SEMI

LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

FEMI

XXXI Congreso Nacional de la Sociedad Española de Medicina Interna

II Congreso Ibérico de Medicina Interna

OVIEDO

17-20 Noviembre 2010

Auditorio-Palacio de Congresos "Principe Felipe"

VII Congreso de la Sociedad Asturiana de Medicina Interna

¿EXISTEN LAGUNAS TERAPÉUTICAS EN EL TRATAMIENTO DE LA ENFERMEDAD DE GAUCHER?

¿QUÉ HAY DE NUEVO?

Pilar Giraldo
Hospital Universitario Miguel Servet

salud servicio aragonés de salud

Hospital Universitario Miguel Servet

Servicio de referencia para Estudio de Enfermedad de Gaucher y otras Lisosomales

Gobierno de Aragón

(BOA 13 Marzo 2006)

er(net) ciberer CENTRO DE INVESTIGACION BIOMEDICA EN RED DE ENFERMEDADES RARAS

FEETEG


GOBIERNO DE ARAGON
salud
servicio aragonés de salud

Grupo multidisciplinar que incluye investigadores básicos bioquímicos y biólogos moleculares e investigadores clínicos especialistas en Hematología, Neurología, Neurofisiología, Radiología, ORL, Atención Primaria, etc.

Investigar en Enfermedades Raras de Depósito Lisosomal es el principal objetivo del Grupo.

Desde 1993, hemos obtenido financiación en convocatorias competitivas del Fondo de Investigación Sanitaria

- Gobierno de Aragón
- Unión Europea
- Fondos privados

Desde 2008 el Grupo está integrado en el Centro de Investigación Biomédica en Red de Enfermedades Raras como la U-752 de CIBERER

Es un Grupo científico independiente y multidisciplinar

Mantiene el Registro Español de Enfermedad de Gaucher desde 1993, cuyas actividades están garantizadas por el cumplimiento de las normas ISO-9001-2000

Coordina el screening, diagnóstico, ensayos clínicos, tratamiento y seguimiento de pacientes con EG

Establece guías y recomendaciones para el diagnóstico y tratamiento de la enfermedad

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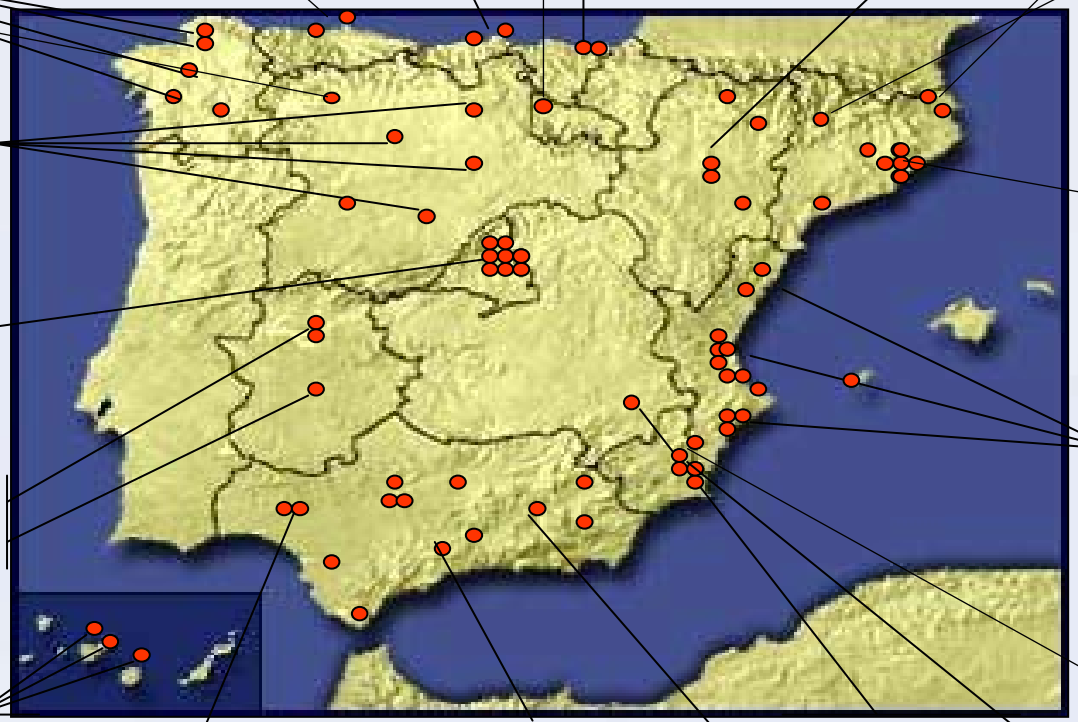
Hospitales



H. Juan Canalejo. A Coruña
H. Virxe da Junqueira
H. Montecelo. Pontevedra
H. Meixoeiro. Vigo
H. Xeral de Galicia

Complejo Hospitalario de León
H General Yagüe. Burgos
H. Clínico Universita Salamanca
H. Río Hortega. Valladolid
H. Ntra. Sra. de Sónsoles. Ávila
H. Virgen de la Concha. Zamora

H. Universitario 12 de Octubre
H. Universitario San Carlos
H. Universitario La Paz
H. Universitario Ramón y Cajal
Hematoclin Médico S.L.
Clínica Santa Elena
H. Gregorio Marañón
H. San Rafael

H. San Pedro de Alcántara
H. Virgen del Puerto. Plasencia
H. Infanta Cristina. Badajoz

H. Universitario de Canarias
H. Ntra. Sra. de la Candelaria
H. Ntra. Sra. del Pino

H. Jerez de la Frontera
H. Puerta del Mar. Cádiz
H. Punta Europa. Algeciras
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H. Virgen Macarena. Sevilla
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H. Motril. Granada

H. Carlos Haya. Málaga
H. Virgen de la Victoria. Málaga
H. General Básico de Ronda
H. Costa del Sol. Málaga

Complejo Hospitalario de Albacete:
H. Santa Mª del Rosell. Murcia
H. General Universitario. Murcia
H. Rafael Méndez
H. Virgen de la Vega
H. Virgen de la Arritxaca

H. Virgen de la Luz. Cuenca

H. de Sagunto
H. General de Elda
H. Universitario La Fe
H. Dr. Peset
H. Fransesc de Borja
H. General de Valencia
H. Clínico de Valencia
H. Lluis Alcanys. Játiva
H. General de Alicante
H. Vega Baja. Alcoy
H. General Universitario. Elche
H. San Vicente. Alicante
H. Marina Baixa. Villajoyosa

H. Universitario Miguel Servet. Zaragoza
H. Universitario Lozano Blesa. Zaragoza
H. San Jorge.
H. de Barbastro. Huesca
H. de Alcañiz. Teruel

H. Marqués de Valdecilla. Santander
Centro de Salud Castro Urdiales

H. Central de Asturias. Oviedo
H. de Cabueñes. Gijón

H. de Galdakao. Bilbao
H. de Cruces. Bilbao

Complejo Hospitalario San Millán. Rioja

H. U. Josep Trueta. Gerona
Hospital Palamós

H. Arnau de Villanova. Lérida

H. Universitario Bellvitge
H. San Juan de Dios
H. Universitario Vall d'Hebrón
H. Clinic i Provincial
H. del Mar
H. General de Manresa
C. Hospitalario Parc Tauli
H. Mutua de Tarrasa
H. San Joan. Reus

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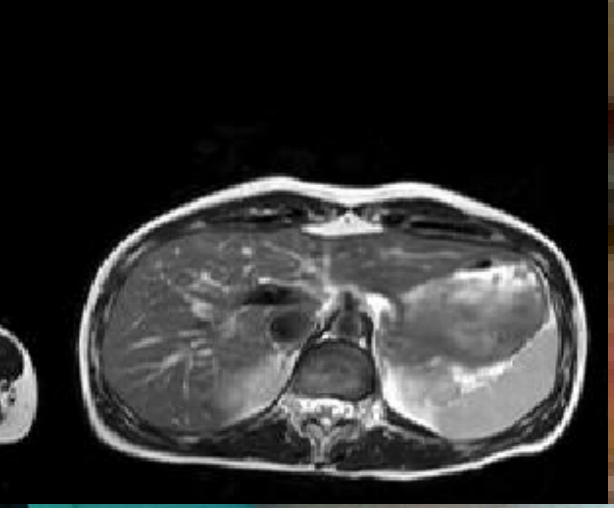

