La enfermedad de Fabry: manejo multisistémico del Internista.

Siete años de experiencia en el tratamiento

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XXXI Congreso Nacional de la Sociedad Española de Medicina Interna

OVIEDO
17-20 Noviembre 2010

Guión de la charla

- Repaso de la enfermedad de Fabry
- Papel del especialista en Medicina Interna en su manejo
- Terapia de reemplazo enzimático
  - Los inicios
  - Evidencia disponible
  - Experiencia a largo plazo
  - Retos futuros
- Otros tratamientos
- Conclusiones

Enfermedad de Fabry

- Enfermedad por depósito lisosómico
- Trastorno, ligado al cromosoma X, del metabolismo de los glicoesfingolipidos
- Deficiencia de Alfa-Galactosidasa A (GLA)

Concepto fisiopatológico tradicional…

- Disfunción del endotelio
- Celular
  - Depósito aumentado de Gb_3
  - Agrandamiento de lisosomas
  - Disfunción y muerte celular
- Órganos
  - Fallo del órgano
  - Hipertropia secundaria (cardiaca)

Pero también…

- La agregación plaquetaria está aumentada[1]
- Los glicoesfingolípidos incrementan la expresión de moléculas de adhesión leucocitaria al endotelio y de la integrina MAC-1 en leucocitos[2]
- Las concentraciones del factor von Willebrand-antígeno también se han visto elevadas[3]

1 DeGraba T et al, Ann Neurol 2000, 47:229-233
2 Sakuraba H et al , Clin Genet 1987, 31:349-35
3 O'Donnell T et al, Symposium on LSD, Cannes, april 2002, abstract p. 73

- Hiperhomocisteinemia en un 21%[1]
- Alteraciones en el remodelado de la matriz extracelular vascular: elevados niveles de MMP-9[2]
- Presencia de Ac anti-cardiolipina en un 14% y de anticoagulante lúpico en un 34%[3]

1 Baron K et al 3rd International symposium on LSD, Santiago de Compostela, 2003
2 Shah JS et al, 5th International symposium on LSD, Valencia, 2005
3 Aggio M et al, 5th International symposium on LSD, Valencia, 2005

- Existencia de factor de crecimiento que estimula la proliferación de células musculares lisas y miocardiocitos *in vitro* [1]
- Elevados niveles de VEGF[2]
- Elevados niveles de MPO en varones con EF[2]

1 Barbey et al, Arterioscler Thromb Vasc Biol, 2006, 26: 839-44
2 Kanesky et al, Neurology 2006, 67: 2045-47

Parece haber algo más…

- Disfunción del endotelio
- Celular
  - Depósito aumentado de Gb_3
  - Agrandamiento de lisosomas
  - Disfunción y muerte celular
- Órganos
  - Fallo del órgano
  - Hipertropia secundaria (cardiaca)

¿Activa el depósito de Gb3 otros procesos secundarios con un papel predominante en la fisiopatología de la EF?

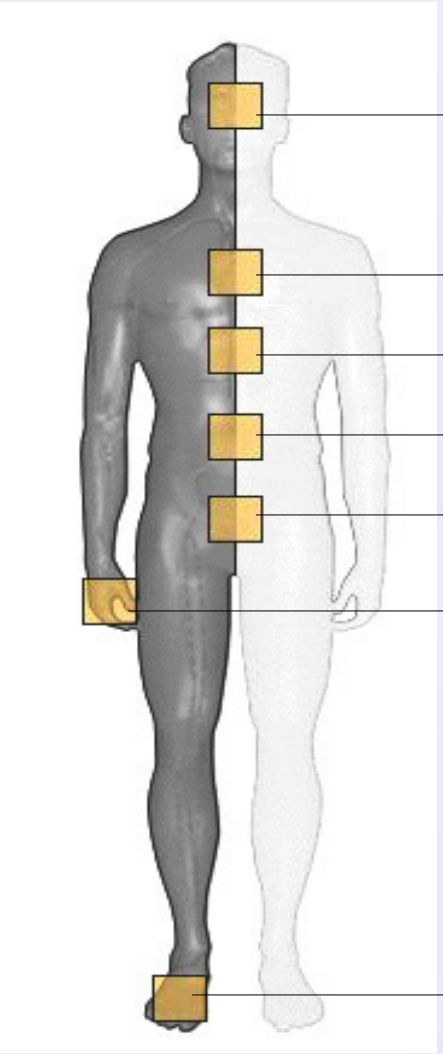
- Prevalencia: 1 cada 40.000[1]–110,000 recién nacidos,[2] aunque una publicación reciente ha sugerido que la incidencia puede ser más elevada (1 cada 3.100 recién nacidos)[3]
- Hasta un 25% de los pacientes reciben diagnósticos erróneos[4]
- Origina disfunción orgánica y muerte precoz en hombres y mujeres[4,5]
- Típicamente la esperanza de vida esta acortada unos 20 años en hombres[6] y 15 en las mujeres[7]

1. Garman & Garboczi. *J Mol Biol* 2004;337:319–35.
2. Meikle *et al. JAMA* 1999;281:249–54.
3. Spada *et al. Am J Hum Genet* 2006;79:31–40.
4. Mehta *et al. Eur J Clin Invest* 2004;34:236–42.
5. Barbey *et al. Curr Med Chem Cardiovasc Hematol Agents* 2004;2:277–86.
6. MacDermot *et al. J Med Genet* 2001;38:750–60.
7. MacDermot *et al. J Mol Genet* 2001;38:769–75.

