## Research letters

## Recombinant human $\alpha$ -glucosidase from rabbit milk in Pompe patients

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Pompe's disease is a fatal muscular disorder caused by lysosomal  $\alpha$ -glucosidase deficiency. In an open-label study, four babies with characteristic cardiomyopathy were treated with recombinant human  $\alpha$ -glucosidase (rhGAA) from rabbit milk at starting doses of 15 mg/kg or 20 mg/kg, and later 40 mg/kg. The enzyme was generally well tolerated. Activity of  $\alpha$ -glucosidase normalised in muscle. Tissue morphology and motor and cardiac function improved. The left-ventricular-mass index decreased significantly. We recommend early treatment. Long-term effects are being studied.

Infantile Pompe's disease is a metabolic myopathy with a rapidly progressive course, and is commonly fatal in the first year of life. The disease presents in the first few months after birth with respiratory and feeding difficulties and hypotonia, and hypertrophic cardiomyopathy is characteristic. Major developmental milestones, such as rolling over, sitting, and standing are not achieved.¹ The late-onset form presents as a slowly progressive proximal myopathy. The disease is caused by lysosomal α-glucosidase deficiency and concomitant storage of lysosomal glycogen.¹

In the development of enzyme therapy for Pompe's disease, production of rhGAA was tested in genetically modified Chinese hamster ovary cells<sup>2,3</sup> and milk of transgenic animals.<sup>4</sup> The two sources seemed suitable, but the high yield in milk and efficacy of the enzyme seen in mice led to large-scale production of rhGAA in transgenic rabbits being chosen.<sup>4</sup> A phase I study of healthy volunteers showed no major side-effects. We report on the first 36 weeks of treatment in patients, during which safety and efficacy data were gathered.

We did a single-centre, open-label pilot study, approved by the institutional review board. Four patients were included with typical symptoms of infantile Pompe's disease (table) and virtual absence of  $\alpha$ -glucosidase. We obtained written informed consent from the parents.

RhGAA was administered intravenously once weekly, at starting doses of 20 mg/kg in babies lighter than 6·5 kg (patients 1 and 2) and 15 mg/kg in babies weighing 6·5 kg or more (patients 3 and 4). Doses were increased to 40 mg/kg for all patients. These doses are generally well tolerated without premedication. Adverse events reported were fever, malaise, erythematous rash, sweating, hypoxia, flushing, and tachycardia. The role of IgE-type antibodies in these responses was not evident, but IgG-type antibodies may be relevant. Adverse events were transient and manageable by adaptation of the infusion rate.

 $\alpha$ -glucosidase activity in muscle on the starting doses

Patient	Onset of symptoms	Head-lag/ axial hypotonia*	Cardiac hypertrophy/ ECG abnormality	Oxygen need*	Age at diagnosis	Date at inclusion
1	At birth	+	+	-	1 month	3 months
2	3 months	+	+	+	4 months	7 months
3	At birth	+	+	-	14 days	2.5 months
4	3 months	+	+	+	6 months	8 months

ECG=electrocardiography. \*During inclusion period.

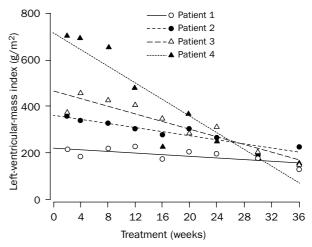
Patients' characteristics

showed a ten-fold increase at 12 weeks of treatment (from 0.15–0.37 nmol/mg per h to 2.1–4.9 nmol/mg per h), but was still lower than normal (8–40 nmol/mg per h). 12 weeks later, with 40 mg/kg RhGAA,  $\alpha$ -glucosidase activity was in the normal range for all four patients. On histological assessment, lysosomal glycogen storage was lowered and tissue morphology improved. The total tissue glycogen content did not change significantly.

Skeletal muscle function and strength improved in all patients, most significantly for patient 1, who had the least severe disease at start of treatment. This infant reached milestones that are beyond realistic expectations for a patient with the disease. At 12 months, he could crawl in a four-point position and stand with the support of one arm. Patient 3, who had more severe disease, learned to touch her feet in play. Her improvement has continued, despite no endogenous acid  $\alpha$ -glucosidase (cross-reactive-immunological-material [CRIM] negative). Patients 2 and 4 also gained strength, most notably in the arms. At start of treatment these two patients (ages 7 months and 8 months) had endstage disease and muscle function was almost lost. Patient 2 became dependent on a respirator during the inclusion period, as did patient 4, after 10 weeks of treatment, during a bout of pneumonia. The two patients, included before age 3 months, developed normal respiration and became outpatients. All patients showed progress in mental development.

The most prominent effect was on the heart. Left-ventricular posterior-wall thickness and left-ventricular-mass index (figure) decreased in all patients from the start of treatment. Patient 4 responded best. Her left-ventricular-mass index at 36 weeks of treatment was less than 30% of baseline. Symptoms of cardiac instability disappeared in all patients, which was life-saving for patient 4. All patients passed the critical age of 1 year.