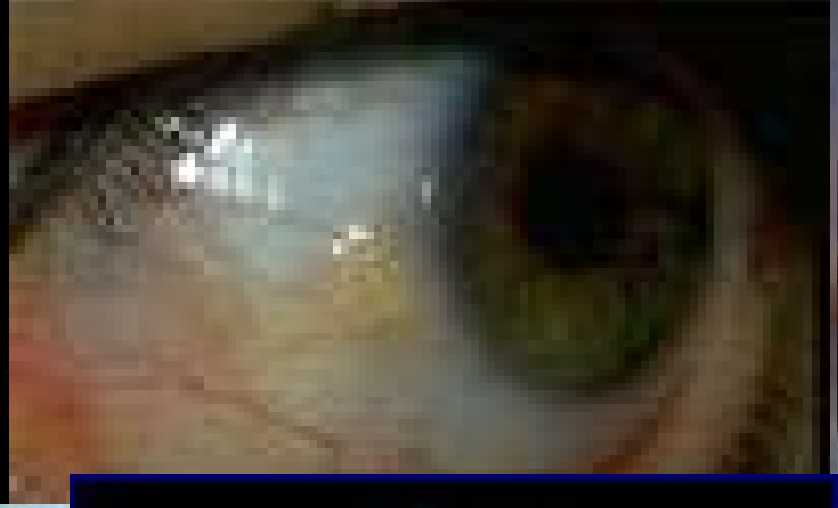

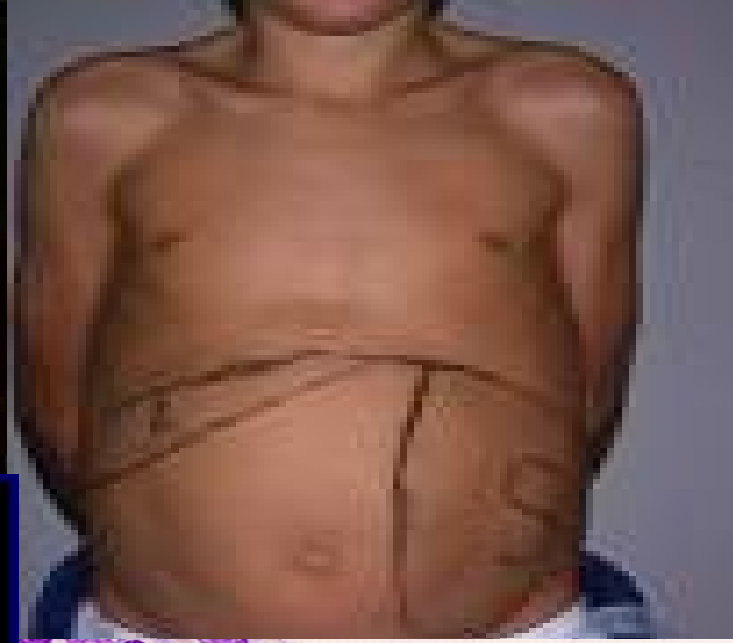

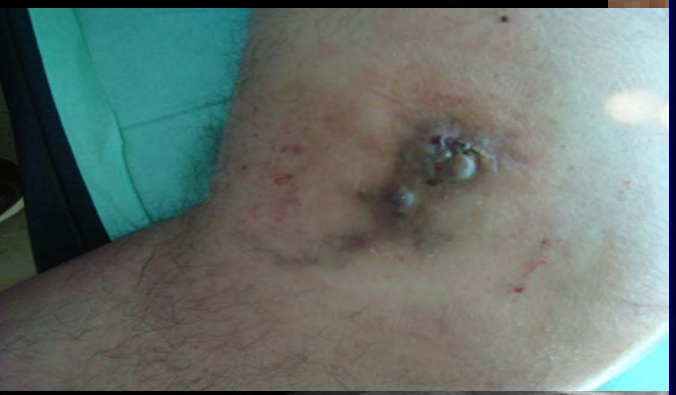

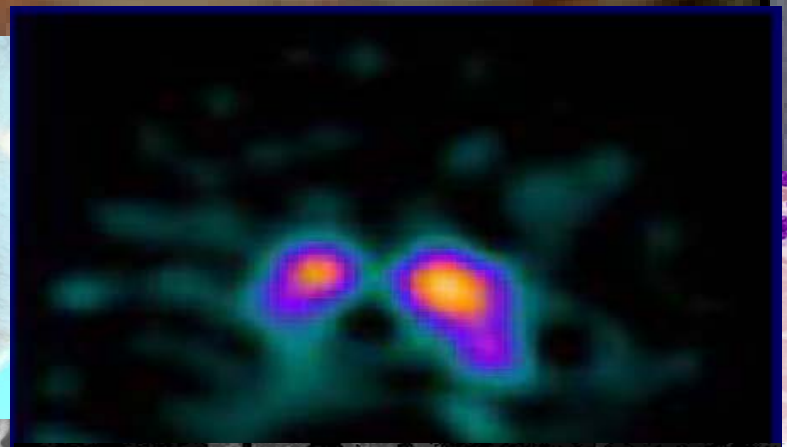

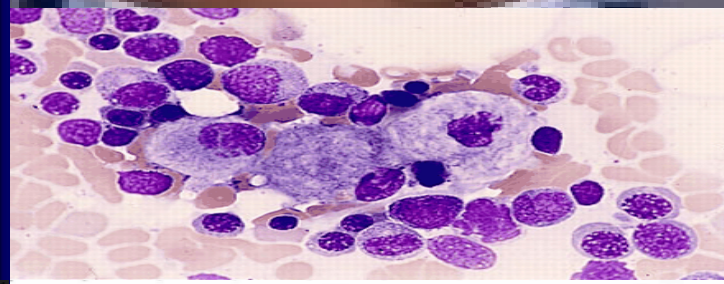

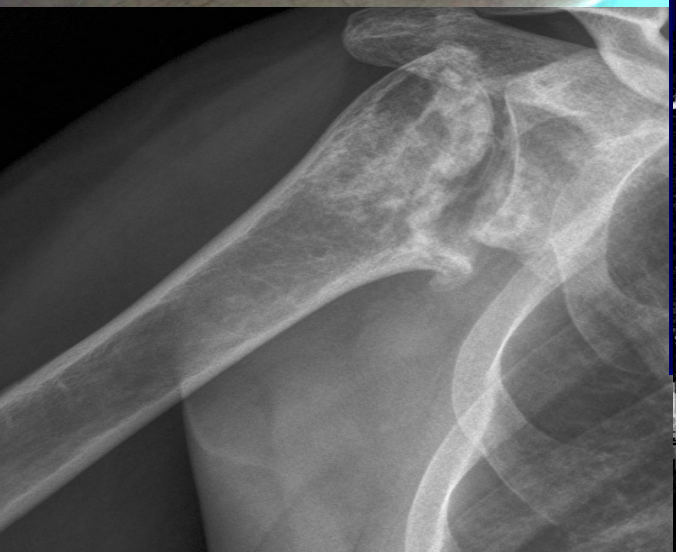

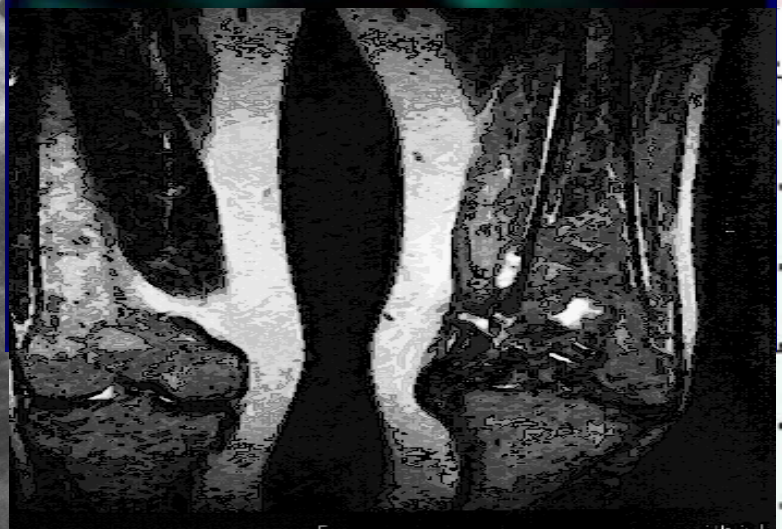


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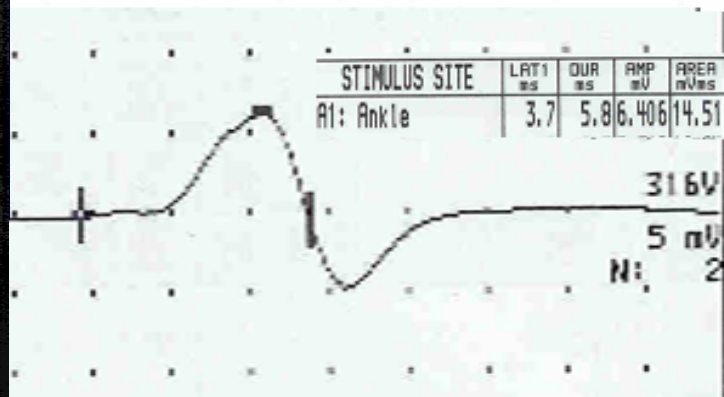
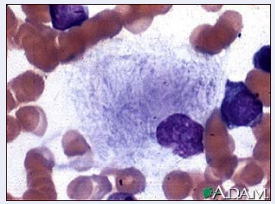
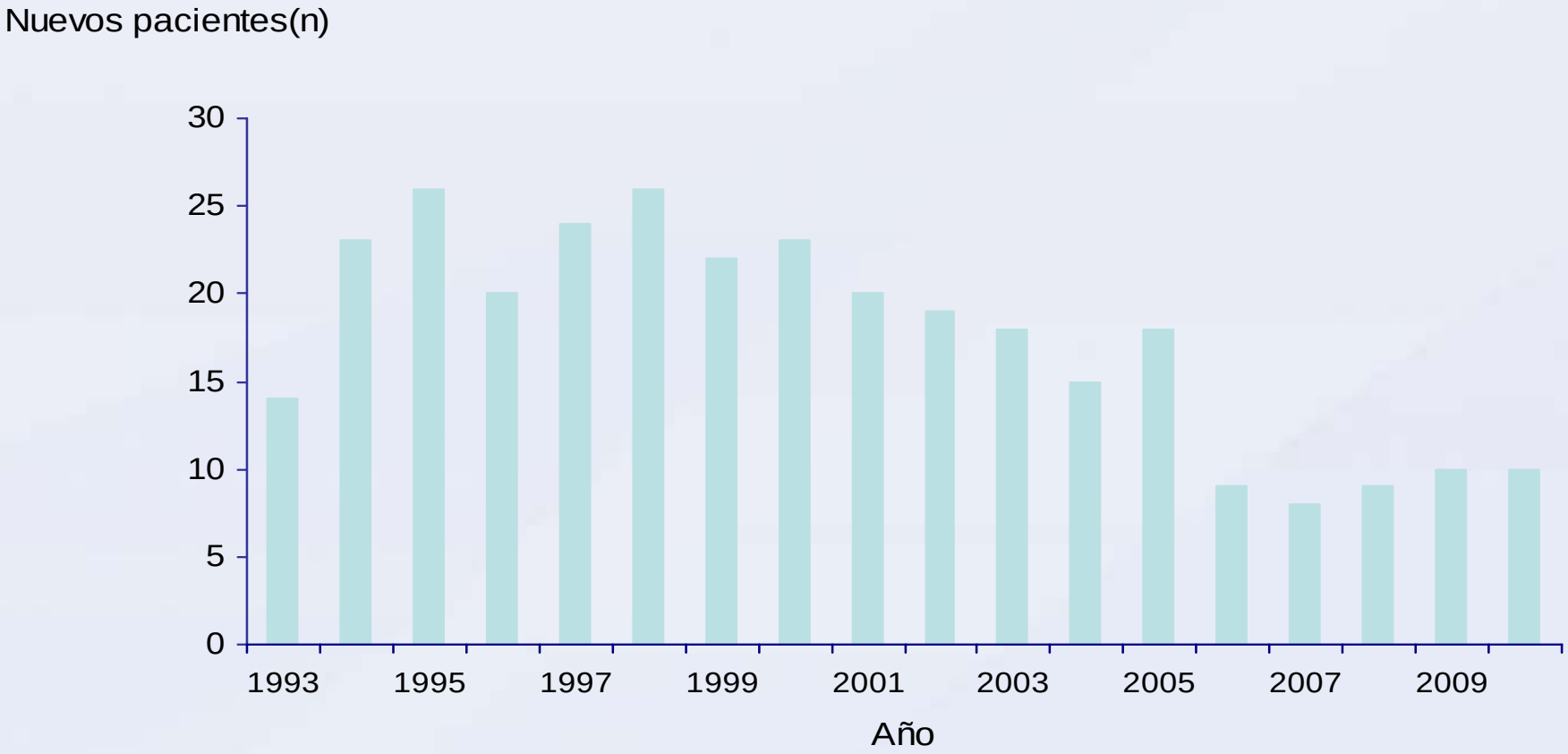

STIMULUS SITE
LAT1 ms
DUR ms
AMP mV
AREA mVms
A1: Ankle
3.7
5.8
6.406
14.51
316V
5 mV
N:

- Enfermedad genética heterogénea
- Correlation genotipo-fenotipo imperfecta



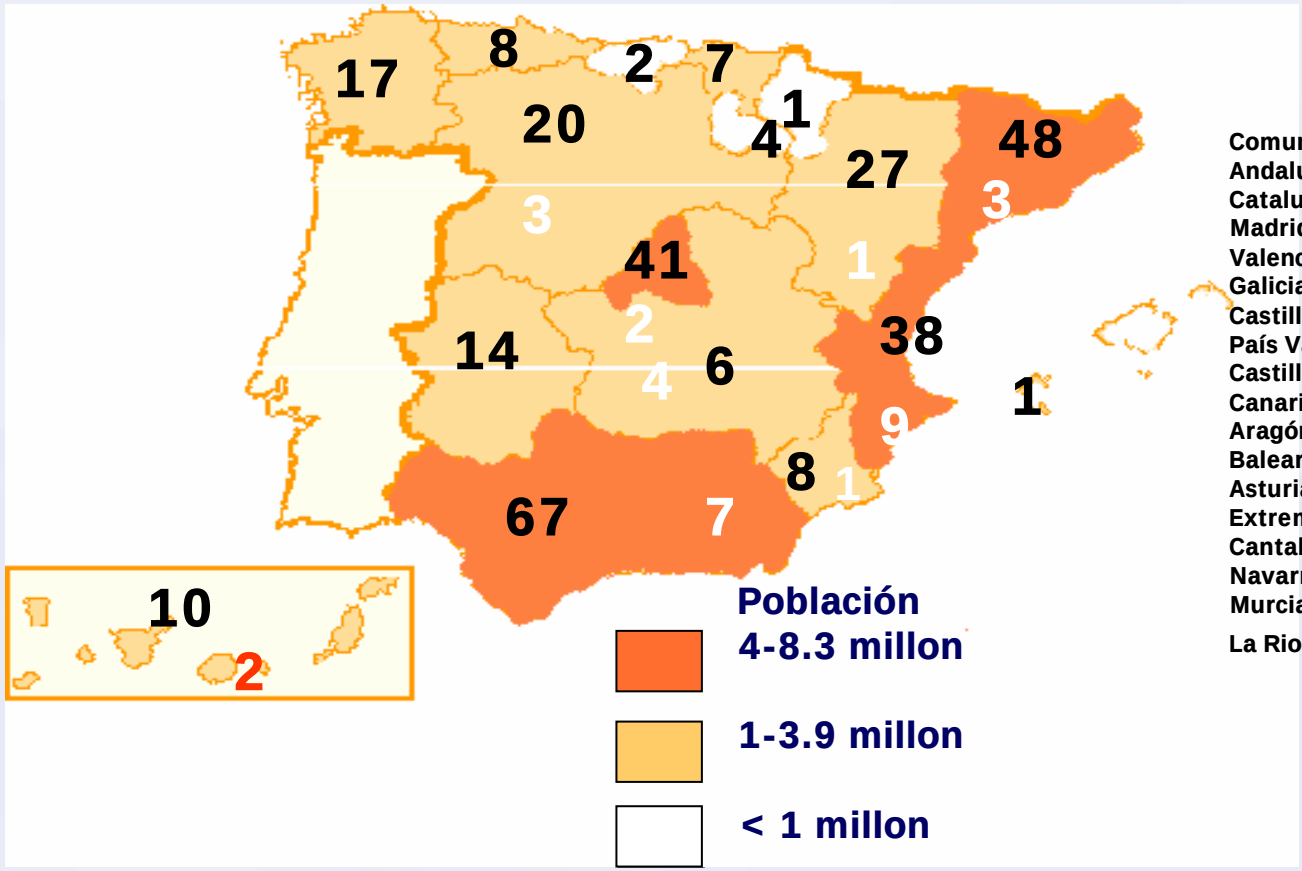
- Enfermedad crónica, degenerativa e invalidante
- No curable con los procedimientos médicos disponibles
- El tratamiento enzimático sustitutivo supuso una revolución a principio de los 90’s, ha mejorado la calidad de vida de los pacientes, pero no es capaz de resolver todos los problemas que plantea la enfermedad ni prevenir complicaciones.

