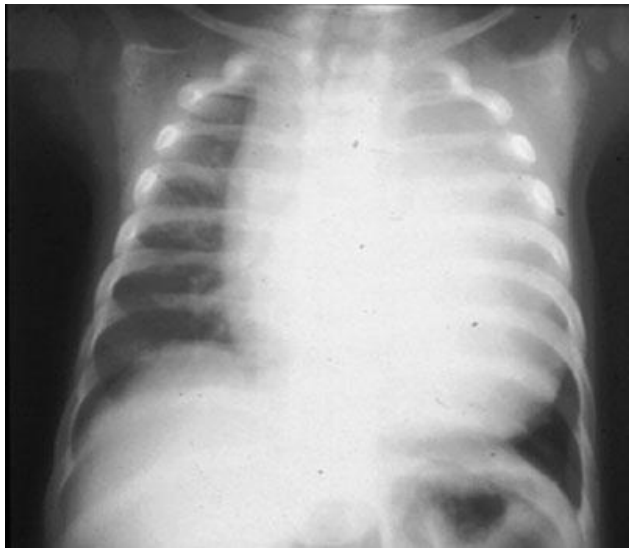
Treatment options for acid maltase deficiency (Pompe)



in the general context of late onset disease

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Disclosures

- Dr Andrew Millar is a full time employee of Genzyme
- The views expressed are the personal professional views of Dr Millar
- Full prescribing information is available here
- Adverse events should be reported
- Reporting forms and information can be found at www.yellowcard.gov.uk
- Adverse events should also be reported to Genzyme
- Tel: 01865 405200

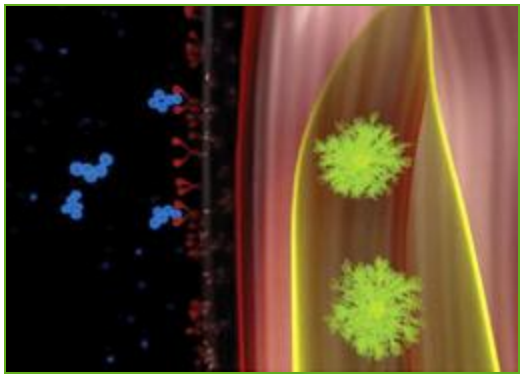
Key messages

- Pompe is a treatable disease
- Extreme rarity means limited research and evidence
- Treatment involves
  - Early diagnosis and initiation
  - Careful regular quantitative monitoring including respiratory function
  - Enzyme replacement therapy -ERT
  - Ventilatory support and interventions
  - Carefully tailored physiotherapy
    - Per-infusion muscle activation and blood flow stimulation
    - Individualised exercise regimens
    - Contractures
    - (measurements as above)
  - Diet and weight control
  - Consideration of investigational methods to increase muscle strength

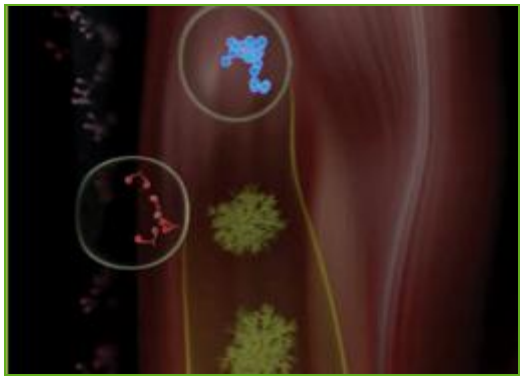
Spectrum of disease

- Two broad types of disease IO & LO
- Widely varied age of onset and speed of progression:
- ~<25% of normal enzyme activity is associated with disease phenotype
- Inexact inverse correlation between residual enzyme activity and severity

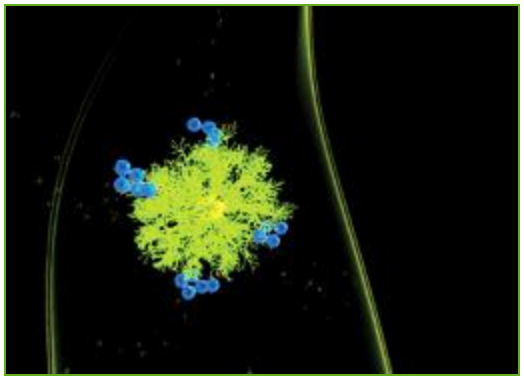
enzyme replacement therapy (ERT) - mechanism



