Editorial Comment

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Fabry disease: is there a role for enzyme replacement therapy?

Treating patients or families with Fabry disease is challenging. Males with this X-linked disease experience life-threatening organ damage to the heart, kidney and cerebrovascular system, and may have advanced disease at presentation; in addition, treatment with enzyme replacement therapy (ERT) is not only extremely expensive, it is of limited effectiveness. Furthermore, because of a manufacturing problem [1], one of the two ERT preparations was in short supply from June 2009 until 2012. In this issue of the *Journal of Internal Medicine*, Weidemann *et al.* [2] from the Wurzburg Fabry centre report that ERT with agalsidase beta (Fabrazyme, Sanofi–Genzyme) did not prevent clinically significant events including sudden cardiac death. Treatment outcomes for 40 patients with advanced Fabry disease were found to be no better than the outcomes of 40 matched patients, selected from the Fabry Registry, who were not treated with ERT as a result of financial constraints. Fifteen significant events were recorded in 13 ERT-treated patients during a follow-up period of at least 60 months (median 6 years); seven of these were deaths (four were stroke and four were end-stage renal disease), six of which were due to cardiac disease. Specifically, male patients with advanced Fabry disease were found to be at risk of developing cardiac fibrosis as evidenced by the finding of late enhancement on cardiac magnetic resonance imaging.

Similarly, results showing the lack of effectiveness of ERT in a prospective follow-up of 57 patients (30 male) treated for a median duration of 5.2 years have been recently reported from the Amsterdam Medical Centre [3]. In the latest review from the Cochrane database [4], it is also concluded that 'there is no robust evidence for ERT in Fabry disease'. Reports of data from the two industry-sponsored registries [5, 6] have confirmed that, in the era of ERT, cardiac disease has overtaken renal failure as the main cause of death in Fabry disease. It seems likely that ERT has limited capacity to prevent progressive ventricular fibrosis and malignant arrhythmias. Infused enzyme is easily able to access fibroblasts, but concern has been raised that access to cardiac and renal cells is suboptimal [7, 8].

Several conclusions emerge from the report by Weidemann and colleagues. First, treatment is certainly not futile; many characteristics of the disease in their cohort appeared to be responding well to ERT. The rate of decline in renal function over 60 months was <4 mL min^{-1} per year which is substantially less than can be expected in untreated patients with Fabry disease. The rate of progression of proteinuria also declined. Secondly, significant benefits were seen in terms of symptoms of Fabry disease that are not life-threatening, such as pain and hypohidrosis, but nonetheless lead to impaired quality of life in these patients.

Weidemann *et al.* are right to emphasize the importance of intensive follow-up of patients with Fabry disease at expert centres so that measures including the insertion of an implantable cardiodefibrillator can be instituted in the event of disease progression. Regular review by cardiologists and nephrologists is also strongly advised, so that optimum supportive care can be delivered to this group of patients.

A crucial question is whether these disappointing results can be translated to agalsidase alpha. This is an alternative ERT preparation (Shire Human Genetic Therapies, Lexington, KY, USA) that is produced in a human fibroblast cell line. The licensed dose is 20% of the dose of agalsidase beta; however, in terms of ERT for Fabry disease, more is not necessarily better. The overall effectiveness of the two preparations at their licensed doses is considered to be similar [9]. Favourable results of long-term agalsidase alpha therapy have been reported [10], although these studies have not been controlled and the clinical outcomes have not been as robust as those quoted by Weidemann and co-workers. Agalsidase alpha has been demonstrated to be extremely effective in patients with life-threatening cardiac disease [11]. It is generally accepted that agalsidase alpha is less immunogenic than agalsidase beta, even when the two ERT preparations are given at the same dose in patients with Fabry disease [12]. Results of antibody tests are not reported by Weidemann *et al.*, but it seems

likely that 70–80% of the patients in their cohort were antibody positive.

The manufacturing platform for agalsidase alpha is less immunogenic, as demonstrated in a recent head-to-head comparison of the Hamster kidney ovary- and human fibroblast-derived cell lines [imiglucerase (Genzyme] and velaglucerase (Shire Human Genetic Therapies], respectively] in Gaucher disease [13]. These antibodies are of disputed clinical significance in Gaucher disease; their incidence is much lower than in Fabry disease, and they would in fact help to target the enzyme to the reticuloendothelial system, a major site of substrate storage. However, such antibodies are very important in Pompe disease, and their role in Fabry disease could extend to restricting access to relevant tissues, reducing substrate clearance and induction of inflammation and fibrosis.

The use of small-molecule 'chaperone' therapy in Fabry disease, both alone and in combination with ERT [14], may offer renewed hope for patients with this disease. There is certainly a need for better and more affordable treatments. The Cambridge clinical pharmacologist D.R. Laurence [15] astutely observed that there were distinct phases in the perception of new treatments and drugs by patients and experts. An early response (first 3–5 years after licensing) was often 'revolutionary' and 'a real advance with definite benefits for patients'. However, once more data became available (approximately 5–7 years), the perception would be more controlled and possibly even negative: 'not only is this treatment useless, it makes patients worse'. Ultimately, it would become accepted wisdom that the intervention (e.g. ERT for Fabry disease) has limited effectiveness, but is indicated for selected patients provided they also receive appropriate ancillary therapy, and that the disease process has not become irreversible.

Conflict of interest statement

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