REGISTRO ESPAÑOL DE ENFERMEDAD DE GAUCHER



Está sometido a la normativa legal y registrado con el nº 1971180032.
Acreditación de calidad según las Normas ISO2000-9001 Num. EC2751/07.

REGISTRO ESPAÑOL DE ENFERMEDAD DE GAUCHER



Comunidad Autónoma	Nº	TI x10^5	Población*
Andalucía	74	0,9	8.353.843
Cataluña	51	0,7	7.475.420
Madrid	43	0,4	6.271.638
Valencia	47	1,0	5.029.601
Galicia	17	0,4	2.784.169
Castilla-León	23	0,7	2.560.031
País Vasco	7	0,3	2.141.860
Castilla-La Mancha	10	0,4	2.095.855
Canarias	13	0,3	2.103.992
Aragón	28	1,4	1.345.473
Baleares	1	0	1.100.000
Asturias	8	0,6	1.058.923
Extremadura	14	1,1	1.097.744
Cantabria	2	0,4	589.235
Navarra	1	0,4	530.819
Murcia	9	0,4	436.870
La Rioja	4	1,5	321.702

*INE Población a 1 enero 2009

Familias	274
Pacientes	353
Portadores	708

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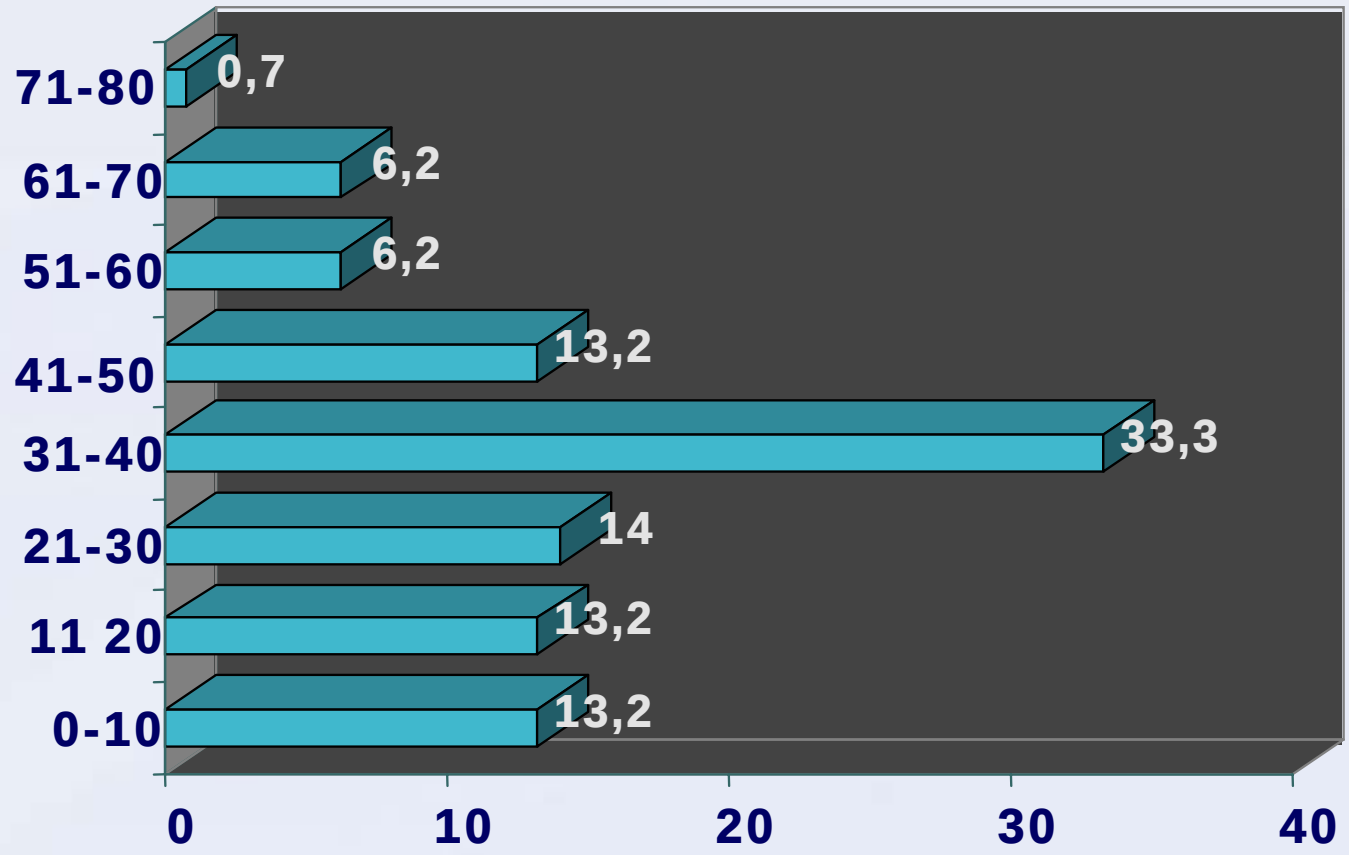
REGISTRO ESPAÑOL DE ENFERMEDAD DE GAUCHER

Edad al diagnóstico



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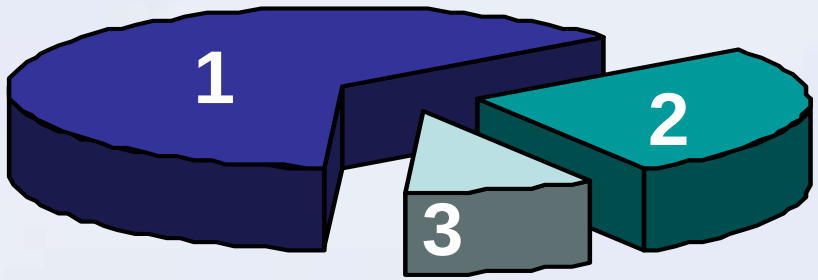
De la información recogida en el Registro Español de la Enfermedad, conocemos que
de los 353 casos registrados desde 1993

Tipos

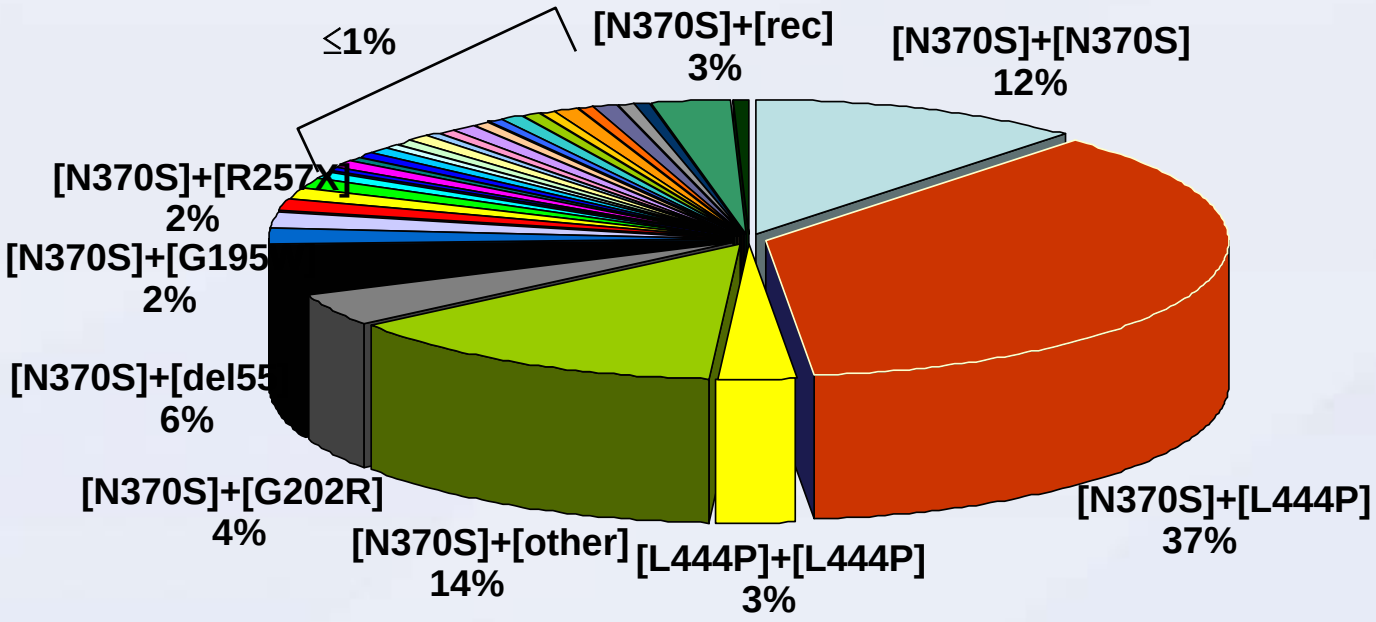


309: 87,6%

19: 5,1%

25: 7,6%

Genotipo de la Enfermedad de Gaucher en España



≤1%
[N370S]+[Y313H]
[G377S]+[G377S]
[N370S]+[c.1098insA]
[N370S]+[c.1392del3]
[N370S]+[E326K;N188S]
[N370S]+[c.500insT]
[N370S]+[c.953delT]
[N370S]+[G113E]
[N370S]+[G325W]
[N370S]+[G377S]
[N370S]+[IV5+1g>t]
[N370S]+[L336P]
[N370S]+[M123T]
[N370S]+[N188S]
[N370S]+[Q169X]
[N370S]+[R257Q]
[N370S]+[R359Q]
[N370S]+[R463C]
[N370S]+[S364R]
[N370S]+[S364N]
[N370S]+[Y412H]
[N370S]+[T134P]
[N370S]+[P391L]
[N370S]+[c.1451-1452delAC]
[N370S]+[IVS4-2a>g]
[N370S]+[R120W]
[N370S]+[RecNciI; c.1263-1317del55]

94,3 tienen N370S

Alfonso P et al J Human Genet 2007

Registro Español de EG

REGISTRO ESPAÑOL DE ENFERMEDAD DE GAUCHER

Genotipo	No (%)	Mujeres %	Edad al Dx	SSI	S-MRI	Esplenectomía (%)	Citopenia (%)	TES (%)
N370S/N370S	39 (12.7)	58.9	**42.2** 2-82	**5.3** 1-13	**3.3** 0-8	**10.7**	**3.5**	**41.0**
N370S/otro	217 (71.1)	50.7	25.7 0.5-77	7.3 1-22	8.7 0-21	27.3	21.2	87.5
otro/otro	49 (16.0)	**38.7***	16.5 0-60	9.7 2-30	7.6 0-14	26.9	23.5	95.9

•p=.001

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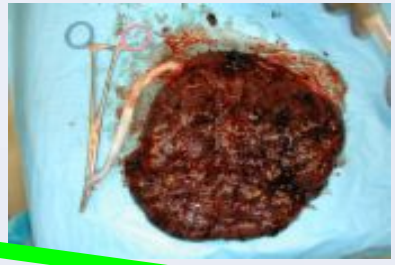
Enfermedad de Gaucher

Edad al diagnóstico	3ª decada
Portadores de N370S	94,3 %
Visceromegalias	95,6 %
Enfermedad ósea	70,4 %
Enfermedad de Parkinson	8,1 %
Neuropatía periférica	10,9 %
Sin tratamiento	20,1 %
Esplenectomía	28,1 %
Cirugía ortopédica	27,5 %