Alglucosidase alfa "docks" on M6P receptors on cell surface



Inside cell, GAA dissociates from M6P receptors, which cycle back to cell surface



Inside lysosome, GAA breaks down glycogen to glucose

Enzyme Replacement Therapy –pre-clinical KO mice studies of three forms of GAA

- Dose response between 20 and 100mg/kg
- Chinese Hamster Ovary cell construct is more effective than other constructs
- Entry to myocytes and effective glycogen clearance are complex
- Cardiac muscle glycogen is much more effectively cleared than from skeletal muscle despite higher initial quantities
- Is this connected with continuous high level metabolic activity and blood flow in comparison to skeletal muscle

GAA ERT Glycogen Clearance –phase I study

Phase I study shows

- clearance of glycogen from muscle biopsies
- considerable restoration of normal muscle architecture
- During four months of ERT

Amalfitano et al. Genet Med 2001;3:132-8

The question of early treatment

- Chien et al; Paediatrics 2009;124,6
- Taiwan new born screening programme
- 5 cases detected in 206,000 live births
- Treatment started between 12 and 34 days of age

Results

- Baseline cardiomegaly reduced over 6 months
- Gross glycogen deposits and damaged muscle architecture greatly improved
- Independent walking in all five treated subjects by about 20 months
- Vast improvement in comparison to historical controls

Early treatment appears to improve outcome

- Small numbers and no randomised comparison
- So what about adults?
  in whom at time of diagnosis histology shows extensive myocyte damage and loss and MRI shows very substantial fatty replacement of muscle

The Late Onset Treatment Study (LOTS)

- A randomized study of alglucosidase alfa in Late-Onset Pompe's disease
- Ans T van der Ploeg et al NEJM 2010

Interpretation:

"In this study population, treatment with alglucosidase alfa was associated with improved walking distance and stabilization of pulmonary function over an 18-month period."

"In summary, our data indicate that alglucosidase alfa treatment, as compared with placebo, has a positive, if modest, effect on walking distance and pulmonary function in patients with late-onset Pompe's disease and may stabilize proximal limb and respiratory muscle strength."

Licensed prescribing information:
"In patients with late-onset Pompe disease the evidence of efficacy is limited"

LOTS –NEJM 2010

- Double blind placebo controlled
- 90 patients (Randomised 2:1 A:P) for 78 weeks

•Very rare disease

•Progressive disease

•Two weekly 3 hr IV infusions of placebo

“limited” misrepresents the reality of conducting studies in this context

Inclusion criteria

- GAA deficiency and 2 mutations
- 8 years or older
- >40m on a 6 minute walk test
- 30-80% of predicted FVC with a postural drop >10%
- Bilateral knee extension <80% of predicted (QMT)

- Exclusion:
  Invasive ventilation
  Non-invasive ventilation while awake and upright

Clinical efficacy

- Co-primary
  6 minute walk test (meters)
  % predicted FVC

- Secondary
  quantitative muscle testing (strength) leg and arm (QMT)
  maximum inspiratory pressure
  maximum expiratory pressure

