TRATAMIENTO DE LA AFECTACIÓN ÓSEA EN LA ENFERMEDAD DE GAUCHER

salud servicio aragonés de salud

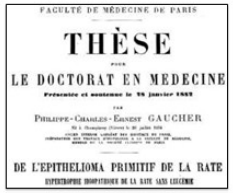
III REUNIÓN ENF. MINORIRATIAS SEMI

Universidad Zaragoza
1542

La Enfermedad de Gaucher: definición

Enfermedad de Gaucher: ¿qué es?

1882: P. Ernest Charles Gaucher



FACULTÉ DE MÉDECINE DE PARIS

THÈSE

POUR

LE DOCTORAT EN MEDECINE

Présentée et soutenue le 28 janvier 1882

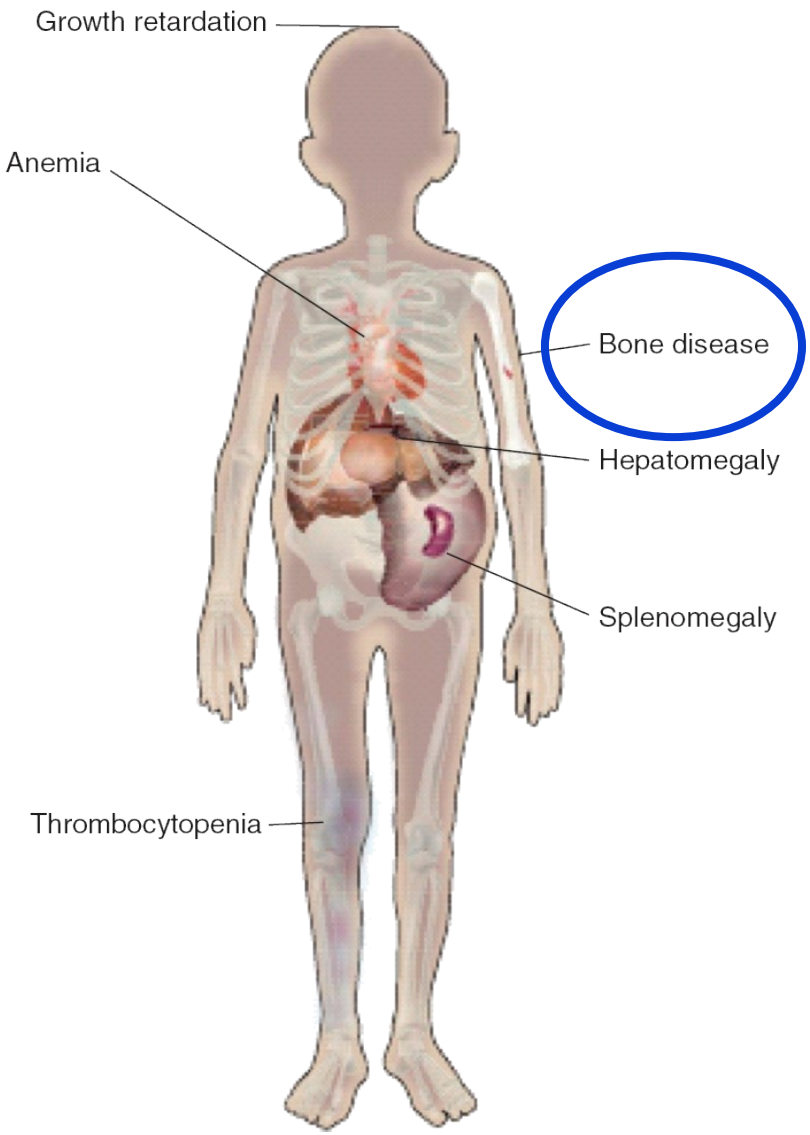
PAR

PHILIPPE-CHARLES-ERNEST GAUCHER

DE L'EPITHELIOMA PRIMITIF DE LA RATE

PREVALENCIA

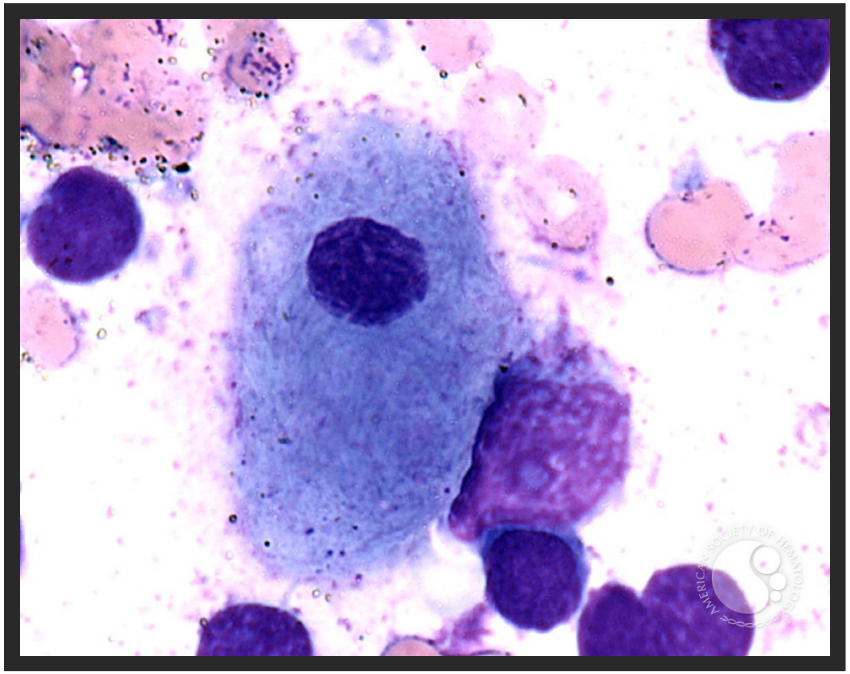
La Enfermedad de Gaucher: definición



Manifestaciones Clínicas óseas

Goldblatt J et al. Clin Ortop Rel Res 1978

¿?



Stowens DW et al. Skeletal complications of GD. Medicine (Balltimore) 1985.

Barak V et al. Eur Cytokine Netw 1999.
Allen MJ et al. QJ Med 1997.
Lichtenstein M et al. Blood Cells Mol Dis 1997.
Hollak CE et al. Blood Cells Mol Dis 1997.