Registro Español de EG

TRATAMIENTO ENZIMATICO SUSTITUTIVO

1990 Alglucerase Genzyme

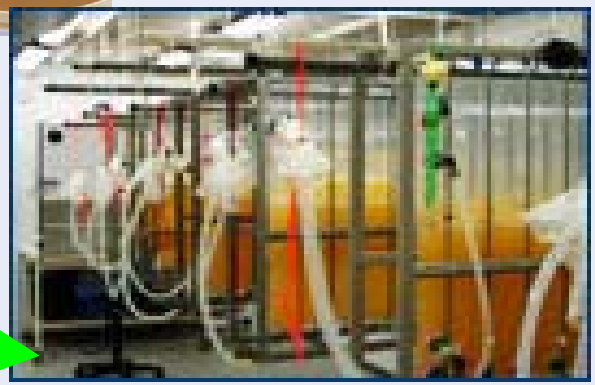


1995 Imiglucerase

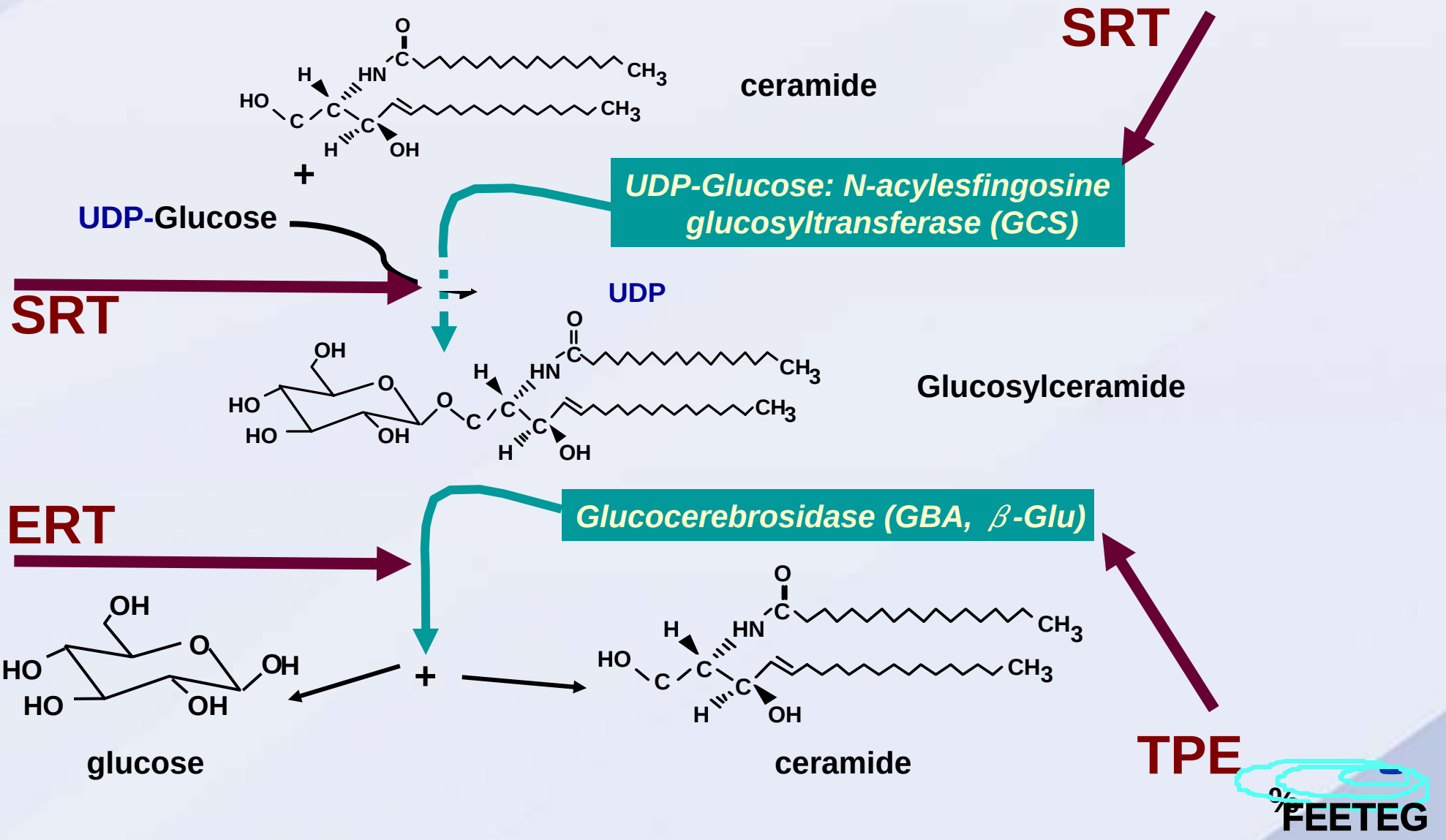
2003 Gene-Activated® Human Glucocerebrosidase (GA-GCB)

Velaglucerase TKT/Shire

2006 Plant Cell Expressed Recombinant Human Gluco-cerebrosidase (prGCD)
Taliglucerase Protalix/Pfizer



ENFERMEDAD DE GAUCHER.TRATAMIENTO



Open Access Publication

Haematologica the hematology journal

Official Journal of the European Hematology Association

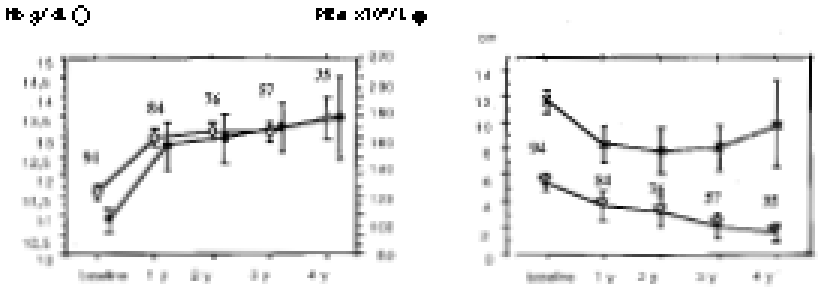
Haematologica 2000; 85:782-788
original paper

Phagocytes & Lymphocytes

Report of the Spanish Gaucher's Disease Registry: clinical and genetic characteristics

PILAR GIRALDO, MIGUEL POCOVI,* JUAN I. PÉREZ-CALVO,* DANIEL RUBIO-FELIX, MANUEL GIRALT ON THE BEHALF OF SPANISH GAUCHER'S DISEASE REGISTRY

Department of Hematology, Miguel Servet University Hospital, *Department of Internal Medicine, Lozano Blesa University Hospital, °Department of Biochemistry, Molecular and Cellular Biology, University of Zaragoza, Zaragoza, Spain



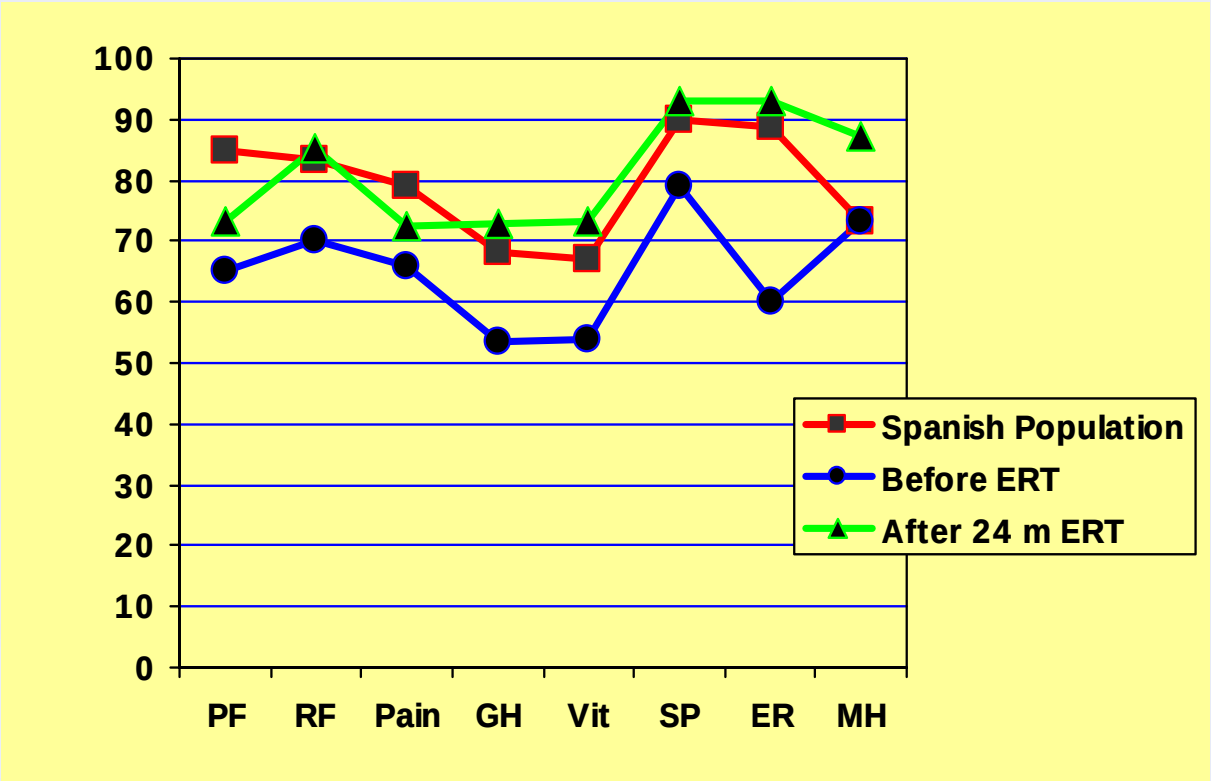
p value	Hb	Platelets	p value	Liver	Spleen
Baseline vs 1y	<.0001	<.0001	Baseline vs 1 y	<.0001	.0035
Baseline vs 2 y	<.0001	<.0001	Baseline vs 2 y	.0023	.0063
Baseline vs 3y	.0001	.0001	Baseline vs 3 y	.0002	.0064
Baseline vs 4 y	.0369	.0109	Baseline vs 4 y	.0069	.0043
1y vs 2y	.0191	.0268	1y vs 2y	.0271	.0035
2y vs 3y	.0951	.1178			
3y vs 4y	.4367	.0931			

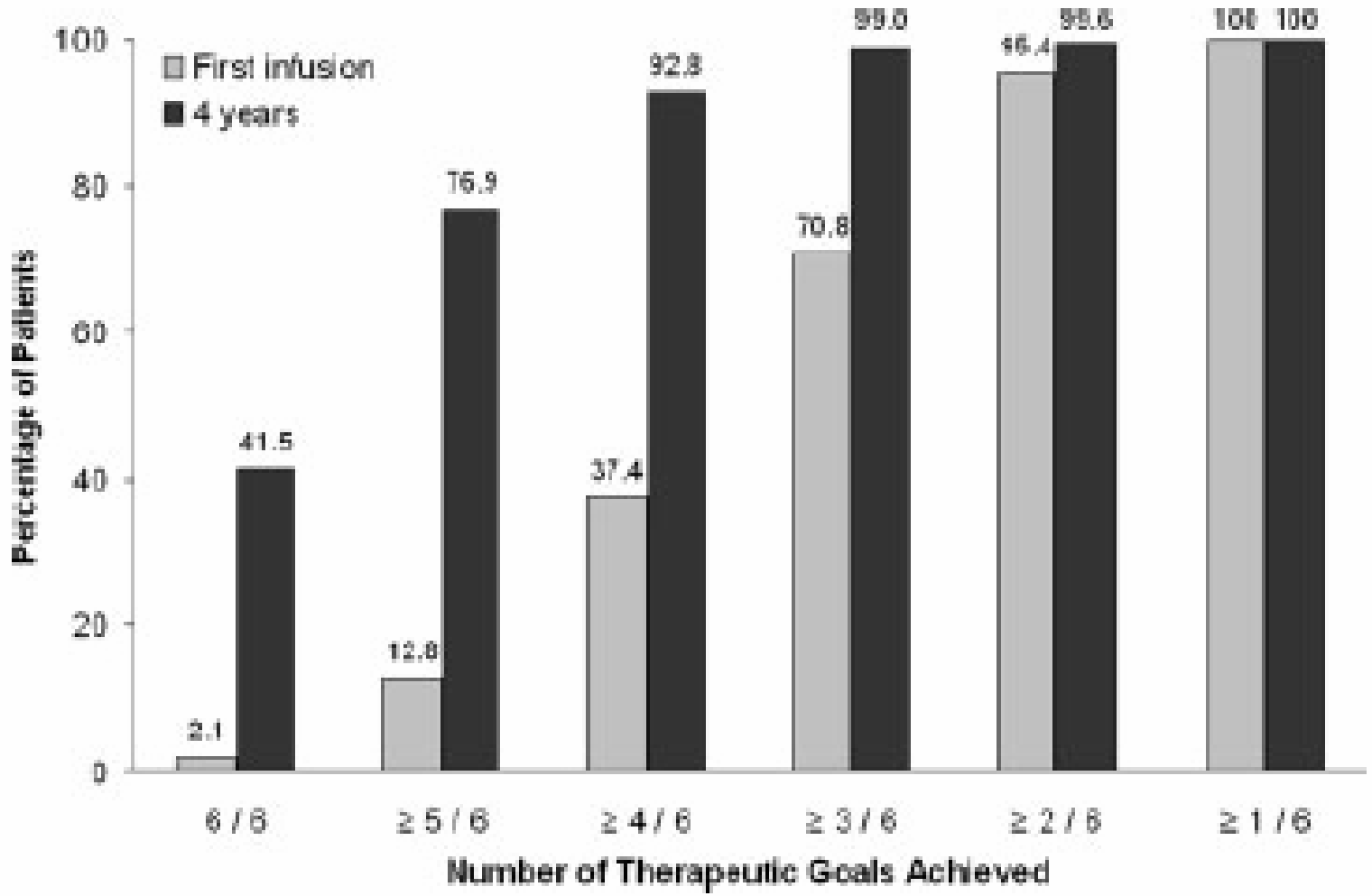
Figure 4. ERT, variation in clinical and hematologic parameters.