RhGAA resulted in uptake of  $\alpha$ -glucosidase in skeletal



**Linear-regression analyses of left-ventricular-mass index** r=-0.74, r=-0.93, r=-0.93, and r=-0.93 for patients 1, 2, 3, and 4, respectively; each p<0.05.

muscle, improved tissue morphology, and stimulated muscle function. The treatment reduced cardiac size, improved cardiac function and clinical condition, and seemed to prolong life. We recommend that treatment be started early. Confirmatory studies in a larger population and long-term follow-up are needed to assess final outcome and quality of life. The milk of transgenic animals seems to be a safe source and opens the way for further exploration of this production method.

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## Opioid use in last week of life and implications for end-of-life decision-making

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This study was prompted by public and professional concern that the use of opioids for symptom control might shorten life. We retrospectively analysed the pattern of opioid use in the last week of life in 238 consecutive patients who died in a palliative care unit. Median doses of opioid were low (26-4 mg) in the last 24 h of life and patients who received opioid increases at the end of life did not show shorter survival than those who received no increases. The doctrine of double effect therefore need not be invoked to provide symptom control at the end of life.

Concern continues among the general public and health professionals over the use of opioids at the end of life and in particular their possible role in shortening patients' lives.¹ Recent court cases in the UK have raised the possibility that the doctrine of double effect (DDE) is used as a cover for euthanasia.² The DDE states that a harmful effect of treatment, even resulting in death, is permissible if it is not intended and occurs as a side-effect of a beneficial action.

We assessed whether symptom control with opioids is associated with shortening of life and how often the DDE is relevant in palliative care. A retrospective case-note review was undertaken of 238 consecutive patients dying in our 62-bed

Time before	Number of patients	Increase in opioid dose per 24 h			
death (h)		>2-fold	1.5-2-fold	>1·5-fold	
120–144	161	4 (2.5%)	2 (1.2%)	6 (3.7%)	
96-120	170	1 (0.6%)	3 (1.8%)	4 (2.4%)	
72-96	188	5 (2.7%)	4 (2.1%)	9 (4.8%)	
48-72	207	6 (2.9%)	9 (4.4%)	15 (7.3%)	
24-48	222	2 (0.9%)	9 (4.1%)	11 (5.0%)	
0-24	239	6 (2.5%)	5 (2.1%)	11 (4.6%)	

Table 1: Patients receiving a greater than 1-5-fold or greater than 2-fold increase in opioid dose per 24 h period before

hospice unit. A prospective study might have influenced practice and so was thought inappropriate. The sample proved representative of our patient population, with an median inpatient stay of 9 days (range 1–182) and a mean age of 69 years (SD 13·7).

Opioid doses (expressed as parenteral morphine equivalents) were recorded over 24 h during the last week of life and the change in dose calculated for each period. The distribution of at least two-fold increases over the last week of life was analysed, and the characteristics of patients who received a marked increase in opioid dose at the end of life were compared with patients receiving a lesser or no increase. A marked increase was defined as either a greater than 1.5-fold increase in opioid dose in 24 h during the last 48 h of life, the post-increase dose was greater than 30 mg per 24 h, or a greater than three-fold increase in the last week, during which the increase was greater than 30 mg. We reviewed case notes of the group with marked dose increase to assess whether the DDE could have been included in the decision-making process.

The mean daily opioid dose increased from 42 mg to 55.5 mg (median 15 mg to 26.4 mg), over the last 7 days of life. 212 (89%) patients received opioids in the last 24 h of life, compared with 145 (61%) patients at admission. The proportions of patients requiring a greater than two-fold increase per 24 h period were very small and were evenly distributed over the week (table 1).

Comparison of the patients who received a marked increase in opioids at the end of life with those who received no increase showed no significant difference in survival from admission, frequency of unexpected death, or description of death (table 2). They were, however, significantly more likely to be receiving opioids for pain and were also more likely to be receiving sedatives. The case-note review did not show any cases in which DDE could have been implicated. The reason for the increase was recorded in all cases and the deterioration in condition was noted before the change in dose.

Marked increase (n=28)	No increase or slight increase (n=210)	p
21 (8-6)	16.4 (3.1)	0.7*
24 (85.7%)	135 (64.3%)	0.01-0.025
9 (32·1%)	63 (30%)	>0.5†
2 (7·1%)	10 (4.8%)	>0.5†
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2 (7·1%)	38 (18·1%)	>0.25†
25 (89-3%)	165 (78.6%)	>0.25†
17 (60-7%)	109 (51.9%)	>0.25†
2 (7·1%)	5 (2.4%)	>0.5†
6 (21·4%)	25 (11.9%)	>0.25†
5 (17-9%)	53 (25·2%)	>0.25†
12 (42.9%)	112 (53-3%)	>0.25†
0	19 (9%)	<0.05-0.10†
	24 (85·7%) 9 (32·1%) 2 (7·1%) 2 (7·1%) 2 (7·1%) 2 (7·1%) 5 (89·3%) 17 (60·7%) 2 (7·1%) 6 (21·4%) 5 (17·9%)	Increase (n=28)

\*t test. † $\chi^2$  test

Table 2: Characteristics of patients compared by increase in opioid dose