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Right or wrong: Lyso Gb-3 measurement affects outcomes?

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Conferencista:

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Co- Autor de las guías de manejo y tratamiento de la enfermedad de Fabry Internacionales.

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Declaración de Conflicto de Intereses:

He recibido honorarios por parte de Biomarin, Sanofi, Pint, Amicus, Idorsia, Protalix, AvroBio, 4DMT y Acelink en concepto de disertante o asesor sobre enfermedad de Fabry. Esto no condiciona el contenido de mi presentación.

La divulgación de imágenes de pacientes ha sido aprobada por los mismos luego de la firma de un consentimiento informado.

Frase de Salvamento:

La información contenida en esta presentación está dirigida exclusivamente al cuerpo médico, con la intención de brindar información científica de interés y deja las consideraciones del autor y no las de SANOFI. Cualquier indicación OFF LABEL mencionada será con el único objetivo de intercambio científico y no representa una promoción. SANOFI no recomienda indicaciones que no estén contenidas en la información para prescribir aprobada de sus productos en Colombia.

CÓDIGO PROMOMAT: MAT-CO-2202393

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Empecemos por el principio:

¿Cómo distinguir los fenotipos?

Los niños CLASICOS experimentan el inicio de los síntomas a una edad más temprana que las mujeres, a una edad promedio de 6 años, en comparación con los 9 años en las mujeres[1]

Edad de inicio de síntomas

Valor de LysoGb3

Edad de eventos serios

Severe clinical events	p.N215S males		Classic males	
	n (%)	Mean age	*n* (%)	Mean age
Cardiac event	18 (31)	52.3 (12.1)	34 (21)	43.3 (10.6)

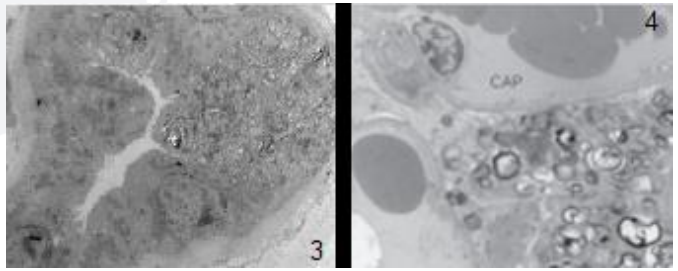
2

¿cómo distinguir los fenotipos?

Actividad enzimática

Clásico ≤ 2%
Tardío 2-25% [6]

Compromiso endotelial



Tipo de mutación

1: Pediatr Res.2008;64(5):550-5, 2:Mol Genet Genomic Med. 2018 12;6(4):492-503, 3:Pediatr Nephrol. 2018;33(11):2095-2101 ,4: J Nephropathology. 2012; 1(3): 194-197, 5:J Med Genet 2015;52(4):262-8; 6: Orphanet J Rare Dis. 2010 Nov 22;5:30.

Recomendaciones y guías…. Siempre en evolución.

The management and treatment of children with Fabry disease: A United States-based perspective

Robert J. Hop
Matthew R. T

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], Stephen Waldek[k], Er

Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document

Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients

Dominique P. Germain[1] | Alain Fouilhoux[2] | Stéphane Decramer[3] | Marine Tardieu[4] | Pascal Pille | Georges Deschênes[8] | Didier

Early indicators of disease progression in Fabry disease that may indicate the need for disease-specific treatment initiation: findings from the opinion-based PREDICT-FD modified Delphi consensus initiative

Molecular Genetics and Metabolism 123 (2018) 416–427, Orphanet Journal of Rare Diseases (2015) 10:36, Mol Genet Metab. 2016;117(2):104-13, Clin Genet. 2019;96(2):107-117, BMJ Open. 2020;10(10):e035182

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Tratamiento temprano: prevenir / estabilizar / revertir el daño orgánico

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

The management and treatment of children with Fabry disease: A United States-based perspective

Robert J. Hopkin [a], John L. Jefferies [a], Dawn A. Laney [b], Victoria H. Lawson [c,d], Michael Mauer [e], Matthew R. Taylor [f], William R. Wilcox [g,*], on behalf of the Fabry Pediatric Expert Panel

Symptomatic patients.

1- Patients reporting Fabry-related symptoms should consider treatment, regardless of age or sex.
2- This includes patients with *mild symptoms*, as any symptoms reflect underlying disease progression.
3- Treat and manage symptomatic girls and boys in the same way, with the same goal of decreasing symptomatology and reducing the risk of disease progression.

Asymptomatic patients.

“Clinicians should consider starting ERT around age 8–10 years in asymptomatic boys with classical Fabry mutations”.

Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients

Dominique P. Germain[1] | Alain Fouilhoux[2] | Stéphane Decramer[3] | Marine Tardieu[4] | Pascal Pillet[5] | Marc Fila[6] | Serge Rivera[7] | Georges Deschênes[8] | Didier Lacombe[9]

- Se debe considerar la ERT para niños y niñas sintomáticos con dolor neuropático, albuminuria patológica, compromiso gastrointestinal grave y dolor abdominal o compromiso cardíaco.
- Para los niños asintomáticos, los criterios de inicio de TRE actualmente siguen el prospecto del producto actual que indica el inicio del tratamiento a partir de los 7 u 8 años de edad.
- Sin embargo, la opinión de este grupo es que los niños asintomáticos pueden beneficiarse de un inicio más temprano de la ERT según los siguientes criterios:

  - *Mutación patogénica relacionada a fenotipo clásico*
  - *Ausencia de actividad enzimática (valor 0)*
  - *Historia de enfermedad severa en la familia*
  - ***Niveles de LYSO-Gb3 mayores a 20 nmol/l***

Clin Genet. 2019 Aug;96(2):107-117.

Enfermedad de Fabry en la infancia: una revisión

Fabry-related signs and symptoms	Earliest report of symptom
Storage of GL-3 found in organs on biopsy	Prenatal
Corneal whorls/verticillata	Newborn
GI problems, including nausea, vomiting, diarrhea, constipation, and abdominal pain	1.0 year
Slow growth in boys (mean height/weight < 50th percentile)	2.0 years
Intermittent acroparesthesia/neuropathic pain triggered by stress, heat, fatigue, or exercise	2.0 years
Hypohidrosis or anhidrosis	2.5 years
Fabry crises of agonizing neuropathic pain, typically begin in the hands and feet and may radiate proximally	2.5 years
Heat, cold, and/or exercise intolerance	3.5 years
Retinal vascular tortuosity	4.0 years
Tinnitus/vertigo	4.0 years
Low GFR	4.0 years
T-wave inversion on electrocardiogram	4.0 years
Trivial cardiac valve disease	4.0 years
Angiokeratoma	4.4 years

Las primeras manifestaciones de la enfermedad de Fabry en el fenotipo clásico están relacionadas al daño del sistema nervioso periférico:

- ***Compromiso gastrointestinal***
- ***Dolor neuropático en manos y pies***

Genet Med. 2015 May;17(5):323-30

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Characterization of Early Symptom Progression in Young Pediatric Patients with Classic Pathogenic Variants in the GLA gene: Data from A Prospective, Multicenter Pilot Study Of Fabry Disease Clinical and Biochemical Findings in Young Pediatric Patients (the MOPPet Study)

DA Laney[a], MF Houde[b], AL Foley[a], DS Peck[c], AM Atherton[d], TL Toler[e], L Manwaring[e], K Nimmons[a], DK Grange[e], C Kidwell[f], BA Heese[g], MD Holida[h], C Auray-Blais[i]

[a]Emory University, Atlanta, GA, USA, [b]Takeda, Deerfield, IL, USA, [c]Mayo Clinic, Rochester, MN, USA, [d]Horizon Therapeutics, Deerfield, IL, USA, [e]Washington University, St. Louis, MO, USA, [f]University of Missouri, Columbia, MO, USA, [g]Mercy Children's Hospital, Kansas City, MO, USA, [h]University of Iowa, Iowa City, IA, USA, [i]Université de Sherbrooke, Sherbrooke, QC, Canada

Study number	Gender	Genotype	type	Predicted Phenotype	alpha-gal, leukocytes (nmol/mg protein/hr)	First symptom(s) reported	Age first symptoms reported (months)
01-01	M	c.1024C>T/p.R342X	Nonsense	Classic	0.9	Heat intolerance and gastrointestinal (chronic gas/bloating)	11
01-08	F	c.777delA	Deletion	Classic	20.6	Heat intolerance, gastrointestinal (abdominal pain and chronic diarrhea alternating with constipation), and neuropathic pain	38
01-09	M	c.777delA	Deletion	Classic	0.2	Heat intolerance, hypohidrosis, and gastrointestinal (chronic diarrhea)	35
[illegible]	M	[illegible]	Splice site	Classic	n/a	Heat intolerance, gastrointestinal (chronic abdominal pain), and neuropathic pain	31
01-051	M	c.679C>T; p.R227X	Nonsense	Classic	1.1	Gastrointestinal (abdominal pain)	28
03-06	M	p.L120P/A121T	Missense	Classic	0.7	Gastrointestinal (chronic constipation) and neuropathic pain	12

Bloated/Gassy
Range: 11-27 months
Mean: 20 months
Mean: 22 months
(n=3 3 males)

Chronic Diarrhea/Loose Stools
Range: 23-42 months
Mean: 34 months
Median: 36 months
(n=6 5 males, 1 female)

Chronic Abdominal Pain
Range: 25 - 51 months
Mean: 38 months
Median: 38 months
(n= 9 7 males, 2 females)

Heat Intolerance/Flushing
Range: 11-42 months
Mean: 28.1 months
Median: 31 months
(n=9 7 males/2 females)

Hypohidrosis
Range: 16-42 months
Mean: 33 months
Median: 35 months
(n=6 6 males)

Anhidrosis
Range: 35 - 48 months
Mean: 41.7 months
Median: 42 months
(n=3 3 males)

Figure 1. Age at First Reported Symptom

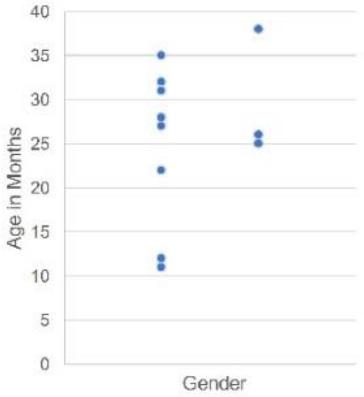
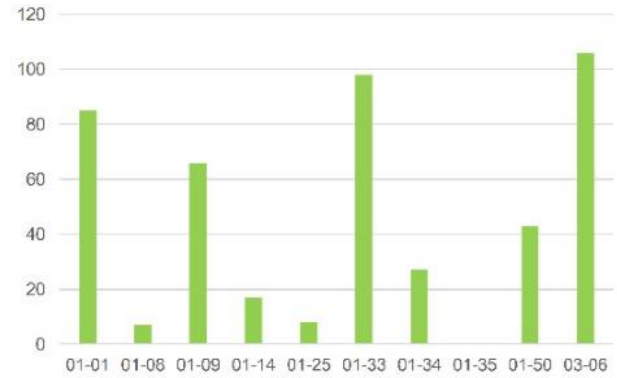


Figure 4. Urine LysoGL3 at reported symptom onset (pg/mmol creatinine) (nl <0)



Conclusions

The results indicate that onset of initial Fabry symptoms prior to age four in children with classic Fabry disease is more common than often recognized. This may be because the symptoms such as bloating or heat intolerance are non-specific and could be underrecognized; however the progression of symptoms do follow a specific pattern of increased severity over time that can clarify relatedness to Fabry.