- En los hombres, la medición de actividad GLA revelará que es baja o ausente[1,2]
- Muchas mujeres tendrán actividad GLA dentro del intervalo normal[3]
- El análisis del DNA confirma el diagnóstico en ambos sexos[1,2]
- Es aconsejable realizar un estudio familiar siempre que sea posible[1,2]

1. Mehta. *Hosp Med* 2002;63:347–50.
2. Barbey *et al. Curr Med Chem Cardiovasc Haematol Agents* 2004;2:277–86.
3. Gupta *et al. Medicine* 2005;84:261–8.

SIGNOS Y SÍNTOMAS. VISIÓN GENERAL



Ictus precoz

Afecación neuropsicológica

Hipertrofia cardíaca

Hipohidrosis

Insuficiencia renal

Angioqueratomas

Acroparestesias

Acroparestesias

Natural history of Fabry disease in females in the Fabry Outcome Survey

P B Deegan, A F Baehner, M-Á Barba Romero, D A Hughes, C Kampmann, M Beck, on behalf of the European FOS Investigators

J Med Genet 2006;**43**:347–352. doi: 10.1136/jmg.2005.036327

See end of article for authors' affiliations

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Revised version received 4 October 2005
Accepted for publication 5 October 2005
Published Online First 14 October 2005

Background: Fabry disease is a rare X linked lysosomal storage disorder resulting from deficiency of α-galactosidase A activity. Although the severity of clinical features in male patients is well described, only recently have studies reported the high prevalence of disabling clinical features in heterozygous females.
Aims: This study sets out to examine the clinical features and natural history of Fabry disease in further detail in a large group of female patients.
Methods: Data were obtained from 303 females enrolled in the Fabry Outcome Survey. Pain was assessed using the Brief Pain Inventory, and health related quality of life (HRQoL) was assessed using the European Quality of Life Questionnaire. A modified version of the Mainz Severity Score Index was also applied. Data on left ventricular mass (LVM) index, mean ventricular wall thickness, and glomerular filtration rate (GFR) were used to assess cardiac and renal involvement.
Results: The most commonly reported clinical features in females were neurological (77%) and cardiac (59%). A history of renal involvement was recorded in 40% of cases. Neurological features were the earliest to develop (mean age: 16 years), whereas cardiac (mean age: 33.5 years) and renal (mean age: 37.3 years) features developed later. LVM index increased exponentially with age. In addition, age was negatively correlated with estimated GFR and HRQoL.
Conclusions: Females with Fabry disease report important age related clinical features and clinical investigation demonstrates evidence of disease progression. This study highlights the importance of careful and longitudinal assessment of female heterozygote patients with Fabry disease.

The (“Dream”) Team

Cardiólogo

Nefrólogo

Gastroenterólogo

Neurólogo

INTERNISTA

Dermatólogo

Pediatra

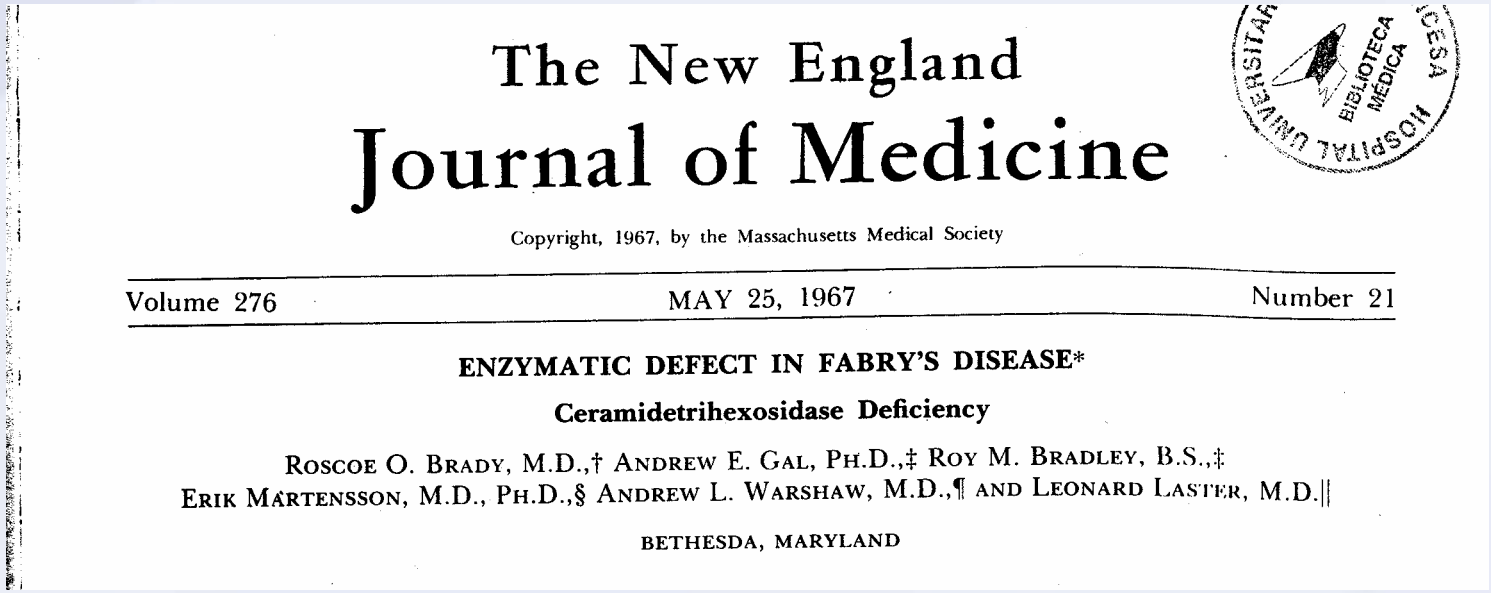
Médico de Familia

Genetista

4.1.9 Atención a pacientes con enfermedades raras, ya sea por no inscribirse en una especialidad definida o por el desarrollo de nuevos conocimientos: Para mantener la continuidad asistencial en la atención de todos estos pacientes el internista ha de estar especialmente preparado para trabajar en equipo en colaboración con otros especialistas hospitalarios, con el médico de familia y con otros profesionales sanitarios.

