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Should eliglustat be first line therapy for patients with type 1 Gaucher disease? Definitions of safety and efficacy

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Enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease (GD) has revolutionized the management and natural history of patients suffering from this metabolic disorder, and has become a milestone in the history of rare genetic disorders.

Eliglustat [1] (Cerdelga™, Sanofi/Genzyme) is the second oral therapy approved for patients with type 1 GD. Like miglustat [2] (Zavesca™, Actelion), approved since 2002–2003, eliglustat is a form of substrate reduction therapy (SRT). It is considered to be better and less toxic when compared to miglustat [3] and was described as being of equivalent efficacy to ERT [4] so that a number of regulatory agencies including the FDA and EMA approved it as first line therapy for patients with GD [5]. The caveat was that this approval did not apply to patients who were CYP2D6 ultra-rapid metabolisers. As an oral agent, its manufacturer decided to market it as “a premium drug” and hence at a cost that is generally higher than ERT.

Mistry et al. [6] have reported the results of the extension trial of ENGAGE, the phase 3 placebo controlled trial of eliglustat, published previously elsewhere [7]. In these additional 9 months, the patients from the eliglustat group continue to do well, whereas those switched from placebo to eliglustat demonstrating improvement in the key disease features, with no new adverse events being reported (albeit there were 2 new cases of second degree AV block). With these additional data, we have decided to revisit the question of whether regulatory agencies were correct in defining the new SRT as first line therapy for patients with GD and suitable CYP2D status, given the attractiveness of oral drug over an intravenous ERT.

The clinical trials for treatment-naïve patients and patients switched from imiglucerase, ENGAGE and ENCORE, respectively, were designed and reported in a novel and potentially misleading manner due to the introduction of new nomenclature and definitions, which created the impression that eliglustat is equivalent in its safety and efficacy to ERT. The impressive list of senior and trusted investigators as authors of these reports further supported this impression.

In the protocol for treatment-naïve patients (ENGAGE) [7], the key efficacy parameters reported by the investigators are presented as “absolute treatment difference” defined as improvement with eliglustat relative to the deterioration of the placebo group. Traditionally, improvement from or deterioration from *baseline*, has been how changes in key parameters (haemoglobin, platelets, spleen and liver size) with ERT and SRT have been reported in GD. A simple comparison of the mean results as changes from baseline shows an inferior improvement in all 4 key disease parameters with eliglustat compared to any of the ERTs studied to date, based on the published data from previously conducted trials [2,9,10,11]. This might well be true for any SRT as a modality, compared to any ERT; it is certainly also true for miglustat. As GD is a benign disorder, if the safety profile and cost were comparable to ERT, perhaps there would be no argument against the acceptance of eliglustat as first line therapy because of the convenience of oral administration. We understand that cost will not be comparable and the safety profile is problematic.

The results of the switch-over trial (ENCORE) [4], were first published over a year ago in The Lancet and updated results were recently published in Blood [1]. In these reports, the key definition of “maintaining stability” as the endpoint of the trial (which on top of proof of

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efficacy is also a measure of the safety parameter of "lack of deterioration"), which was accepted by the FDA and EMA, is far more generous than the definition of the same parameters during the previous switch-over protocols (imiglucerase to velaglucerase alfa [12] or to taliglucerase alfa [13] or certainly to miglustat [14]). For example, in the switch over trial with velaglucerase alfa, patients would be defined as "deterioration" and should have been withdrawn from the trial if haemoglobin levels dropped ≥ 1 g/L below baseline (in the ENCORE study haemoglobin concentrations were allowed to drop by 1.5 g/L to meet the definition of maintaining stability); similarly, if the platelet count dropped > 20% from baseline (25% for eliglustat) and the liver and spleen volumes were not permitted to increase > 15% each. In previous studies, meeting any of these end points resulted in cessation of study medication whereas in ENCORE, organ volume increases up to 20% and 25% respectively were considered therapeutic success. Supervising regulatory agencies must protect the safety of clinical trial subjects, and we question whether these seemingly arbitrary differences in the assessment of safety represent an inconsistent stance. In the switch study involving miglustat, when patients switched from imiglucerase to miglustat [14], lack of deterioration for any of these key disease features was defined as not exceeding a 5% change from baseline (down for the haematological parameters and up for the liver and spleen).