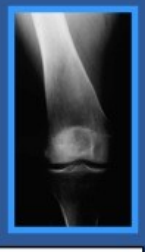
Aspectos fisiopatológicos mal conocidos

Existe un modelo animal de experimentación poco válido

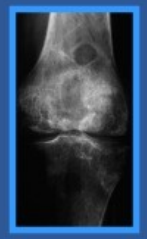
EVALUACIÓN DE LA AFECTACIÓN ÓSEA EN LA E. GAUCHER

EVALUACIÓN DE LA AFECTACIÓN ÓSEA EN LA E. GAUCHER

RADIOGRAFÍA

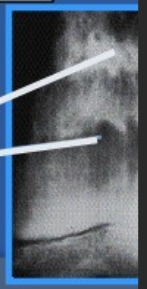


MATRAZ (Erhlenmeyer)



LESIONES OSTEOLÍTICAS

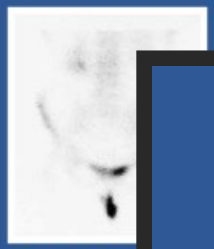
DE



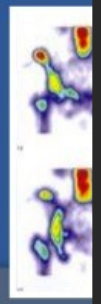
OSTEOESCLEROSIS

OSTEOLISIS

GAMMAGRAFÍA

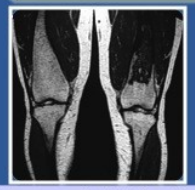


MDP- Tc

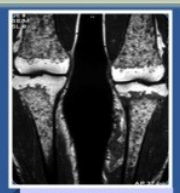


SPECT

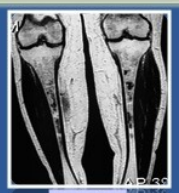
RESONANCIA MAGNÉTICA NUCLEAR



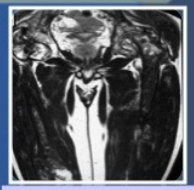
Erhlenmeyer-flask-deformity



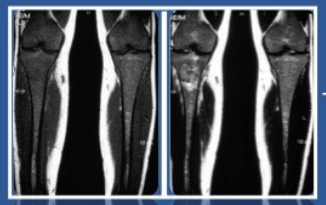
Afectación Epífisis



Infartos



Necrosis cabeza femoral



T1

T2

CRISIS ÓSEA

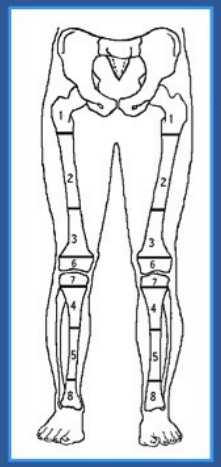
(increase in signal intensity on T2-weighted images)