ORDEN SCO/227/2007, de 24 de enero, por la que se aprueba y publica el programa formativo de la especialidad de Medicina Interna.

BOE núm. 33 Miércoles 7 febrero 2007



The New England
Journal of Medicine

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Volume 276 MAY 25, 1967 Number 21

ENZYMATIC DEFECT IN FABRY'S DISEASE*

Ceramidetrihexosidase Deficiency

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ERIK MÅRTENSSON, M.D., PH.D.,§ ANDREW L. WARSHAW, M.D.,¶ AND LEONARD LASTER, M.D.||

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BIBLIOTECA MEDICA HOSPITAL UNIVERSITARIO

1967: R.O. Brady et al. purifican la ceramidatrihexosidasa a partir de placenta humana.

1970: C.A. Mapes et al. infunden plasma fresco a pacientes con EF.

REPLACEMENT THERAPY FOR INHERITED ENZYME DEFICIENCY

Use of Purified Ceramidetrihexosidase in Fabry's Disease

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Abstract Ceramidetrihexosidase, which is lacking in patients with Fabry's disease, has been highly purified from human placental tissue. This enzyme was administered intravenously to two patients with Fabry's disease. The patients tolerated the procedure very well. The enzyme was rapidly cleared from the blood and was taken up to a major extent by the liver. In one patient, the level of circulating ceramidetrihexoside decreased from 53 to 22 nmoles per 10 ml of plasma 40 minutes after the enzyme was administered. In the other, who received 2/5 less enzyme, the level of circulating ceramidetrihexoside decreased from 67 to 45 nmoles per 10 ml of plasma. Infusions of normal fresh plasma or leukocytes and platelets suspended in plasma yielded results resembling the effect obtained with purified enzyme. Plasma infusion had no demonstrable effect. (N Engl J Med 289: 9-14, 1973)

Table 1. α-Galactosidase Activity in Plasma of Patients with Fabry's Disease after Infusion of Fresh Normal Human Plasma, Platelet-Enriched and Leukocyte-Enriched Plasma, and Purified Placental Ceramidetrihexosidase.

Material Infused	Case No.	α-Galactosidase Activity*	
		Increase over pre-infusion level (%)	Half-time of increased enzyme activity
Fresh normal plasma	1	0	–
Enriched plasma	1	+ 68	3.5 hr.
Ceramidetrihexosidase (5 mg of protein)	1	> + 540	~ 12 min
Ceramidetrihexosidase (3 mg of protein)	2	+ 100	~ 10 min

*Measured with 4-methylumbelliferyl-α-D-galactopyranoside as substrate.[13]

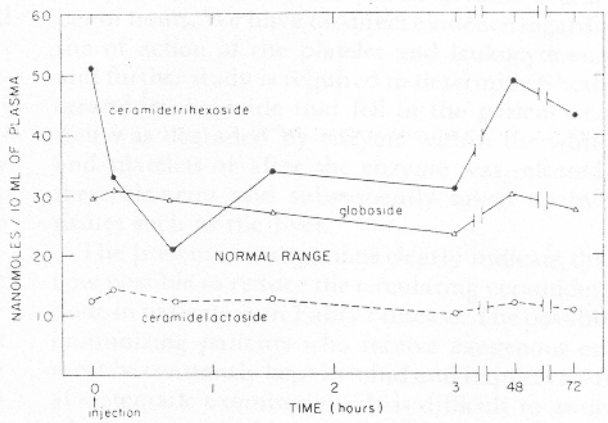

Figure 2. Effect of Infusion of Ceramidetrihexosidase on Plasma Glycolipids in Case 1.

Enzyme Replacement Therapy in Fabry Disease

A Randomized Controlled Trial

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Context Fabry disease is a metabolic disorder without a specific treatment, caused by a deficiency of the lysosomal enzyme α-galactosidase A (α-gal A). Most patients experience debilitating neuropathic pain and premature mortality because of renal failure, cardiovascular disease, or cerebrovascular disease.

Objective To evaluate the safety and efficacy of intravenous α-gal A for Fabry disease.

Design and Setting Double-blind placebo-controlled trial conducted from December 1998 to August 1999 at the Clinical Research Center of the National Institutes of Health.

Patients Twenty-six hemizygous male patients, aged 18 years or older, with Fabry disease that was confirmed by α-gal A assay.

Intervention A dosage of 0.2 mg/kg of α-gal A, administered intravenously every other week (12 doses total).

Main Outcome Measure Effect of therapy on neuropathic pain while without neuropathic pain medications measured by question 3 of the Brief Pain Inventory (BPI).