Patients

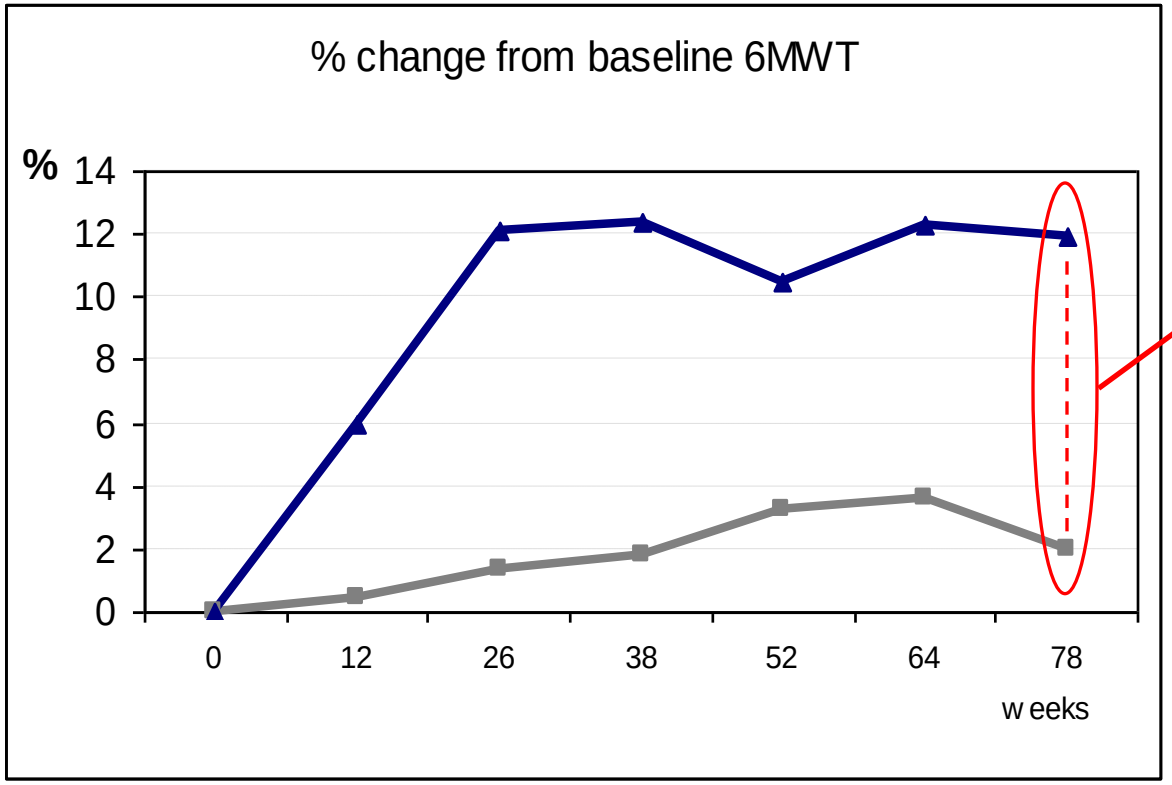
90 enrolled and 81 completed (5 Mz and 4 Pl dropped out)

	Mz (60)	Placebo (30)
Age: mean (range)	45.3 (6-70)	42.6: (10-68)
Male : female	34 : 26	11 : 19
Age at symptom onset	30 (5-59)	24 (2.7-43)
Disease duration	9 (0.3 -25)	10 (0.5 – 31.3)
% normal GAA	11 (0-47)	10 (0-32)
SF-38	34	35
6 min walk test	332 (77-626)	318 (41 -608)
FVC % predicted	55 (31-78)	53 (30-78)

