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Enzyme-replacement therapy for Anderson-Fabry disease

Anderson-Fabry disease (AFD) is a lysosomal storage disorder due to an X-linked inborn error of glycosphingolipid catabolism resulting from the deficient activity of α-galactosidase A (α-Gal A).[1] The effect is the accumulation of globotriaosylceramide (Gb_3) in various organs. The disease manifests primarily in affected hemizygous males and to some extent in heterozygous (carrier) females.

The clinical features include corneal and lenticular opacities, acroparaesthesia, angiokeratomas, hypohidrosis, and end-organ disease (kidneys, heart, and brain). Acroparaesthesia is the earliest, prominent symptom during the first two decades of life and commonly remains undiagnosed unless other manifestations provide diagnostic clues. Most affected males have proteinuria and ultimately develop renal failure. The clinical course can also be complicated by cardiac and cerebrovascular disease which, combined with renal failure, leads to early mortality. The median survival is 50 years (IQR 40–56) for hemizygous males and 70 years (57–78) for obligate females.[2,3]

AFD is a rare "orphan" pan-ethnic disorder, with an estimated prevalence of 1 in 117 000 males.[4] However, the frequency may be underestimated because some patients with residual enzyme activity have disease characterised predominantly by cardiac abnormalities.[5] Indeed, in one study, screening of patients with cardiomyopathy revealed an underlying deficiency of α-Gal A in 3–9%.[6]

Advances in the application of molecular genetic techniques have enabled the development of directed protein therapies. In Gaucher's disease enzyme replacement has become the current standard of care. Slow substrate turnover, restricted sites of abnormalities, and targeted macrophage delivery of the recombinant enzyme contribute to the success of therapy.[7] The absence of primary central-nervous-system involvement in type 1 Gaucher's disease (the commonest subtype) also obviates the need for medicines to breach the blood-brain barrier.

Now two randomised trials of enzyme-replacement therapy for AFD have been completed.[8,9] Despite fundamental differences between the two trials, which were conducted independently, both studies suggested that enzyme-replacement therapy for AFD was well tolerated and likely to be effective.

These studies, one by National Institutes of Health (NIH) investigators and the other by the Mount Sinai Study Group (MSSG), differed in the enzyme preparation used and in the dose per infusion (panel). Whether potency (specific enzyme activity), which was provided for only one formulation, affected therapeutic effect is not certain. Enzyme uptake probably occurs through receptors for mannose-6-phosphate, mannose, and asialoglycoprotein. The wide distribution of these receptors may have influenced clinical response through competitive, non-specific enzyme uptake, and enzyme-glycosylation patterns (which were not provided) could have altered bioavailability and efficacy.

The trials also differed in their entry criteria. Importantly, patients in the MSSG trial were not selected for pain symptoms and remained on analgesics throughout the study. This factor and the instrument used for assessment may have prevented demonstration of a significant improvement in pain between treated and placebo groups in the MSSG study.

Initial renal function was quite well preserved among patients in both studies. In the NIH study, improvement in renal function in the treated group compared with the placebo group was largely accounted for by a more rapid deterioration of function in the latter group. The decline in renal function observed in the placebo group was, however, subsequently reversed during the open-label phase. Since deterioration in renal function has not been shown to reverse spontaneously in AFD, preservation of renal function (in the treatment group) should be considered a major advance. There were no reports of deterioration in renal function among any of the MSSG patients.

Both studies examined changes in kidney histology. The NIH examined for changes in glomerular architecture, abnormalities that probably account for the loss of renal function characteristic of AFD. The MSSG looked for changes in the lipid deposits within renal interstitial capillaries since the underlying microvascular disease may play a prominent role in renal abnormalities in AFD. The NIH study suggested that, compared with placebo treatment, enzyme replacement decreased Gb_3 concentrations in kidney tissue, but not significantly. The MSSG noted that, compared with the placebo group, enzyme-treated patients had a significant decrease in Gb_3 in the kidney. Both studies reported significant decreases in urine-sediment and plasma Gb_3 concentrations. The importance of plasma and vascular Gb_3 with respect to renal function is uncertain since the total vascular Gb_3 content is a small component of the total renal Gb_3 accumulation,[10] and studies of treatment with plasmapheresis or phlebotomy did not seem to alter the natural history of the disease.[1] Irrespective of which histological finding correlates best with renal function, advanced changes (eg, glomerular sclerosis) are probably irreversible. Thus, early intervention may slow progression of the disease, but this point needs to be confirmed by studies started early in the disease and continued for a long time.