Results Mean (SE) BPI neuropathic pain severity score declined from 6.2 (0.46) to 4.3 (0.73) in patients treated with α-gal A vs no significant change in the placebo group (P = .02). Pain-related quality of life declined from 3.2 (0.55) to 2.1 (0.56) for patients receiving α-gal A vs 4.8 (0.59) to 4.2 (0.74) for placebo (P = .05). In the kidney, glomeruli with mesangial widening decreased by a mean of 12.5% for patients receiving α-gal vs a 16.5% increase for placebo (P = .01). Mean inulin clearance decreased by 6.2 mL/min for patients receiving α-gal A vs 19.5 mL/min for placebo (P = .19). Mean creatinine clearance increased by 2.1 mL/min (0.4 mL/s) for patients receiving α-gal A vs a decrease of 16.1 mL/min (0.3 mL/s) for placebo (P = .02). In patients treated with α-gal A, there was an approximately 50% reduction in plasma glycosphingolipid levels, a significant improvement in cardiac conduction, and a significant increase in body weight.

Conclusion Intravenous infusions of α-gal A are safe and have widespread therapeutic efficacy in Fabry disease.

JAMA. 2001;285:2743-2749 www.jama.com

FABRY DISEASE IS A RARE X-LINKED recessive glycosphingolipid storage disorder that is caused by a deficiency of the lysosomal enzyme α-gal A (α-galactosidase A).[1] Its incidence has been estimated to be 1:117 000 births.[2] Globotriaosylceramide (Gb_3), the glycosphingolipid substrate of this enzyme, accumulates within vulnerable cells, tissues, and organs of affected patients. Affected cell types include endothelial cells, pericytes, smooth muscle cells of the vascular system, renal epithelial cells, myocardial cells, and dorsal root ganglia neuronal cells.[3-5]

Clinical onset of the disease typically occurs during childhood or adolescence with recurrent episodes of se-

SAFETY AND EFFICACY OF RECOMBINANT HUMAN α-GALACTOSIDASE A REPLACEMENT THERAPY IN FABRY'S DISEASE

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Table 1 Overview of clinical efficacy of enzyme replacement therapy for Fabry disease

	Agalsidase alfa	Agalsidase beta
Neuropathic pain	• Significant reduction in pain scores compared with placebo[29]	• Small, insignificant decrease[45] • Reduction in pain in both active and placebo groups[33]
Acroparesthesia	• Significant reduction in prevalence from baseline[41a]	
Nerve function	• Significant improvement in cold and heat sensation threshold in the foot[46] • No change in thermal threshold in the thigh[48]	• Significant improvement in nerve function[47]
Vestibular/auditory	• Improved vestibular function with no change in auditory function[48] • Improved hearing[50]	

Effects of enzyme replacement therapy in Fabry disease—A comprehensive review of the medical literature

Olivier Lidove, MD[1], Michael L. West, MD[2], Guillem Pintos-Morell, MD[3], Ricardo Reisin, MD[4], Kathy Nicholls, MD[5], Luis E. Figuera, MD[6], Rossella Parini, MD[7], L. R. Carvalho, MD[8], Christoph Kampmann, MD[9], Gregory M. Pastores, MD[10], and Atul Mehta, MD[11]

DOI: 10.1097/GIM.0b013e3181f13b75

Genetics IN Medicine • Volume xx, Number xx, xx 2010

Table 1 Overview of clinical efficacy of enzyme replacement therapy for Fabry disease

	Agalsidase alfa	Agalsidase beta
Kidney	• Stability of measured GFR more than 2 yr of treatment, no effect on proteinuria, proteinuria >1 g/day predicts continued decline in GFR[32]	• Stability of creatinine clearance and proteinuria[51]
	• Stability of eGFR in men with Stage 1 or 2 CKD[30] during a 4.5-yr period	• Stability of eGFR and proteinuria[52b]
	• Improved creatinine clearance compared with placebo.[29] Stability of measured GFR	• Reduction in major clinical events (primarily renal). Proteinuria >1 g/day predicts continued decline in eGFR[35]
	• Stable or improved eGFR in women, improved proteinuria in women with baseline exceeding 300 mg/day[38]	• Stable eGFR with 4.5 yr ERT. Proteinuria >1 g/day predicts continued decline in eGFR[34,53]
		• Proteinuria > 1 g/day or GFR < 90 predicted continued loss of GFR during ERT[54]
		• Sustained reduction in proteinuria when combined with ACE inhibitors or ARBs[55]
Dialysis—transplant patients	• Slight increase in eGFR in transplant patients[56]	• Reduction in pain and GI involvement[57]
		• Increase in LVM in dialysis patients, decrease in transplant patients[44c]

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Table 1 Overview of clinical efficacy of enzyme replacement therapy for Fabry disease

	Agalsidase alfa	Agalsidase beta
Heart	• No change in LVM, small increase in fractional shortening[41] • Significant reduction in MRI-measured LVM compared with placebo[31] • Improved cardiac conduction[29] in one case • Significantly reduced LVM in women with LVH, improved NYHA scores[38] • Significantly improved heart rate variability in boys[19]	• Reduction in heart rate and reduction in LVEDV. No change in LVM[58] • No change in LVM[59] • Reduction in MRI-measured LVM and LV wall thickness[60] • Reduction in LVM and improved LV function and exercise capacity in patients without fibrosis[61] • Reduction in LVM[62] • Reduction in LVM and improvement in regional wall function[63] • Significant reduction in LV wall thickness in patients with preserved kidney function[54] • Reduction in LVM in patients without fibrosis, no effect in patients with fibrosis[64] • No effect on LVM[65]

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Table 1 Overview of clinical efficacy of enzyme replacement therapy for Fabry disease