PERMITE MONITORIZAR LA RESPUESTA DEL HUESO AL TRATAMIENTO

Rosenthal DI et al. J Bone Joint Surg Am 1986

EVALUACIÓN DE LA AFECTACIÓN ÓSEA EN LA E. GAUCHER

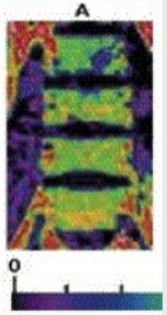
RESONANCIA MAGNÉTICA COMO MÉTODO CUANTITATIVO



Rosenthal- Score Rosenthal DI et al. J Bone Joint Sur Am 1986

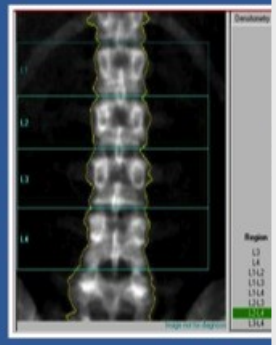
RESONANCIA MAGNÉTICA COMO MÉTODO CUANTITATIVO: QCSI*

normal



DE ELECCIÓN ACTU… A TR…

RESONANCIA MAGNÉTICA COMO MÉTODO CUANTITATIVO: ABSORCIOMETRÍA DE DOBLE ENERGÍA DE RX (DEXA)



TÉCNICA ÚTIL P…

MÉTODOS CUANTITATIVO

MARCADORES BIOLÓGICOS CLÁSICOS

QUITOTRIOSIDASA PLASMÁTICA (QT):

- Se eleva x 1000 veces en pacientes con síntomas.
- Método más utilizado para iniciar el tratamiento y monitorizarlo.
- INCONVENIENTES:
  - 6% población déficit absoluto.
  - 35% duplicación de 24 bp en el Exón 10.

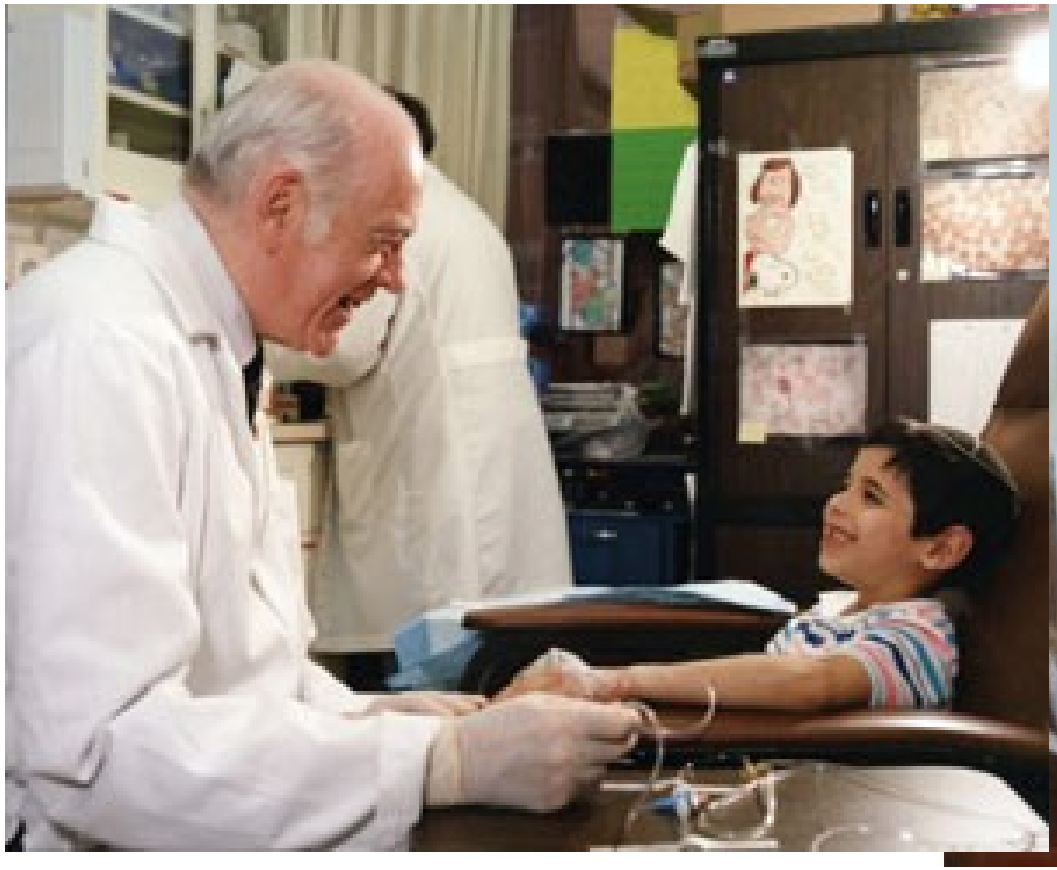
2. CCL 18/ PARC:

- Se eleva de 10 a 50 veces .
- Alternativa para pacientes deficientes de QT.

MALA CORRELACIÓN CON LA AFECTACIÓN ÓSEA

van Breemen et al. BBA 2007
Hollak C et al. J Clin Invest 1994
Boot RG et al. Blood 2004

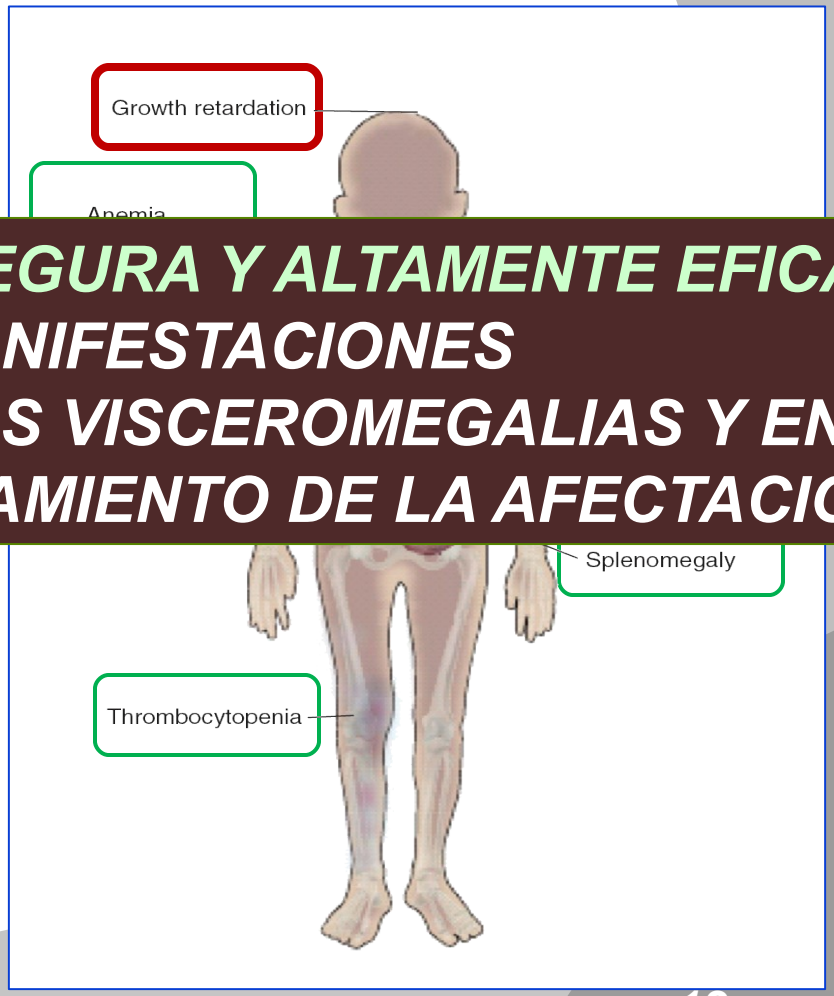
El tratamiento en la Enfermedad de Gaucher



Profesor R. O. Brady

Original Ceredase Bottles (año 1991)

