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Enzyme Replacement Therapy for Anderson-Fabry Disease*

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Anderson-Fabry disease (AFD) is an X-linked recessive multisystemic disorder caused by a deficiency of the lysosomal enzyme alpha–galactosidase A (AGAL). The incidence of AFD is estimated to be 1 in 117,000 live births for males[1]; however, recent newborn screening surveys suggest that the incidence may be much higher, up to 1 in 3100.[2] Although most reports have focused on symptomatic male patients, females with AFD can develop disease-related problems.[3] Clinically, AFD is characterized by major renal, cardiac, and cerebrovascular complications consequent to the progressive deposition of an incompletely metabolized substrate, globotriaosylceramide (Gb_3), in multiple cell types, and by the attendant mechanisms of tissue injury that remain to be more fully defined. Renal and cardiac failure are prominent sources of morbidity and likely account for the reduced survival among affected males and females (in whom median age of death is 50–57 years and 70–72 years, respectively).

Enzyme replacement therapy (ERT), the first specific treatment for AFD, consists of regular intravenous infusion of a recombinant enzyme formulation. Two forms of recombinant AGAL exist: agalsidasealfa (Replagal®, Shire Human Genetic Therapies, Cambridge, Massachusetts) and agalsidase beta (Fabrazyme®, Genzyme Corporation, Cambridge, Massachusetts). Agalsidasealfa is generated by the activation of the AGAL gene in a continuous human cell line, whereas agalsidase beta is produced in a Chinese hamster ovary mammalian cell expression system, transduced with the human AGAL sequence. A sizable percentage of people receiving ERT for AFD have seroconverted (ie, developed antibodies)—the frequency of developing antibodies against agalsidasealfa and agalsidase beta has been reported to be 55% and 83%, respectively, of individuals treated.[4,5] Recent studies have shown that the presence of antibodies may influence Gb_3 storage in skin capillaries and Gb_3 excretion in urine, but no relationship between antibody formation and plasma Gb_3 levels or clinical outcome has been established thus far.[6]

We examined randomized and quasirandomized controlled trials to evaluate the effectiveness and safety of ERT compared with placebo, other interventions, or no interventions for treating AFD. Changes in Gb_3 concentration in plasma and tissue (ie, endothelial cells), death, and pain (acroparesthesia and Fabry crises) were our primary outcomes.

We identified 6 studies (n=223) comparing either agalsidasealfa or beta with placebo or each other; however, the methodologic quality of these studies was largely poor.

Two trials compared agalsidasealfa with placebo and reported on Gb_3 concentration in plasma and tissue; aggregate results were nonsignificant. One study reported pain scores, with a significant improvement at up to 3, 5, and 6 months for patients receiving treatment. A significant difference was observed in pain-related quality of life after 5 months and up to 6 months , but at no other time points. Neither study reported deaths.

One of the 3 trials comparing agalsidase beta with placebo reported on Gb_3 concentration in plasma and tissue, and showed significant improvement in kidney, heart, and composite results (renal, cardiac, and cerebrovascular complications and death) (**Figure**). No significant difference was found between groups for death; none of the studies reported on pain.

Only one trial compared agalsidasealfa to agalsidase beta. There was no significant difference between groups for any serious or other adverse events.

This review highlights the need for continued research on the use of ERT for AFD.

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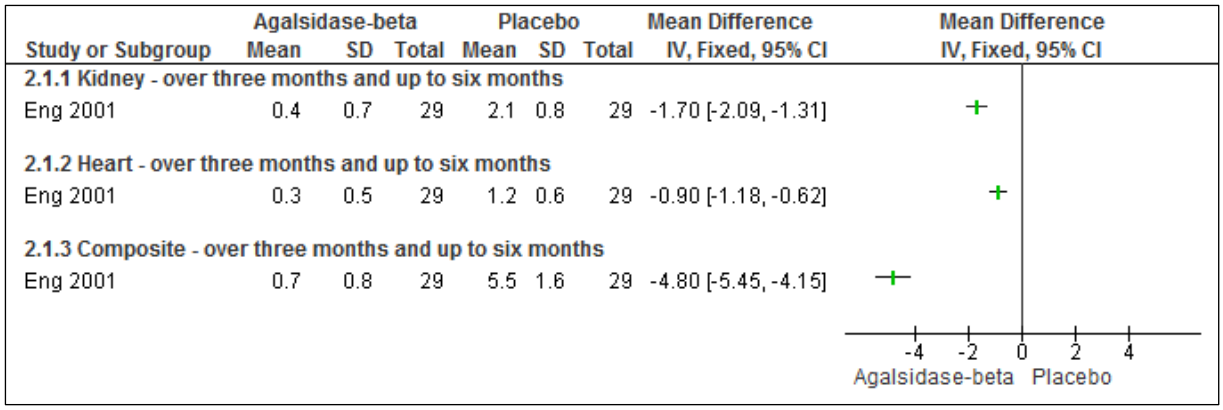

Figure. Agalsidase Beta vs Placebo: Microvascular Endothelial Deposits of Gb_3

Abbreviations: Gb_3, globotriaosylceramide; SD, standard deviation.