Qual Life Res. 2005 Mar;14(2):453-62.

Quality of life related to type 1 Gaucher disease: Spanish experience.

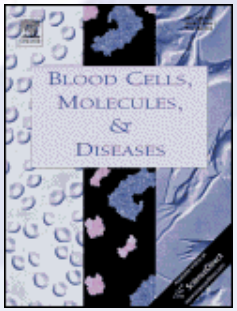
Giraldo P, Solano V, Pérez-Calvo JI, Giralt M, Rubio-Félix D; Spanish Group on Gaucher disease.





195 patients

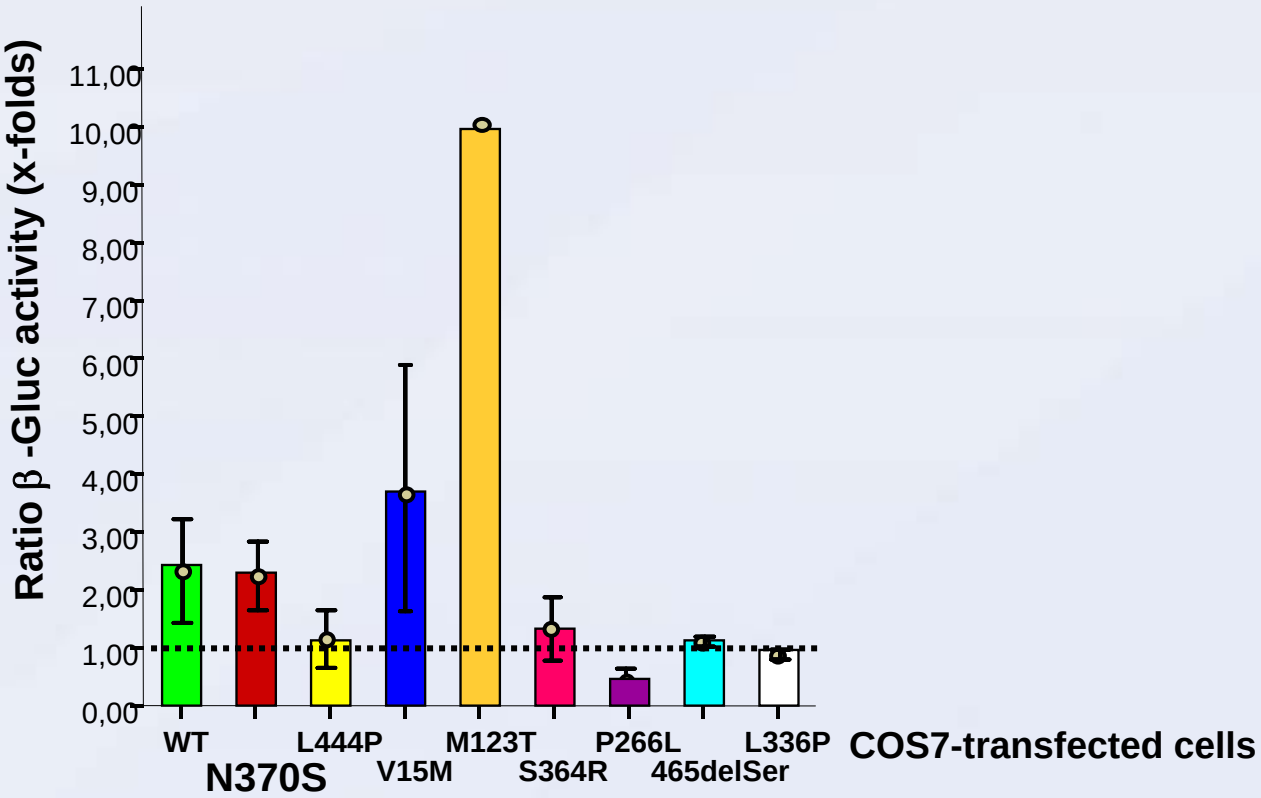
Weinreb N. Am J Hematol 2008

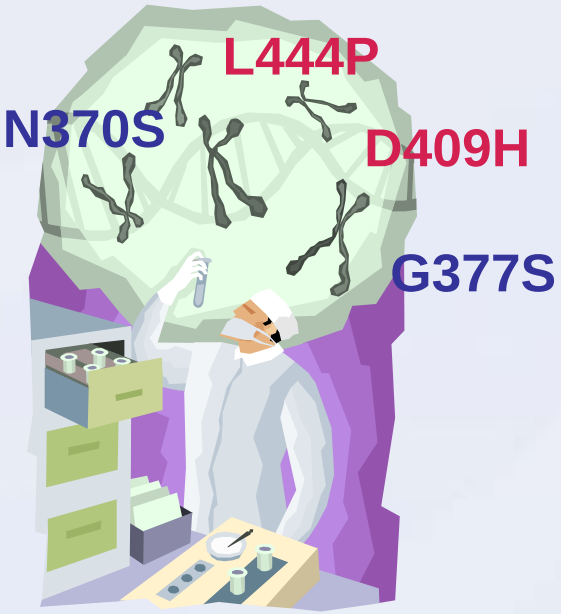


Blood Cells Mol Dis. 2005 Sep-Oct;35(2):268-76.

Miglustat (NB-DNJ) works as a chaperone for mutated acid beta-glucosidase in cells transfected with several Gaucher disease mutations.

Alfonso P, Pampín S, Estrada J, Rodríguez-Rey JC, Giraldo P, Sancho J, Pocoví M.



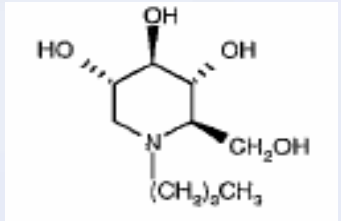


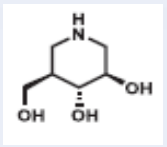
Genotipo

El tipo de mutación influye en la actividad enzimática residual, y por tanto en la cantidad de material acumulado y gravedad de la enfermedad.

TRATAMIENTO POR REDUCCION DE SUSTRATO

iminosugar obtained from leaves of *Morus alba*





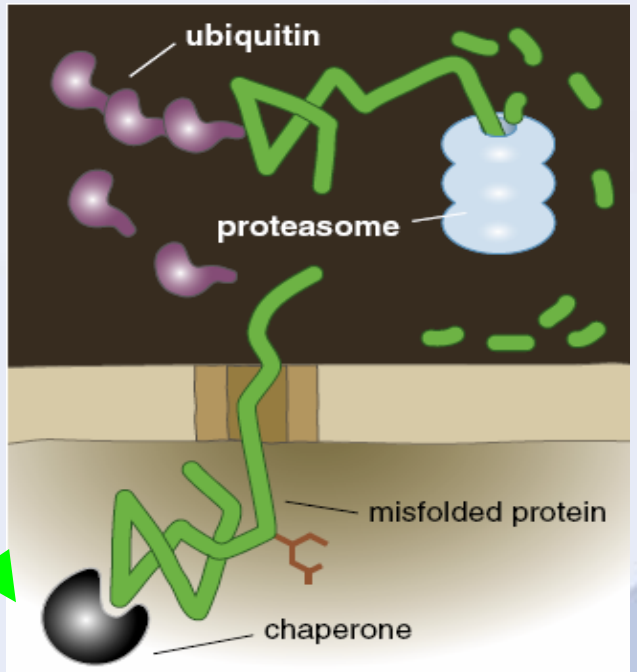
Pharmacological Chaperones

Sphingomyelin ← **Ceramide** → Galactosylceramide

Miglustat Zavesca → ***Glucosylceramide sintasa***

Glucosylceramide

Ganglio series | ***Lacto (neo) series*** | **Globo series**



ZAGAL (**Za**vesca en **Ga**ucher **L**eve)

Trás la aprobación de miglustat en la UE (2004)

- Diseño y objetivos
  - Establecer un protocolo asistencial para recoger de forma homogénea los datos de seguridad, eficacia y calidad de vida en los pacientes tratados al menos durante un año, en práctica clínica habitual.
  - Garantizar la seguridad y utilización apropiada de miglustat en un protocolo de práctica clínica habitual.

Tratamiento

- Siguiendo las recomendaciones del European Working Group on Gaucher Disease Advisory Council

Giraldo P et al Haematologica 2006

ZAGAL Study

Study period: May 2004 - April 2009

Baseline assessment

Complete clinical exam	X
Blood counts	X
Biochemical and other analytical data	X
Imaging evaluation (MRI, DEXA, plain Xray	X
Detailed neurological exam and superficial electroneurogram in sural and peroneal nerves	X
Cognitive test and memory impairment screen for dementia assessment	X

RECOMMENDATION: A low carbohydrate diet (i.e: sucrose, maltose, starch…) during first weeks on therapy

ZAGAL Study. Baseline characteristics

Study period: May 2004 - April 2009		
Characteristics	Naïve=1 1	
Male, n (%)	4	30
Female, n (%)	7	70
Age, mean years±SD	46.4	±16.9
Age at diagnosis, mean years±SD	37.4	±17.7
Severity score index, mean (range)	5.8	1-9
Hb g/dL, mean ±SD	10.8	1.2
Platelets x10^9/L, mean ±SD	90.0	20.0
Spleen cm, mean ±SD	5.0	2.0

Data from naïve patients treated by miglustat or ERT (6 m)

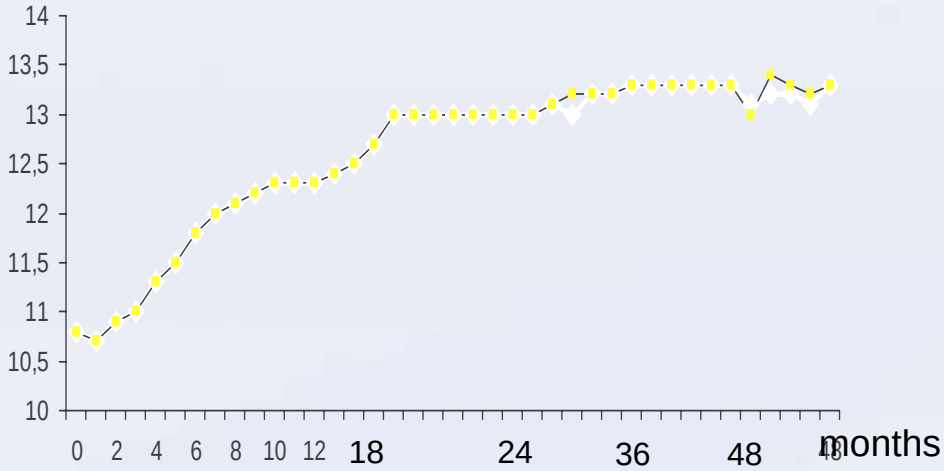
	Miglustat n=11	ERT* n=40	P
Patient characteristics			
Age, mean (range) years	46.7 (21-74)	37.4 (17-52)	0.021
Gender M/F	4/7	19/21	-
SSI, mean (range)	5.80 (4-9)	6.80 (1-10)	0.683
Genotype N370S or G377S (%)	100	100	-
Prior spleen removal	2	0	-
Disease markers			
Spleen, mean ↓ (cm)	9.2 (1.5-18)	4.2 (0-8.0)	0.308
Liver, mean ↓ (cm)	0.2 (0-10)	4.3 (1.6-5.7)	0.014
Hb, mean ↑ (g/dL)	0.77 (0.2-1.8)	0.81 (0-4.0)	0.856
Platelets, mean ↑ (x 10^9/L)	41.5 (10-116)	32.7 (0-95)	0.324
CT activity , mean ↓ (%)	38.2 (20.6-42.8)	42.8 (0-80.2)	0.136

REMARKS: Efficacy of SRT results at 6 months are comparable to those observed in patients treated with ERT for 6 months

