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XXXIV Congreso Sociedad Andaluza de Medicina Interna (SADEMI)

V Encuentro de Enfermería de Medicina Interna de Andalucía

14, 15 y 16 de Junio 2018
CAMPUS DE LA SALUD
- GRANADA -

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CAMPUS DE LA SALUD
- GRANADA -

Actualización en enfermedad de Fabry

Alberto Ortiz, MD, PhD
Jefe de Servicio de Nefrología e Hipertensión
IIS-Fundacion Jimenez Diaz
Profesor Titular de Medicina, U Autónoma de Madrid
Coordinador, RETIC REDINREN
Madrid, Spain

Conflict of interest

- Consultant: Sanofi Genzyme
- Speaker fees: Sanofi Genzyme, Shire, Amicus

Molecular Genetics and Metabolism 123 (2018) 416–427

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

Fabry disease revisited: Management and treatment recommendations for adult patients

Alberto Ortiz[a,*], Dominique P. Germain[b], Robert J. Desnick[c], Juan Politei[d], Michael Mauer[e], Alessandro Burlina[f], Christine Eng[g], Robert J. Hopkin[h], Dawn Laney[i], Aleš Linhart[j], Stephen Waldek[k], Eric Wallace[l], Frank Weidemann[m], William R. Wilcox[i]

Abstract | Full Text | Images | References | **Supplemental Materials**

Title	Description	Type	Size
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	Appendix B	pdf	.37 MB
	Appendix C	pdf	.36 MB
	Appendix D	pdf	.37 MB
	Appendix E	pdf	.3 MB
	Appendix F	pdf	.27 MB
	Appendix G	pdf	.3 MB
	Appendix H	pdf	.26 MB

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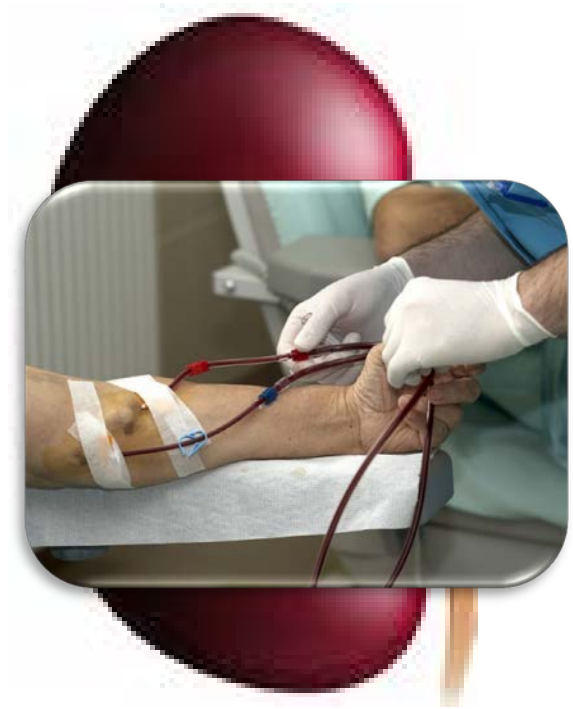
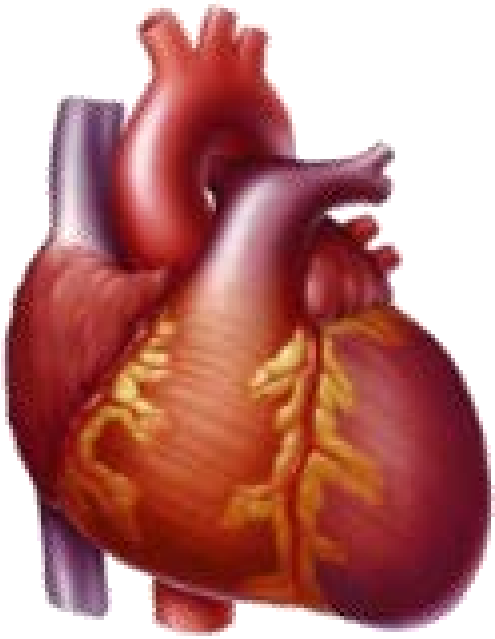
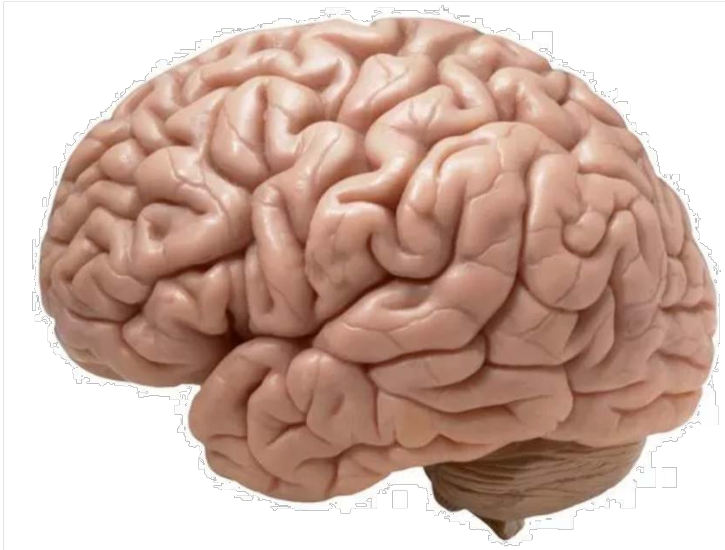


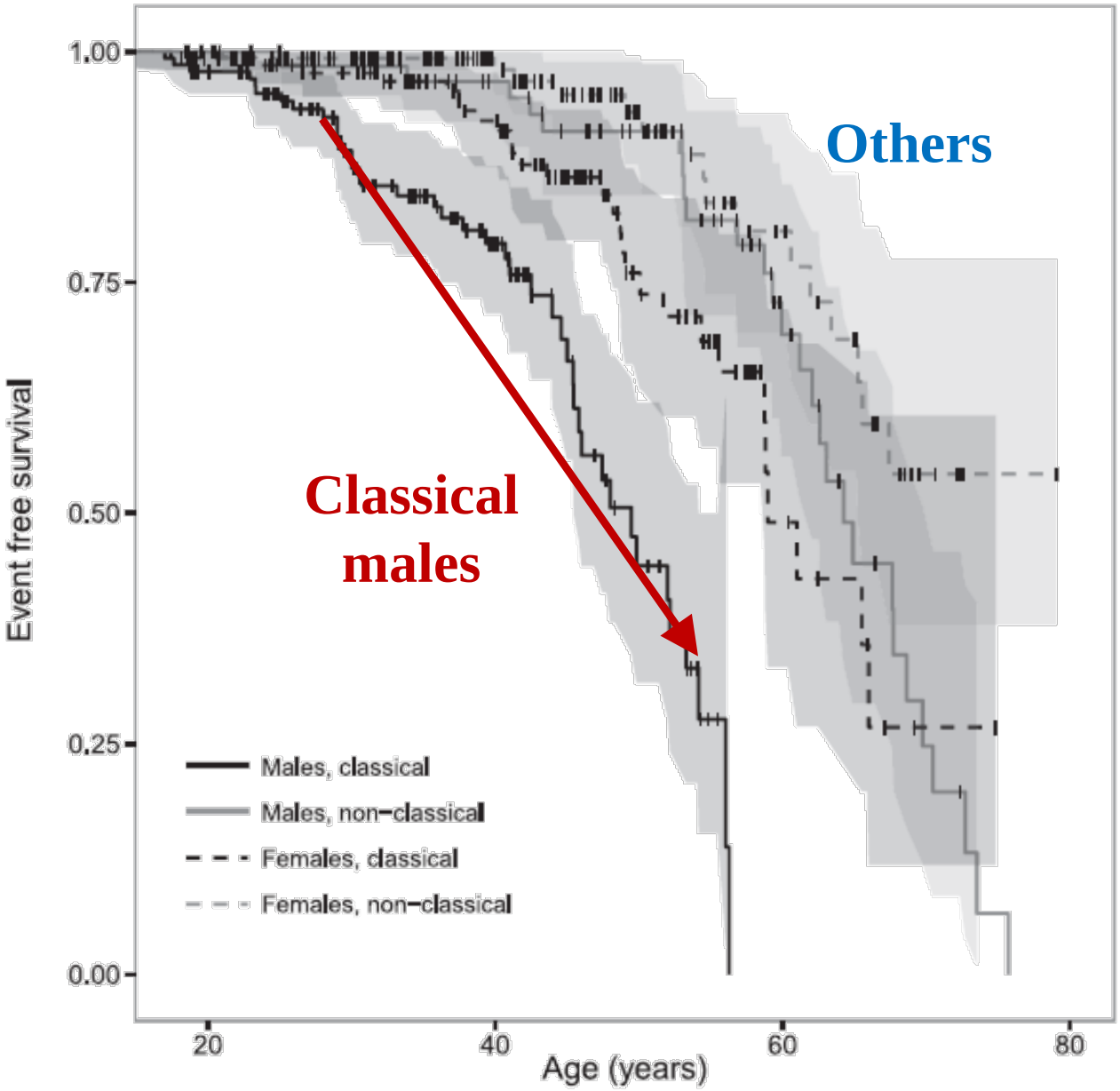




X-linked

Classical males vs other Fabry patients

Natural history
Severe events



Arends M, et al. J Am Soc Nephrol 2017 May;28(5):1631-1641

ERT: agalsidase

For **all**

Chaperone: migalastat

Not for all: **amenability**

Med Clin (Barc). 2017;148(3):132–138

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Diagnosis and treatment

Diagnosis and treatment of Fabry disease☆

Diagnóstico y tratamiento de la enfermedad de Fabry

Alberto Ortiz[a,b,*], Maria Dolores Sanchez-Niño[a,b]

Carta al Editor

Diferencias entre agalsidasa α y agalsidasa β en el tratamiento de la enfermedad de Fabry

Differences between agalsidase α and agalsidase β in the treatment of Fabry disease

Sr. Editor:

Jordi Pérez-López
Alfonso Domínguez Gil-Hurlé
Mónica López Rodríguez

Med Clin (Barc). 2017 Sep 20;149(6):270

Reply☆

Respuesta

Dear Editor,

Med Clin (Barc). 2017 Sep 20;149(6):271-272.