The levels of urinary biomarkers support some initial hypotheses as the total urinary biomarkers levels were elevated in all male subjects with the two subjects reporting earliest onset of symptoms (01-01 and 03-06) having the highest baseline urinary lyso-GB3. Two out of the three female patients had urinary biomarkers that were elevated, but much lower than the male subjects.

¿Pero la agalsidasa Beta, a que edad puede indicarse?

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FABRAZYME safely and effectively. See full prescribing information for FABRAZYME.

FABRAZYME® (agalsidase beta) for injection, for intravenous use

Initial U.S. Approval: 2003

RECENT MAJOR CHANGES

Indications and Usage (1)	3/2021
Warnings and Precautions (5.1, 5.2)	3/2021

INDICATIONS AND USAGE

Fabrazyme is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 1 mg/kg body weight given every two weeks as an intravenous infusion. (2.1)
- Ensure appropriate medical support is available when Fabrazyme is administered because of the potential for anaphylaxis and severe infusion-associated reactions. (2.1, 5.1, 5.2)
- Administer antipyretics prior to infusion. (2.1)
- See the full prescribing information for the recommended infusion rate. (2.1)

DOSAGE FORMS AND STRENGTHS

For injection: 5 mg or 35 mg lyophilized cake or powder in a single-dose vial for reconstitution (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylactic and severe hypersensitivity reactions have occurred during Fabrazyme infusions. If severe hypersensitivity or anaphylactic reactions occur, immediately discontinue the infusion and provide necessary emergency treatment. Readministration to patients who have previously experienced severe or serious hypersensitivity reactions to Fabrazyme should be done only after careful consideration of the risks and benefits of continued treatment, and only under the direct supervision of qualified personnel with appropriate medical support measures readily available. (5.1)
- Infusion-Associated Reactions: Pretreat patients who experience infusion-associated reactions with an antipyretic and antihistamine. If an infusion-associated reaction occurs, decrease the infusion rate, temporarily stop the infusion, and consider administration of additional antipyretics, antihistamines, and/or steroids. If a severe infusion-associated reaction occurs, discontinue the infusion and initiate appropriate anaphylaxis treatment. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥20%) are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2021

8.4 Pediatric Use

The safety and effectiveness of Fabrazyme have been established in pediatric patients based on adequate and well-controlled studies in adults, a single-arm, open-label study in 16 pediatric patients with Fabry disease aged 8 to 16 years, and additional data in 24 patients with Fabry disease aged 2 to 7 years *[see Clinical Pharmacology (12.2) and Clinical Studies (14)]*.

https://products.sanofi.us/Fabrazyme/Fabrazyme.pdf

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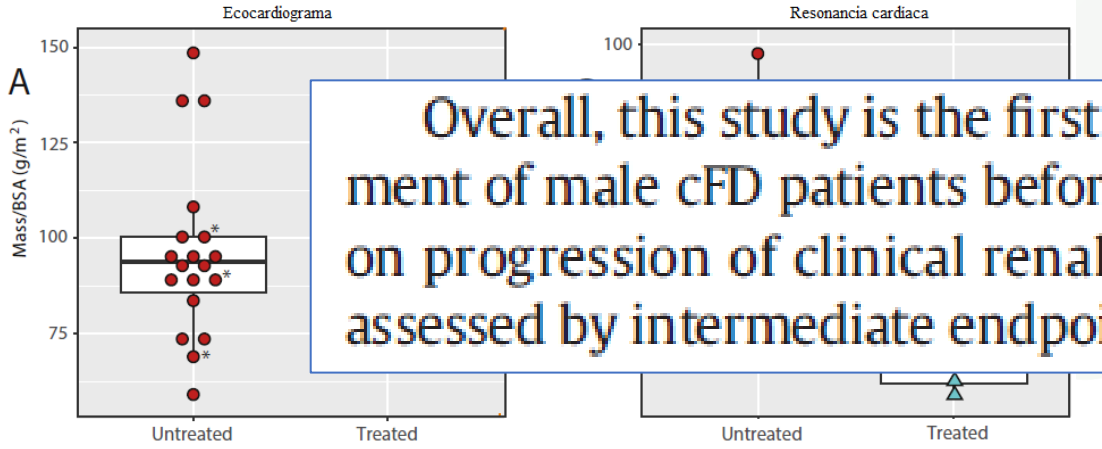
Early start of enzyme replacement therapy in pediatric male patients with classical Fabry disease is associated with attenuated disease progression

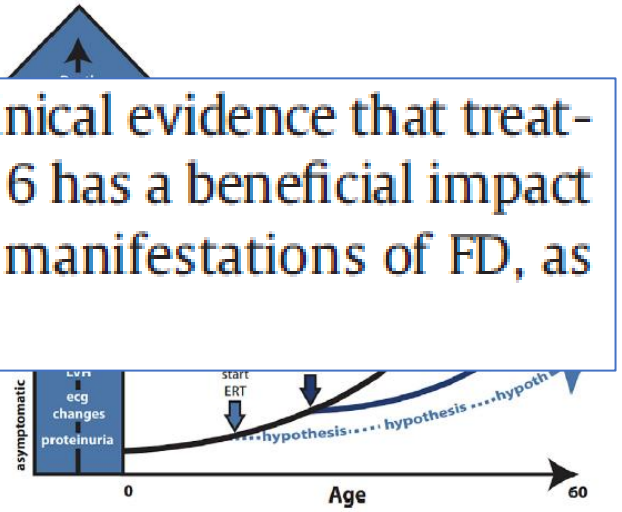
El estudio FIELD fue un ensayo controlado aleatorizado para evaluar el efecto de diferentes dosis de agalsidasa-beta en pacientes ***hombres pediátricos con fenotipo clásico***.
Seguimiento de 7 pacientes a 9 años de tratamiento con agalsidasa beta 1 mg/kg.
Resultados:

ALBUMINURIA: no tratados (mediana: 3,3 mg/mmol, rango: 0-200 mg/mmol), tratados (mediana: 0,4 mg/mmol, rango: 0-8,8 mg/mmol, p = 0,04). El IFG no fue distinto.

La masa del VI en ecocardiograma: 94 g/m^2, no tratado versus 80 g/m^2 en el grupo tratado (p=0,02).
La masa del VI por resonancia magnética: 68 g/m^2 no tratado versus 53 g/m^2 en tratados (p = 0,02)



Overall, this study is the first to provide clinical evidence that treatment of male cFD patients before the age of 16 has a beneficial impact on progression of clinical renal and cardiac manifestations of FD, as assessed by intermediate endpoints.



Criterios tempranos de inicio de tratamiento

Early initiation of enzyme replacement therapy in classical Fabry disease normalizes biomarkers in clinically asymptomatic pediatric patients

Paciente 1 (niño) diagnosticado por screening familiar a la edad de 6 meses: Mut I317T Complicaciones graves y tempranas en la historia clínica familiar

A los 5 años y 3 meses: estudios en relación a EF; límites normales para su edad

El nivel de lysoGb3 en plasma fue de 35 ng/ml (normal <5 ng/ml). La marcada elevación de los niveles plasmáticos de lysoGb3 como reflejo de la carga de enfermedad y el fenotipo clásico llevó a iniciar TRE con agalsidasa beta 1 mg/kg.

Los niveles de LysoGb3 disminuyeron a 5,1 ng/ml después de 4 meses de ERT y se normalizaron después de 8 meses de TRE

Paciente 2 (niño) diagnosticado de DF a la edad de 2 años y 1 mes: Mut: 95_546dupl352; 800_801ins217 Complicaciones graves y tempranas en la historia clínica familiar

A los 3 años y 6 meses: estudios en relación a EF; límites normales para su edad

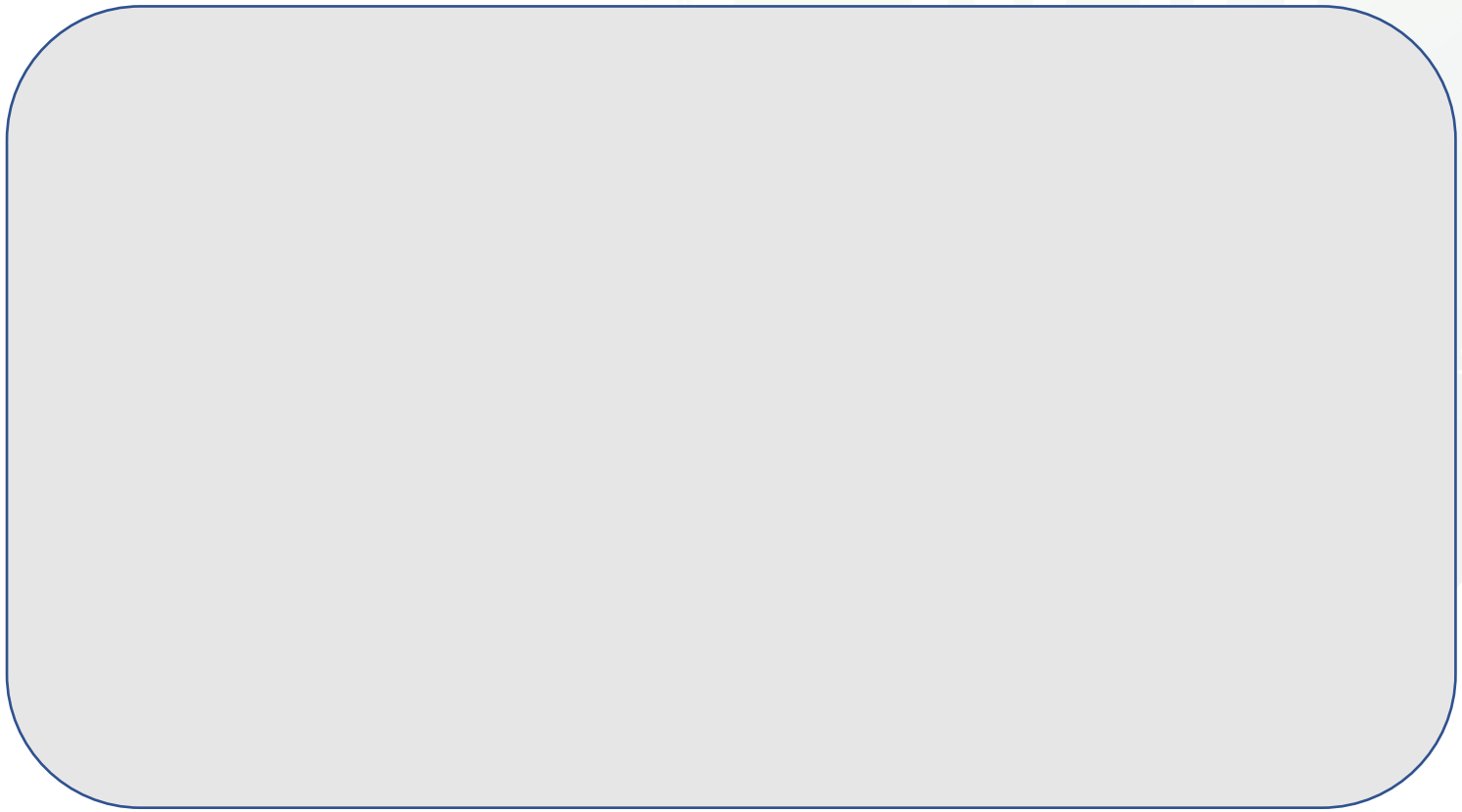
El nivel de lysoGb3 en plasma fue de 52,2 ng / ml. La elevación >10 veces de los niveles plasmáticos de lysoGb3 como un reflejo de la carga de enfermedad y el fenotipo clásico severo llevó a iniciar TRE con agalsidasa beta 1 mg/kg

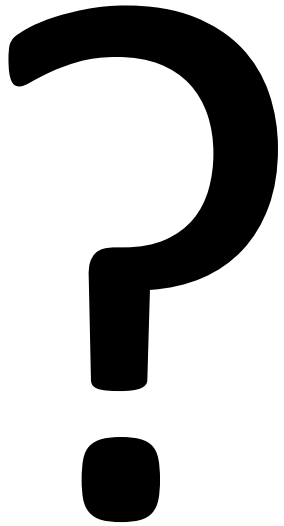
Los niveles de LysoGb3 se normalizaron después de 10 meses de TRE por debajo del nivel de cuantificación

Kritzer A, et al. Mol Genet Metab Rep. 2019;21:100530.