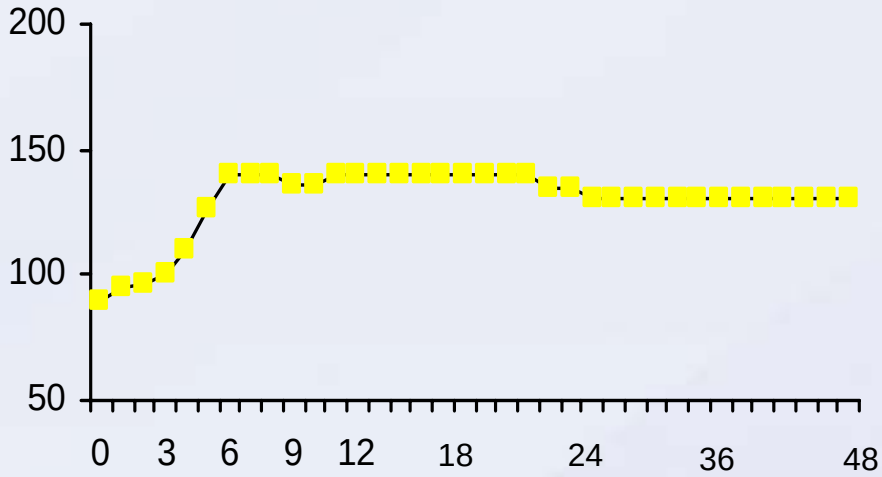
Giraldo P et al. *Haematologica* 2006;91:125-28

GD1 patients on miglustat. Follow-up to 48 months

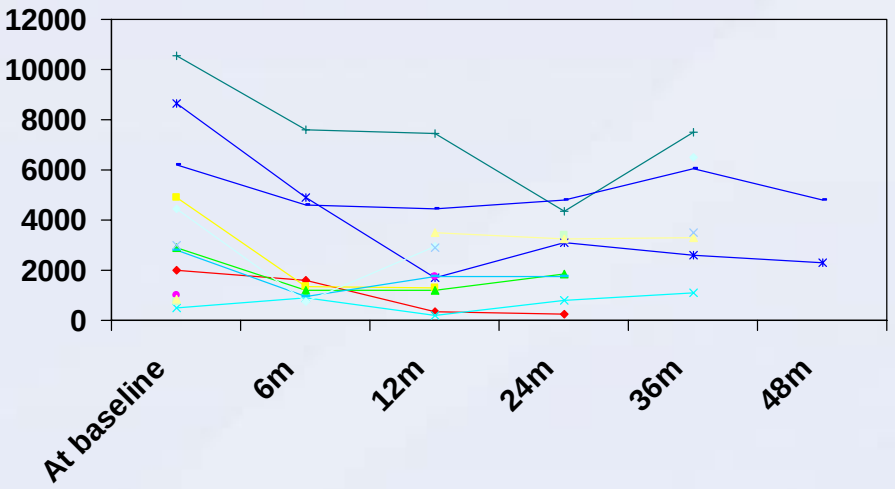
Hb g/dL



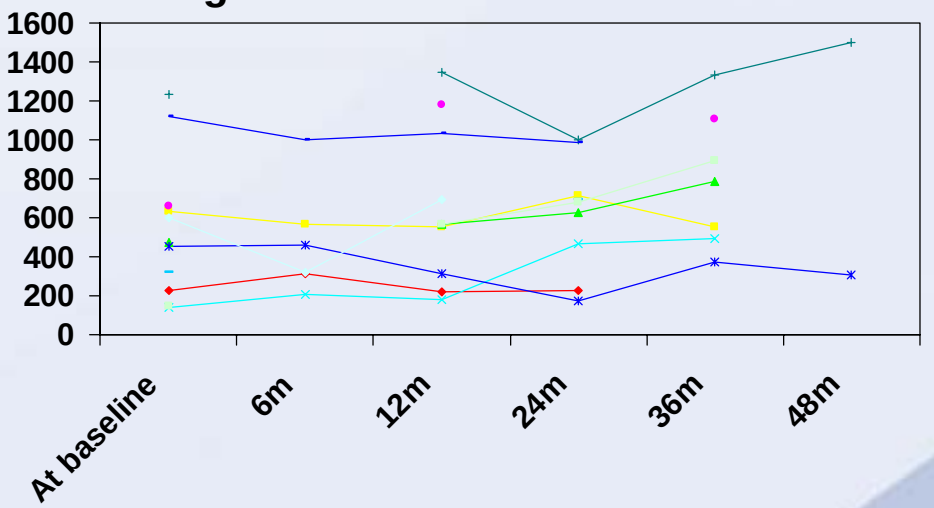
Platelets x 10^9/L



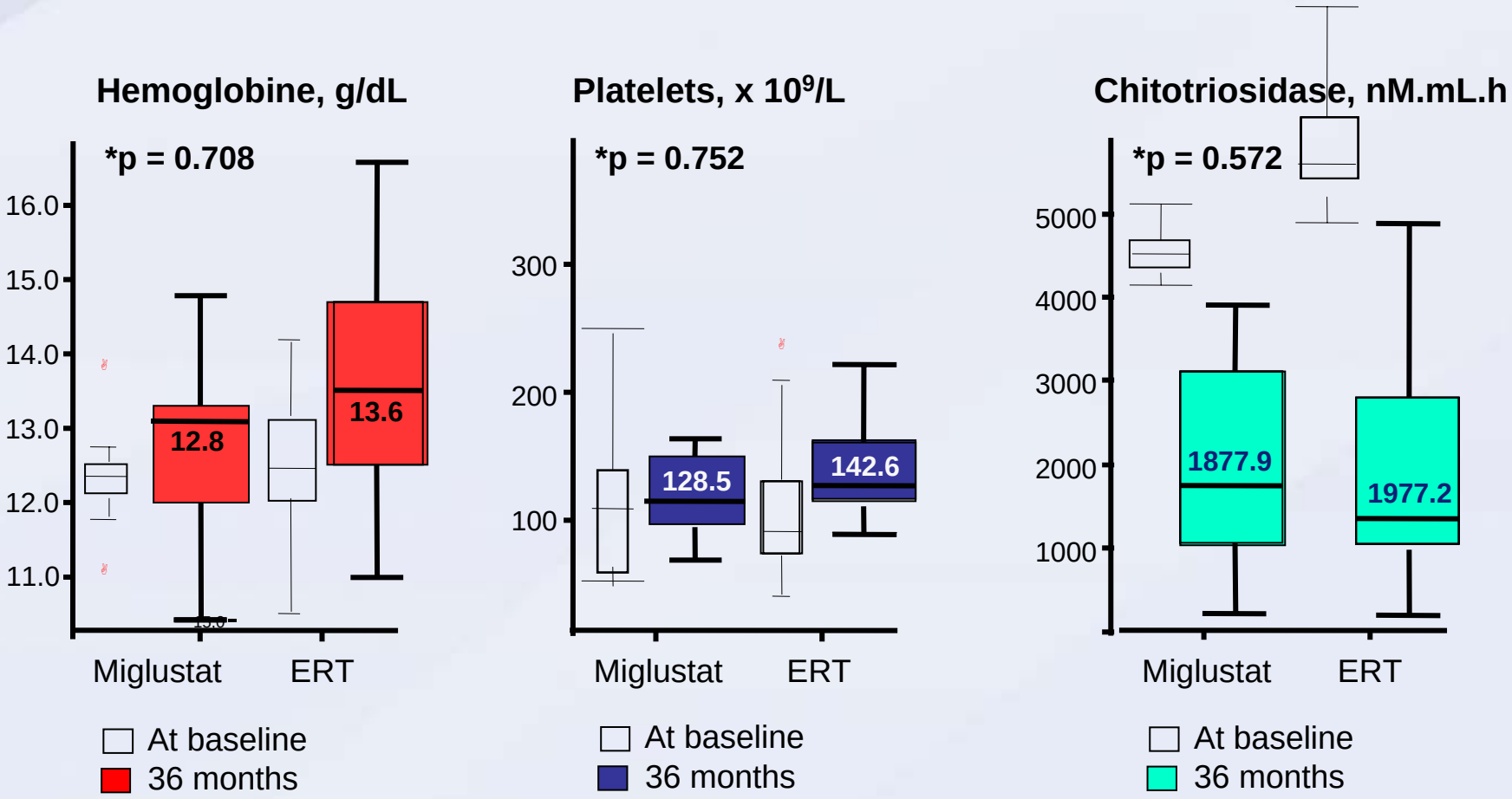
CT nM/mL.h



CCL-18 ng/mL

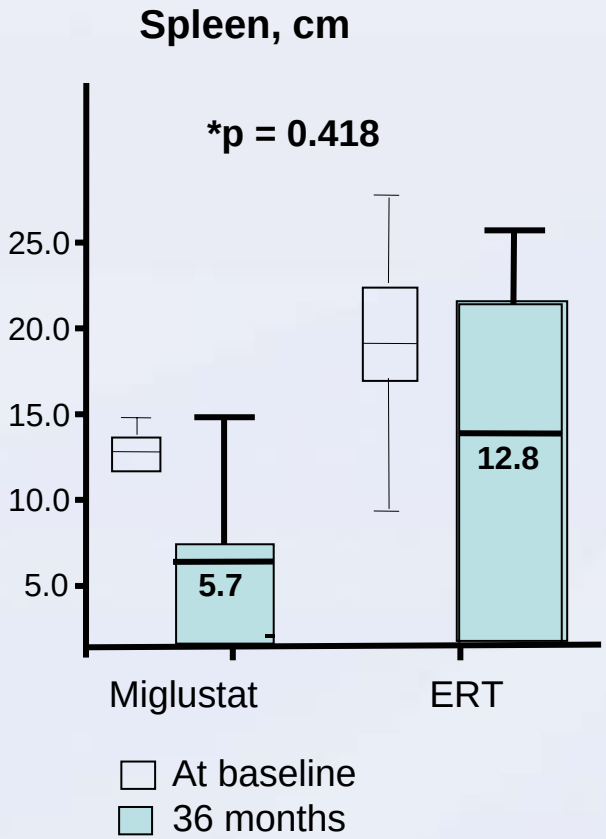


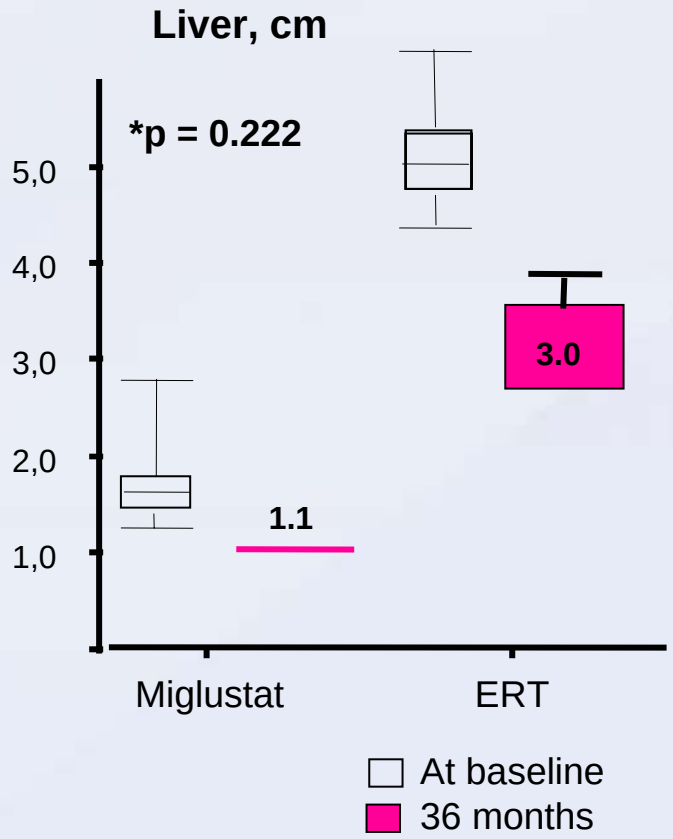
Data from naïve patients treated by miglustat (10) or ERT (29) during 36 months



REMARKS: Naïve patients with similar characteristics at 36 months on ERT or SRT do not showed significant differences in the outcomes related therapy

Data from naïve patients treated by miglustat (10) or ERT (29) during 36 months





Desabastecimiento de Imiglucerasa

Desde Junio 2009, como consecuencia del desabastecimiento de imiglucerase por problemas de fabricación se han producido modificaciones en el tratamiento de los pacientes con EG.

En Septiembre 2009, el EWGGD trás una reunión de consenso estableció unas recomendaciones para identificar y monitorizar a los pacientes con mayor riesgo de sufrir progresión o complicaciones.

Desabastecimiento de Imiglucerasa

En España hemos recogido los datos de seguimiento de 50 pacientes con EG tipo 1 y realizado análisis previo y tras 6 meses de desabastecimiento, con el objetivo de observar y obtener un perfil de la situación.