Extrarenal involvement contributes considerably to morbidity in AFD. Although selection of patients was not

Comparison of enzyme-replacement studies of AFD

	NIH	MSSG
Design		
Entry criteria	Age ⩾18 years; neuropathic pain	Age ⩾16 years; serum creatinine ≤2·2 mg/dL
Patients (and mean age)		
α-Gal A-treated	14 males (34·0 years)	27 males; 2 females (32·0 years)
Placebo	12 males (34·4 years)	29 males (28·4 years)
Enzyme source and dose	Human cells (agalsidase alfa, Replagal); 0·2 mg/kg, 12 doses over 24 wk; 20 min increased to 40 min midway into study; no premedications	Chinese hamster ovary cells (agalsidase beta, Fabrazyme); 1·0 mg/kg, 11 doses over 20 wk; 4–6 h (0·25 mg/min); premedication (1000 mg paracetamol, 25–50 mg hydroxyzine)
Specific activity	$3·4\times10^{6}$ nmol/h per mg protein	Not available
Outcome measures		
Primary	Effect on neuropathic pain (assessed by Brief Pain Inventory) while without analgesics	% of patients with clearance of renal interstitial capillary microvascular endothelial Gb3 deposits
Secondary	GFR; renal histology (glomerular count, glomerular and tubulointerstitial morphology, glycolipid inclusions)	GFR; clearance of microvascular endothelial Gb_3 deposits in heart and skin
	..	Pain (Short-form McGill Pain Questionnaire)
	..	Quality of life (Short-form General Health Survey SF-36)
	Gb_3 in plasma, kidney, 24 h urine sediment	Gb_3 in plasma, kidney, heart, skin, 24 h urine sediment
Duration of the study	24 weeks randomised, 24 weeks open label	20 weeks randomised, 24 weeks open label
Findings		
Safety*		
Infusion reactions	57% (rigors)	59% (48% rigors; 24% fevers)
Developed IgG antibodies	21% by ELISA, 64% by immunoprecipitation, both at 6 months	88% by ELISA at 1 year
Pain	Consistent and progressive decline in pain scores (p=0·02), compared with placebo; 4/11 discontinued analgesics *vs* none in placebo group (p=0·03)	Treated group had significant change from baseline, indistinguishable from placebo (p>0·05)
Quality of life (QOL)	Pain-related QOL improved (p=0·05), compared with placebo	Compared with baseline: significant improvement in physical and emotional roles for treated group, and in physical role and body-pain components for placebo group
Gb_3 clearance		
Plasma	54% decrease	Undetectable (<1·2 ng/μL) after week 20
Kidney tissue	20% decrease	23·3 % decrease
Urine sediment	28·9% decrease	34·1% decrease
Kidney histology (Reported differently)	Improved: 20% increased fraction of normal glomeruli (p=0·01); 33% decrease in mesangial widening (p=0·01); other (extrarenal) tissues not examined histologically	Improved: 69% had "0" scores (ie, no or trace microvascular endothelial Gb_3 deposits; p<0·001); also noted in skin (p<0·001) and heart (p<0·001).
Renal function	Treatment arm had stable GFR measured by creatinine clearance (p=0·02) and inulin clearance (p=0·19) compared with placebo	Serum creatinine concentration stable; baseline GFR provided with no follow-up data, although reported as unchanged (p=0·19)
Cardiac change	Improved cardiac conduction (ie, decrease in QRS-complex duration [P=0·047]); one patient in placebo group developed right-bundle branch block that resolved during open-label treatment	No significant change from baseline
Other	Increased body weight (p=0·02)	..

GFR=glomerular-filtration rate. Gb_3=globotriaosylceramide. *In both studies safety monitored by antibodies to α-Gal A, electrocardiography, echocardiography, and clinical monitoring for adverse effects. [Data from the European labels of the products: overall, 55% of patients treated with Replagal developed IgG antibodies, and 83% of patients treated with Fabrazyme developed IgG antibodies].

based on cardiac abnormalities, a significant decrease in duration of the QRS complex was noted among the NIH patients, and a bundle-branch block resolved with enzyme-replacement therapy in one patient in this study. Neither study reported central-nervous-system changes with treatment.