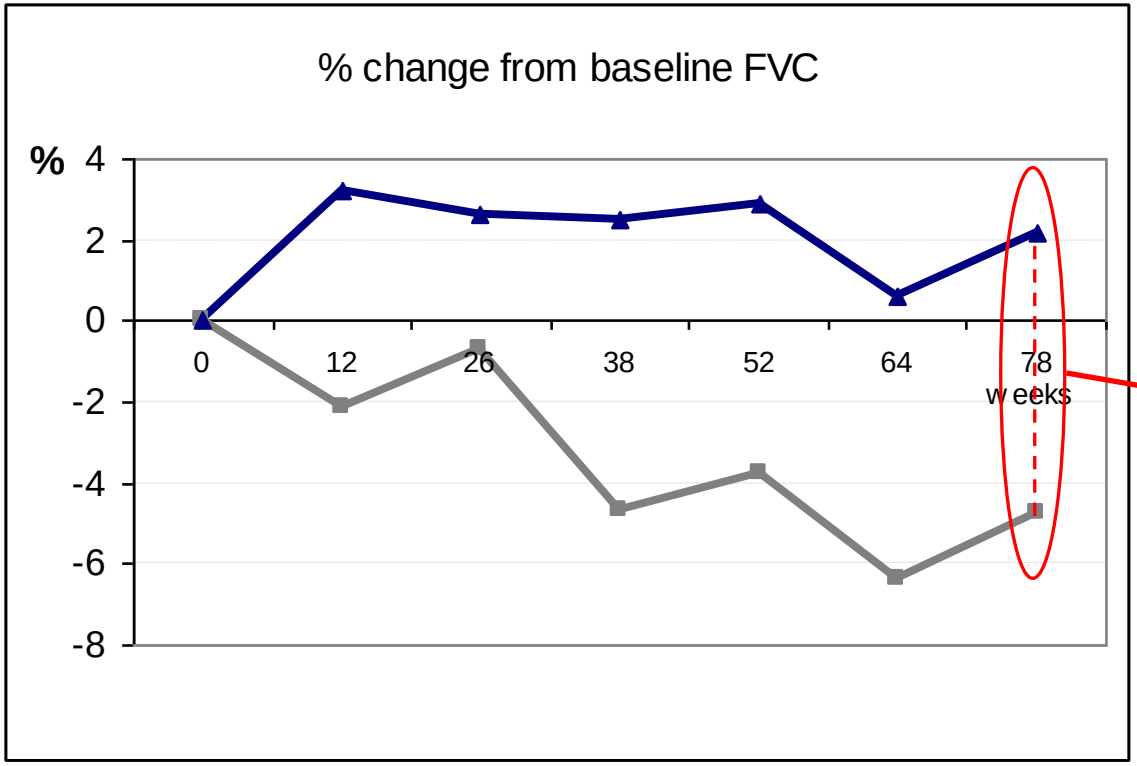
6 minute walk test –Primary end-point

- This has not previously been assessed serially in Pompe disease
- COPD clinical trial measure:
  - "walk as far as you can in six minutes" -normals ~ 6-700 metres
  - used for about 10 years and reviewed in Eur Resp J 2008
    -not referenced in NEJM publication
    - → "≥10% change from baseline is important"
- ?Applicability to AMD -respiratory function, core stability and muscle strength

6 minute walk test results redrawn as percentage change from baseline



FVC results (3.4% predicted difference) redrawn as percentage change from baseline



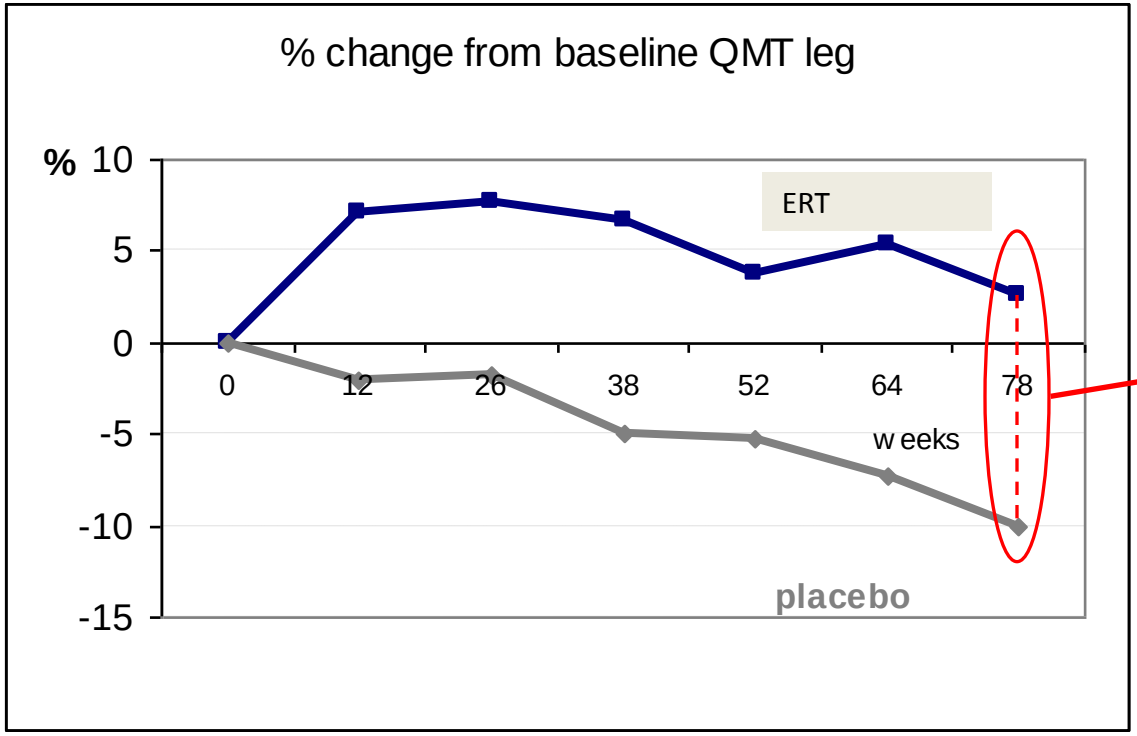
comparative change in percent predicted ~3.4%

comparative percentage change from baseline ~7%

Baseline “percent predicted”:

