SYNERGY BETWEEN THE PHARMACOLOGICAL CHAPERONE 1-DEOXYGALACTONOJIRIMYCIN AND AGALSIDASE ALPHA IN CULTURED FIBROBLASTS FROM PATIENTS WITH FABRY DISEASE

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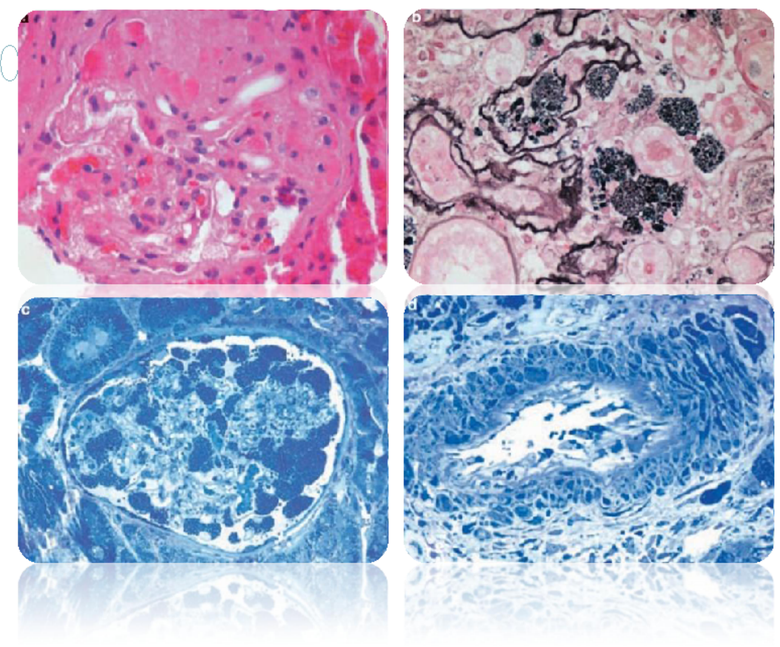
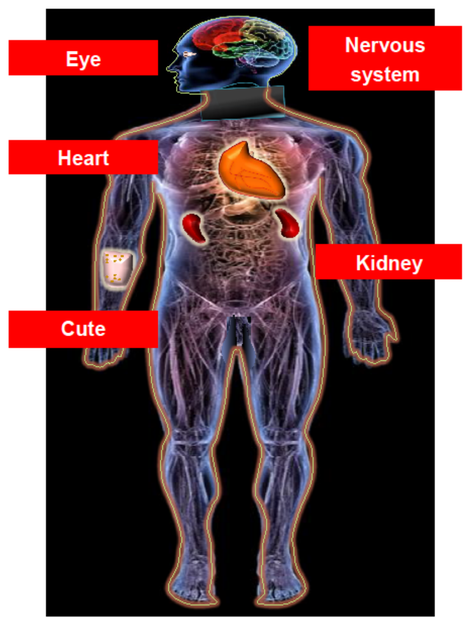
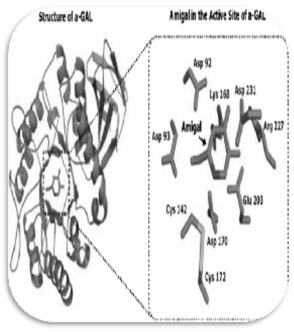
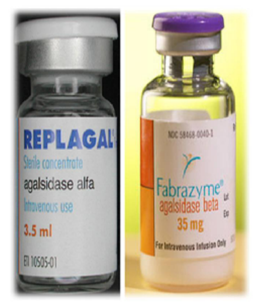


Background Fabry disease (FD) is an X-linked inherited disease due to alpha-galactosidase A (alpha-Gal A) deficiency. Enzyme replacement therapy (ERT) with recombinant human alpha-galactosidase A (rh-alpha-Gal A) is now available for the treatment of FD and in most patients results in clinical improvement or stabilization. Two recombinant rh-alpha-Gal A preparations are presently approved for ERT, agalsidase alpha, and agalsidase beta. However, ERT efficacy may vary in different tissues and its long-term effects remain to be defined.



Aim of the study. As a strategy to improve the efficacy of ERT, we tested the combination of rh-alpha-Gal with the chaperone molecule 1-deoxynojirimycin (DGJ) in cultured FD fibroblasts with negligible residual enzyme activity. In our previous study, compared to the effects of rh-alpha-Gal A alone, co-administration of DGJ and agalsidase beta resulted in better correction of intracellular alpha-Gal A activity, and increased amounts of the enzyme within the lysosomal compartment The present study aimed to evaluate if agalsidase alpha has the same synergistic effects too.