- **What is known about enzyme activity?**

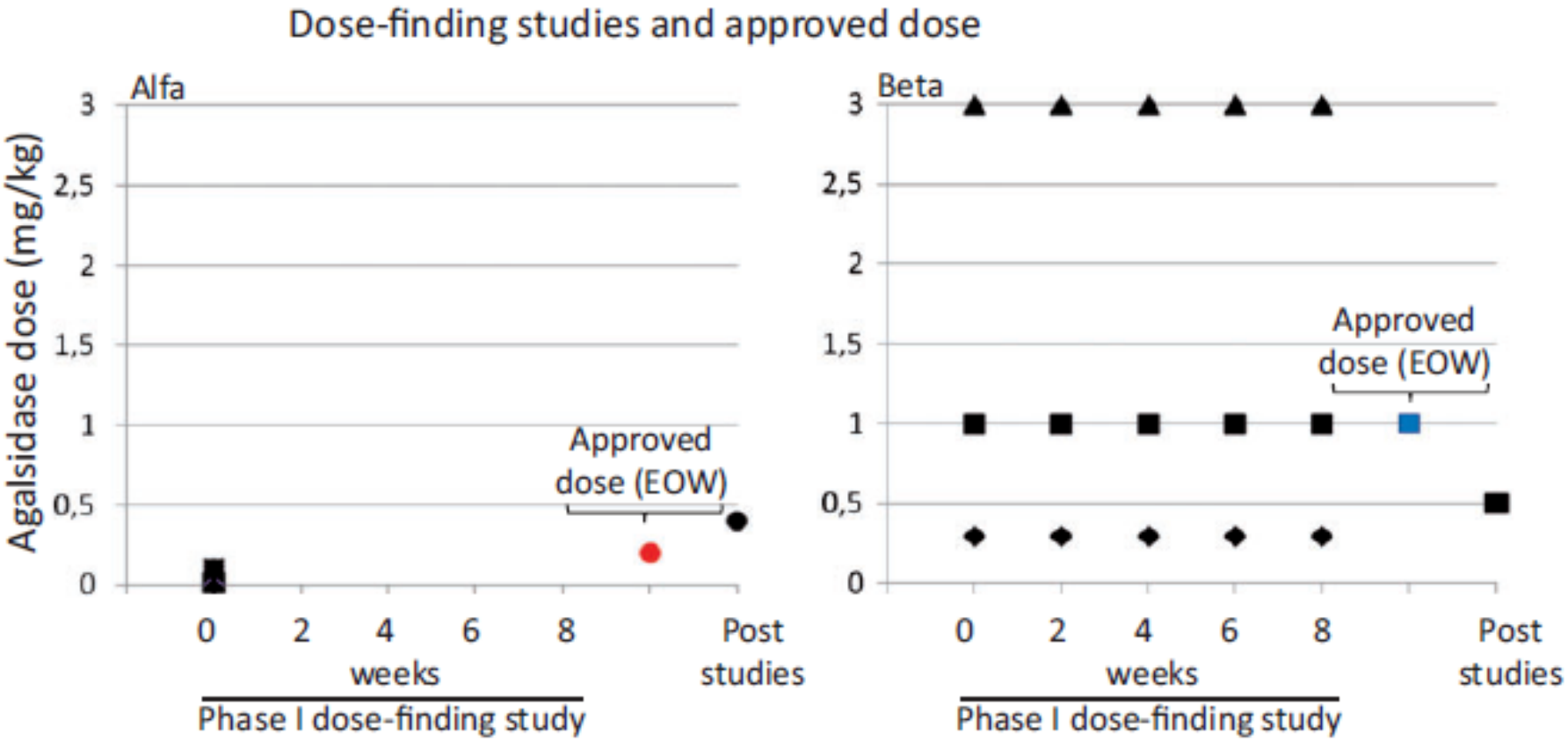
“agalsidasa alfa y agalsidasa beta no son moléculas idénticas y, consecuentemente, sus **regímenes óptimos de dosificación son distintos** ”

“La agalsidasa **alfa** tiene un **menor** contenido de ácido siálico y de **manosa-6-fosfato**, lo que le confiere un patrón de glicosilación más parecido al humano”

Pérez-López J et al. Med Clin (Barc). 2017 Sep 20;149(6):270

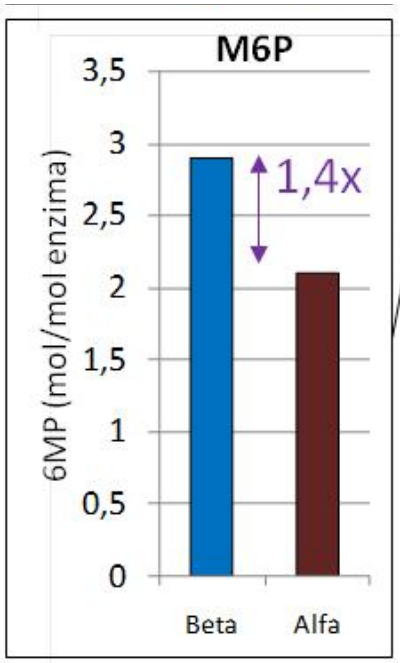
Ambas son proteínas recombinantes humanas

"agalsidasa alfa y agalsidasa beta no son moléculas idénticas y, consecuentemente, sus **regímenes óptimos de dosificación son distintos** " Pérez-López J et al. Med Clin (Barc). 2017 Sep 20;149(6):270



Ortiz A, Sanchez-Niño MD. Nephrol Dial Transplant. 2018 Apr 18. doi: 10.1093/ndt/gfy089. [Epub ahead of print]

“La agalsidasa **alfa** tiene un **menor** contenido de ácido siálico y de **manosa-6-fosfato**, lo que le confiere un patrón de glicosilación más parecido al humano.” Pérez-López J et al. Med Clin (Barc). 2017 Sep 20;149(6):270



Ortiz A. Med Clin (Barc). 2017 Sep 20;149(6):271-272.

- What is known about enzyme activity?

- **And about enzyme antigenicity?**

"y a diferencia de la agalsidasa-beta, (alfa) no contiene ácido N-glicolilneuramínico (reconocido **xenoantígeno** causante de **reacciones inmunes** y de procesos inflamatorios crónicos)"

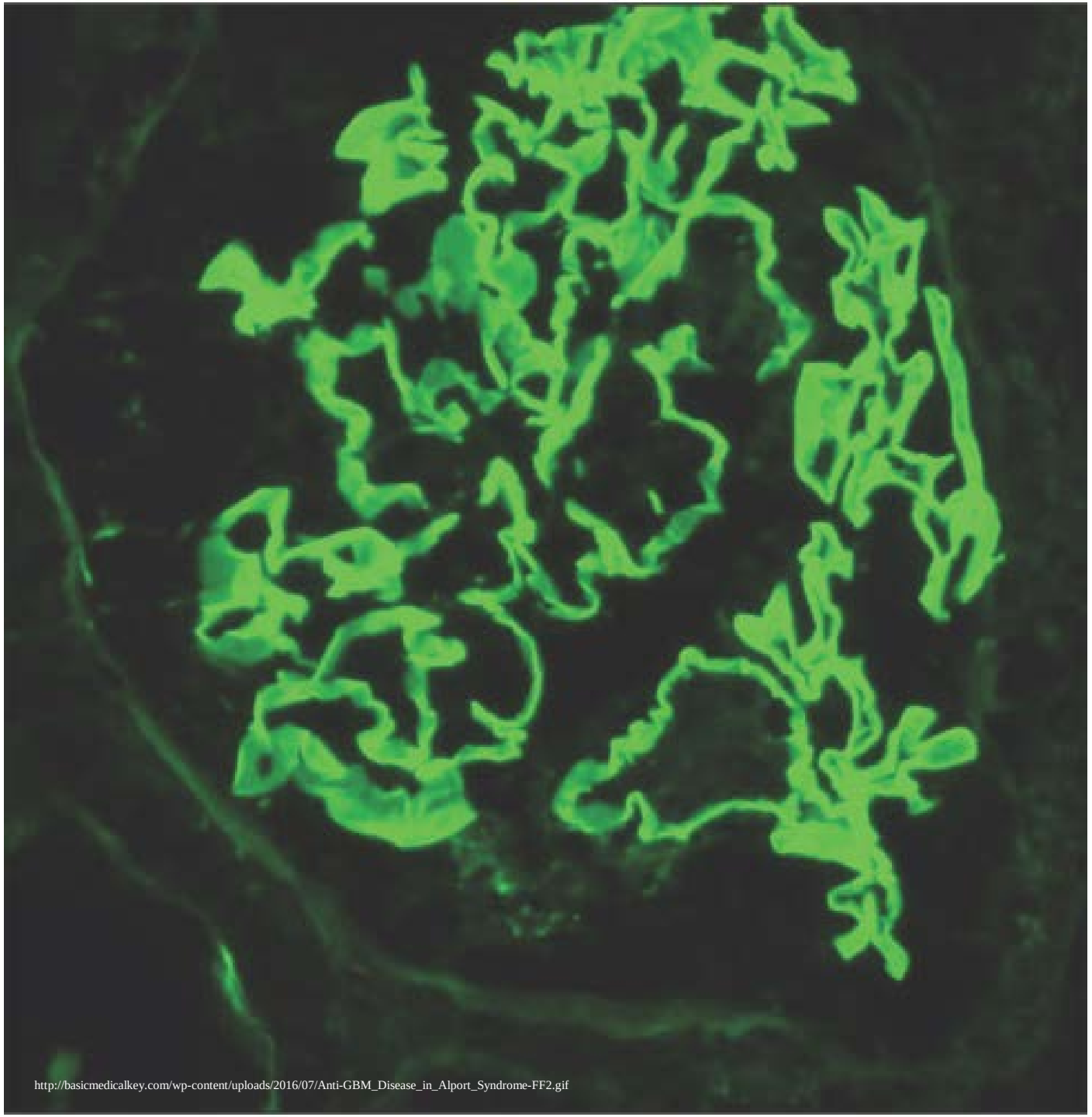
Pérez-López J et al. Med Clin (Barc). 2017 Sep 20;149(6):270

If this were true:

a) Other CHO-generated proteins would generate Ab in 40-80% of patients, e.g. **EPO**
b) Ab would develop in both males and **females**
c) And would **not be cross-reactive**

Anti-GBM antibodies in Alport patient receiving a kidney graft

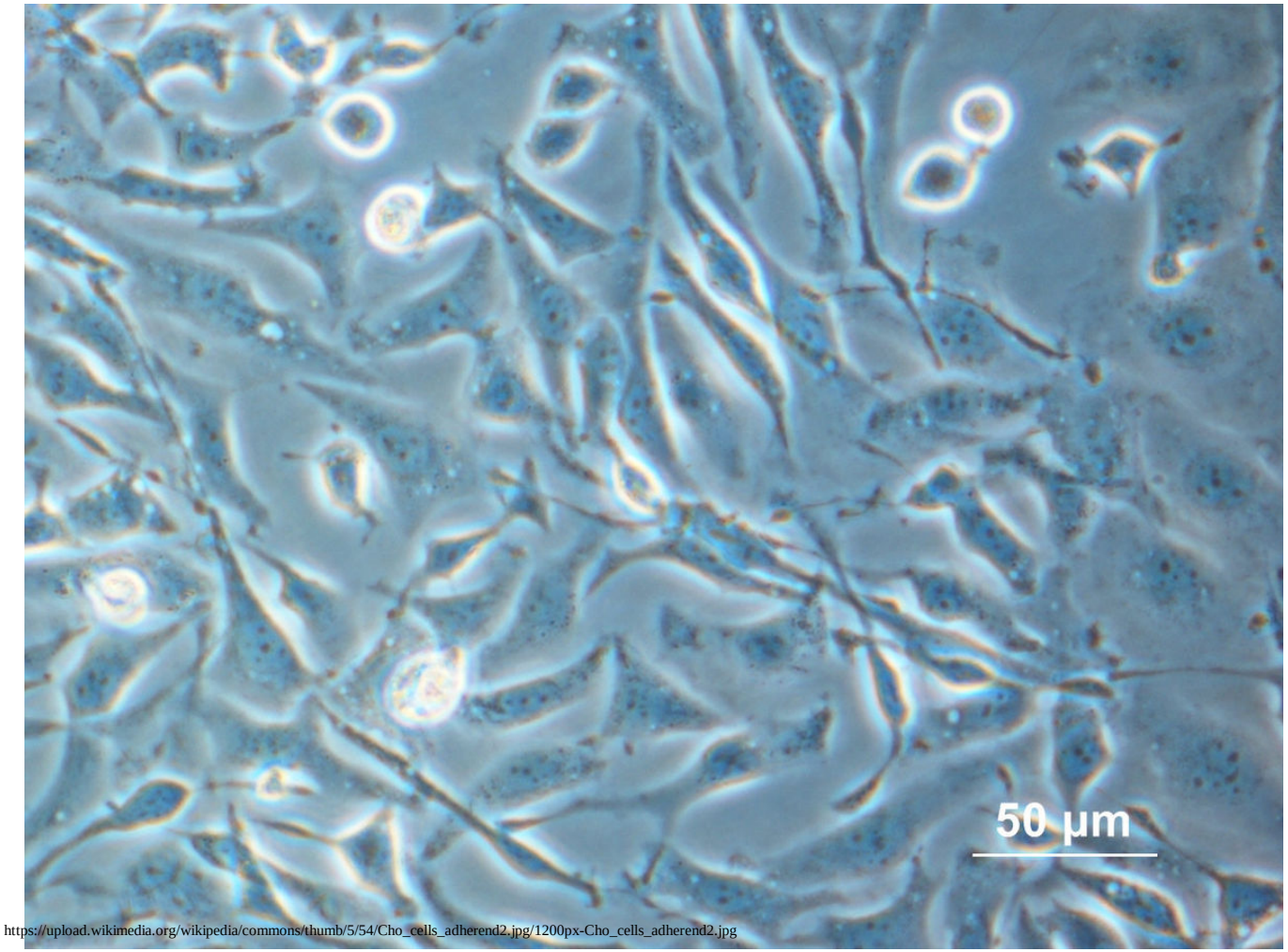
Alport patients **lack** certain **GBM** components (type IV collagen)



http://basicmedicalkey.com/wp-content/uploads/2016/07/Anti-GBM_Disease_in_Alport_Syndrome-FF2.gif