- 55% in treatment group
- 53% in placebo group

Leg muscle strength (3.2% predicted difference) redrawn as percentage change from baseline



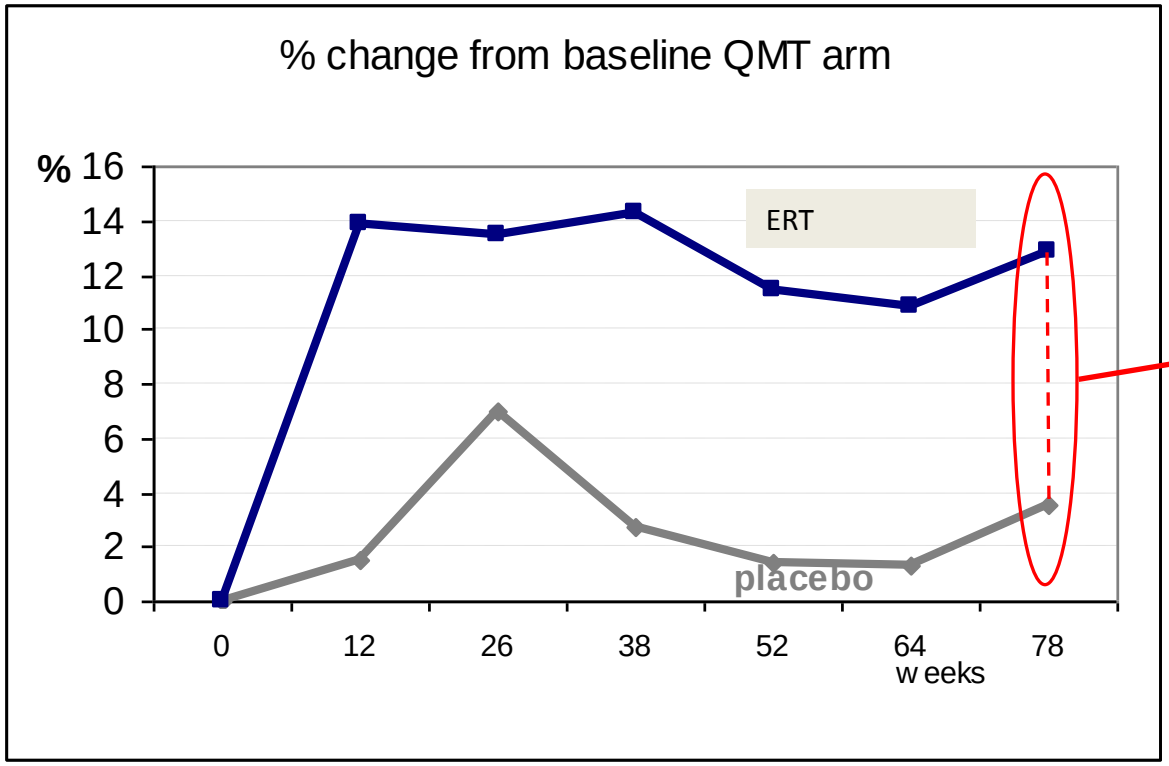
comparative change in percent predicted ~3.2%

comparative percentage change from baseline ~12%

Baseline “percent predicted”:

- 38% in treatment group
- 33% in placebo group

Arm muscle strength (3.6% predicted difference) redrawn as percentage change from baseline