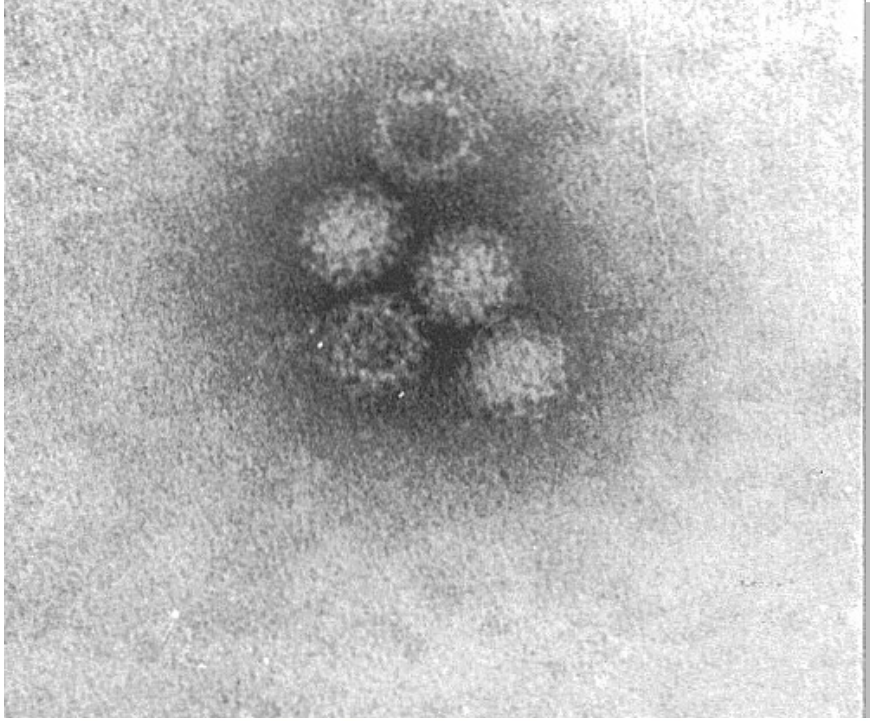
El tratamiento en la Enfermedad de Gaucher



IMIGLUCERASA ES SEGURA Y ALTAMENTE EFICA
CONTROL DE LAS MANIFESTACIONES
HEMATOLÓGICAS, LAS VISCEROMEGALIAS Y EN
PREVENCIÓN Y TRATAMIENTO DE LA AFECTACIÓ

Weinreb NJ. Expert Opin Pharmacother 2008

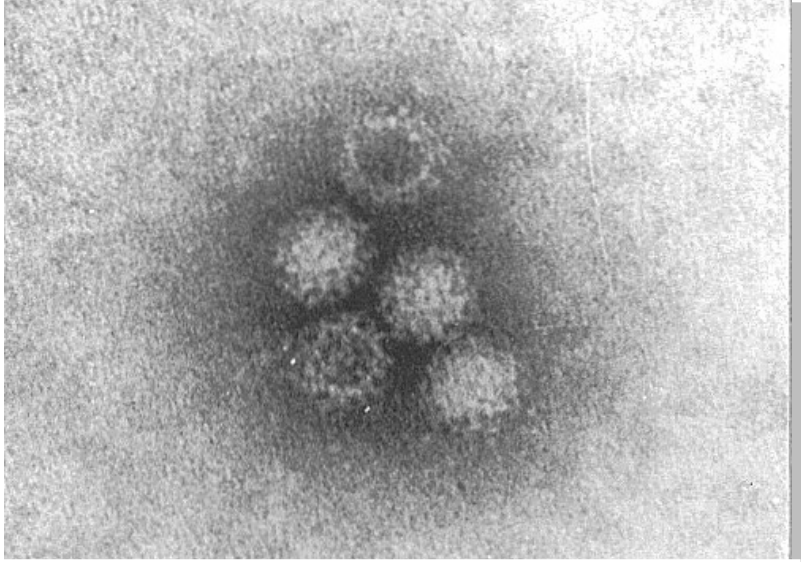
Año 2009
Vesivirus 2117



Hollak C. BCMD Sept 2009

	Total number of living Gaucher disease patients	On ERT	On SRT	Children[a]	Type III	Drug interruption or significant dose reduction
France	530	240	25	39	10	240
Israel	>800	250[c]	0	30	2	200
Czech Republic	31	23	5	2	1	17
Italy	unknown	224[c]	4	39	18	71
Spain	324	170	40	25	10	140
Greece	99	51[c]	3	11	6	unknown
Germany	300	250[c]	unknown	40	10	200
Poland		54	0	13	17	20
Portugal		80[c]	4	2	0	80
United Kingdom		232	<20	39	unknown	200
The Netherlands		59	4	8	4	46
Hungary	25	23	unknown	4	unknown	19
Eastern European Countries[e]	Unknown	[illegible]	unknown	33		[illegible]
		1732		271	78	1277