Hamster

Chinese Hamster cells (CHO cells)



https://upload.wikimedia.org/wikipedia/commons/thumb/5/54/Cho_cells_adherend2.jpg/1200px-Cho_cells_adherend2.jpg

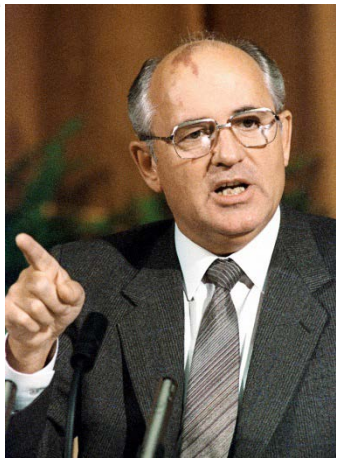
More than 30 years of human recombinant EPO

The Lancet · Saturday 22 November 1986

EFFECT OF HUMAN ERYTHROPOIETIN DERIVED FROM RECOMBINANT DNA ON THE ANAEMIA OF PATIENTS MAINTAINED BY CHRONIC HAEMODIALYSIS

CHRISTOPHER G. WINEARLS[1] DESMOND O. OLIVER[2]
MARTIN J. PIPPARD[3] CECIL REID[3]
MICHAEL R. DOWNING[4] P. MARY COTES[3]

1986



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http://www.abc.net.au/news/image/3980674-3x4-700x933.jpg
https://en.wikipedia.org/wiki/List_of_leaders_of_the_Soviet_Union#/media/File:RIAN_archive_359290_Mikhail_Gorbachev.jpg

Winearls CG, et als. Lancet. 1986 Nov 22;2(8517):1175-8

Evidence suggests lack of endogenous protein rather than xenoantigens as cause for antibodies

"Ambas moléculas tienen, por tanto, distintos perfiles de inmunogenicidad, que explicaría una **menor formación de anticuerpos IgG** contra el fármaco en el caso de la agalsidasa alfa [2]."
Pérez-López J et al. Med Clin (Barc). 2017 Sep 20;149(6):270

Vedder AC et al. PLoS One. 2007;2:e598

- **RCT** open-label comparison of 34 patients with FD treated with either agalsidase-alfa or agalsidase-beta each at 0.2 mg/kg EOW over 12 and 24 months
- Among other endpoints of the study, anti-agalsidase antibodies developed in:
  - 4/8 **males** with agalsidase-alfa
  - 6/8 **males** with an unapproved dose of agalsidase-beta
  - **p = 0.30**, Chi Square, **p = 0.60**, Fisher exact test

No females developed antibodies

Bibliografía

1. Togawa T, Takada M, Aizawa Y, Tsukimura T, Chiba Y, Sakuraba H. Comparative study on mannose 6-phosphate residue contents of recombinant lysosomal enzymes. Mol Genet Metab. 2014;111:369–73.
2. Vedder AC, Linthorst GE, Houge G, Groener JE, Ormel EE, Bourma BJ, et al. Treatment of Fabry disease: Outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. PLoS One. 2007;2:e598.

EOW, every other week
The recommended dose of Fabrazyme is 1 mg/kg body weight administered once every 2 weeks as an intravenous infusion.
Fabrazyme SmPC 2017

Evidence suggests lack of endogenous protein rather than xenoantigens as cause for antibodies

Lenders M et al. *J Am Soc Nephrol* 2016;27:256–264: serum-mediated inhibition

- To determine the agalsidase inhibition status of **168** patients (68 male) with FD, outcomes of inhibition-positive patients were compared with those of inhibition-negative patients

Males, **main risk factor was nonsense mutation**:

Nonsense in 6/23 (**26**.1%) patients **without** serum-mediated inhibition

Nonsense in 13/18 (**72**.2%) patients **with** serum-mediated inhibition

$p<0.01$

Inhibition did **not depend on the initial ERT** compound initially used (agalsidase-alfa or -beta)

No females developed antibodies

EOW, every other week

IgG

- Develop in patients treated with **agalsidase alfa or agalsidase beta**[1,2,3]
- Ab **cross-reactive: agalsidase alfa and agalsidase beta**[1,2,3]

[4] IgG **less frequent** in protein positive and **females**

1. Nakano S et al. PLoS One. 2015;10:e0128351
2. Linthorst et al. Kidney Int 2004;66:1589-95
3. Goker-Alpan IMD Reports - DOI 10.1007/8904_2015_483
4. Lenders et al. J Am Soc Nephrol 27: 256–264, 2016. doi: 10.1681/ASN.2014121226

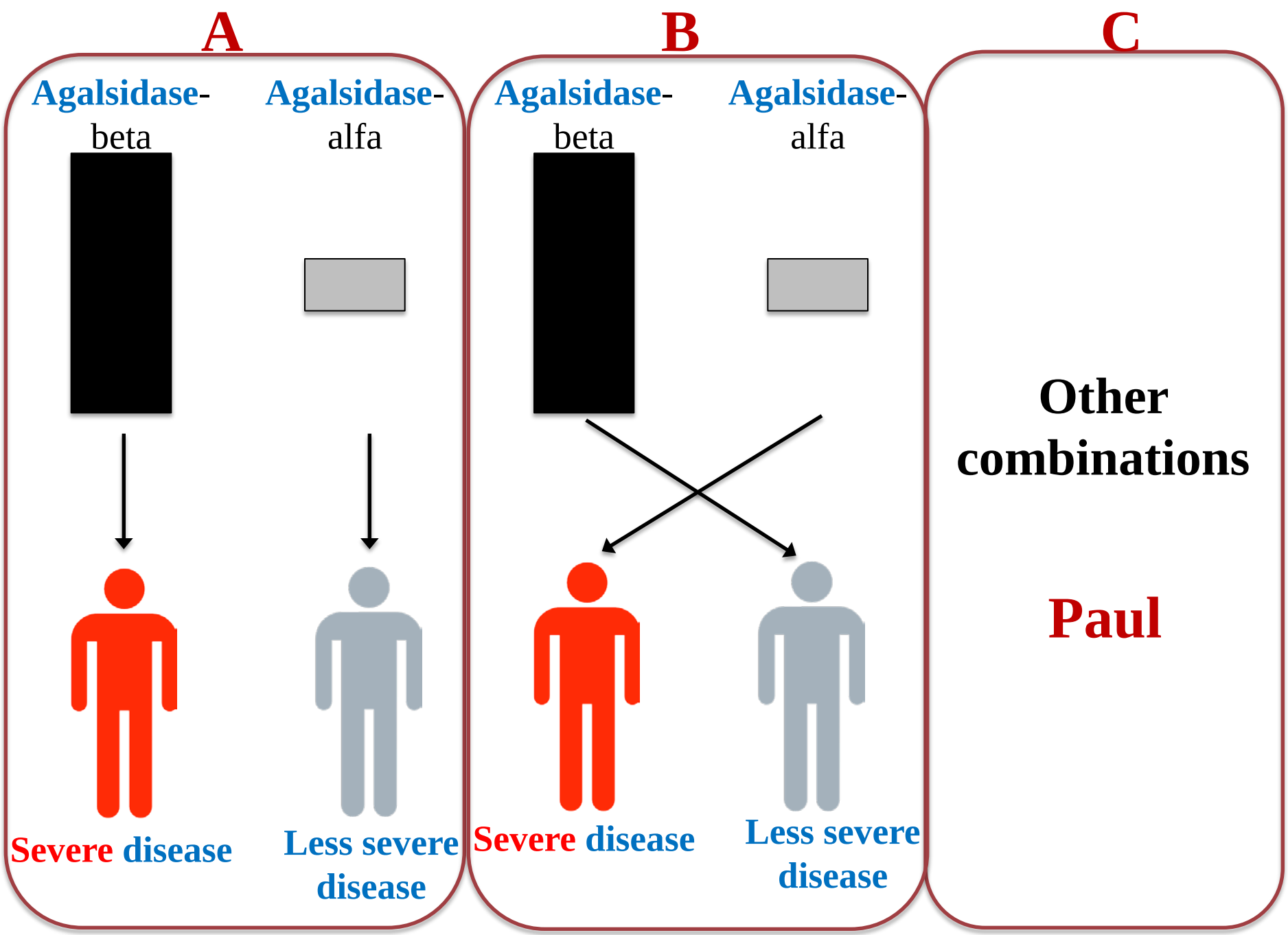
- What is known about enzyme activity?
- And about enzyme antigenicity?
- **What do experts think?**

What´s in a Fabry prescriber´s mind?

Agalsidase- beta

Agalsidase- alfa

https://imgur.com/gallery/Am8qRh1



Bars represent dose of ERT. Note that these are different molecules and differ by more than just dose.

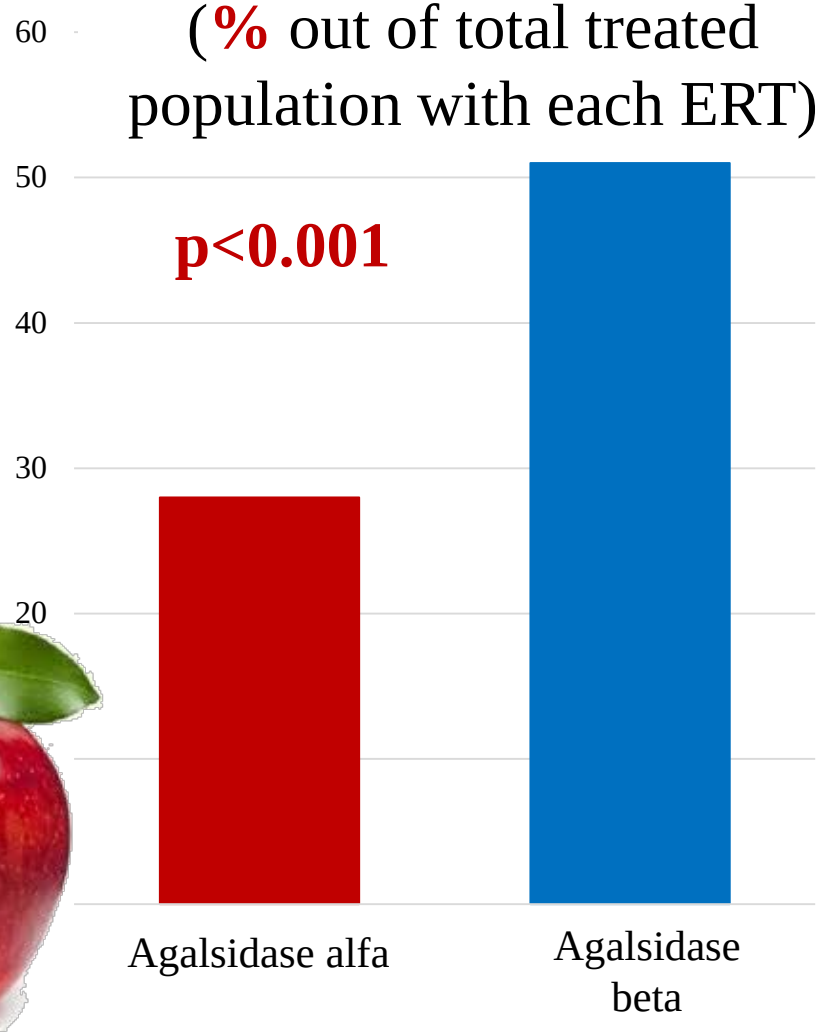

Paul

How were patients distributed between **Agalsidase-alfa** 0.2 mg/kg/2weeks and **Agalsidase-beta 1.0** mg/kg/2 weeks in a recent multicenter observational study?

