, the patient can follow the rate escalation protocol in home setting after the first six months study. The disease burden and the clinical evolution during the infusion rate variations are evaluated with FASTEX calculated one year after the baseline; each patient will be asked to complete a patient reported outcome questionnaire at the end of the study to evaluate whether the reduction of infusion time has improved the Quality of Life.

Table 1
Dilution and infusion rates.

Dilution	Dose	Duration	Rate
1st phase (from 1st to 8th infusion)			
500 ml SS with 2 vials (70 mg)	15 mg/h	280 min (4 h, 40′)	107 ml/h
250 ml SS with 1 vial (35 mg)	15 mg/h	140 min (2 h,20′)	107 ml/h
2nd phase (from 9th infusion onwards)			
9th infusion			
500 ml SS with 2 vials (70 mg)	20 mg/h	210 min (3 h,30′)	143 ml/h
250 ml SS with 1 vial (35 mg)	20 mg/h	105 min (1 h,45′)	143 ml/h
10th infusion			
500 ml SS with 2 vials (70 mg)	25 mg/h	168 min (2 h,48′)	178 ml/h
250 ml SS with 1 vial (35 mg)	25 mg/h	84 min (1 h, 24′)	178 ml/h
11th infusion			
500 ml SS with 2 vials (70 mg)	30 mg/h	140 min (2 h,20′)	215 ml/h
250 ml SS with 1 vial (35 mg)	30 mg/h	70 min (1 h,10′)	215 ml/h
12th infusion			
500 ml SS with 2 vials (70 mg)	35 mg/h	120 min (2 h)	250 ml/h
250 ml SS with 1 vial (35 mg)	35 mg/h	60 min (1 h)	250 ml/h

SS Saline solution.
From 13th Infusion onwards: same as the previous one.

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