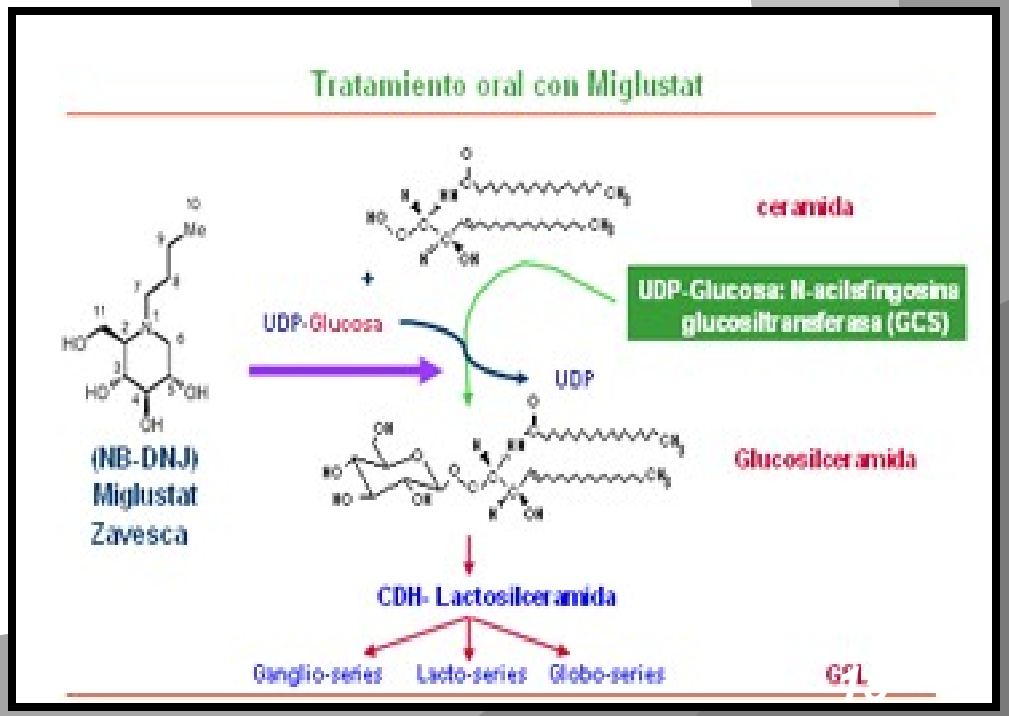
Año 2009
Vesivirus 2117



Access to unlicensed treatments: since the companies Protalix and Shire inform us about opportunities for expanded access use of their enzymes (taliglucerase and velaglucerase, respectively) before licensing, how can this be managed and by what means can consolidated applications for patients with urgent need be made?

Carla E.M. Hollak [a,*], Stephan vom Dahl [b], Johannes M.F.G. Aerts [c], Nadia Belmatoug [d], Bruno Bembi [e],

EMEA (2009) Miglustat (Zavesca®) summary of product characteristics. Retrieved 15 May, 2009, from http://www.emea.europa.eu/humandocs/PDFs/EPAR/zavesca/H-435-PI-en.pdf



The role of the iminosugar *N*-butyldeoxynojirimycin (miglustat) in the management of type I [illegible]pathic) Gaucher disease:

Table 3
Discontinuations per country observation.