	Agalsidase alfa	Agalsidase beta
QoL	• Significantly improved QoL in women[66]	• No change[58] • Improvements in SF-36 Health Status Survey—General Health, Mental component[45] • Improvements in both active and placebo groups[33]
CNS	• Strokes occur during treatment[30] • Increase in number of white matter lesions[67] • Appearance and disappearance of white matter lesions[68] • Correction of abnormally elevated cerebral blood flow and cerebrovascular responses[69,70]	• Strokes occur during treatment[53] • Increase in number of white matter lesions[43]
Sweat function	• No change 2 days or 2 weeks after treatment[71] • Improved sweat function[46] • Apparent improvement in sympathetic skin response[72]	

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	Agalsidase alfa	Agalsidase beta
GI	• Reduced severity and frequency of GI pain[73]	
MSSI	• Significant reduction in total, general, neurologic, and cardiovascular scores[74] • Improvement in total, neurologic, and cardiovascular scores in women[38] • Significant reduction in MSSI in men and women[75]	
Cardiopulmonary function	• Improvement in NYHA classification in women[38]	• No significant changes[76]
Children	• Well tolerated, appears to decrease pain[36] • Significantly improved heart rate variability in boys, decrease in pain medication[19]	• Well tolerated, GI involvement improved[37]
Women	• Improved LVM and QoL[66] • Improvements in heart, kidney, pain, and MSSI[38]	

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Genetics IN Medicine • Volume xx, Number xx, xx 2010

Anticuerpos frente a la TRE

	Agalsidasa α	Agalsidasa β
Prevalencia (Regulatory documents, CFDI)	11 - 24%	60 - 89%
Sexo	Hombres	Hombres y mujeres
Tipo	IgG	IgG, IgE
Relevancia Clínica	?	?

Ensayos clínicos-Registros de Resultados

Ensayos controlados aleatorizados (RCT)

- Generalmente un pequeño grupo de pacientes
- Pequeña cantidad de centros de tratamiento
- Esquema rígido de visitas y de administración de dosis
- Tratamientos concurrentes y enfermedades concomitantes restringidos
- Tratamientos que se emplean para los fines a los que están destinados
- Marco temporal relativamente corto
- Proporcionan pruebas de la *eficacia* de los tratamientos en un entorno altamente controlado para reducir los sesgos

Registros de Resultados

- Grupo grande y variado de pacientes
- Muchos centros de tratamiento (multinacionales)
- Esquema de visitas y de administración de dosis de conformidad con la práctica clínica normal
- Sin restricciones sobre los tratamientos concurrentes y enfermedades concomitantes
- Tratamientos que se usan de conformidad con la práctica clínica normal
- Marco temporal prolongado
- Proporcionan pruebas de la *efectividad* de los tratamientos en la realidad

El uso de tratamientos en la realidad es diferente del uso de tratamientos en el entorno controlado de un RCT

Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data

*A Mehta, M Beck, P Elliott, R Giugliani, A Linhart, G Sunder-Plassmann, R Schiffmann, F Barbey, M Ries, J T R Clarke, on behalf of the Fabry Outcome Survey investigators**