Existen criterios de Switch?

Cuándo consideramos que hay falla terapéutica?
Cuando debo cambiar a mayor dosis?



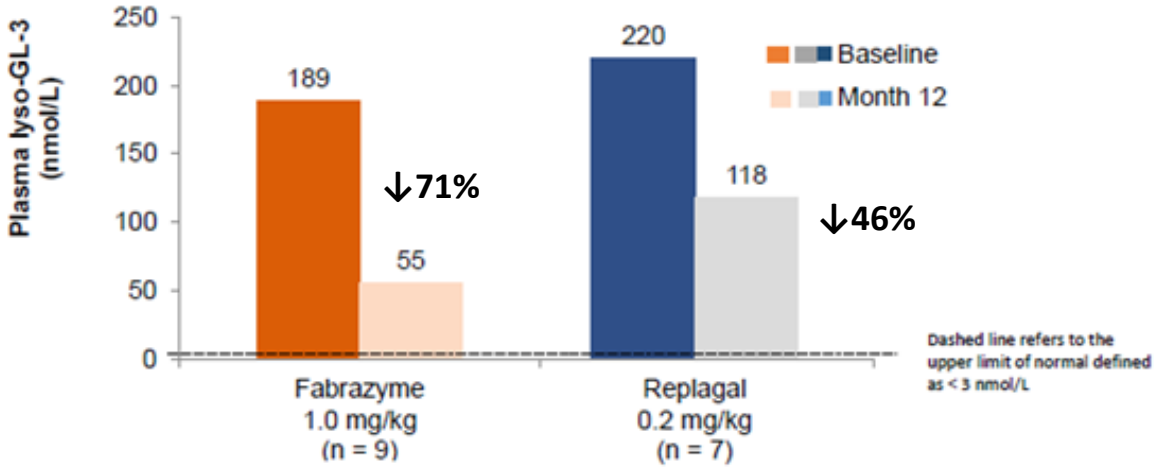


Reduction of elevated plasma globotriaosylsphingosine in patients with classic Fabry disease following enzyme replacement therapy

Patients with ***classical manifestations of Fabry disease*** receiving ERT for a minimum period of one year were analyzed on plasma concentrations of lysoGb3 and Gb3. All patients (22 males and 21 females) showed increased plasma lysoGb3 levels prior to ERT

Greater decline in male patients in plasma lyso-GL-3 after treatment with Fabrazyme vs Replagal

- In male patients plasma Lyso-GL-3 decline was greater with Fabrazyme 1.0 mg/kg EOW than with Replagal 0.2 mg/kg EOW (p = 0.003*)
  - Also greater than with lower dose Fabrazyme (0.2 mg/kg EOW) (p = 0.046*)



EOW, every other week; lyso-GL-3, globotriaosylsphingosine.
*p < 0.05 statistically significant.

Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: an international cohort study

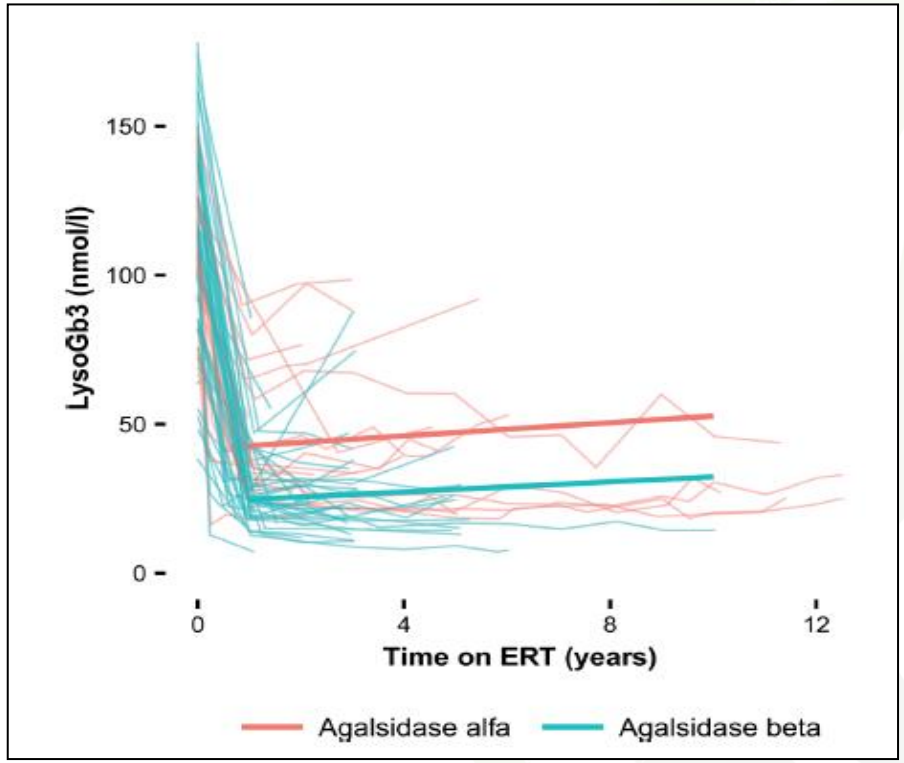
El tratamiento con agalsidasa beta en dosis más altas en comparación con agalsidasa alfa ¿no produce una diferencia en los eventos clínicos a corto plazo?

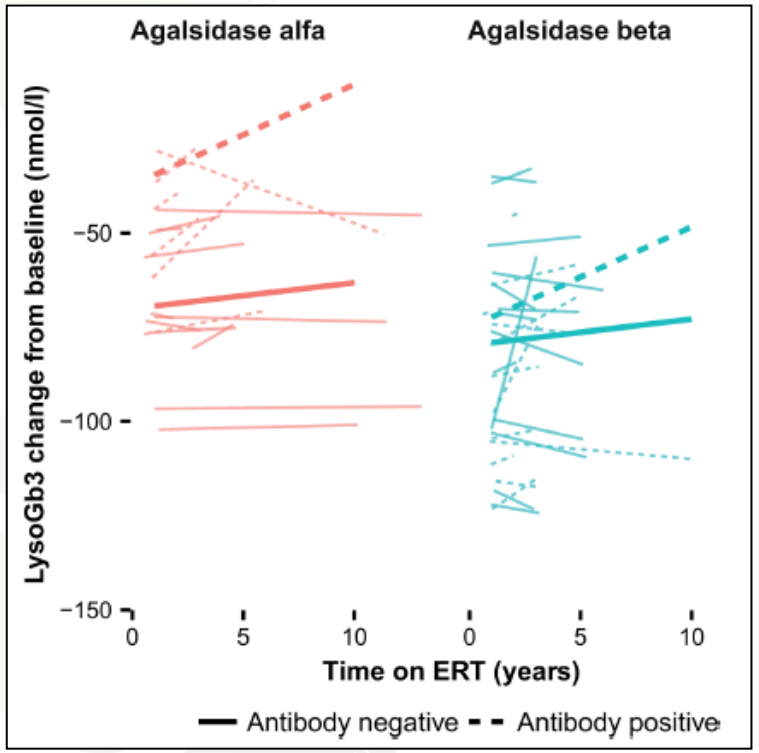
Se observó una MEJOR respuesta bioquímica (↓ lysoGb3), AUN en presencia de anticuerpos, y se observó una mejor reducción de LVMi con agalsidasa beta (OR 2,27, p=0,03)

Patient characteristics at start of ERT

	Agalsidase alfa (0.2 mg/kg)	Agalsidase beta (1.0 mg/kg)	p-value
Patients	248	139	
Men, classical	69 (28%)	71 (51%)	<0.001
Men, non-classical	47 (19%)	7 (5%)	0.22
Women, classical	95 (38%)	43 (30%)	0.14
Women, non-classical	37 (15%)	18 (13%)	0.86
ERT start <18 years of age	15 (6%)	3 (2%)	0.13
Follow-up time (years)	5.2 (0.8–14.4)	3.8 (0.8–12.1)	<0.001
Events before initiation of ERT			
Dialysis/renal transplant	8 (3%)	12 (9%)	0.007
PM/ICD	21 (8%)	9 (7%)	0.87
Stroke	22 (9%)	17 (12%)	0.09
Any of the above	46 (19%)	31 (22%)	0.08
Lyso-Gb3 (nmol/L)	10 (0.7–146)	80 (2.0–178)	<0.001
eGFR (mL/min/1.73 m^2)	89 (10–159)	86 (10–140)	0.009
CKD category A3	44/195 (23%)	42/113 (37%)	0.008

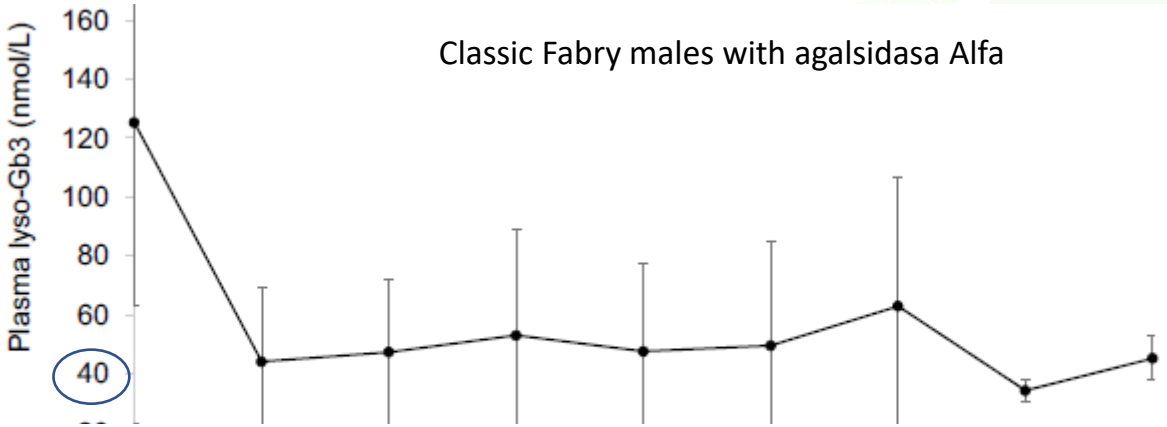
Cómo responde el Lyso-Gb3 a las diferentes dosis?