- Academic Medical Center, The Netherlands;
- Royal Free London NHS Foundation Trust, UK
- University Hospital Wuerzburg, Germany
- Cohort 1b, CFDI, Canada

Classical men

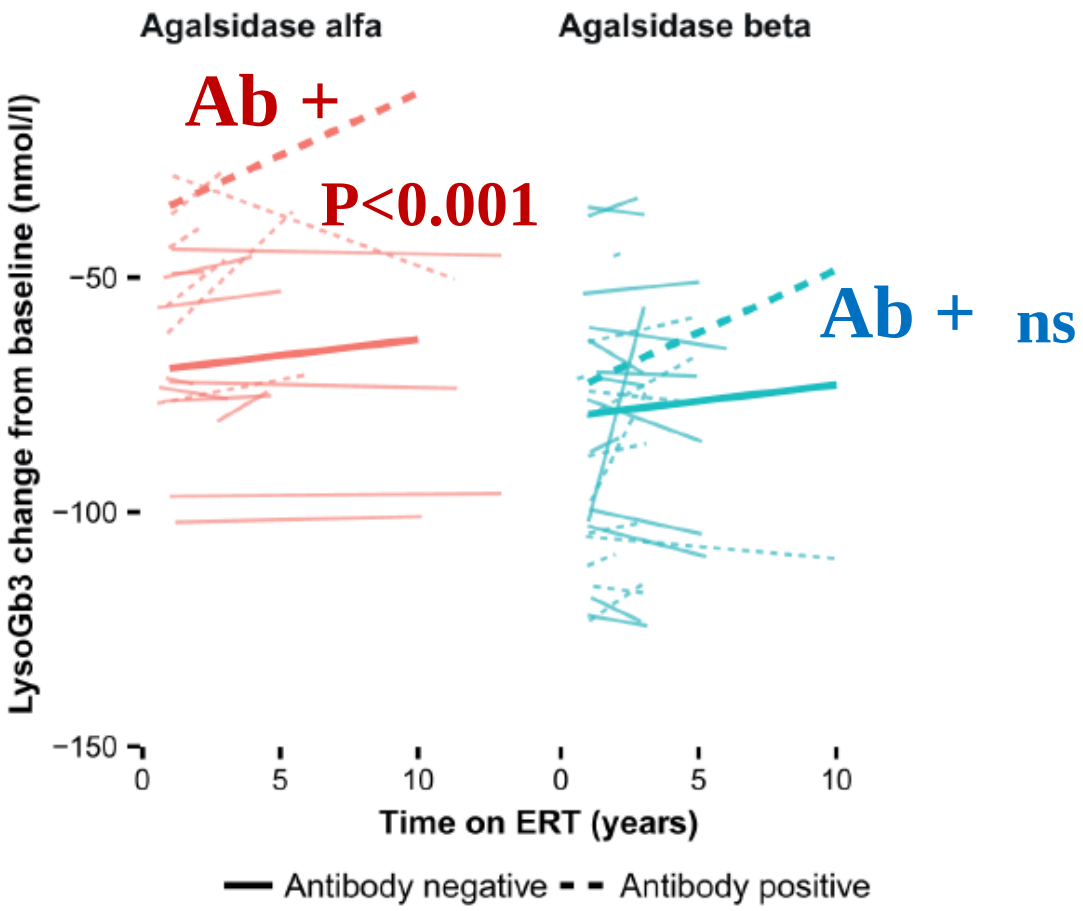
(**%** out of total treated population with each ERT)



The correct response is **A**

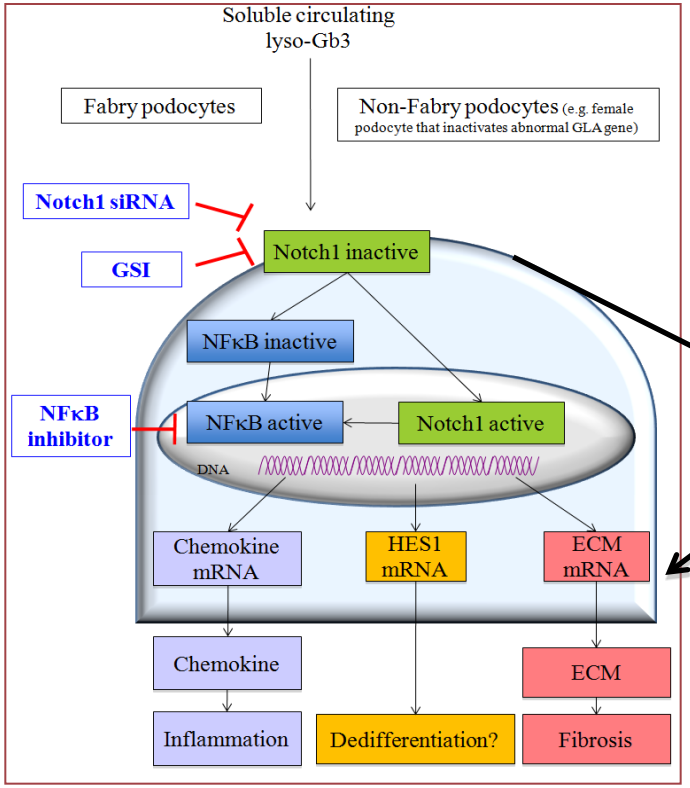
Arends M et al. J Med Genet Published Online First: 07 February 2[illegible] 10.1136/jmedgenet-2017-104863

Ab: Does it matter?



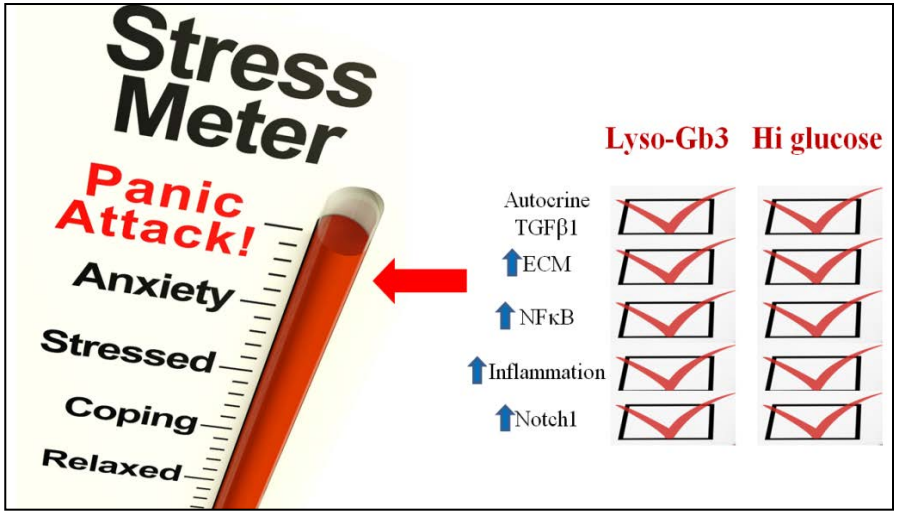
Arends M et al. J Med Genet Published Online First: 07 February 2018. doi: 10.1136/jmedgenet-2017-104863

Lyso-Gb3 Promotes Podocyte Stress



TGF-β1

Effect of lyso-Gb3 on Fabry nephropathy[1,2]



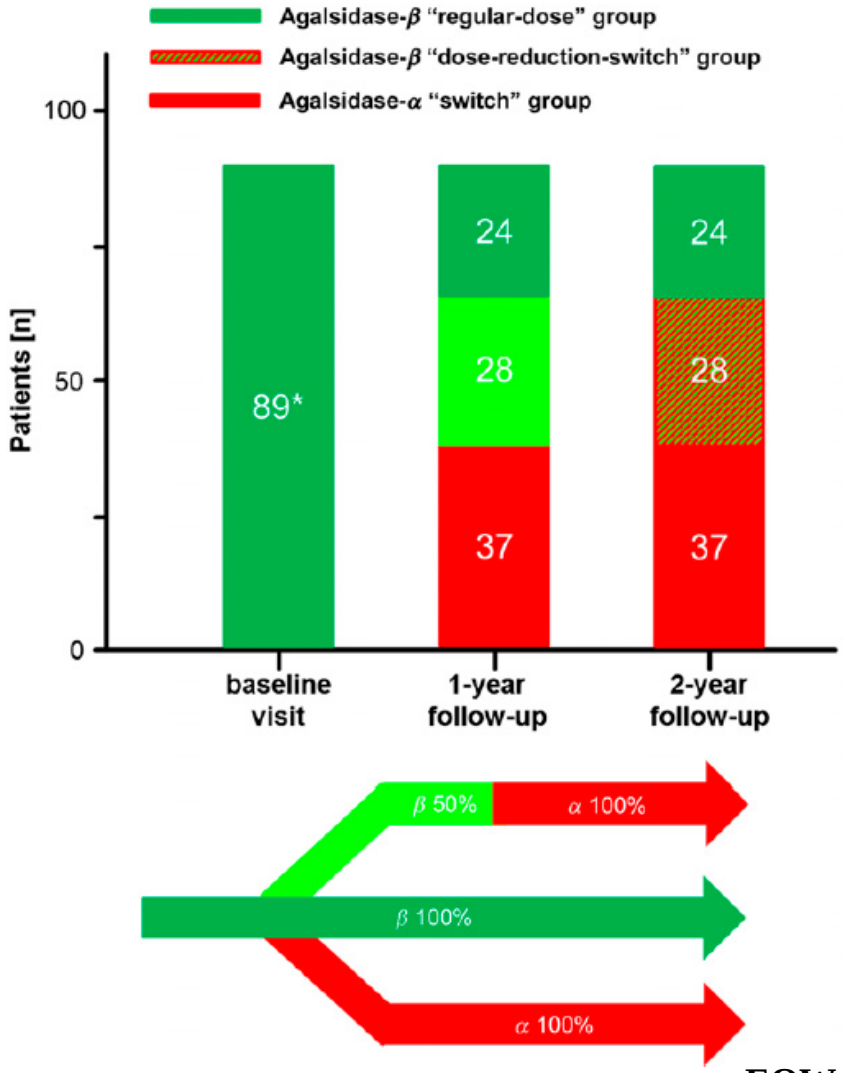
TGF-β1, transforming growth factor beta 1.