Lancet 2009; 374: 1986–96

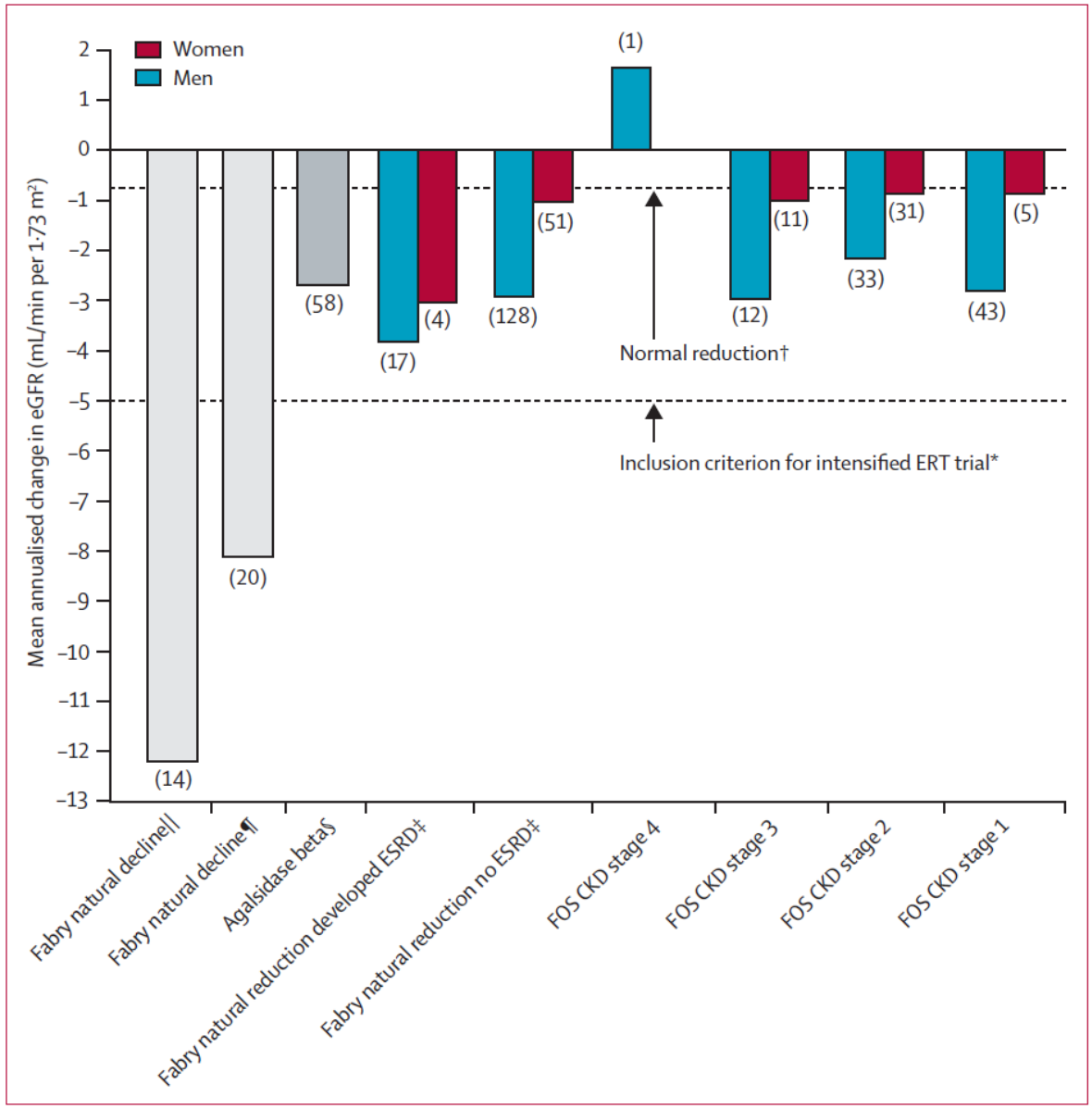
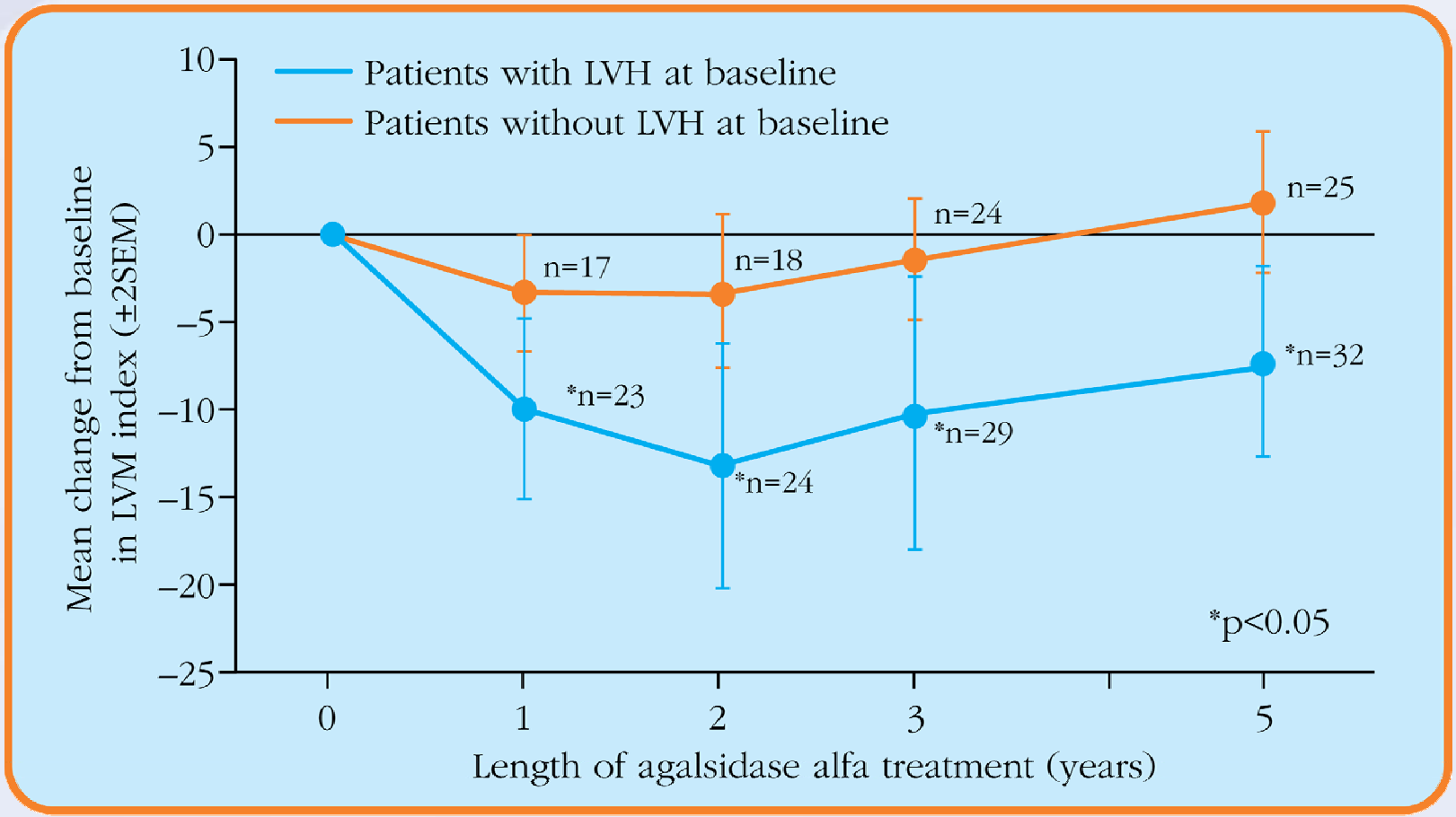