To further support our contention, one can learn from the placebo arm of the ENGAGE trial, which recruited quite severely affected patients, to the extent that several ethics committees (IRBs) were not prepared to approve the study; with an entry criterion of splenomegaly being 6 to 30 multiples of normal (mean volume in the group was 6.5 to 30) the mean deterioration over 9 months was only 2.26%. This "lack of significant deterioration" was also shown during the global shortage of imiglucerase (see below) and was observed 17 years ago, when in the first real life data of 15 patients with type 1 GD who had been treated with ERT from 5 to 56 months and then withdrew from ERT for 8 to 47 months, the majority of the patients not only maintained stability but some actually continued to improve. In the ENCORE study 16% of the patients did not maintain stability even under these generous criteria [8]. None of the patients in the switch-over trials from imiglucerase to velaglucerase alfa or to taliglucerase alfa reached deterioration values.

These issues would not have arisen had imiglucerase been used as a comparator to eliglustat in the ENGAGE study of untreated patients and if placebo had been used as the comparator in the stable patients in the ENCORE study. In a report from Goldblatt et al. [15] (again during the imiglucerase shortage) it was shown that most adult patients stable on ERT can progress extremely slowly after withdrawal of ERT with the appearance of disease stability for a prolonged period. The authors of this study concluded that "…data of this nature emphasise the necessity for the use of a drug-free placebo group in clinical trials of new drugs for maintenance therapy for patients with stable Gaucher disease after previously receiving ERT."

In the switchover study of imiglucerase to velaglucerase alfa, all patients remained stable, and in the similar studies of taliglucerase alfa and miglustat, only three patients (in each study) did not meet the stability criteria.

To date, there has been no response to requests to re-analyse the data in the ENCORE study such that outcomes would be in line with previous definitions of deterioration. Published data guiding professionals involved in the management of patients with rare diseases must be presented reliably and transparently. We do not know whether eliglustat is equally as effective and safe as imiglucerase (or other ERTs) but a simple analysis of presumably available data would answer the question.

Last but not least, in a paper in this issue reporting adverse events (AEs) among all 393 patients who had participated in all clinical trials of eliglustat to date [16], the majority of AEs were described as "non-serious, occasional, non-severe and did not lead to drug discontinuation". We became concerned about the issue of cardiac AEs in the report in which it was stated "…The frequency of cardiac events considered related to eliglustat (5%) was similar to the frequency not related to eliglustat (6%); 7 patients (2%) experienced palpitations considered related and 13 patients (3%) experienced palpitations considered not related to eliglustat. Related and not related events of syncope were reported with the same frequency (1%)." The paper does not detail what each of these AEs was, and how the relation to eliglustat was determined, nor are we informed why palpitations and syncope are not considered cardiac. We interpret these data as demonstrating an overall incidence of 17% of cardiac AEs, quite an alarming percentage for a cohort of patients with a benign disease given decades of safe and effective ERT therapy. Furthermore, in the phase 2 report of eliglustat by Lukina et al. [17], there was a mean time-averaged change from baseline in electrocardiographic PR interval of-3 to 7 ms and for QRS interval of 1 to 4 milliseconds which resulted in a package insert statement regarding an increased risk of arrhythmia.

Therefore, until we can be satisfied that the concerns described have been explained, we recommend that eliglustat be considered as a second line therapy for patients unwilling or unable to get ERT.

Conflict of interest

AZ has received honoraria from Shire, Pfizer and Genzyme.

JG has received travel support from Genzyme, Amicus, Actelion, Pfizer, Shire and Protalix.

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