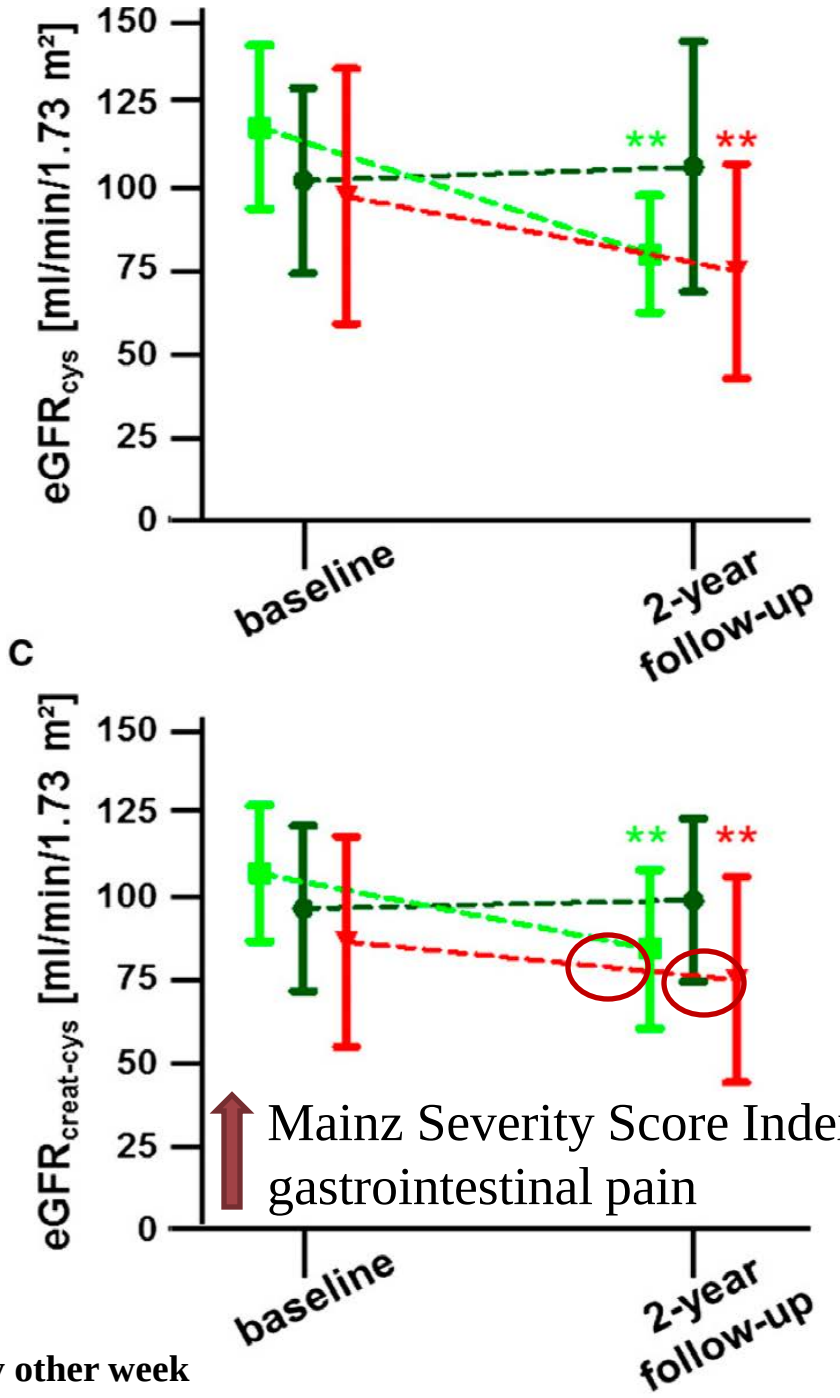
100 nM lyso-Gb3

1. Sanchez-Niño MD, et al. Nephrol Dial Transplant. 2011;26:1797-802.
2. Sanchez-Niño MD, et al. Human Mol Genet. 2015;24:5720-32.

- What is known about enzyme activity?
- And about enzyme antigenicity?
- What do experts think?
- **What did we learn from the shortage?**

2 years of dose-reduction of agalsidase-β 1.0 mg/kg/eow and/or switch to agalsidase-α 0.2mg/kg/eow and eGFR



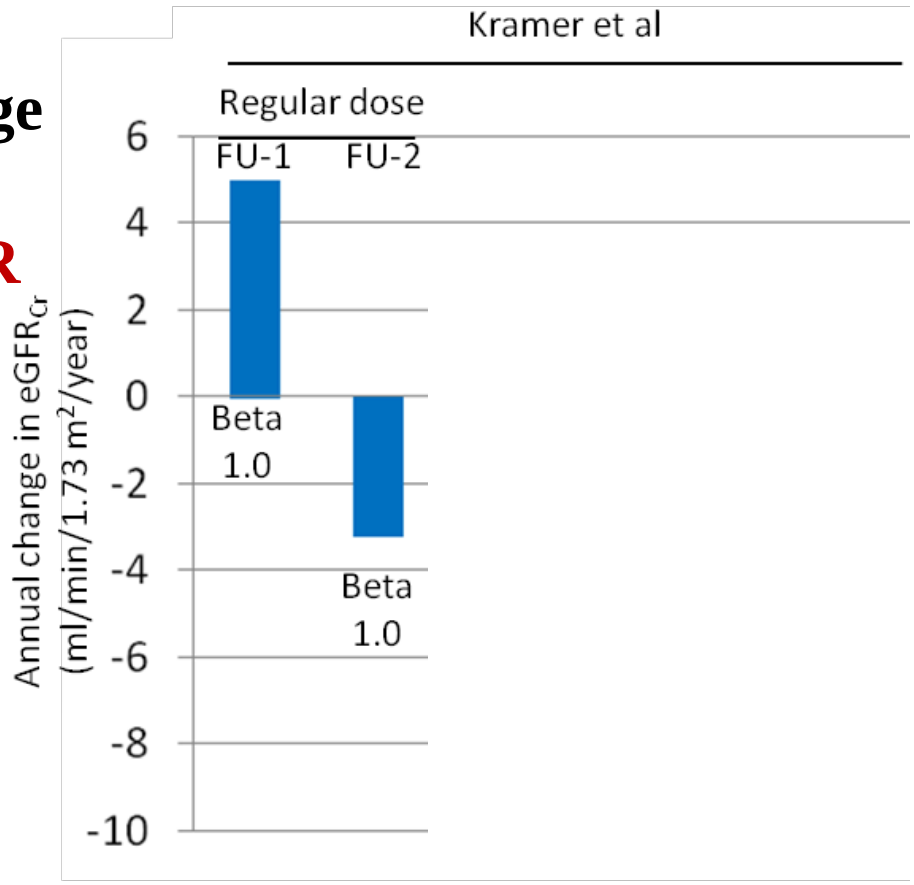


Lenders et al. JASN 2015

EOW = every other week

Dose and the shortage: impact of switching back to agalsidase beta 1.0 mg/kg/EOW

Change in eGFR



Ortiz et al. Nephrol Dial Trasplant 2018. Elaborated with data from:
Krämer J et al. Nephrol Dial Transplant 2017 Nov 23. doi: 10.1093/ndt/gfx319. [Epub ahead of print]
www.fda.gov/ohrms/dockets/ac/03/briefing/3917B2_01_TKT%20Replagal%20Background%20.pdf

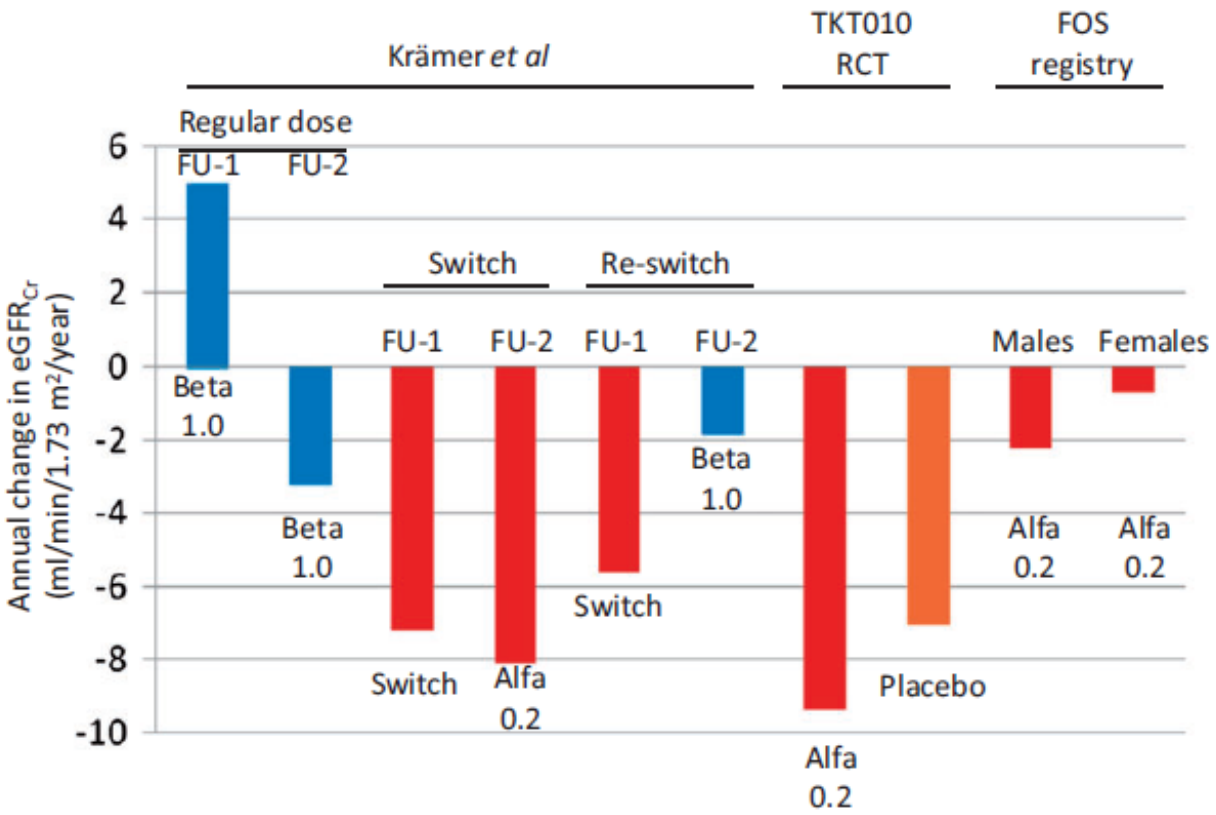
Nephrol Dial Transplant (2018) 1–6
doi: 10.1093/ndt/gfy089

ndt
Nephrology Dialysis Transplantation

Enzyme replacement therapy dose and Fabry nephropathy

Alberto Ortiz[1,2] and Maria Dolores Sanchez-Niño[1,2]

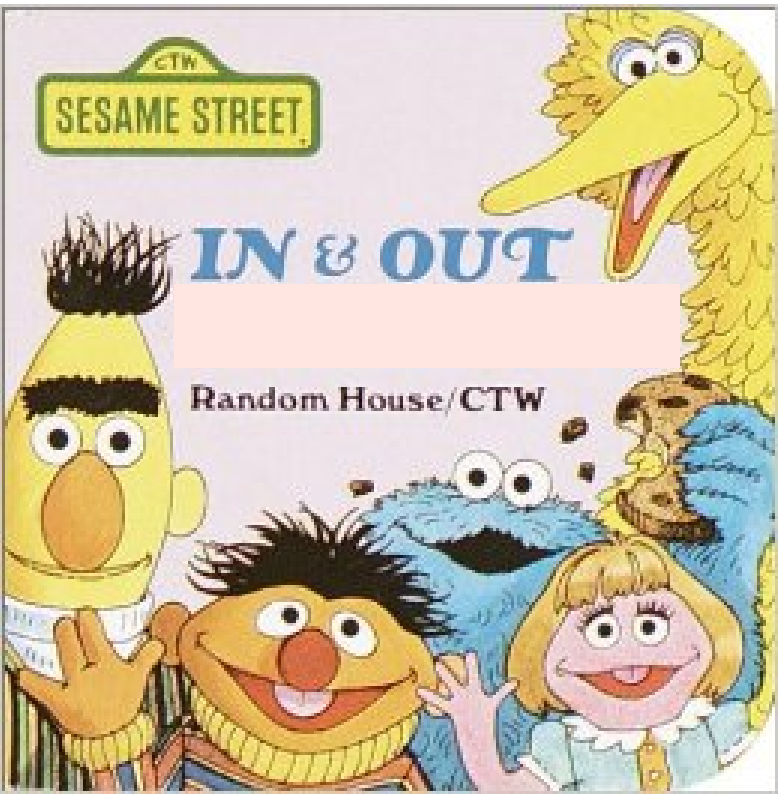
[1]Department of Nephrology and Hypertension, IIS-Fundacion Jimenez Diaz, School of Medicine, UAM, Madrid, Spain and [2]REDINREN, Madrid, Spain