Figure 4: **Mean yearly fall in estimated glomerular filtration rate according to stage of chronic kidney disease at baseline in male and female patients with Fabry's disease during 5 years of treatment with agalsidase alfa**
Data are plotted according to baseline stage of chronic kidney disease. Patient numbers are shown in parentheses. Data from previous studies for the expected natural fall in renal function in patients with Fabry's disease and the effects of agalsidase beta are plotted for reference and comparison. ERT=enzyme replacement therapy. FOS=Fabry Outcome Survey. CKD=chronic kidney disease. ESRD=end-stage renal disease. eGFR=estimated glomerular filtration rate. *Schiffmann et al.[20] †Lindeman et al.[23] ‡Schiffmann et al.[16] §Germain et al.[21] ¶Schwarting et al.[9] ||Branton et al.[24]

Lancet 2009; 374: 1986–96



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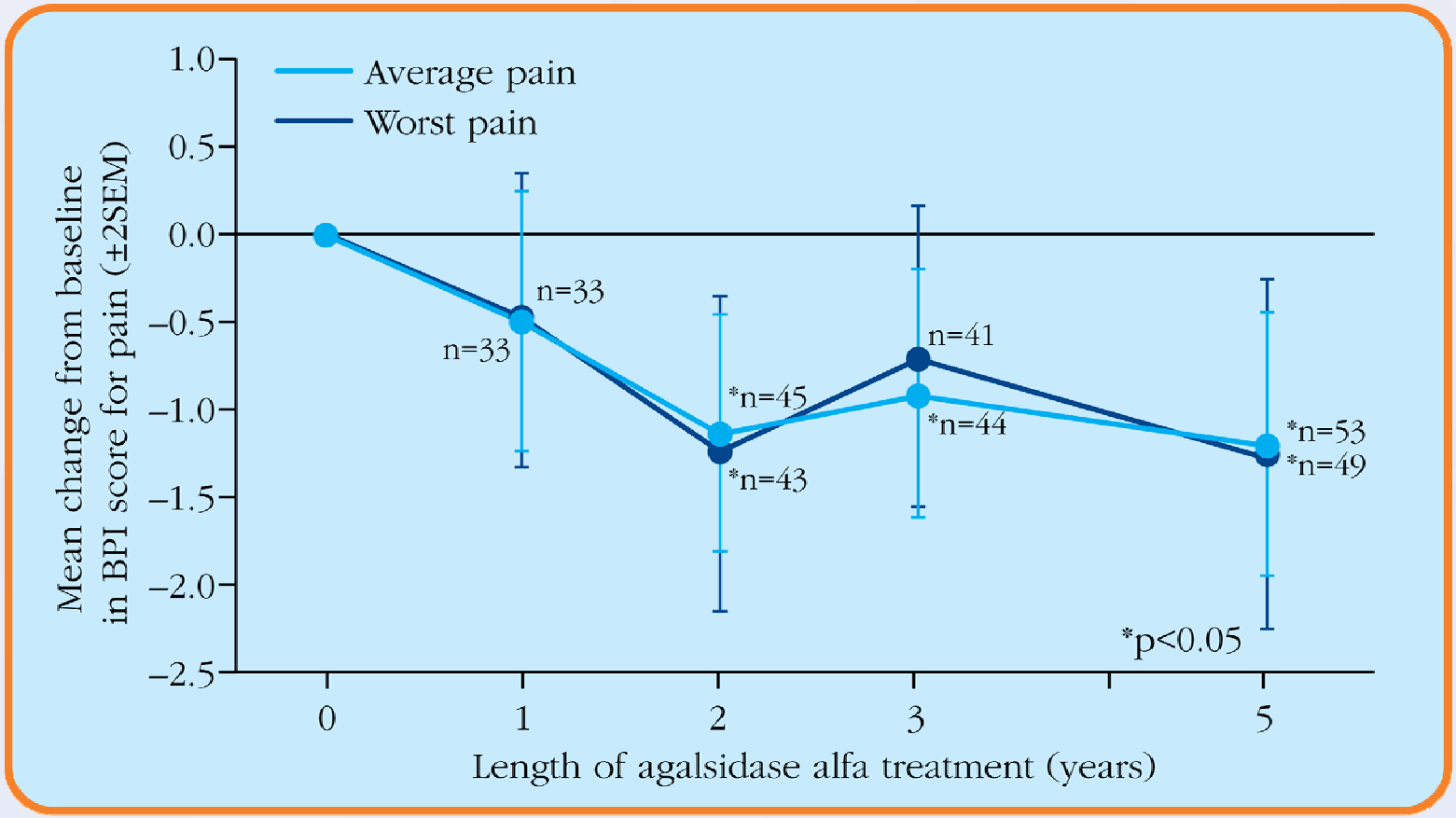
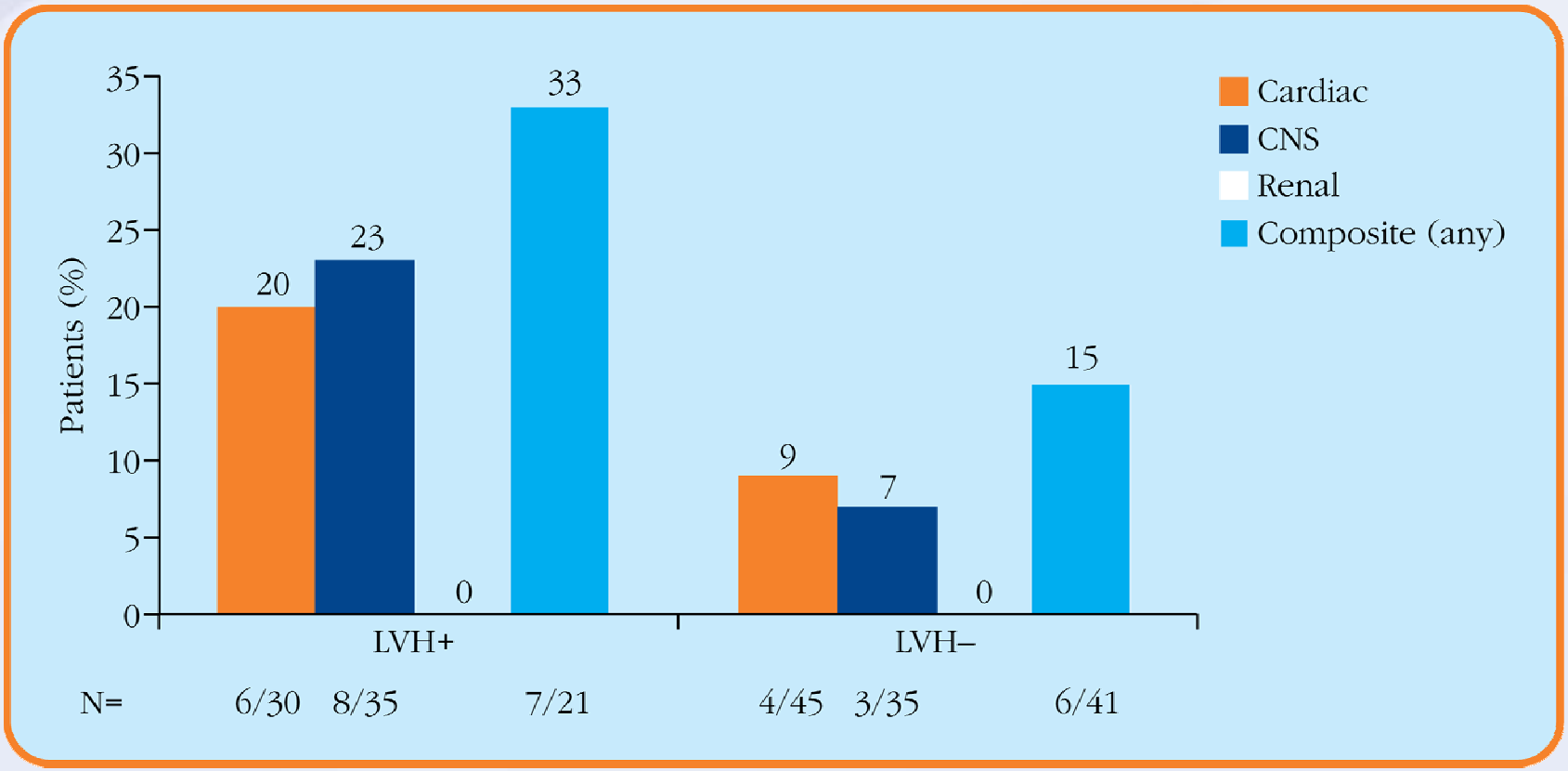