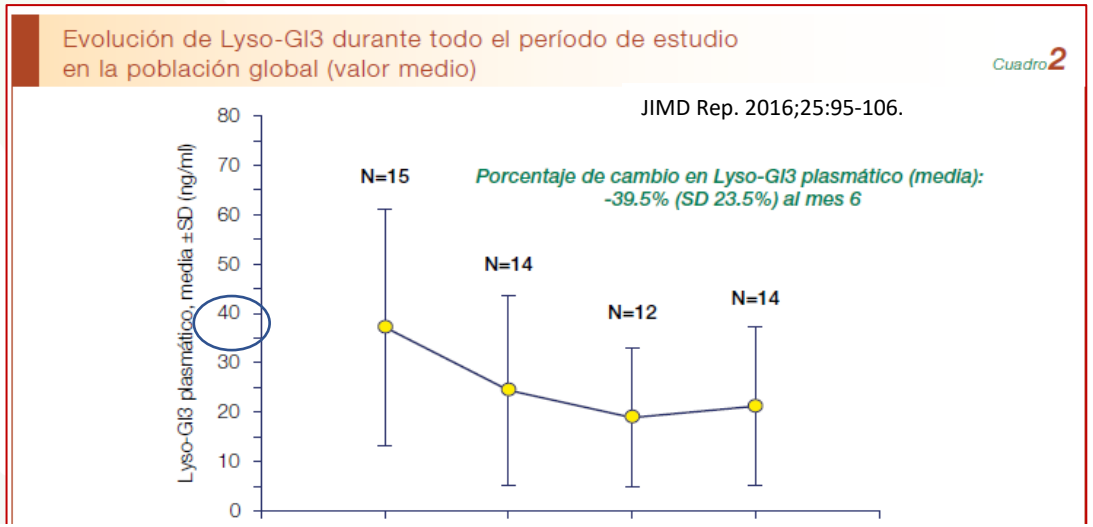




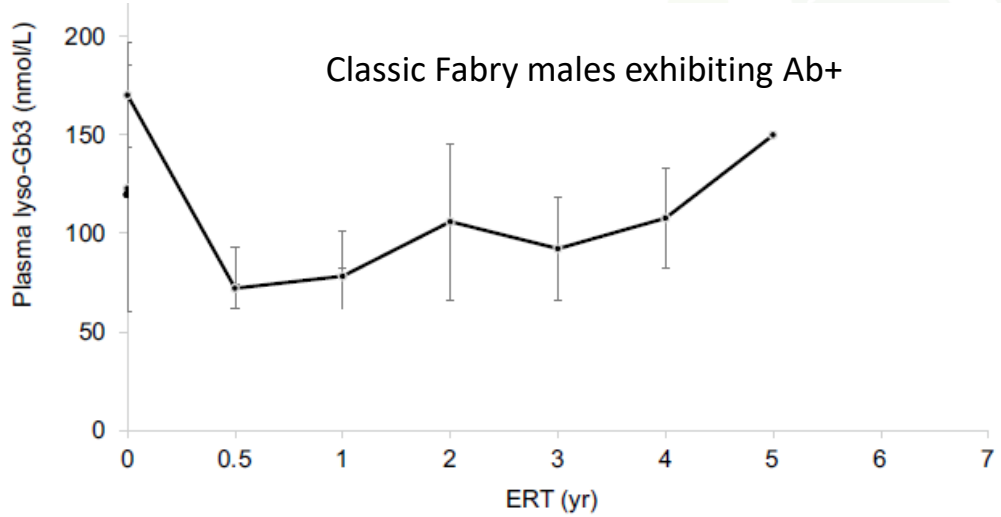
- In patients treated with agalsidase alfa, the presence of antibodies was associated with a less prominent decrease in lyso-Gb3 following ERT, resulting in 34.77 nmol/L (95%CI 23.65–45.88, p<0.001, adjusted for baseline lyso-Gb3 concentrations) higher lyso-Gb3 concentrations in the antibody-positive group compared with the antibody-negative group
- In patients receiving agalsidase beta, the decrease in lyso-Gb3 after ERT initiation was minimally affected by the presence or absence of antibodies ($\beta_{AB+ \text{ vs } AB-}$: 6.72 nmol/L, 95%CI –1.43–14.87, p=010)

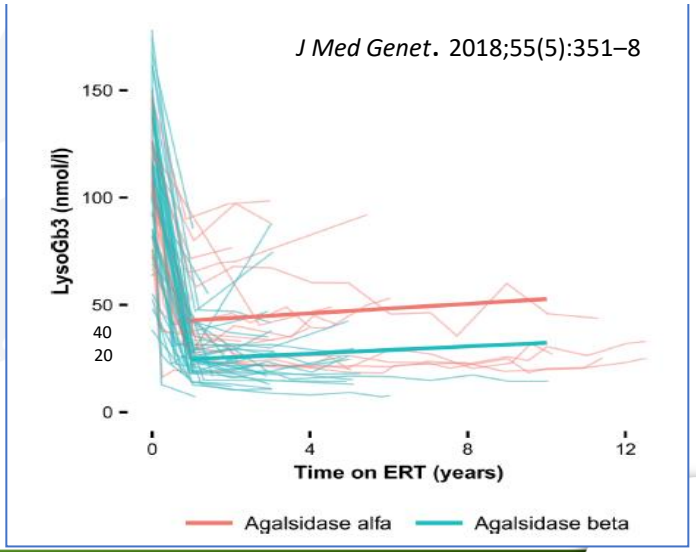
Plasma lyso-Gb3: a biomarker for monitoring fabry patients during enzyme replacement therapy





- La dosis de 0.2 mg/kg de agalsidasa Alfa reduce el nivel de LysoGb3 en un nivel medio de 40 nm/L y la dosis de 1 mg/kg de agalsidasa Beta a 20 nmol/L.





Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

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

Favourable effect of early versus late start of enzyme replacement therapy on plasma globotriaosylsphingosine levels in men with classical Fabry disease

Maarten Arends [a,*], Frits A. Wijburg [b], Christoph Wanner [c], Frédéric M. Vaz [d], André B.P. van Kuilenburg [d], Derralynn A. Hughes [e], Marieke Biegstraaten [a], Atul Mehta [e], Carla E.M. Hollak [a], Mirjam Langeveld [a]

Patient characteristics at start of ERT.

	Initiation of ERT < 25	Initiation of ERT ≥ 25	p-Value
Patients	21	64	
Age at start ERT (years)	18.0 (9.5–24.6)	41.7 (25.0–64.9)	<0.001
Agalsidase alfa as first ERT	6 (29%)	17 (27%)	0.99
Agalsidase beta as first ERT	15 (71%)	47 (73%)	0.99
Missense mutation	10/21 (48%)	32/64 (50%)	0.99
Nonsense mutation	11/21 (52%)	27/64 (42%)	0.46
Splice site mutation	0/21 (0%)	5/64 (8%)	0.33
aGAL activity (% of mean reference)	1.1 (0.0–8.6%)	2.9 (0.0–8.6%)	0.02
LysoGb3 before ERT (nmol/L)	114 (84–124)	112 (32–175)	0.92
Acroparesthesia	21/21 (100%)	59/62 (95%)	0.57
Angiokeratoma	12/20 (60%)	53/64 (83%)	0.06
Cornea verticillata	14/19 (74%)	39/61 (64%)	0.58
eGFR (mL/min/1.73 m^2)	125 (89–139)	87 (10–136)	<0.001
CKDA category A2 or higher	9/19 (47%)	31/37 (84%)	0.02
CKDA category A3	0/19 (0%)	24/37 (65%)	<0.001
LVMI (g/$m^{2.7}$)	34 (21–64)	52 (24–150)	<0.001
WML	5/16 (31%)	15/18 (83%)	0.004
Clinical event(s) before ERT	1/21 (5%)	23/64 (36%)	<0.001

The median lysoGb3 determined at the time point closest to 1 year after ERT initiation was lower for the early-treatment compared with the late-treatment group (24.4 vs 27.7 nmol/L, p = 0.04). ***In addition, 10/21 (48%) patients in the early-treatment group reached a lysoGb3 concentration <20 nmol/L compared to 15/64 (22%) in the late-treatment group***.

Thus, the odds ratio for a lysoGb3 <20 nmol/L in early versus late-treatment group was 2.93 (95% CI: 0.92–9.39, p = 0.052). When adjusted for lysoGb3 at baseline, first ERT preparation and the average ERT dose, the adjusted OR was 7.38 (95% CI: 1.91–34.04, p = 0.006)

Pronóstico

"Lyso-Gb3 associates with adverse long-term outcome in patients with Fabry disease"

66 pacientes (26 hombres y 40 mujeres, edad media 44 años), análisis de Lyso-Gb3 en plasma como factor asociado a eventos clínicos adversos a largo plazo.

Eventos: ESRD 5, fibrilación auricular, marcapasos y/o desfibrilador implantable, accidente cerebrovascular o muerte (lo que ocurra primero).
De 50 pacientes en TRE, 6 fueron tratados con agalsidasa-β, 44 con agalsidasa-α

Clinical outcomes	Classic males N=21	Classic females N=36	Later-onset males N=5	Later-onset females N=4
Death, n (%)	4 (20)	1 (2.8)	0 (0)	0 (0)
Composite outcome*, n (%)	9 (43)	9 (25)	1 (20)	0 (0)

El Lyso-Gb3 basal y la exposición acumulada al Lyso-Gb3 antes del tratamiento fueron las variables de exposición primarias.
Para calcular la exposición acumulativa de Lyso- Gb3; previa al tratamiento se multiplicaron el nivel basal por la edad en años de los pacientes al inicio de la TRE.

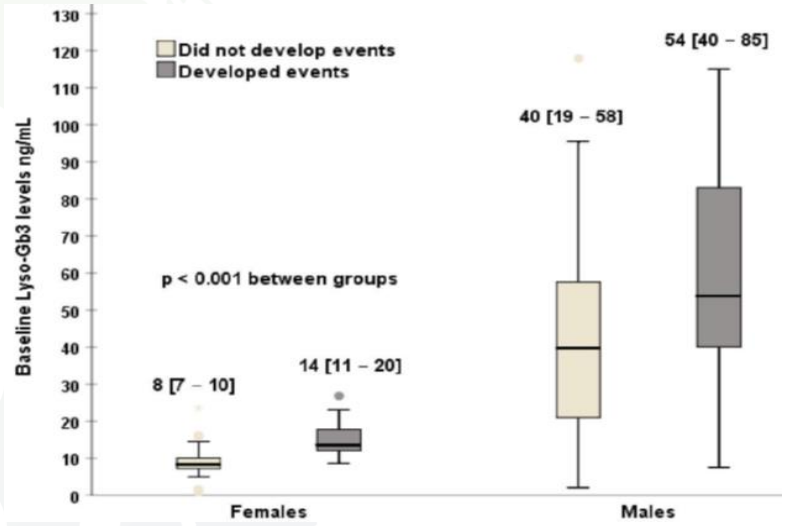
Durante la mediana de seguimiento de 68 (40-80) meses, el primer evento ocurrió en 19 (29%) de la población de pacientes.