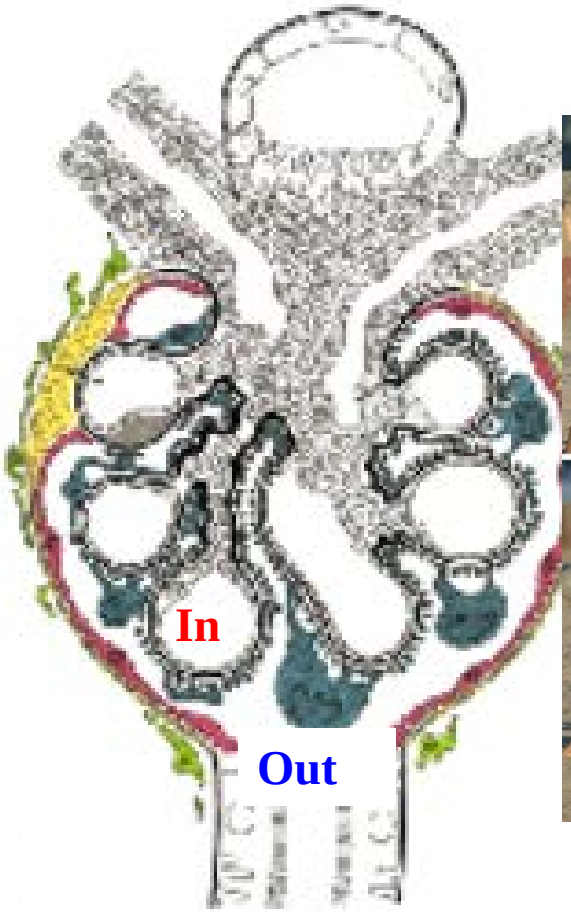


Ortiz A, Sanchez-Niño MD. Nephrol Dial Transplant. 2018 Apr 18. doi: 10.1093/ndt/gfy089. [Epub ahead of print]

Sesame Street issues: In and out

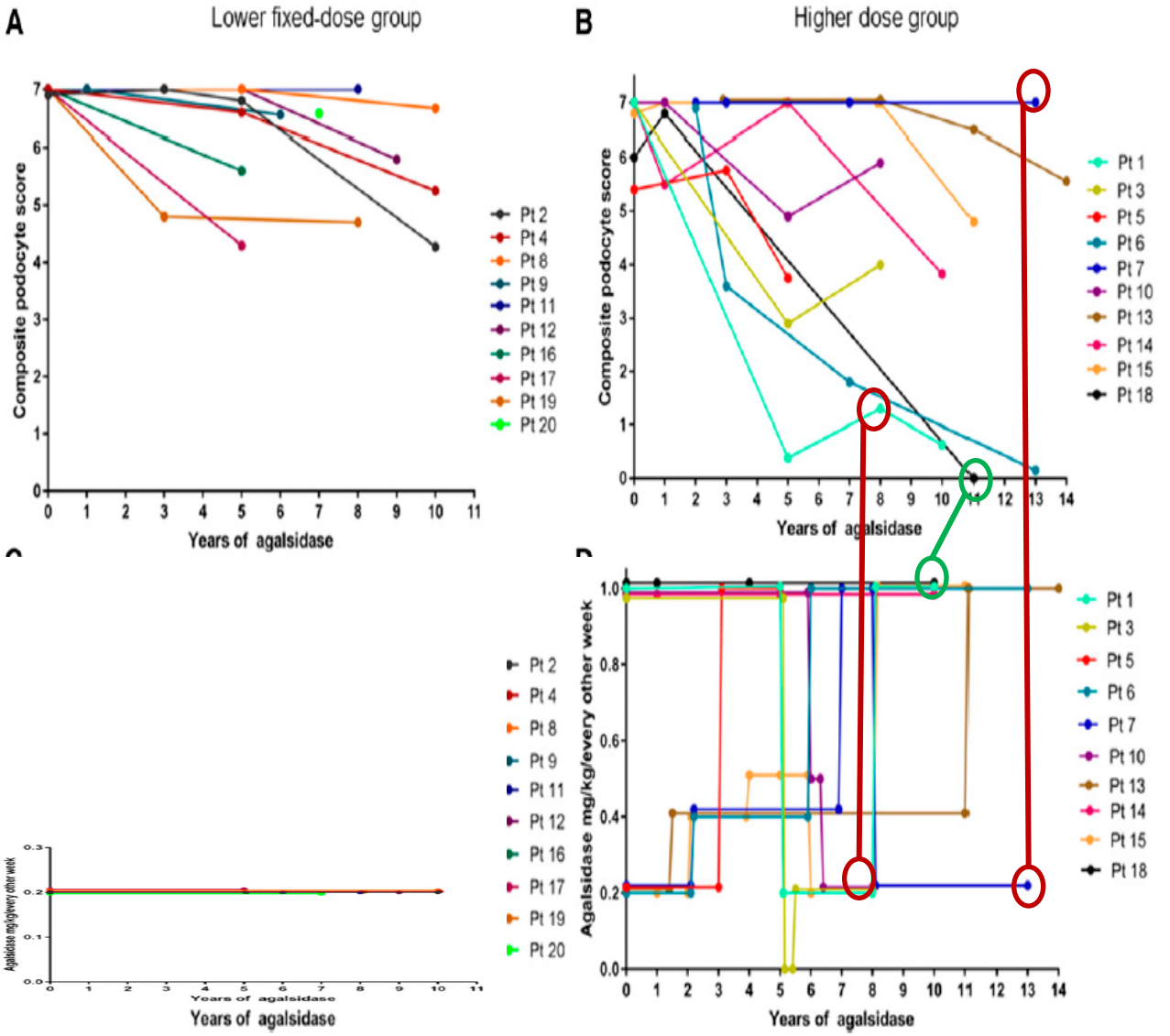
Beware of **larger** molecules!





Long-Term Dose-Dependent Agalsidase Effects on Kidney Histology in Fabry Disease

- Reduction of **podocyte Gb3** correlated with **cumulative dose**
- Residual plasma **Lyso-Gb3** correlated with **cumulative dose** in men



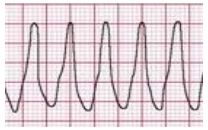
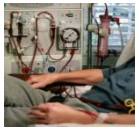
Efficacy and safety of Fabrazyme (agalsidase beta) in patients aged 0-7 years has not been established.
Per approved leaflet in Brazil, Fabrazyme (agalsidase beta 1mg/kg/every two weeks) is indicated in adults and adolescents aged 16 years and older.

Skrunes R et al. Clin J Am Soc Nephrol. 2017 Jun 16. pii: CJN.01820217. doi: 10.2215/CJN.01820217.

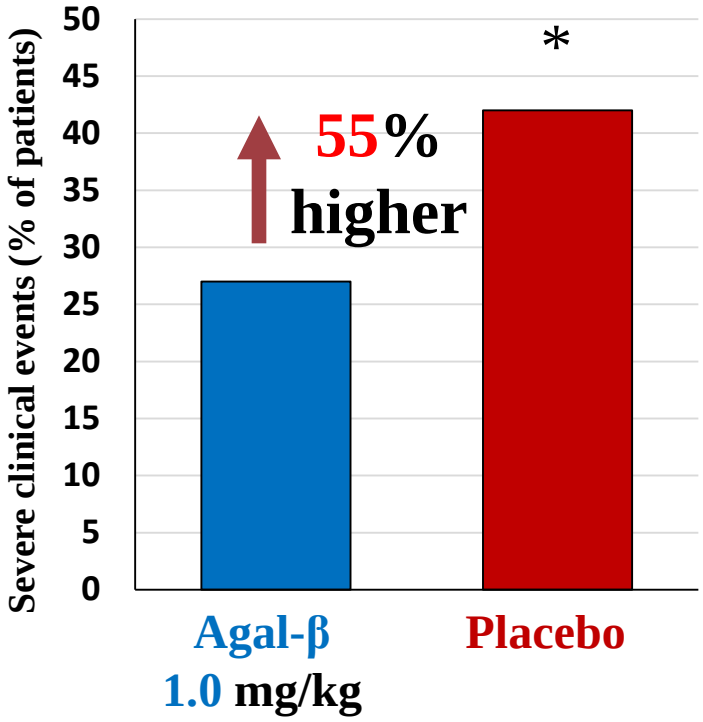
- What is known about enzyme activity?
- And about enzyme antigenicity?
- What do experts think?
- What did we learn from the shortage?
- **What about severe clinical events?**

1. RCT
2. Registry data
3. Meta-analysis

Severe clinical events in phase IV RCT

Agal-β 1.0 Phase IV RCT



Not significant

Sample size 114 **Estimated sample size 600**

Data from Banikazemi et al, Ann Intern Med 2007,
West et al, http://garrodsymposium.com/garrod2016/posters/#p104; accessed July 18, 2016 and clinicaltrials.gov
Figure from Ortiz et al, Med Clin 2017

1. RCT

2. Registry data

ERT at 1 mg/kg/2 weeks with agalsidase beta was associated with a decrease in incidence of severe clinical events* AFTER 6 months of treatment

Fabry registry data: 1044 patients

Median age at start ERT: 40 years = late!!

Non-classical mutations excluded from analysis!

* severe clinical events were defined as: death , renal, cardiac event or stroke.

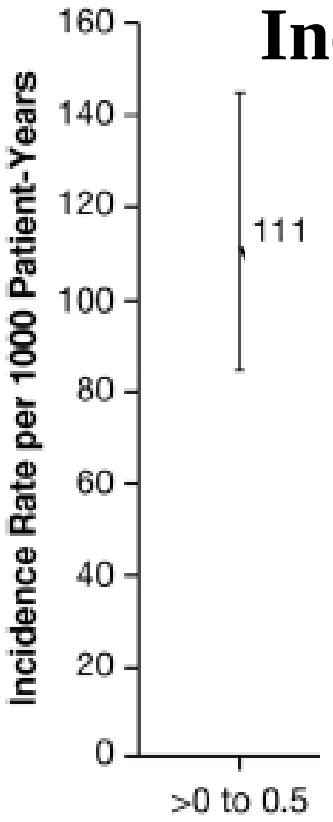
Ortiz at al J Med Genet. 2016 Jul;53(7):495-502.

ERT at 1 mg/kg/2 weeks with agalsidase beta was associated with a decrease in incidence of severe clinical events* AFTER 6 months of treatment

Fabry registry data: 1044 patients

Median age at start ERT: 40 years = late!!

Incidence rate within the first 6 months of ERT



* severe clinical events were defined as: death , renal, cardiac event or stroke.