Lancet 2009; 374: 1986–96

	n	Mean baseline QoL deviation score	Mean QoL deviation score at year end	Mean change in QoL deviation score	p value*
Year 1	41	−0·24 (0·29)	−0·15 (0·26)	0·09 (0·25)	0·0247
Year 2	48	−0·24 (0·30)	−0·13 (0·23)	0·11 (0·23)	0·0026
Year 3	44	−0·25 (0·29)	−0·19 (0·25)	0·06 (0·24)	NS
Year 5	51	−0·24 (0·30)	−0·17 (0·28)	0·07 (0·25)	0·0483

Data are mean (SD) and are mean deviation scores from EuroQol values for the general population. Baseline values for each comparison are different because data were not available at every timepoint for all patients. QoL=quality of life. NS=not significant. *Paired *t* test, significance at p<0·05.

Lancet 2009; 374: 1986–96



La prevención de su aparición, así como el tratamiento de la HVI puede reducir la aparición de otras complicaciones de la EF

Lancet 2009; 374: 1986–96

The glass ceiling….?

- Poco acceso al SNC
- Es necesario determinar cuando se ha alcanzado el punto de “no retorno” en la afectación orgánica
- Algunos pacientes bajo TSE sufren otras complicaciones por progresión de la enfermedad
- Ausencia de un biomarcador fiable de severidad y de eficacia de tratamiento

Terapia génica…

- Valor potencial en pacientes con EF
- Hasta el momento no hay estudios prometedores en humanos
- Expresión a largo plazo de los genes transducidos
- Cuestiones de seguridad

Conclusiones

- La enfermedad de Fabry es una enfermedad de depósito lisosomal multisistémica, grave y progresiva que disminuye la calidad y esperanza de vida de quienes la padecen
- Supone un reto para el Internista identificar a los potenciales pacientes, mejorando su diagnóstico y liderando la atención clínica a los mismos

- La TRE ha supuesto una revolución en el manejo de estos pacientes, mejorando la afectación orgánica por la enfermedad así como su calidad de vida y posiblemente la historia natural
- Hay evidencia clínica que muestra la efectividad y seguridad de la TRE a largo plazo
- Los estudios apuntan conceptualmente al inicio precoz de la TRE, posible situación de beneficio máximo