Event	Number of patients suffering the first event
Pacemaker and/or ICD implantation*	7
New-onset of Atrial fibrillation	3
kidney transplantation	1
chronic dialysis requirement	1
stroke	1
myocardial infarction	1
death	5
	Total 19

Pronóstico

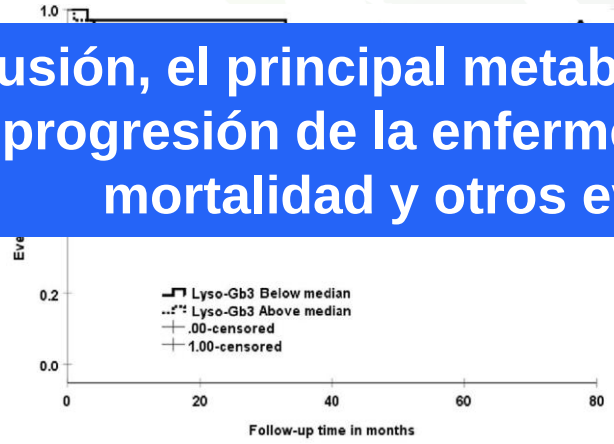
"Lyso-Gb3 associates with adverse long-term outcome in patients with Fabry disease"

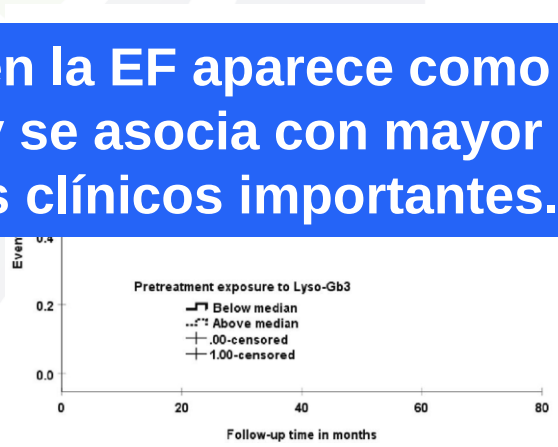
En hombres y mujeres, los niveles séricos de Lyso-Gb3 fueron significativamente mayor en pacientes que desarrollaron eventos versus pacientes sin eventos



En la curva Kaplan-Meier, la mediana de plasma Lyso-Gb3 basal y de exposición acumulada pre-tratamiento dividen los pacientes CON o SIN eventos, aún mejor que la edad, el sexo y el fenotipo.!!!

En conclusión, el principal metabolito en la EF aparece como un marcador de la progresión de la enfermedad y se asocia con mayor riesgo de mortalidad y otros eventos clínicos importantes.



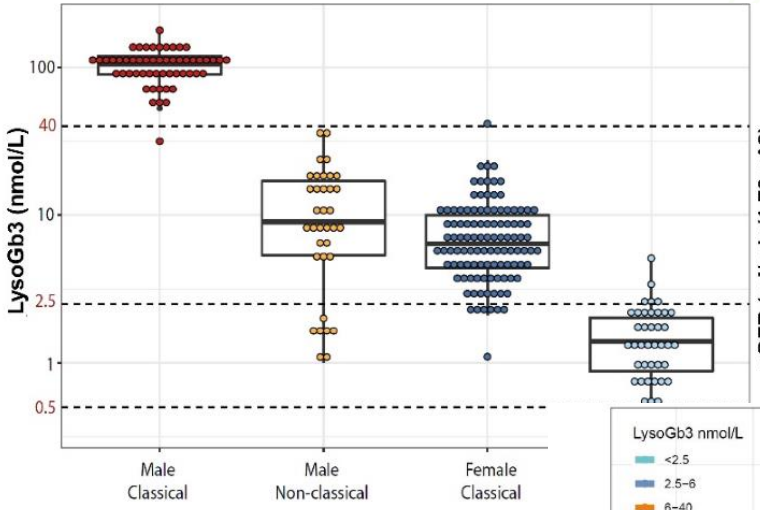


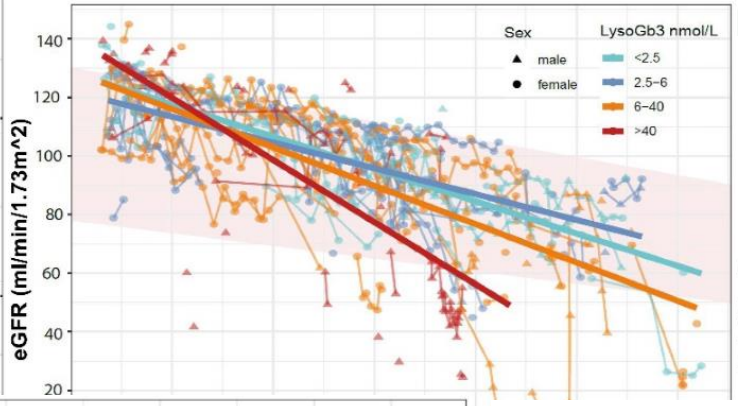
Plasma lysoGb3 in relation to Fabry disease course

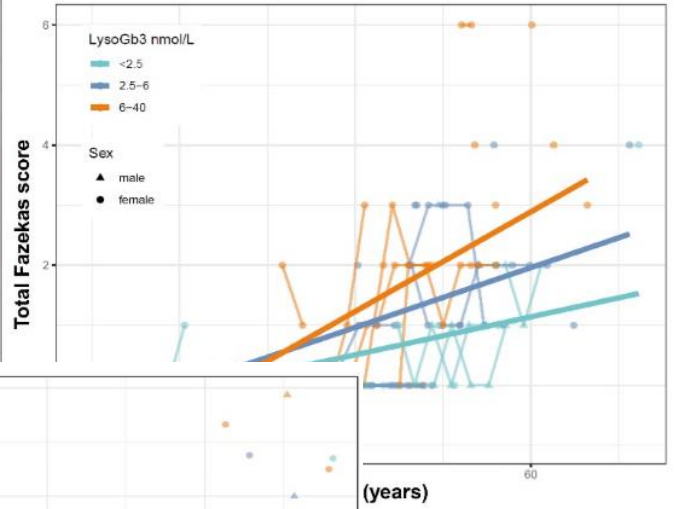
S.J. van der Veen, M. el Sayed, C.E.M. Hollak, A.B.P. van Kuilenburg and M. Langeveld
Amsterdam University Medical Centers (AUMC)

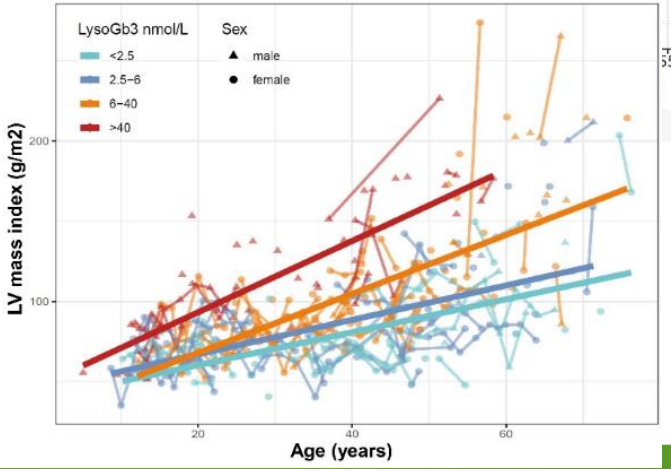
Methods

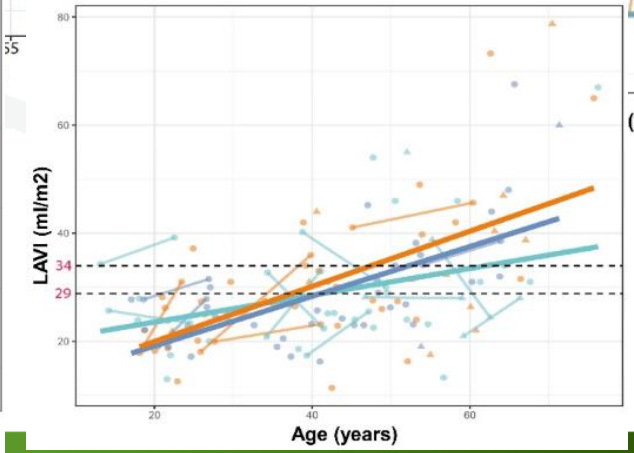
We investigated the stability of lysoGb3[2] levels over time and defined correlations between plasma lysoGb3 concentrations and renal function, cardiac imaging and cerebral manifestations in 237 untreated Fabry patients (multiple measurements per patient).











Conclusions

- Plasma lysoGb3 is stable over time in untreated FD patients (fig. 1a)
- LysoGb3 classifies clinical phenotypes with >95% acc. (fig. 1b).
- lysoGb3 correlates with renal function and morphological and functional parameters of cardiac disease in untreated FD patients (fig. 2, 3, 5).
- Measuring lysoGb3 in untreated FD patients aids prediction of the expected disease course, facilitating clinical decision making.

A nivel TISULAR: 1 mg/kg se asocia a mayor remoción del sustrato intracelular

Los beneficios de la agalsidasa en la histología renal en pacientes jóvenes ***con enfermedad de Fabry***

Dosis bajas
(6 casos)

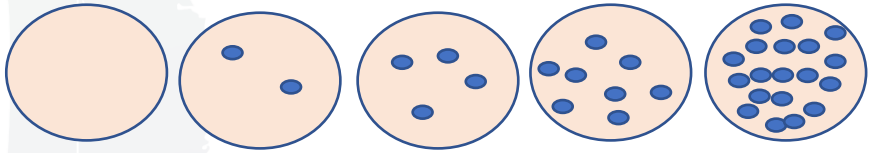
- 0.2 mg/kg Agal Alfa cada 14 días (2,4,6,8,11)
- 0.2 mg/kg Agal Beta cada 14 días (10)

Dosis Alta
(3 casos)

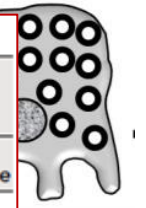
- 1 mg/kg Agal Beta cada 14 días (1,3,9)

Evaluar remoción de Gb3 intracelular en vivo:

Score de inclusiones (0 a 4)