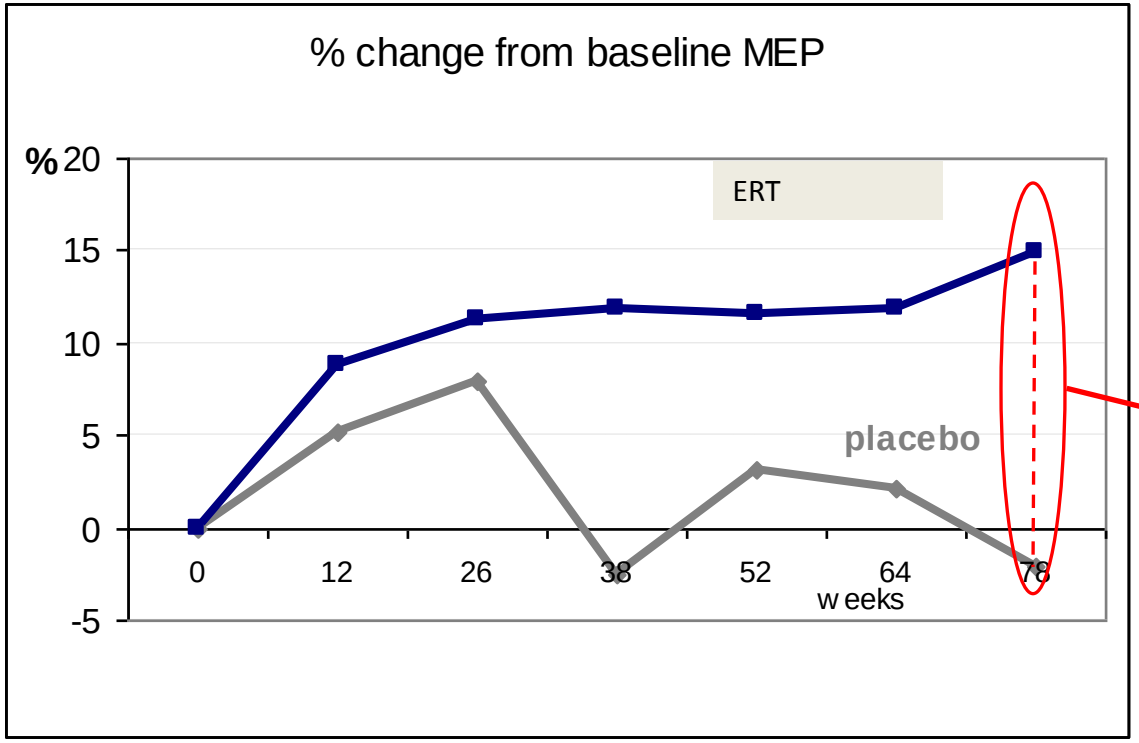
comparative change in percent predicted ~3.6%

comparative percentage change from baseline ~10%

Baseline “percent predicted”:

- 56% in treatment group
- 57% in placebo group

Expiratory pressure (3.8% predicted difference) redrawn as percentage change from baseline



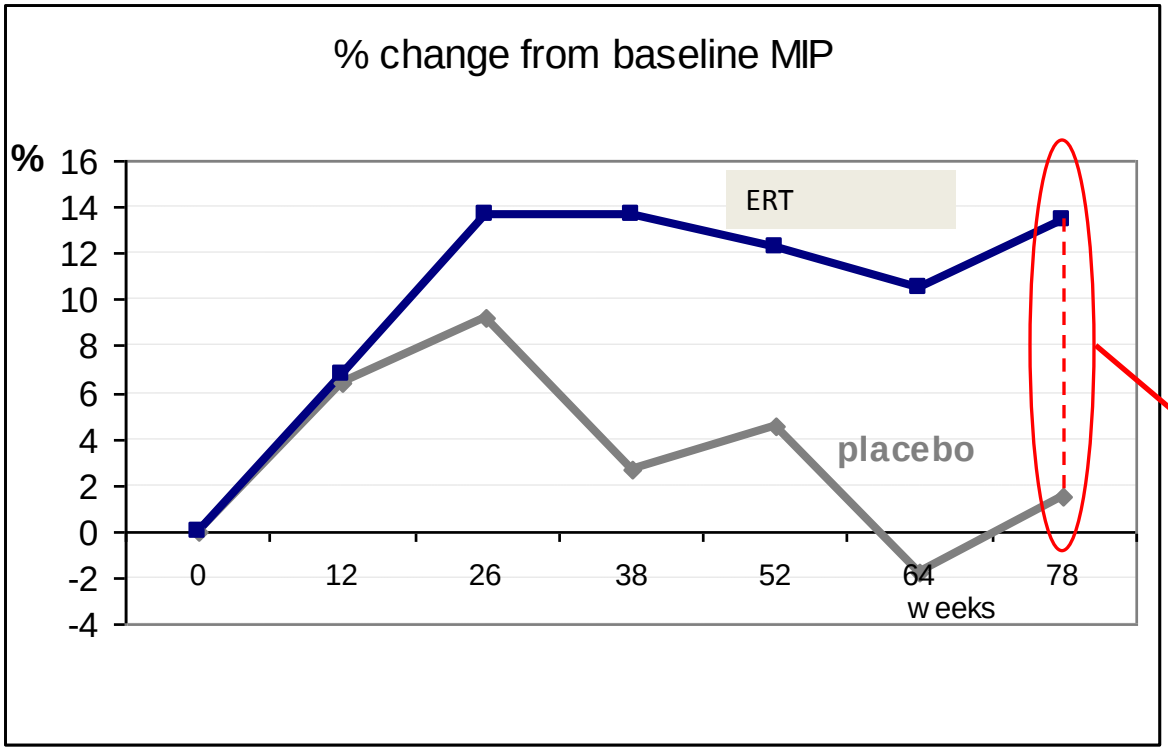
comparative change in percent predicted ~3.8%