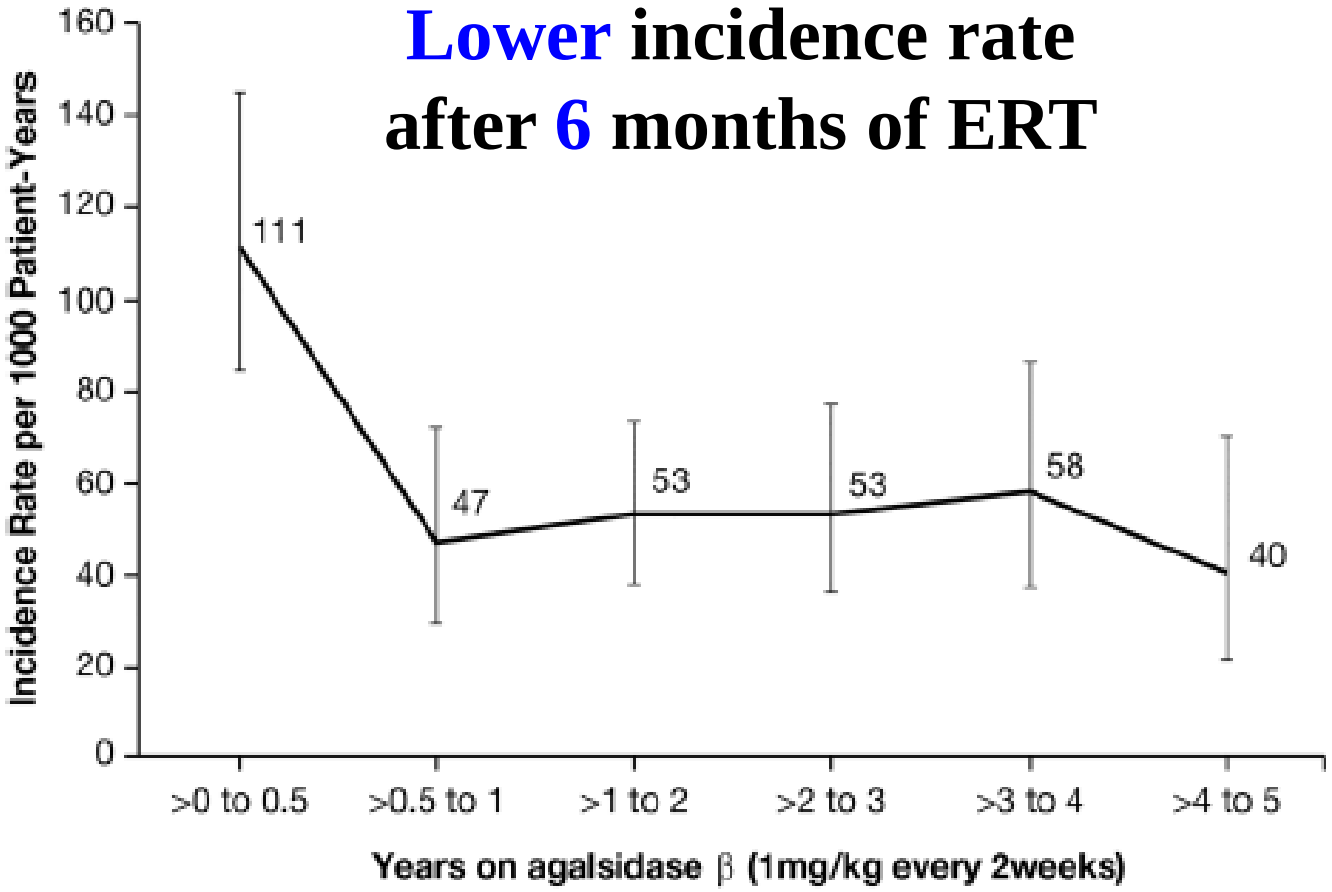
Ortiz at al J Med Genet. 2016 Jul;53(7):495-502.

ERT at 1 mg/kg/2 weeks with agalsidase beta was associated with a decrease in incidence of severe clinical events* AFTER 6 months of treatment

Fabry registry data: 1044 patients

Median age at start ERT: 40 years = late!!

Lower incidence rate after 6 months of ERT



* severe clinical events were defined as: death , renal, cardiac event or stroke.

Ortiz at al J Med Genet. 2016 Jul;53(7):495-502.

"echamos en falta los resultados publicados en **más de 3.000** pacientes tratados a largo plazo (**15 años**) con **agalsidasa-alfa** a la dosis aprobada y que apoyan los beneficios del tratamiento tanto en la progresión del daño renal como cardíaco y que, además, evidencian su efecto beneficioso sobre la morbimortalidad[3]."

Molecular Genetics and Metabolism Reports 3 (2015) 21–27

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: http://www.journals.elsevier.com/molecular-genetics-and-

FOS data were extracted for **740** treated patients who were followed for a median of **~ 5** years

cement in Fabry

Michael Beck [a,*], Derralynn Hughes [b], Christoph Kampmann [a], Sylvain Larroque [c], Atul Mehta [b], Guillem Pintos-Morell [d], Uma Ramaswami [b], Michael West [e], Anna Wijatyk [f], Roberto Giugliani [g], the Fabry Outcome Survey Study Group

[a] University Medical Center, University of Mainz, Department of Paediatrics, Mainz, Germany
[b] Royal Free London NHS Foundation Trust, University College of London, UK
[c] Shire, Zug, Switzerland
[d] Department of Pediatrics, University Hospital "Germans Trias i Pujol," Badalona, Universitat Autònoma de Barcelona, Spain
[e] Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada
[f] Shire, Lexington, MA, USA
[g] Medical Genetics Service HCPA/Dep Genet UFRGS and INAGEMP, Porto Alegre, Brazil

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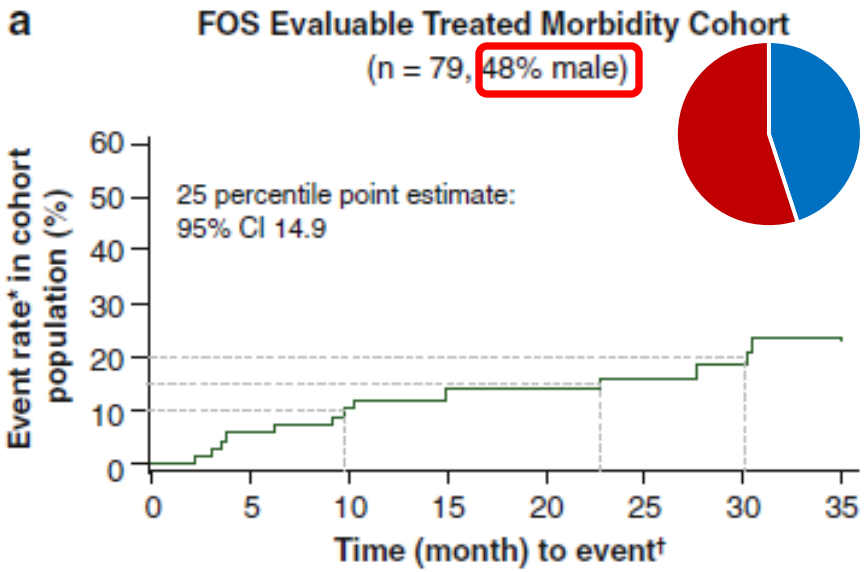
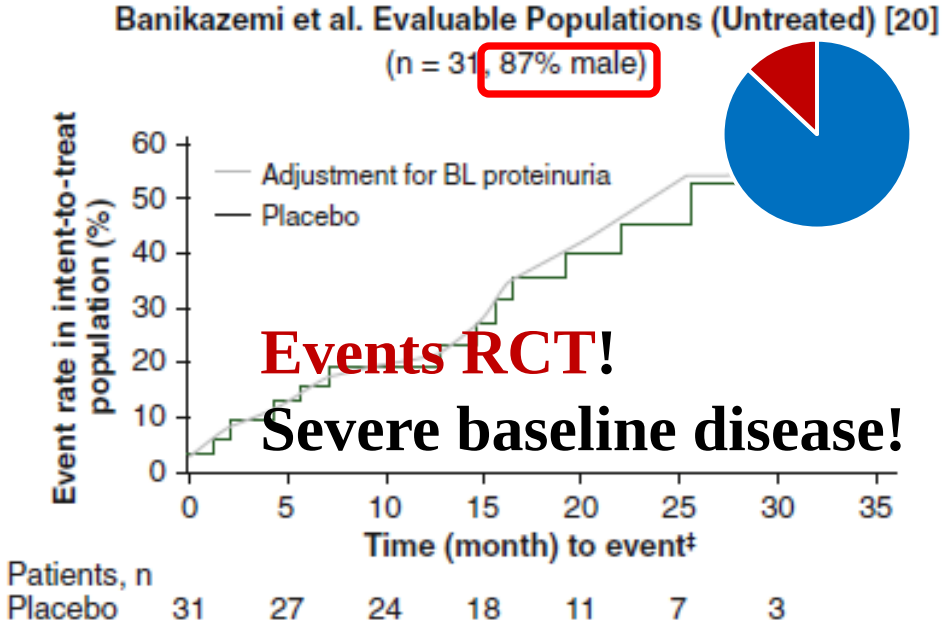
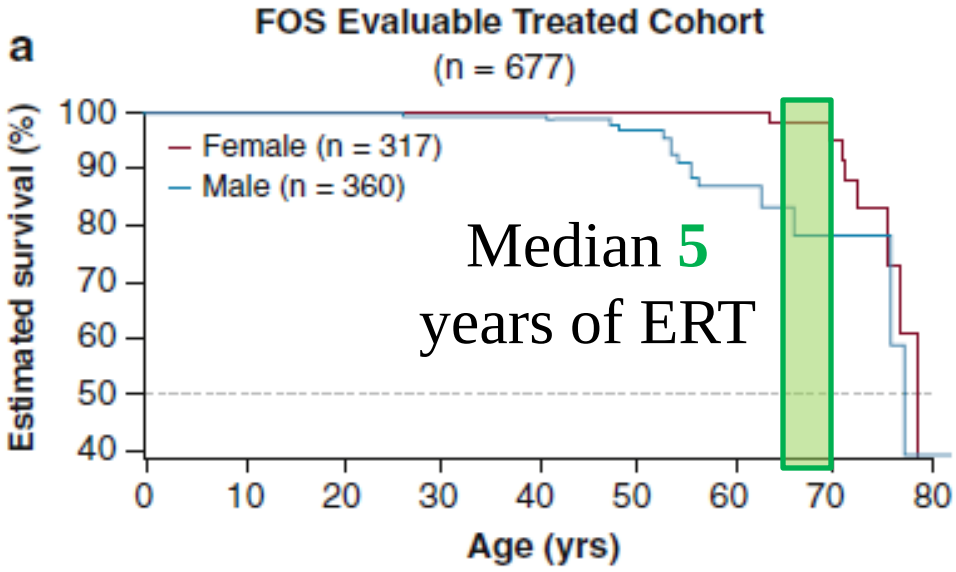
ABSTRACT

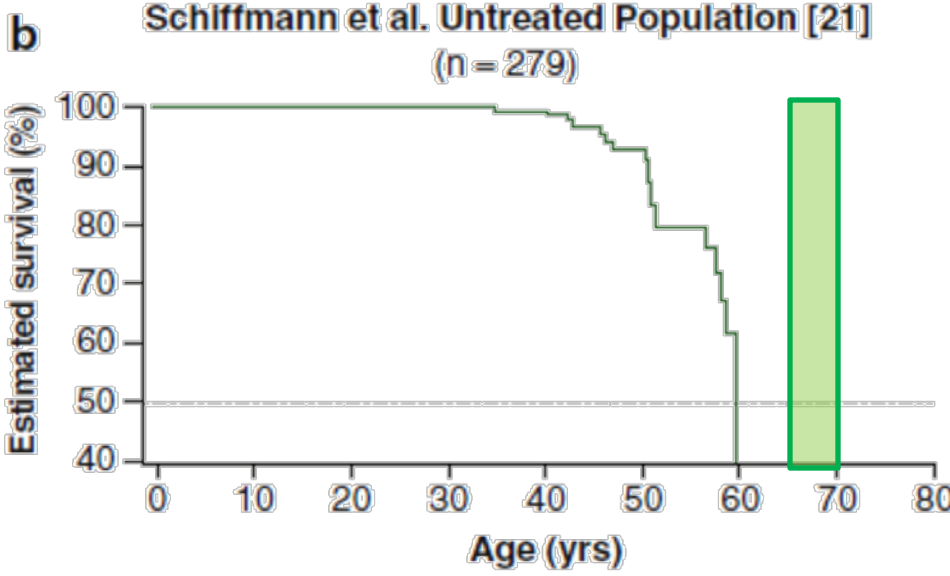
Outcomes from 5 years of treatment with agalsidase alfa enzyme replacement therapy (ERT) for Fabry disease in patients enrolled in the Fabry Outcome Survey (FOS) were compared with published findings for untreated patients with Fabry disease. Data were extracted from FOS, a Shire-sponsored database, for comparison with data from three published studies. Outcomes evaluated were the annualized rate of change in estimated glomerular filtration rate (eGFR) and left ventricular mass indexed to height (LVMI) as well as time to and ages at a composite morbidity endpoint and at death. FOS data were extracted for 740 treated patients who were followed for a median of ~5 years. Compared with no treatment, patients treated with agalsidase alfa demonstrated slower decline in renal function and slower progression of left ventricular hypertrophy. Treated male patients with baseline eGFR <60 mL/min/1.73 m^2 had a mean (standard error of the mean [SEM]) annualized change in eGFR of −2.86 (0.53) mL/min/1.73 m^2/y compared with −6.8 (1.5) in the published untreated cohort. The mean (SEM) rate of LVMI increase with treatment was 0.33 (0.10) g/$m^{2.7}$/y in males and 0.48 (0.09) in females, compared with 4.07 (1.03) in untreated males and 2.31 (0.81) in untreated females. Morbidity occurred later in treated patients, with ~16% risk of a composite morbidity event (26% in males) after 24 months with ERT versus ~45% without treatment, with first events and deaths also occurring at older ages in patients administered ERT (e.g., estimated median survival in treated males was 77.5 years versus 60 years in untreated males). Findings from these retrospective comparisons of observational data and published literature support the long-term benefits of ERT with agalsidase alfa for Fabry disease in slowing the progression of renal impairment and cardiomyopathy. Treatment also appeared to delay the onset of morbidity and mortality. Interpretation of these findings should take into account that they are based on retrospective comparisons with previously published data.


a
FOS Evaluable Treated Morbidity Cohort
(n = 79, 48% male)
25 percentile point estimate:
95% CI 14.9
Event rate* in cohort population (%)
Time (month) to event†


Banikazemi et al. Evaluable Populations (Untreated) [20]
(n = 31, 87% male)
Adjustment for BL proteinuria
Placebo
Event rate in intent-to-treat population (%)
Time (month) to event‡
Patients, n
Placebo 31 27 24 18 11 7 3
Events RCT!
Severe baseline disease!