Score de Vacuolización



Change of podocyte scores and albumin-to-creatinine ratio after 5 years of ERT

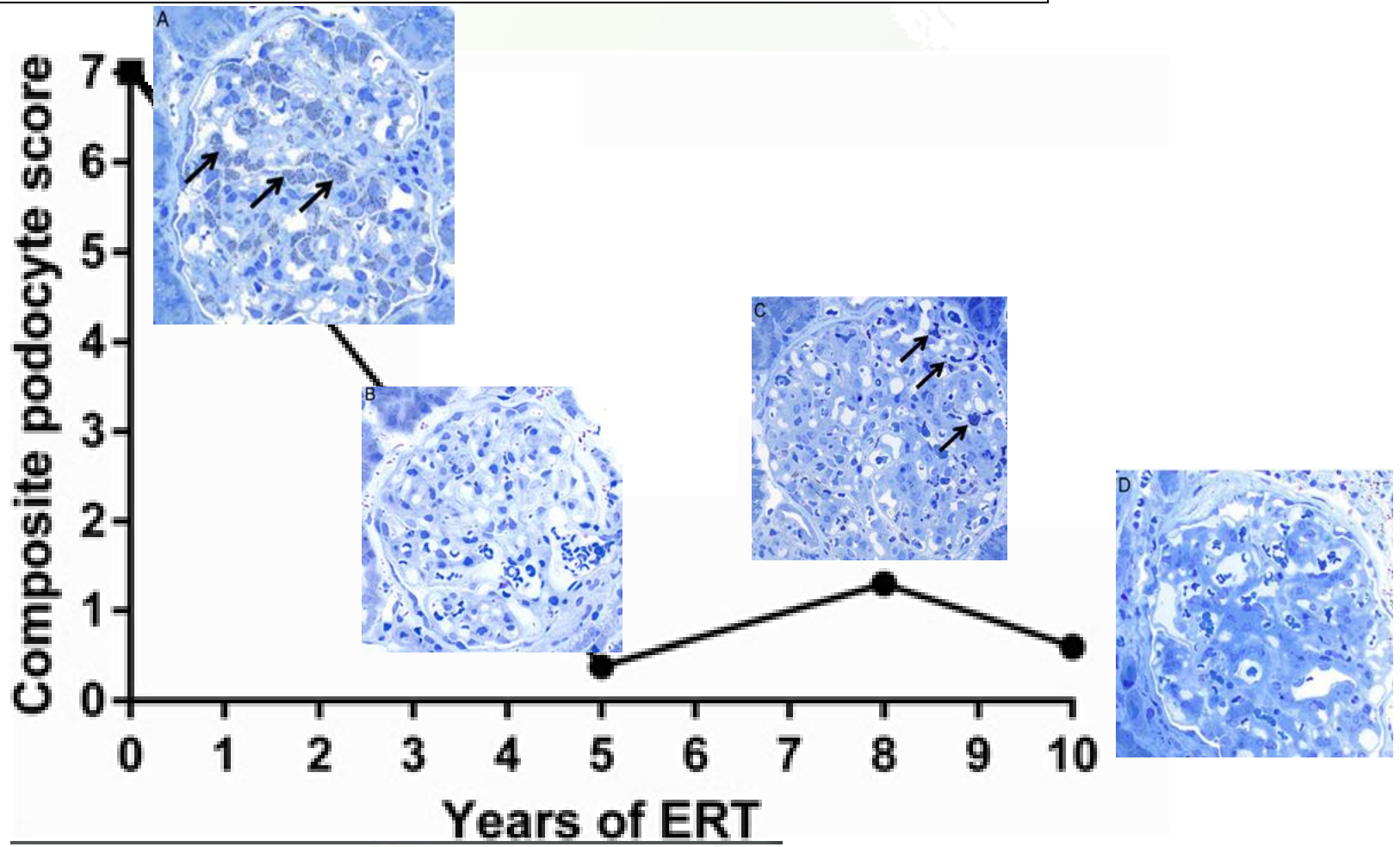
Treatment (agalsidase)	GL3 Inclusion Score (Toluidine Semithin Sections)		Vacuolization Score (PAS Sections)		Composite Score (Inclusions and Vacuolization)		Albumin-to-Creatinine Ratio	
	Change (95% CI)	*P* Value	Change (95% CI)	*P* Value	Change (95% CI)	*P* Value	Change (95% CI)	*P* Value
0.2 mg/kg EOW (6 patients, group 1)	0	1.0	−0.03 (−0.23 to 0.16)	1.0	−0.05 (−0.25 to 0. 15)	0.54	−0.88 (−2.1 to 0.3)	0.12
0.4–1.0 mg/kg EOW (6 patients, group 2)	−1.89 (−3.6 to −0.16)[a]	0.037	−1.1 (−2.3 to 0.08)[a]	0.062	−3.0 (−5.9 to −0.1)[b]	0.044	−0.13 (−8.9 to 8.6)	0.35
1.0 mg/kg EOW (4 patients)	−2.84 (−4.37 to−1.3)[c]	0.010	−1.66 (−3.18 to −0.14)[c]	0.040	−4.5 (−7.5 to −1.5)[c]	0.018	−4.2 (−6.0 to −2.5)[c] *	0.005

Tøndel et al. J Am Soc Nephrol 2013;24(1):137-48

Reaccumulation of globotriaosylceramide in podocytes after agalsidase dose reduction in young Fabry patients

Nephrol Dial Transplant (2016) 0: 1–6

Rannveig Skrunes[1,2], Einar Svarstad[1,2], Kristin Kampevold Larsen[3], Sabine Leh[2,3] and Camilla Tøndel[2,4]



Kidney biopsy specimens stained with toluidine blue.
(A) Baseline, composite podocyte score 7.0.
(B) 5 years of agalsidase-β 1.0 mg/ kg/eow, composite podocyte score 0.4.
(C) 3 years of agalsidase-α 0.2 mg/kg/eow, composite podocyte score 1.3.
(D) 2 years after reinstating agalsidase-β 1.0 mg/kg/eow, composite podocyte score 0.6.

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

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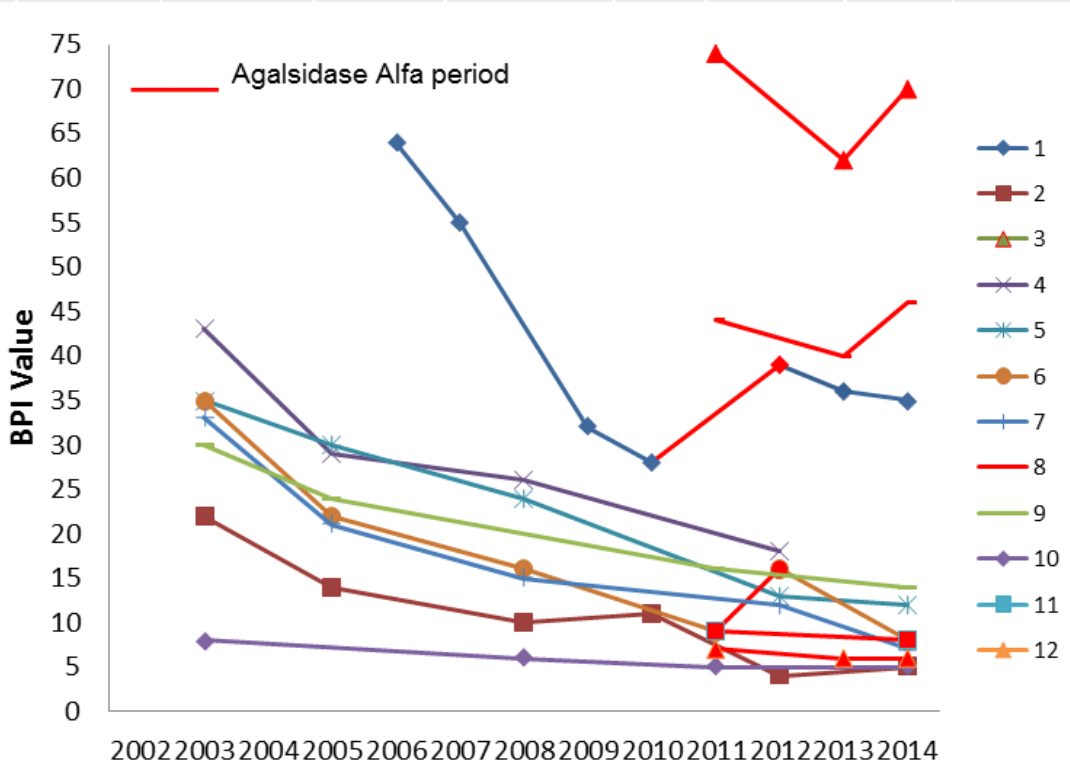
Fabry disease and enzyme replacement therapy in classic patients with same mutation: different formulations – different outcome?

J. Politei[a], A.B. Schenone[a], G. Cabrera[b], R. Heguilen[c] and M. Szlago[a]

pat	gender	age at onset symp	age a ERT in									ERT progression
1	M	9	46	8	0.1[b]	L415P	yes	+	2	+	+	Beta-Alfa (14 m)-Beta
2	M	9	31									Beta
3	M	7	33									Alfa
4	M	8	20									Beta
5	M	6	20									Beta
6	M	7	21									Beta- Alfa (34 m)-Beta
7	M	9	18									Beta
8	M	10	22									Alfa
9	F	20	50									Beta
10	F	18	46									Beta
11	F	22	52									Alfa
12	F	15	21									Alfa



a: alpha GAL A activity in leucocytes NV 30.5-57.7 nmol/hora/mg de proteínas. b: alpha GAL A activity in Dried Blood Spot NV 4-31.5 umol/h/l. LVH: Left ventricular hypertrophy Prot: Proteinuria > 300mg/día

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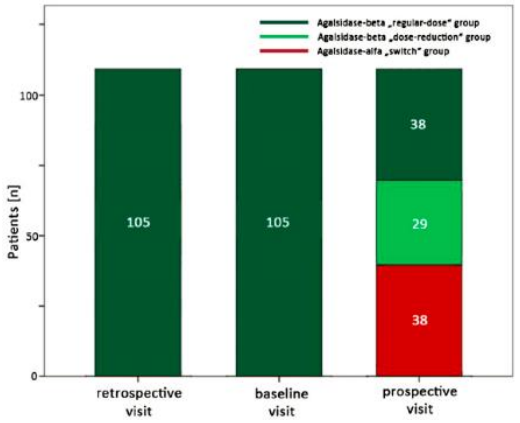
Patients with Fabry disease after enzyme replacement therapy dose reduction versus treatment switch.

Table 7. Changes in FD-related symptoms

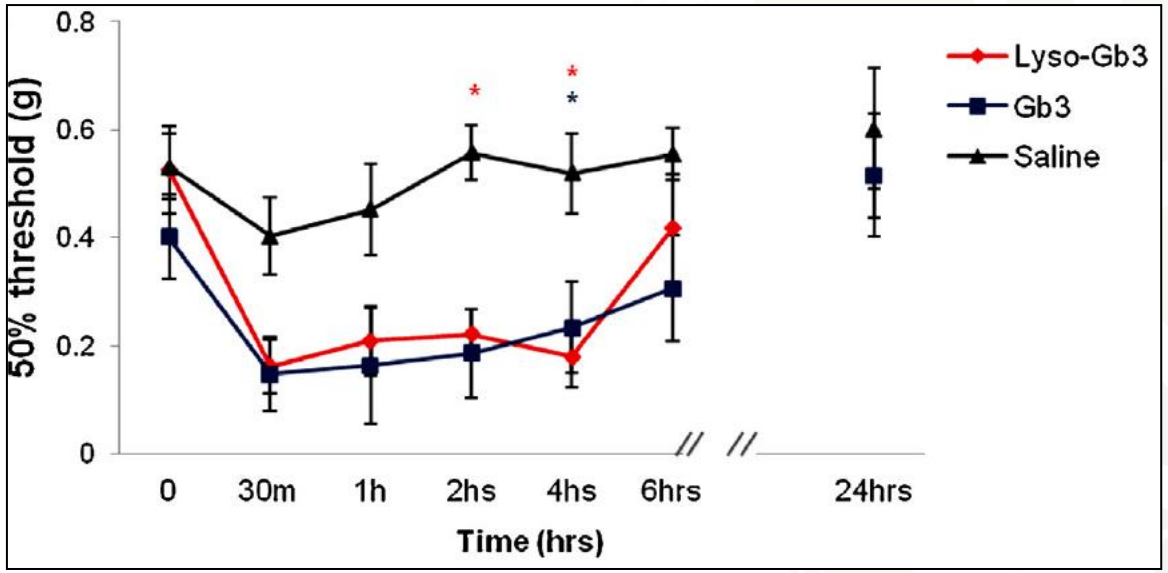
Measure	1-Year Retrospective Visit	*P* Value	Baseline Visit	*P* Value	1-Year Follow-Up Visit
Agalsidase-alfa switch group					
Angiokeratoma	16 (42)	1.00	16 (42)	0.25	19 (50)
Edema	8 (21)	1.00	8 (21)	0.13	12 (32)
Gastrointestinal pain	5 (13)	1.00	5 (13)	0.03	11 (29)
Diarrhea (d/mo)	0.8±1.8	0.92	0.8±1.7	0.05	2.0±5.1
Hypohidrosis	17 (45)	1.00	18 (47)	0.63	16 (42)
Cornea verticillata	19 (50)	1.00	19 (50)	1.00	20 (53)
Tinnitus	6 (16)	0.13	10 (26)	1.00	10 (26)
Hypoacusis	6 (16)	1.00	6 (16)	0.25	9 (23)
Paresthesia	21 (55)	1.00	22 (58)	0.69	20 (53)
Pain attacks	6 (16)	0.25	3 (8)	0.03	9 (24)
Chronic pain	11 (29)	0.63	9 (24)	0.04	14 (38)
Pain crises	5 (13)	0.50	7 (18)	1.00	6 (16)
TIA	0	—	0	—	2 (5.2)
Stroke	0	—	0	—	0
Fatigue	9 (24)	0.63	11 (19)	0.38	14 (37)
DS3 score	13.5±7.9	0.18	14.6±8.4	0.43	15.3±8.3
MSSI score	18.1±10.3	0.93	18.1±9.8	0.004	19.9±9.6