Se han excluido del análisis a los niños, pacientes que han pasado a otro tipo de tratamiento enzimático o a tratamiento oral.

Desabastecimiento de Imiglucerasa

	No	%	Mean ±SD	Max	Min
Age years			45.3±15.3	84	18
SSI at Dx			8.7±3.8	19	3
CT activity nM/mL.h			13,383±12,783	54,780	0
CCL18/PARC ng/mL			776±1,198	3,895	50
Gender M/F	25/25	50/50			
Previous spleen removal	11	20.8			
Previous Bone disease	39	78.0			
Genotype: N370S/N370S N370S/other Other/other	 5 42 3	 10 84 6			

Giraldo P et al Blood Cells Mol Dis 2010

Desabastecimiento de Imiglucerasa

ERT	50% reduction (N=17)					Discontinuation (N=23)				
	No	%	Mean ±SD	Max	Min	No	%	Mean ±SD	Max	Min
Years of ERT			10.3±3.3	15	4			10.1±4.1	15	1
Dose (eow)			34±10	60	20			45±17	60	10
SSI before ERT			7.6±3.2	14	3			9.8±4.5	19	5
Previous orthopedic procedures	4	23.5				13	56.5			
Previous spleen removal	6	35.3				3	13.0			
Bone crisis during withdrawal	7	41.2				1	4.3			
Support therapy during withdrawal	4	23.5				4	17.4			
Genotype: N370S/N370S N370S/Other Other/Other	 1 15 1	 5.8 88.2 5.8				 2 18 3	 8.7 78.3 13.0			

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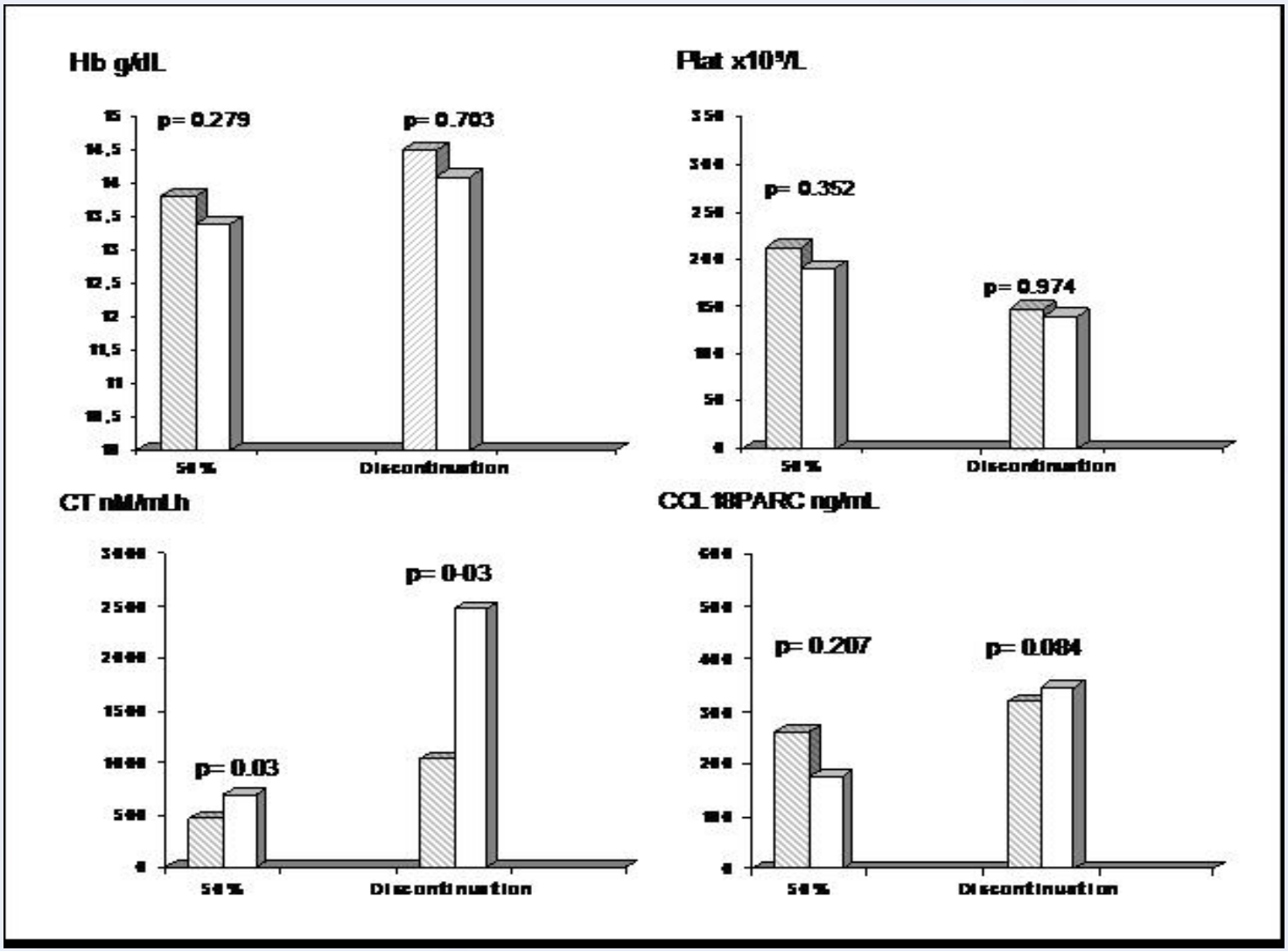
Desabastecimiento de Imiglucerasa



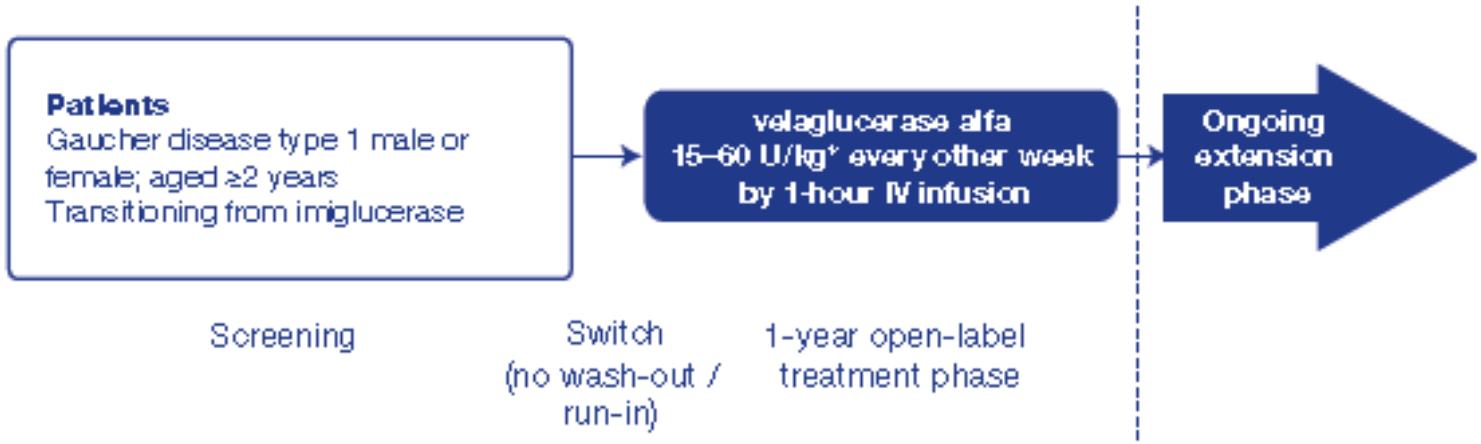
Giraldo P et al Blood Cells Mol Dis 2010

CLINICAL AND IMMUNOLOGICAL RESPONSE IN PATIENTS WITH TYPE 1 GD TRANSITIONING FROM IMIGLUCERASE TO VELAGLUCERASE ALFA: ONGOING EXTENSION OF STUDY TKT034
Mardach R et al

OBJECTIVE

- The TKT034 extension (HGT-GCB-044) was designed to provide an ongoing evaluation of the safety of velaglucerase alfa in patients with GD1 who transitioned from imiglucerase to velaglucerase alfa (**Figure 1**).

FIGURE 1. Design of TKT034 and its extension trial



*Patients received the same number of units of velaglucerase alfa as their prior imiglucerase treatment.
IV, intravenous.

41 patients

>2 y

30 m previous

Imiglucerase

15-60 U/kg/2 w

Hb & Plat stables x 6m

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CLINICAL AND IMMUNOLOGICAL RESPONSE IN PATIENTS WITH TYPE 1 GD TRANSITIONING FROM IMIGLUCERASE TO VELAGLUCERASE ALFA: ONGOING EXTENSION OF STUDY TKT034

Mardach R et al

TABLE 1. Characteristics of study participants (at Baseline of T

Baseline factor	n=38
Age, n (%)	
2–17 years	9 (24)
2–4 years	0
5–17 years	9 (24)
≥18 years	29 (76)
Gender, n (%)	
Male	18 (47)
Female	20 (53)
Clinical parameters, median (range)	
Hemoglobin concentration, g/dL	13.8 (10.7, 16.5
Platelet count, x 10^3/L	162 (29, 399)

FIGURE 2. Hemoglobin concentration change from Baseline (n=38)

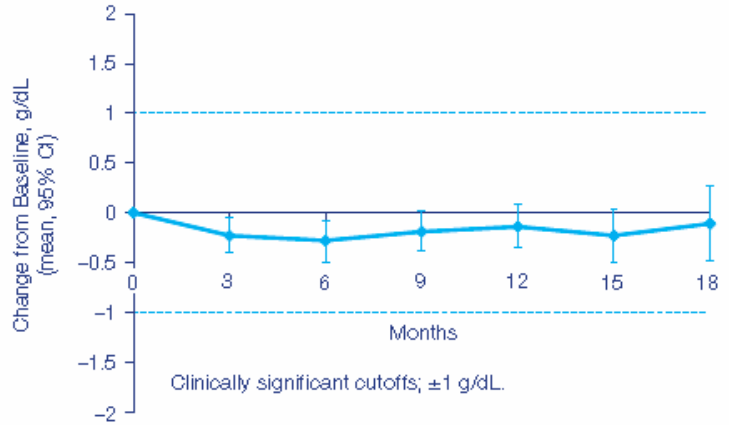
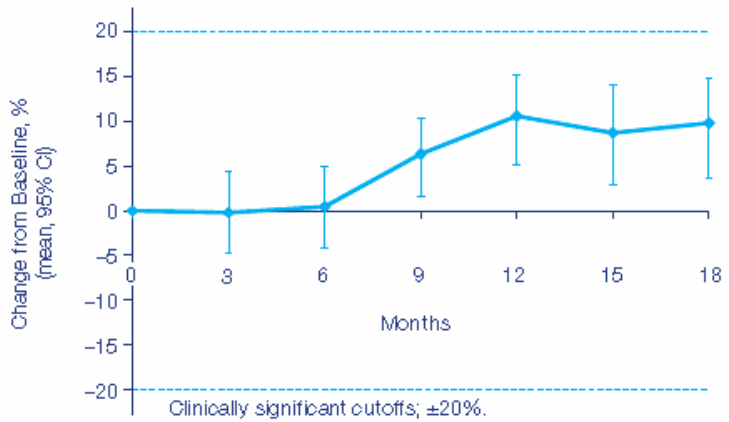


FIGURE 3. Percent change from Baseline in platelet count (n=38)



CLINICAL AND IMMUNOLOGICAL RESPONSE IN PATIENTS WITH TYPE 1 GD TRANSITIONING FROM IMIGLUCERASE TO VELAGLUCERASE ALFA: ONGOING EXTENSION OF STUDY TKT034

Mardach R et al

TABLE 2. TKT034 safety summary (n=40 safety population; 12 months)

	Patients, n (%)				
Adverse events (AEs)	**Total (n=40)**	**15 U/kg (n=14)**	**30 U/kg (n=12)**	**45 U/kg (n=7)***	**60 U/kg (n=7)**
Experienced ≥1 treatment-emergent AE†	34 (85)	11 (79)	11 (92)	6 (86)	6 (86)
Experienced ≥1 drug-related AE	11 (28)	5 (36)	3 (25)	2 (29)	1 (14)
Experienced ≥1 infusion-related AE‡	9 (23)	5 (36)	2 (17)	1 (14)	1 (14)
Experienced ≥1 severe AE	5 (13)	0	2 (17)	1 (14)	2 (29)
Possibly/probably treatment related	0	0	0	0	0
Experienced ≥1 life-threatening AE	0	0	0	0	0
Experienced ≥1 serious AE	4 (10)	0	1 (8)	3 (43)	0
Possibly/probably treatment related	1 (3)	0	0	1 (14)	0
Discontinued due to an AE	1 (3)	0	0	1 (14)	0
Deaths	0	0	0	0	0
Developed anti-velaglucerase alfa antibodies	0	0	0	0	0

*1 patient who received 50 U/kg of imiglucerase was categorized in the 45 U/kg velaglucerase alfa group. This patient was to receive a prescribed dose of 50 U/kg (4000 U/82 kg) of velaglucerase alfa; the patient's first infusion was discontinued after 30 minutes due to a hypersensitivity reaction to velaglucerase alfa so the patient only received 12.7 U/kg but they were categorized into the 45 U/kg group for analysis purposes.