	Spain	France	UK	US	Italy	Other[a]	Total
Patients, n	39	28	16	13	6	13	115
Discontinuations, n (%)	5 (13%)[b]	19 (68%)[b]	11 (69%)[b]	4 (31%)[b]	2 (33%)[b]	8 (62%)[b]	49 (43%)[c]
Reasons, n							
Tolerability	4	12	7	2	1	6	32 (28%)[c]
Non-medical	1	3	2	1	–	–	7 (6%)[c]
Insufficient efficacy	–	1	1	1	–	1	5 (4%)[c]
Switch to ERT	–	3	–	–	1	1	4 (3%)[c]
Death[d]	–	–	1	–	–	–	1 (1%)[c]

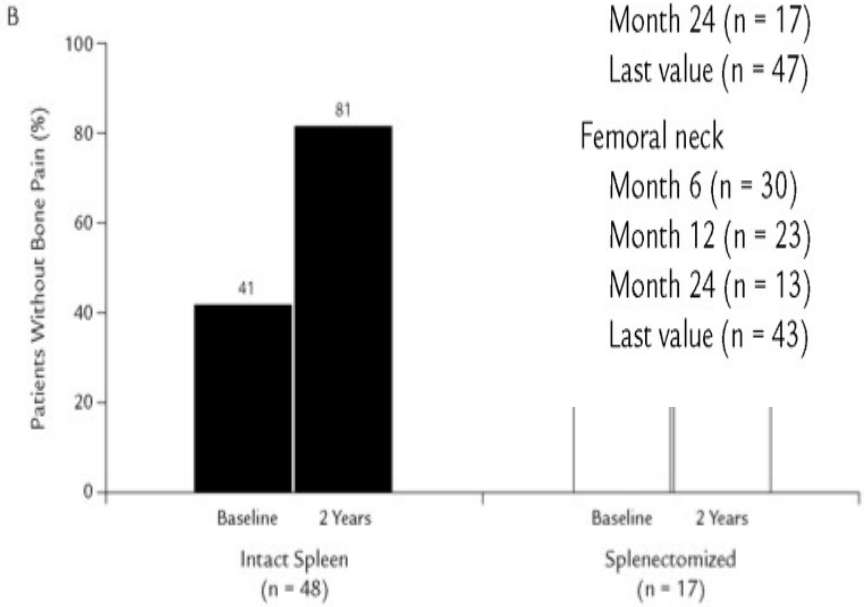
to issues of p[illegible]

- A discussion of potential adverse effects [illegible] compared with imiglucerase, should be undertaken with the patient before drug is prescribed.
- The safety and efficacy of NB-DNJ for patients with severe Gaucher disease (i.e. those with haemoglobin 9 g/dL or less, platelet count 30 × 10[illegible]/L or less, and rapidly evolving osseus disease) has not been established.

erapeutics/Volume 29, Number 8, 2007

Bone Disease in Adults with Type 1
oled Analysis of Three Multinational,

orah Elstein, PhD[2]; Martin Hrebícek, PhD[3]; and



Site/Time Point	Baseline, Mean (SD)	Mean (SE)	95% CI	P
Lumbar spine				
Month 6 (n = 29)	-0.83 (1.16)	0.15 (0.06)	0.02-0.27	0.022
Month 12 (n = 26)	-0.98 (1.17)	0.19 (0.07)	0.05-0.34	0.012
Month 24 (n = 17)	-1.46 (1.11)	0.21 (0.08)	0.05-0.38	0.015
Last value (n = 47)	-1.18 (1.16)	0.21 (0.05)	0.11-0.32	<0.001
Femoral neck				
Month 6 (n = 30)	-0.63 (1.43)	0.23 (0.06)	0.12-0.34	<0.001
Month 12 (n = 23)	-0.73 (0.96)	0.21 (0.08)	0.04-0.38	0.017
Month 24 (n = 13)	-0.82 (0.78)	0.18 (0.08)	0.01-0.18	0.039
Last value (n = 43)	-0.76 (1.27)	0.27 (0.06)	0.15-0.38	<0.001

)	8/39 (21)	11/61 (18)
)	4/41 (10)	9/72 (13)
)	3/41 (7)	7/72 (10)


VPRIV™
(velaglucerase alfa
for injection)
400 units/vial
Shire
Rx Only

Elelyso™
(taliglucerase alfa)
units/vial
200 units/vial

Walton-Bowen et al. Gaucher Registry 2000.