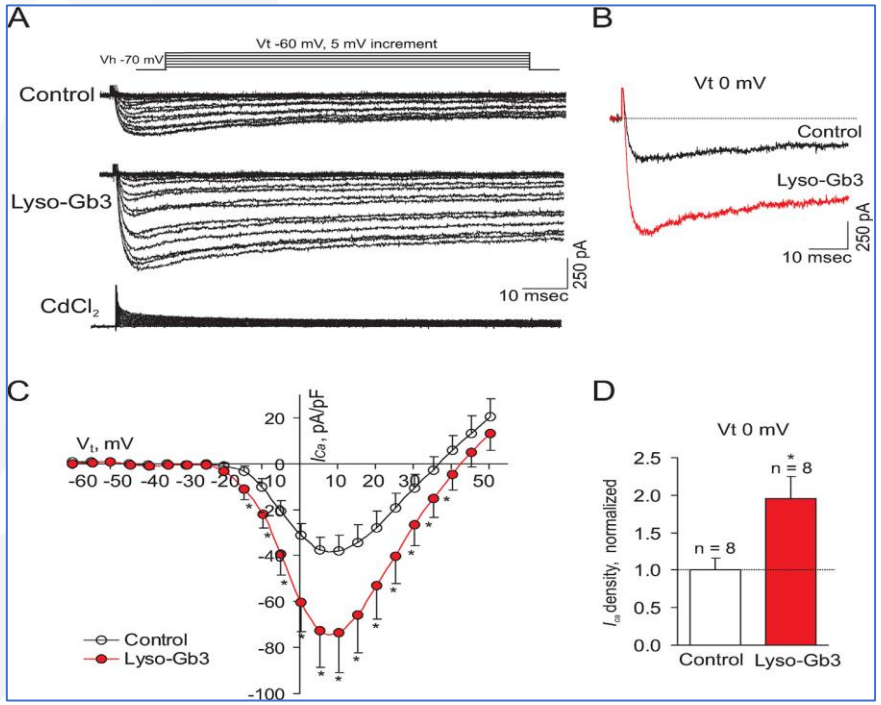


Conclusions: "renal function declined and FD-related symptoms increased after dose reduction and after switch to agalsidase-alfa. In this respect, ***a higher frequency of pain attacks, pain crises, and gastrointestinal symptoms was observed and caused an increase in the MSSI score".***

The Fabry disease-associated lipid Lyso-Gb3 enhances voltage-gated calcium currents in sensory neurons and causes pain

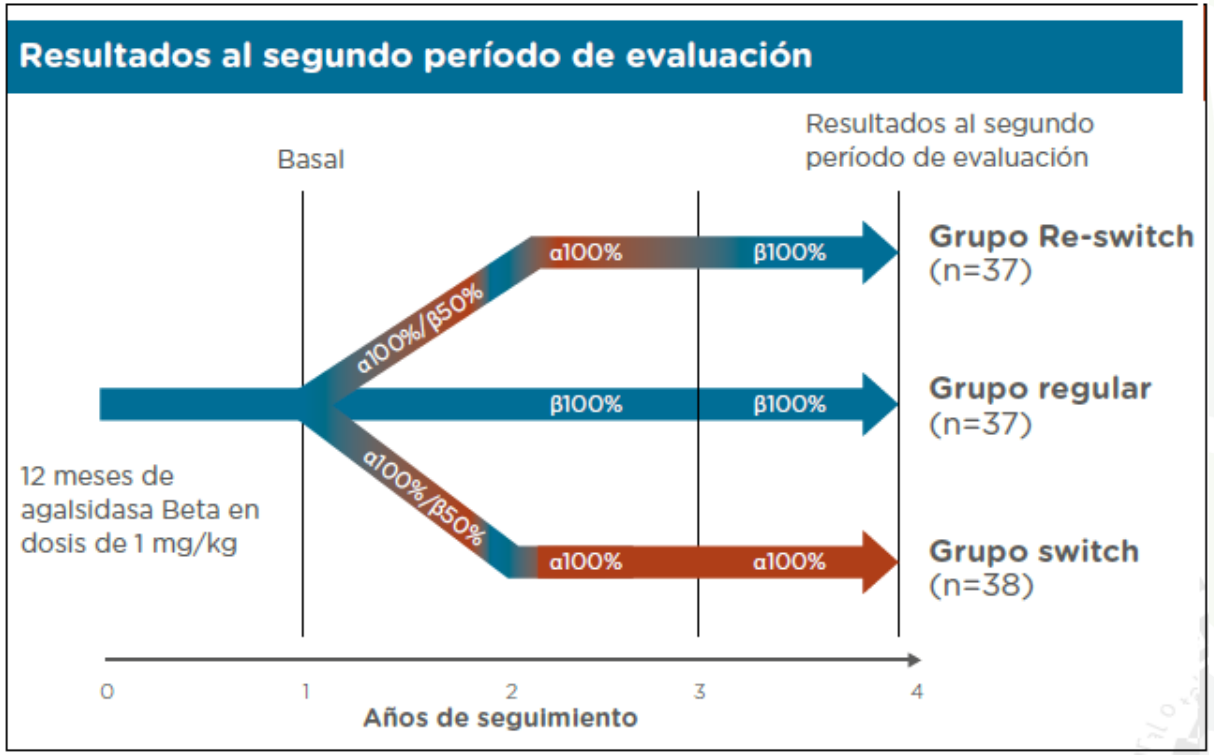
Mechanical withdrawal thresholds were evaluated by applying von Frey hairs in mices.
Prior testing animals received a plantar injection of Gl3, Lyso Gl3 o saline sol.

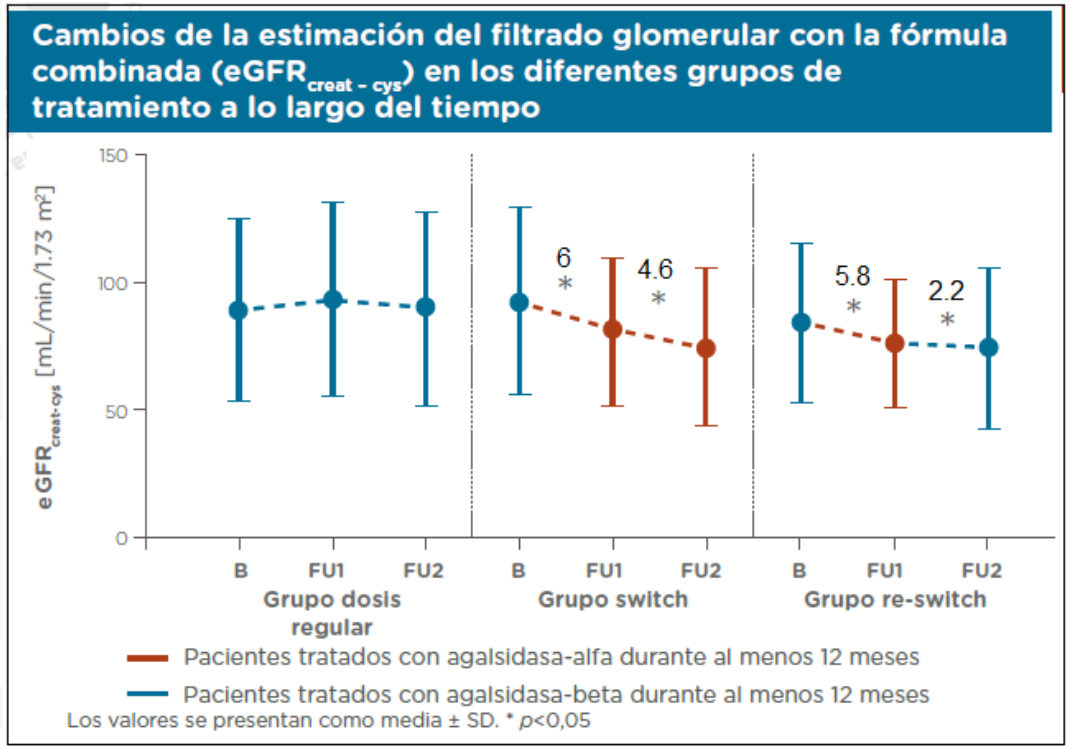




Both lipids significantly reduced pain thresholds.

FUNCIONAL TISULAR a largo plazo: 1 mg/kg se asocia a mejores resultados?





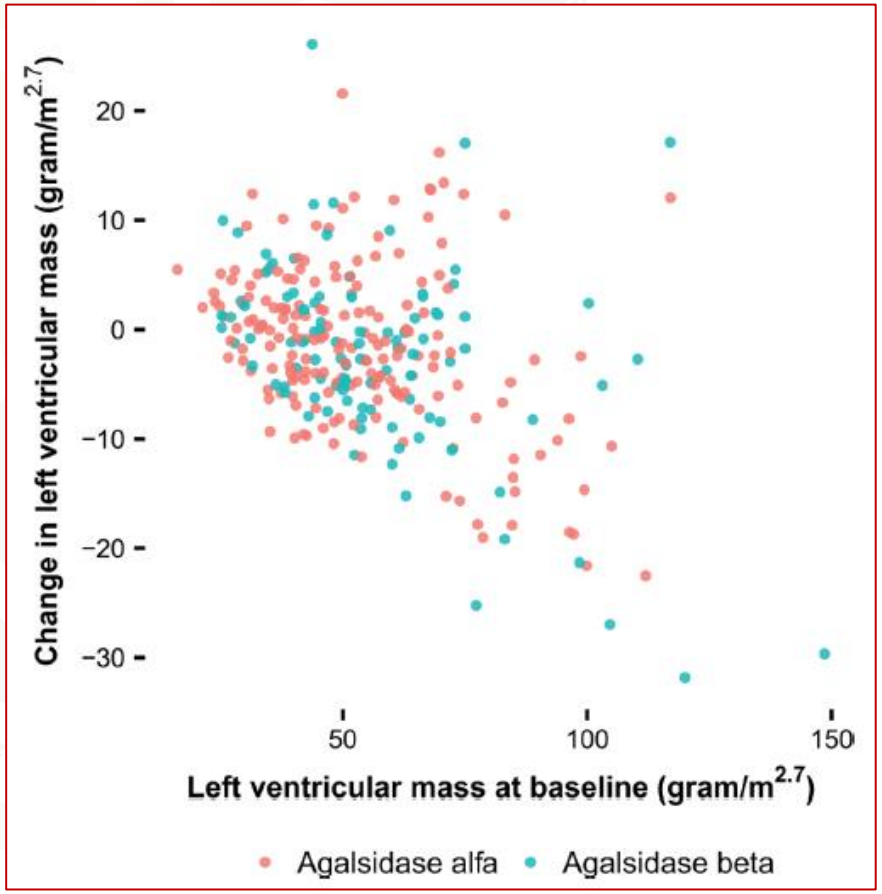
Luego del cambio desde agalsidasa beta a agalsidasa alfa, los pacientes experimentaron una disminución continua en la índice de filtrado glomerular, mientras que esta disminución se atenuó en los pacientes que regresaron al tratamiento con dosis de 1 mg/kg de agalsidasa beta. La disminución del nivel de lisoGb3 puede indicar una mejor respuesta al tratamiento en el último grupo.