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ORIGINAL ARTICLE

Synergy between the pharmacological chaperone 1-deoxygalactonojirimycin and the human recombinant alpha-galactosidase A in cultured fibroblasts from patients with Fabry disease

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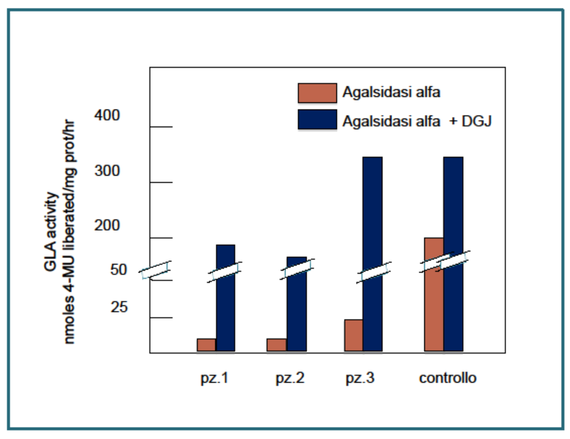
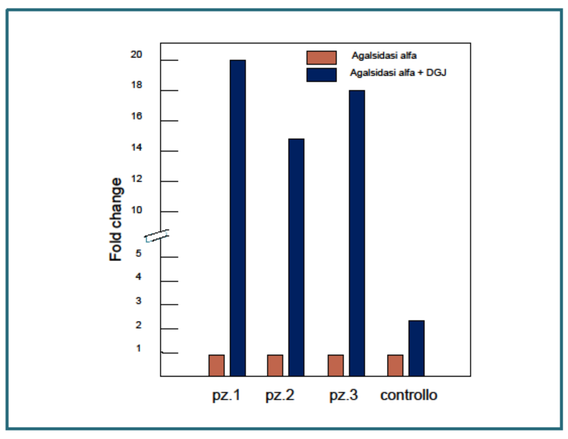
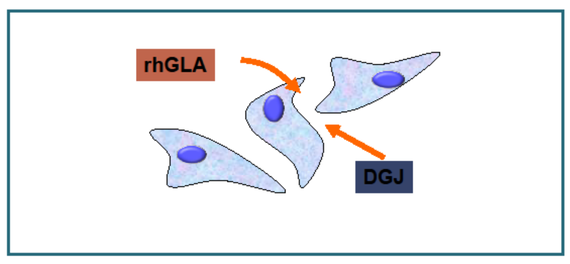
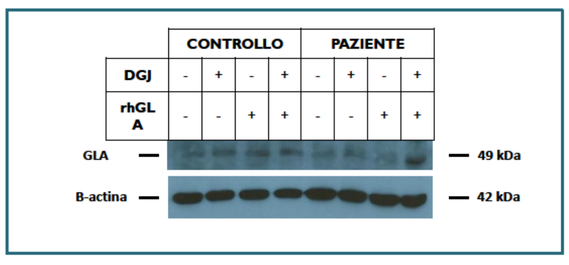
Methods: Fibroblasts from 3 male FD patients and from one control patient, derived from skin biopsies, were incubated with agalsidase alpha (5 nmol/l) for 24 h, in the absence or in the presence of 20 µmol/l DGJ, after a 72h incubation with DGJ alone.
Alpha-Gal A activity was assayed by using the fluorogenic substrate 4-methylumbelliferyl-alpha-D-galactopyranoside (Sigma-Aldrich). To study alpha-Gal A immunoreactive material, fibroblast extracts were subjected to western blot analysis.









Results: When the cells where co-incubated with DGJ and rh-alpha-Gal A we observed a highly improved correction of intracellular activity (an increase da 15 a 20 volte); none of the cell lines showed significant increases in baseline activity when incubated with the chaperone alone. A western blot analysis showed a large increase in alpha-Gal A protein in cells treated with rh-alpha-Gal A and DGJ, compared to the cells treated with rh-alpha-Gal A alone.

Conclusions: In conclusion, this study provides additional evidence for a synergistic effect between ERT and DGJ and supports the idea that the efficacy of combination protocols may be superior to ERT alone. Although these studies were done in vitro and require further confirmation in vivo, our results hold promise for the treatment of FD patients and suggest that this approach can be extended to any other lysosomal storage disease for which ERT and chaperones are available. The efficacy of combination of ERT and DGJ on renal tissue remain to be defined.

References

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