†A treatment-emergent adverse event was defined as one that occurred on or after the day of the first infusion until 30 days after the patient's last infusion.

‡An infusion-related adverse event was defined as one that (1) began either during or within 12 hours after the start of the infusion, and (2) was judged as possibly or probably related to study drug.

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, HEAD-TO-HEAD, PHASE III STUDY OF VELAGLUCERASE ALFA ENZYME REPLACEMENT THERAPY COMPARED WITH IMIGLUCERASE IN PATIENTS WITH TYPE 1 GD. TKT039

TABLE 1. Baseline characteristics

	Velaglucerase alfa 60 U/kg (n=17)	Imiglucerase 60 U/kg (n=17)
Age, n (%)		
2–17 years	4 (24)	5 (29)
2–4 years	0	4 (24)
5–17 years	4 (24)	1 (6)
Male gender, n (%)	8 (47)	8 (47)
Prior splenectomy, n (%)	10 (59)	10 (59)
Clinical parameters, median (range)[1]		
Hemoglobin concentration, g/dL	11.4 (9.7–14.4)	10.6 (8.1–13.1)
Platelet count, x 10^3/L	172 (44.0–310.5)	188 (63.0–430.5)
Spleen volume[2], Multiples of Normal	9.5 (7.0–31.5)	7.0 (3.0–44.5)
Liver volume, Multiples of Normal	1.6 (0.8–4.9)	1.6 (0.7–2.8)
Chitotriosidase[3], nmol/mL/h		
Wild type (n=10/11)	40,686 (15,815–99,393)	36,319 (23,408–112,777)
Heterozygotes (n=5/5)	21,885 (15,237–23,716)	15,037 (5665–49,695)
CCL18, ng/mL	1637 (763–3038)	1849 (806–5902)

[1]Mean of screening and Baseline medians. [2]The 20 splenectomized patients were excluded. [3]2 patients were excluded from the velaglucerase alfa arm: 2 copies of the 24 bp mutation (n=1); low levels of chitotriosidase activity (<5000 nmol/mL/h) at Baseline despite not having the mutation on either allele (n=1). 1 patient was excluded from the imiglucerase arm because the patient had 2 copies of the 24 bp mutation.

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FIGURE 2. Change in hemoglobin concentration with velaglucerase alfa or imiglucerase from Baseline to Month 9

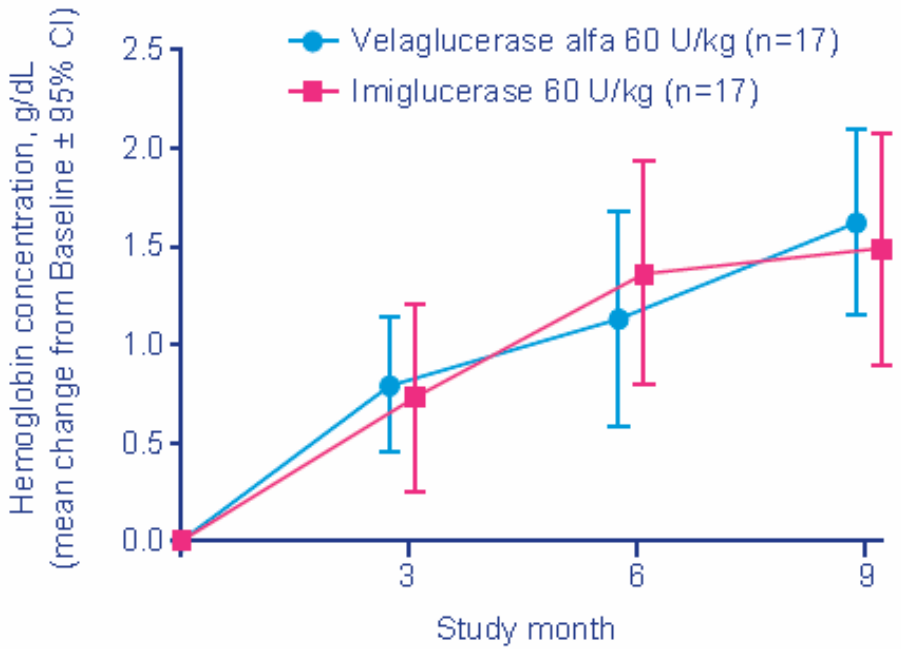

TABLE 2. Primary outcome: hemoglobin concentration (g/dL) change from Baseline (non-inferiority test)

Study population	Mean change from Baseline: Velaglucerase alfa 60 U/kg	Mean change from Baseline: Imiglucerase 60 U/kg	Mean treatment difference (Velaglucerase alfa – Imiglucerase)	Lower limit of the 97.5% one-sided CI[1]
ITT population, n=17 per group	1.624	1.488	0.135	−0.596
PP population, n=15 per group	1.677	1.520	0.157	−0.599

[1]Obtained from a two-sample t-test.

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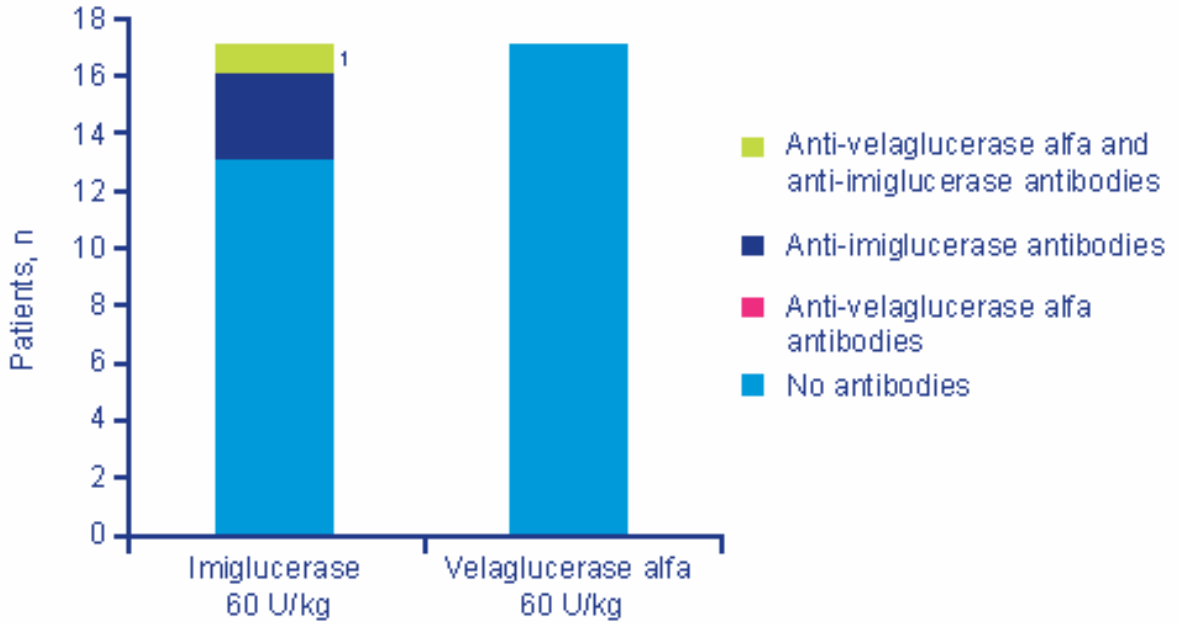
TABLE 3. Safety summary: treatment-emergent[1] AEs

	Patients, n (%)	
Description	Velaglucerase alfa 60 U/kg (n=17)	Imiglucerase 60 U/kg (n=17)
≥1 drug-related AE	8 (47.1)	6 (35.3)
≥1 infusion-related AE	5 (29.4)	4 (23.5)
≥1 severe or life-threatening AE	3 (17.6)	2 (11.8)
Possibly/probably treatment related	2 (11.8)	1 (5.9)
≥1 serious AE	3 (17.6)	0
Possibly/probably treatment related	1 (5.9)	0
Discontinued due to an AE	0	0
Developed anti-drug antibodies	0	4 (23.5)

[1]A treatment-emergent AE was defined as one that occurred on or after the time of the first infusion until 30 days after the patient's last infusion.

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, HEAD-TO-HEAD, PHASE III STUDY OF VELAGLUCERASE ALFA ENZYME REPLACEMENT THERAPY COMPARED WITH IMIGLUCERASE IN PATIENTS WITH TYPE 1 GD. TKT039

FIGURE 3. Development of anti-drug antibodies by study group



[1]The development of anti-velaglucerase alfa antibodies in this patient was attributed to cross-reaction in the assay because he had never been exposed to velaglucerase alfa.

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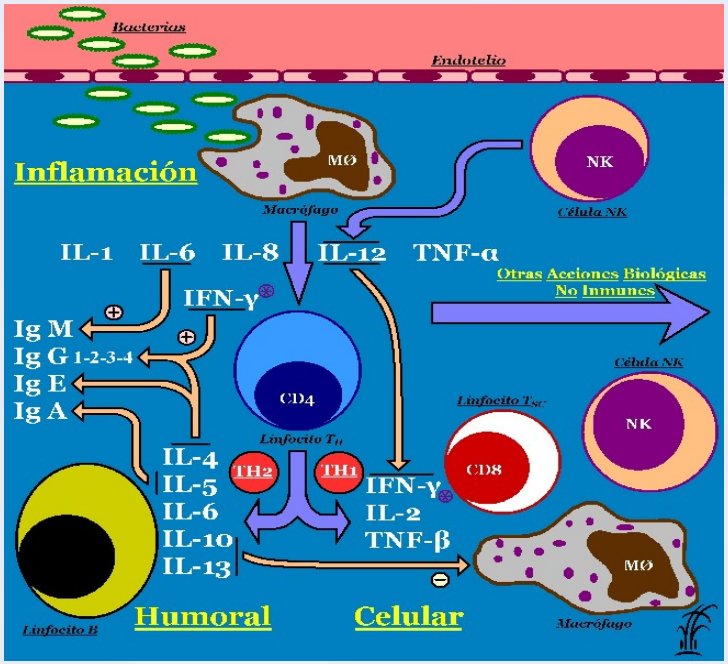
Enfermedad de Gaucher

Se produce toda una cascada de acontecimientos provocados por el acúmulo de sustrato y la activación crónica del macrófago que tienen como consecuencia



↑ Actividad de enzimas macrofágicas
QT, ACE, Ph Alc

↑ Activación del sistema inmune:
Hipergammaglobulinemia
Aumento de depósitos férricos

↑↓ Desequilibrio en citoquinas inflamatorias

FEETEG

Enfermedad de Gaucher. Problemas no resueltos

Activación del sistema inmune

- Sobrecarga de hierro
- Gammapatías mono y policlonales
- Desequilibrio de citoquinas inflamatorias
- Estress oxidativo

Otras enfermedades relacionadas

- Mayor prevalencia de colelitiasis
  Ben Harosh-Katz M et al J Clin Gastroenterol 2004
- Fibromialgia Brautbar A et al Q J Med 2006
- Artropatia Inflamatoria Javier RM et al Presse Med 2007
- Neoplasia de Fost M Blood Cells Mol Dis 2006

Portadores y otras enfermedades relacionadas

Los portadores tienen el 50% de la actividad enzimática pero no tienen acúmulo de sustrato aunque pueden tener otras alteraciones.

Cardiovascular risk factors, low HDL-cholesterol

Pocovi M et al Lancet 1998

Neurological comorbilities (Parkinson, tremor, epilepsy)

Giraldo et al Med Clin 2008

Otras enfermedades relacionadas

Type and number of neurological symptoms observed in 110 GD patients and 297 first and second degree relatives (carriers 213)

	GD patients	Relatives carriers	Relatives Non carriers
Parkinson Disease	8	15	1
Epilepsy	1	6	3
Tremor	2	7	0
Peripheral Neuropathy	10	1	0
Uncordinated movements	1	0	0
Concentration difficulties	4	0	0
Hearing loss	9	1	1
Strabismus	2	0	0
Saccadic movements	1	0	0
Others*	5	5	0

Giraldo et al in press

jose luis cano

Ilustración para el libro
“Cuando yo era niño”
de Santiago Ramón y Cajal