comparative percentage change from baseline ~17%

Baseline “percent predicted”:

- 32% in treatment group
- 31% in placebo group

Inspiratory pressure (3.8% predicted difference) redrawn as percentage change from baseline



comparative change in percent predicted ~3.85%

comparative percentage change from baseline ~12%

Baseline “percent predicted”:

- 40% in treatment group
- 43% in placebo group

Conclusions

- Clear statistically significant arrest in the steady decline of muscle (and respiratory) function similar to other studies (LOPOS)
- Improvements in muscle strength and function

Summarised comparison

	change in % predicted from baseline	% change from baseline
FVC	3.4	7
QMT leg	3.2	12
QMT arm	3.8	10
MEP	3.6	17
MIP	3.9	12
6MWT	-	10

10% increase in 6MWT

- Defined in respiratory clinical trials as “important”
- 10% improvement for any human athletic endeavour is substantial
- All adults over about 30 decline >~0.5% per year
- However, we would all like more……

Strothotte (J Neurol (2010) 257:91–97) is consistent with LOTS

- Open label study of 12 months ERT
- In patients who could complete 6MWT
- baseline: 341m (SD 149; median 342)
- one year: 393m (SD 157; median 412) (p = 0.026)
- ~15% change from baseline
- 5 patients who exercised during infusions did remarkably well
- Was ERT delivery to active muscle with increased blood flow more effective –analogous to cardiac muscle in animal models?

Strothotte conclusions

- Increases in 6MWT look clinically useful
- Per-infusion muscle activation and increased blood flow may increase clinical benefit
- May not be feasible to separate this possible benefit from that of exercise alone

Modification of the natural history of AMD by nutrition and exercise therapy (Slonim et al Muscle Nerve 35: 70–77, 2007)

- Open label study of up to 5 years exercise (ergometer and resistance training)
- With low carbohydrate and high protein diet
- Arrest of decline of physical capacity or improvement in all compliant patients
- Would exercise and careful intensive nutrition be additive to ERT, particularly in a milieu of muscle with the damaging and deleterious effects of glycogen accumulation controlled by ERT?

Respiratory monitoring and support (Mellies; Resp Med (2009) 103, 477)

- Regular measurement of FVC
  incl supine and erect –*diaphragmatic weakness*
- …
  - <60% predicted –at risk of sleep disordered breathing
  - <40% predicted –strong predictor of continuous nocturnal hypoventilation; consider NIPPV
  - <25% -strong predictor of respiratory failure
- Progression is insidious and regular monitoring with early intervention is best practice

Physiotherapy, exercise and more….

- Standardised regular quantitative measurement of
  - strength,
  - functional capacity
  - vital (respiratory) capacity
- Muscle activation and blood flow stimulation during infusions (?including respiratory muscles)
- Muscle strength and functional capacity building exercise programmes and support
- Treatment of muscle contractures and posture

Nutrition and investigational approaches

- Weight loss
  very difficult when immobile, but major impact on mobility
- High protein diet & creatine supplements (with exercise)
  - Investigate treatments of sarcopenia
    - growth hormone
    - ACE inhibitors
    - anabolic steroids
- Stem cell approaches may be ideal in the milieu of progressive disease controlled by ERT…..

Conclusions

- Pompe is a treatable disease
- Evidence is difficult to gather
- Treatment is multi-factorial and investigational
- Systematic regular measurement is essential
  - including respiratory function and readiness for early intervention
- ERT arrests or slows muscle and respiratory decline
- Early treatment may best conserve function
- Muscle activation during infusions may increase effect
- Exercise programmes may increase strength and function
- Nutrition and weight loss may be important
- Contractures should be corrected
- Investigational treatments may be considered