Survival


a
FOS Evaluable Treated Cohort
(n = 677)
Female (n = 317)
Male (n = 360)
Median 5 years of ERT
Estimated survival (%)
Age (yrs)


b
Schiffmann et al. Untreated Population [21]
(n = 279)
Estimated survival (%)
Age (yrs)

1. RCT

2. Registry data

3. Meta-analysis

“Tampoco hacen ninguna referencia a una reciente revisión sistemática del grupo Cochrane, en la que se concluye que tras revisar todas las evidencias publicadas de los ensayos con ambos TSE, no se ha identificado superioridad de uno sobre el otro a las dosis aprobadas[4].”

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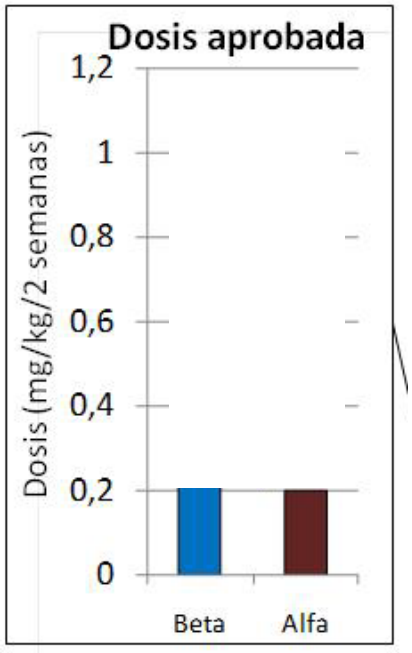
El Dib

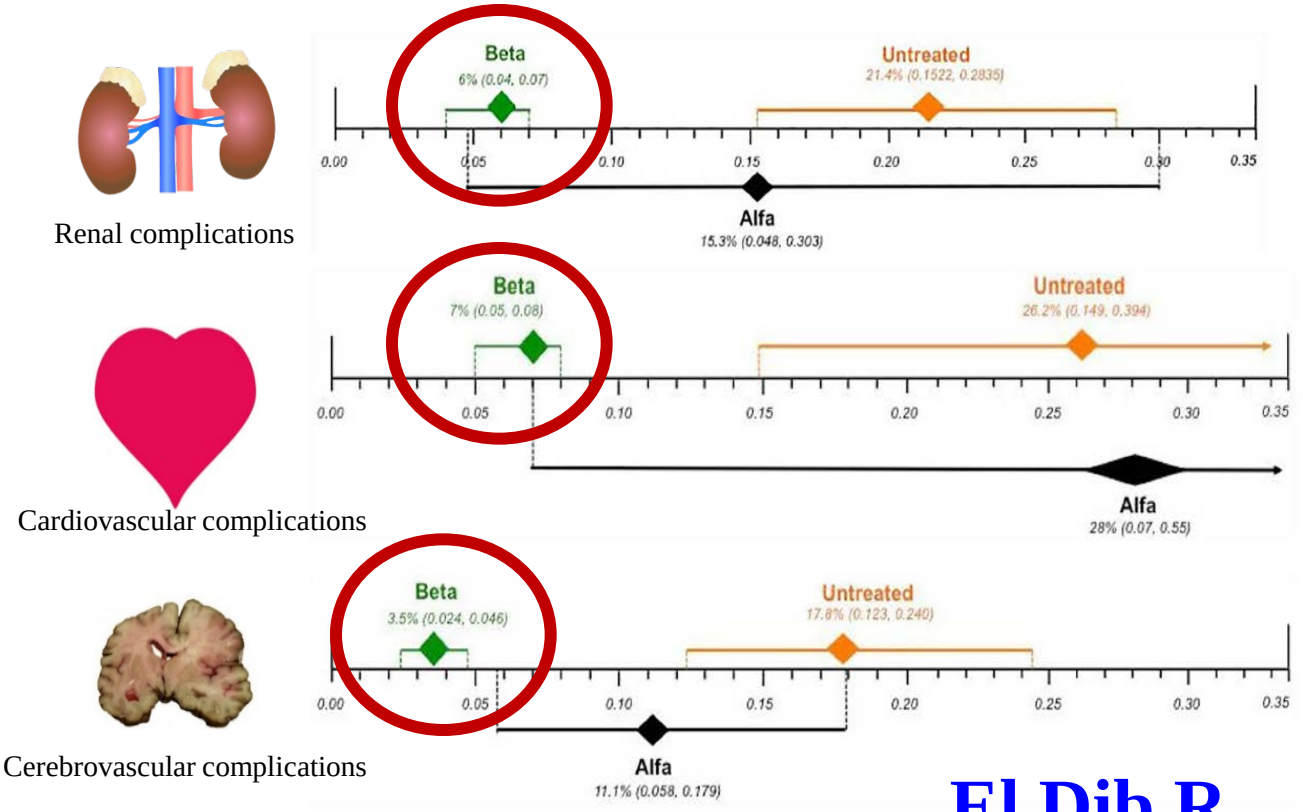
no



ERT and hard outcomes: fresh news!

Enzyme replacement therapy for Anderson-Fabry disease: A **complementary** overview of a **Cochrane** publication through a linear regression and a pooled analysis of proportions from **cohort studies**

Comparison of the plotted proportional meta-analysis, according to ERT regimens, for severe complications



El Dib R et al. PLoS One. **2017 Mar 15**;12:e0173358

Take home message

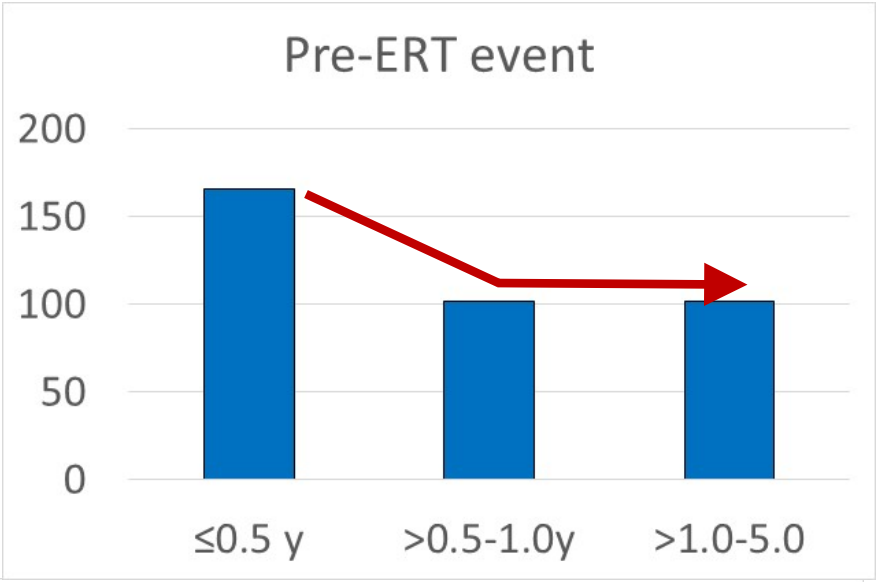
1. Therapy for all (ERT) vs therapy for some (oral chaperone)

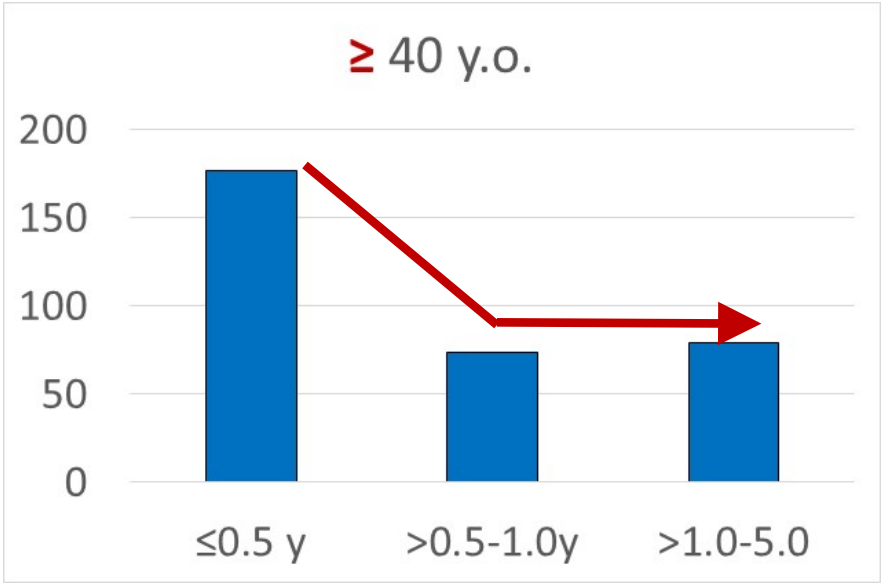
2. Key driver of **antibody** responses is **severity** of mutation

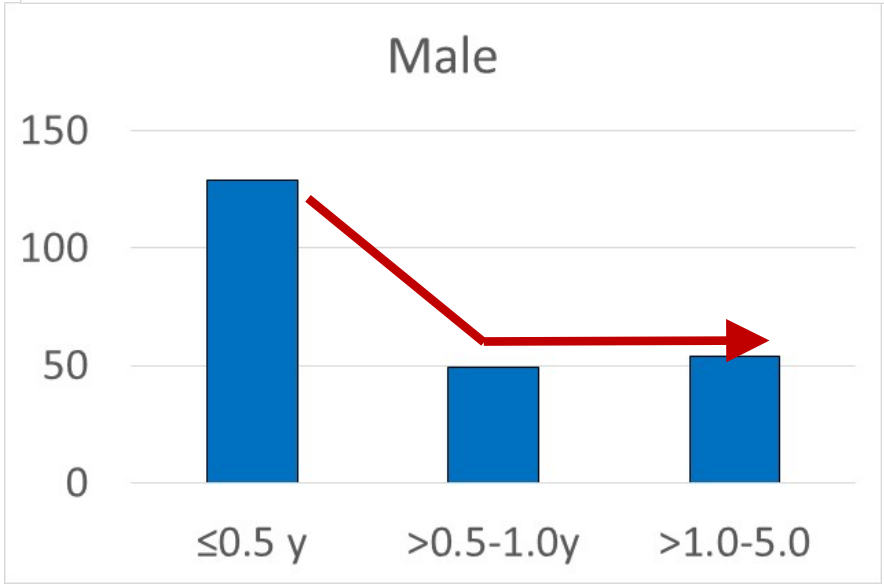
3. ERT **dose-response** for lyso-Gb3 and nephropathy

4. Agalsidase **beta 1.0** mg/kg EOW associated with **lower events rate** in placebo-controlled RCT, large registry databases and meta-analysis

Incidence rates of severe clinical events per 1000 patient years while on agalsidase beta: higher risk populations







Ortiz at al for the Fabry Registry, J Med Genet 2016