FUNCIONAL TISULAR a largo plazo: 1 mg/kg se asocia a mejores resultados?

Agalsidasa alfa versus agalsidasa beta para el tratamiento de la enfermedad de Fabry: un estudio de cohorte internacional

Table 1 Patient characteristics at start of ERT

	Agalsidase alfa (0.2 mg/kg)	Agalsidase beta (1.0 mg/kg)	P value
Patients	248	139	
Men, classical*	69 (28%)	71 (51%)	<0.001
Men, non-classical	47 (19%)	7 (5%)	0.22
Women, classical	95 (38%)	43 (30%)	0.14
Women, non-classical	37 (15%)	18 (13%)	0.86
ERT start <18 years of age	15 (6%)	3 (2%)	0.13
Follow-up time (years)	5.2 (0.8–14.4)	3.8 (0.8–12.1)	<0.001
Events before initiation of ERT			
Dialysis/renal transplant	8 (3%)	12 (9%)	0.007
PM/ICD	21 (8%)	9 (7%)	0.87
Stroke	22 (9%)	17 (12%)	0.09
Any of the above†	46 (19%)	31 (22%)	0.08
LysoGb3 (nmol/L)	10 (0.7–146)	80 (2.0–178)	<0.001
eGFR (mL/min/1.73 m^2)	89 (10–159)	86 (10–140)	0.009
CKD category A3	44/195 (23%)	42/113 (37%)	0.008
LVMI (g/m$^{2.7}$)	49 (15–117)	52 (20–148)	0.14
Use of ACEi/ARBs	89/248 (36%)	52/139 (37%)	0.83
Hypertension	109/236 (39%)	62/137 (45%)	0.23
BMI (kg/m^2)	26 (±4.9)	25 (±5.6)	0.30
HDL cholesterol (mmol/L)	1.5 (±0.4)	1.5 (±0.4)	0.92
LDL cholesterol (mmol/L)	2.7 (±0.9)	2.7 (±0.8)	0.76
Total cholesterol (mmol/L)	4.8 (±1.1)	4.7 (±1.0)	0.51
Triglycerides (mmol/L)	1.2 (0.2–5.9)	1.2 (0.3–3.6)	0.18



El IMVI disminuyó en mayor proporción después del primer año de tratamiento con agalsidasa beta (OR 2,27, P = 0,03)

FUNCIONAL TISULAR a largo plazo: 1 mg/kg se asocia a mejores resultados?

Terapia de reemplazo enzimático para la enfermedad de Fabry: una revisión complementaria de un estudio Cochrane a través de regresión lineal y análisis agrupado de proporciones de estudios de cohortes

Revisión sistemática de estudios clínicos de cohortes con análisis agrupado de proporciones y una regresión lineal de pacientes con enf. de Fabry en terapia con agalsidasa alfa o beta.
77 estudios de cohortes con 15.305 participantes resultaron elegibles.

Table 1. Characteristics of patients undergoing ERT: Comparison among different regimens for AFD patients.

	Total	Alfa	Beta	Untreated
Total cohort studies	77	29	31	20[$]
Total number of patients	15,305	2,840	3,598	8,867
Mean percentage of males[*£]	66.4	65.9	74.7	49.1
Mean age[*€] (years)	35.1	34.4	33.1	41.2

FUNCIONAL TISULAR a largo plazo: 1 mg/kg se asocia a mejores resultados?

Renal complications, agalsidase alfa 15.3% [95% CI 0.048, 0.303; I2 = 77.2%, p = 0.0005]; agalsidase beta 6% [95% CI 0.04, 0.07; I2 = not applicable]; and untreated patients 21.4% [95% CI 0.1522, 0.2835; I2 = 89.6%, p<0.0001].

Effect differences favored agalsidase beta compared to untreated patients.

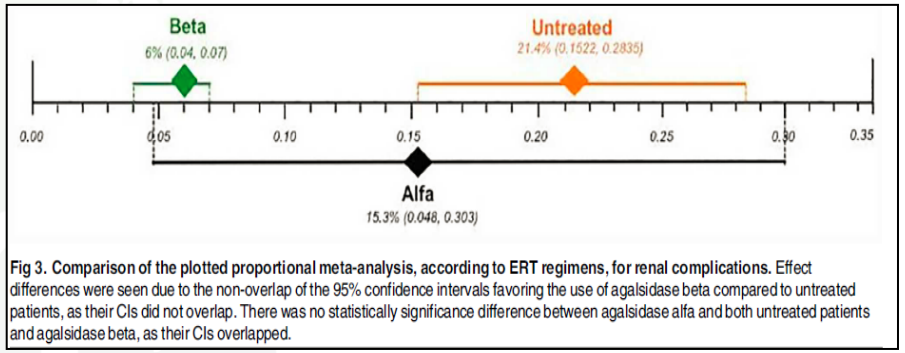


Fig 3. Comparison of the plotted proportional meta-analysis, according to ERT regimens, for renal complications. Effect differences were seen due to the non-overlap of the 95% confidence intervals favoring the use of agalsidase beta compared to untreated patients, as their CIs did not overlap. There was no statistically significance difference between agalsidase alfa and both untreated patients and agalsidase beta, as their CIs overlapped.

Cardiovascular complications, agalsidase alfa 28% [95% CI 0.07, 0.55; I2 = 96.7%, p<0.0001]; agalsidase beta 7% [95% CI 0.05, 0.08; I2 = not applicable]; and untreated patients 26.2% [95% CI 0.149, 0.394; I2 = 98.8%, p<0.0001].

Effect differences favored agalsidase beta compared to untreated patients

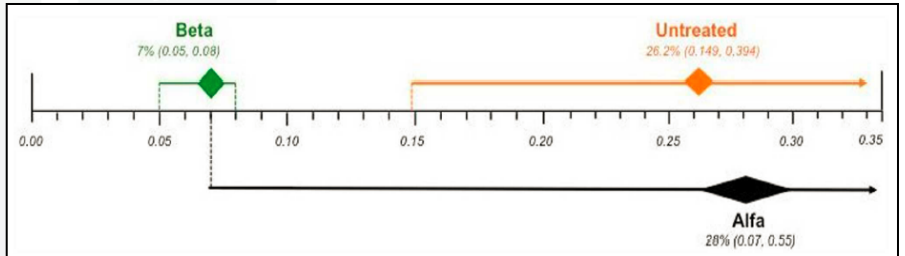


Fig 4. Comparison of the plotted proportional meta-analysis, according to ERT regimens, for cardiovascular complications. Effect differences were seen due to the non-overlap of the 95% confidence intervals favoring the use of agalsidase beta compared to untreated patients, as their CIs did not overlap. There was no statistically significance difference between agalsidase alfa and both untreated patients and agalsidase beta, as their CIs overlapped.

Cerebrovascular complications, agalsidase alfa 11.1% [95% CI 0.058, 0.179; I2 = 70.5%, p = 0.0024]; agalsidase beta 3.5% [95% CI 0.024, 0.046; I2 = 0%, p = 0.4209]; and untreated patients 18.3% [95% CI 0.129, 0.245; I2 = 95% p < 0.0001].

Effect differences favored agalsidase beta over alfa or untreated patients.

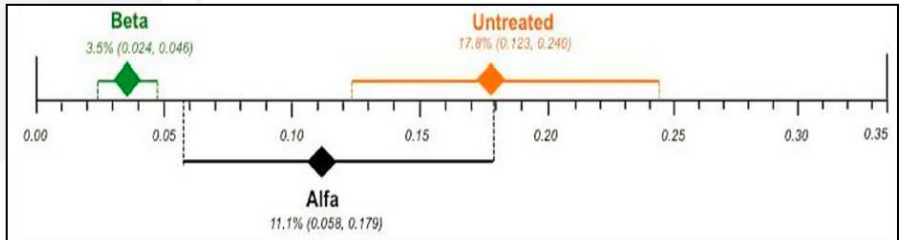


Fig 5. Comparison of the plotted proportional meta-analysis, according to ERT regimens, for cerebrovascular complications. Effect differences were seen due to the non-overlap of the 95% confidence intervals favoring the use of agalsidase beta compared to both untreated patients and agalsidase alfa, as their CIs did not overlap. There was no statistically significance difference between agalsidase alfa and untreated patients, as their CIs overlapped.

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¿Las guías internacionales actuales acuerdan con estas metas terapéuticas al momento de iniciar una TRE?

Amsterdam UMC
Universitair Medische Centra

Sphinx
Amsterdam
Lysosome Center

Protocol

Diagnosis, evaluation and treatment of Fabry disease in the Netherlands

Version 6, April 2020

Updated by:
M. Langeveld, C.E. Hollak, S. Klein van Loon, S. van der Veen, M. el Sayed, E. Eskes

Fabry disease specific therapies

Enzyme replacement therapy

Choice of drug is up to the treating physician and the patient. Given a more robust reduction of the biomarker plasma lysoGb3 and a potential better effect on cardiac hypertrophy and complication rate in agalsidase-beta versus agalsidase-alfa treated patients[14,15], in most patients agalsidase-beta will be prescribed.

2018 Canadian Fabry Disease Guidelines

Canadian Fabry Disease Treatment Guidelines 2018

Sandra Sirrs, Daniel G. Bichet, R. Mark Iwanochko, Aneal Khan, David Moore, Gavin Oudit and Michael L. West

Toronto Ontario

Oct 4 2019

On the basis of these data, agalsidase beta may be considered as the first option in male patients with a classic phenotype who are started on disease specific therapy. Some males with classical phenotypes may prefer agalsidase alfa for other reasons (for example, shorter infusion times) and patient preferences should be considered in choosing a drug. Either drug could be considered for patients with nonclassic phenotypes, women, or older patients.

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Conclusiones

- ***En niños clásicos, aprendimos que hay que tratar temprano, AUN ANTES DE LOS SINTOMAS, para lograr normalizar el LysoGb3***
- ***Debemos proponernos metas terapéuticas y evaluar la respuesta al tratamiento***
- ***La UNICA meta terapéutica a corto plazo es la reducción del LYSOGb3 en formas clásicas.***
- ***Las guías internacionales DEJAN CLARO que la dosis de 1 mg/kg tiene mayor eficacia respecto a la dosis de 0.2 mg/kg***

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