Both groups reported development of antibodies to recombinant α-Gal A. This development is expected since most AFD patients are negative for immunological cross-reacting material.[1] Patients in both studies tolerated the entire course of treatment and, except for one patient with a positive skin test in the MSSG study, none withdrew because of infusion-related reactions. More importantly, antibody formation did not influence therapeutic outcomes in either study, and titres fell over time. However, long-term studies are needed to find out whether the development of antibodies, including subtypes (eg, IgG or IgE, neutralising or non-neutralising), are important considerations in choice of preparation. Breakthrough adverse reactions (ie, those occurring

despite premedication) encountered in the MSSG study may be attributed to glycosylation differences between the two formulations. Post-translation modifications are species specific and are expected to differ between Chinese-hamster-ovary and human cells

Marketing authorisation for both formulations has recently been given in the European Union, so additional data on safety, efficacy, cost, and, importantly, quality of life should be forthcoming. The appropriate time to start enzyme replacement was not addressed in either trial. Nor was the specific benefit of this treatment in heterozygous (carrier) females, among whom a recent study conducted at the Royal Free Hospital in London has shown that AFD has a profound medical, psychosocial, and financial impact.[3]

If the cost of enzyme replacement for Gaucher's disease is anything to go by, that for AFD will be high, and possibly prohibitively so in certain parts of the world. Nonetheless, with two companies competing to adopt this orphan disease, perhaps market forces will drive costs down. The value of any treatment approach needs to be weighed against the costs associated with extensive resource utilisation and loss of productivity due to reduced lifespan. In addition, if alternative therapeutic options, such as galactose infusion, gene therapy, and substrate-synthesis inhibitors[11–13] are approved, the cost of enzyme replacement may be further reduced (eg, by alterations in dose size and frequency).

For now what the two trials in AFD have done is to show that enzyme-replacement therapy can be extended to a second lysosomal-storage disease. The responses obtained in both studies during the brief period of therapy not only demonstrate control but also potential for reversal of the disease process. Thus in patients with lysosomal storage disorders, the management paradigm has shifted from one of predictive genetic counselling and palliative care, to one of early diagnosis and possibility of active intervention.

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Veterinary link to drug resistance in human African trypanosomiasis?

See page 625

Antimicrobial drug resistance has become a major issue in the treatment of infectious diseases. Many antibiotics are obsolete, and the antimalarial drug, chloroquine, has been rendered useless in many parts of the world because of the emergence of resistance. Drug resistance has also become a serious problem in the treatment of animal trypanosomiases.[1] Within the past decade it has become clear that resistance to melarsoprol, the principal drug[2] used against late-stage human African trypanosomiasis (HAT), or sleeping sickness, has also emerged in *Trypanosoma brucei gambiense* in the field, with treatment failure rates of 30% reported among patients in Northern Uganda.[3] A link between the emergence of antimicrobial resistance in man and imprudent use of drugs in livestock has been evident for several years. New observations reported by Eric Fèvre and colleagues in today's *Lancet* show that trypanosomes infectious for man can be introduced into new areas by mass movement of animals. This work has clear implications for the spread of the disease. It also raises the spectre that selection of resistance to veterinary trypanocides could also lead to cross-resistance to drugs used in the treatment of African trypanosomiasis in man.

That resistance has arisen to melarsoprol is, at first glance, somewhat surprising. HAT is relatively uncommon when compared with, say, malaria (estimates of 300 000 cases of sleeping sickness compared with 300 million of malaria annually). Melarsoprol is not used prophylactically, and it should be given parenterally in a clinic or ward, not by self-administration. Therefore the conditions that have normally been implicated in the selection of drug-resistance—ie, widespread use, imprudent use associated with self-administration, and improper prophylactic dosing—do not seem to be relevant to melarsoprol.

On the other hand, throughout the tsetse belt in Sub-Saharan Africa, livestock are treated with various trypanocides, commonly administered at the discretion of farmers, and frequently given over long periods as prophylaxis[1]. Although the drugs used to treat human tyrpanosomiasis differ from those for the disease in animals, there is a potential for the development of cross-resistance between human and animal trypanocides. Crucially, cross-resistance between diminazene, used in the treatment of animal trypanosomiasis, and melarsoprol used in the treatment of African trypanosomiasis in man can be selected with relative ease[4] because both drugs, or their active metabolites, can