Cox T. JIMD 2008

DeMayo RF. AJ Roeng 2008

Weinreb N. AJ Hemat 2008

Mistry P. BJ Haemat 2009

Mistry PK. BCMD 2011

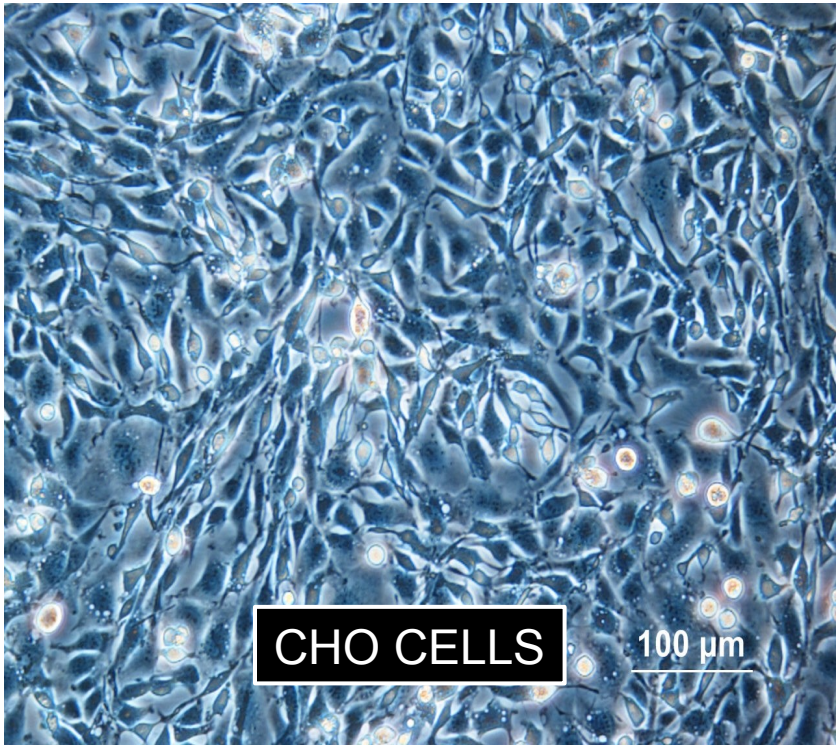
Giuffrida G. Hematology Reports 2012

Weinreb NJ AmJMed 2002.

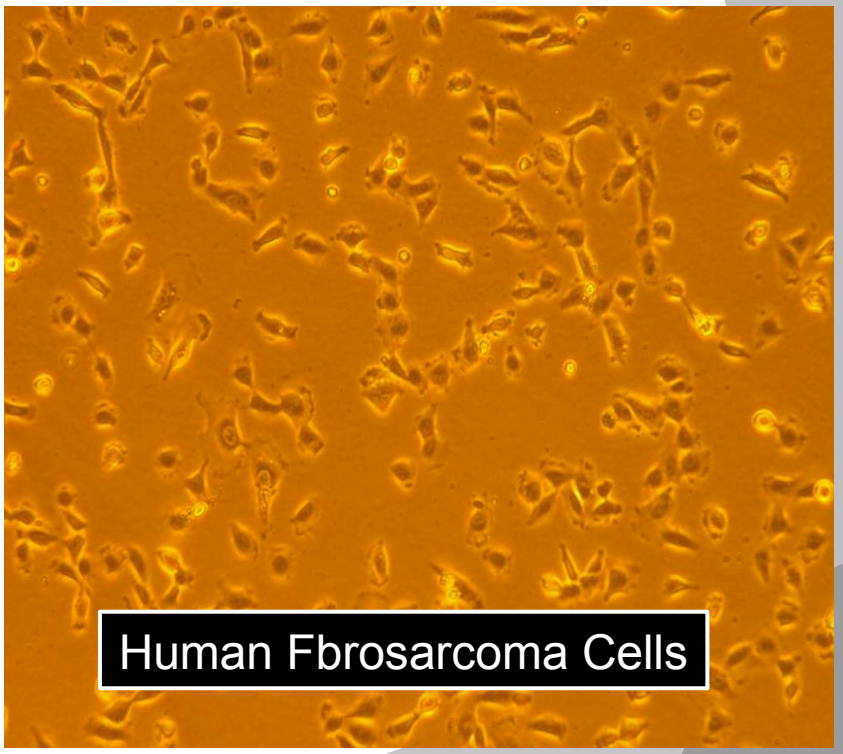
Andersson H. Pediatrics 2008.

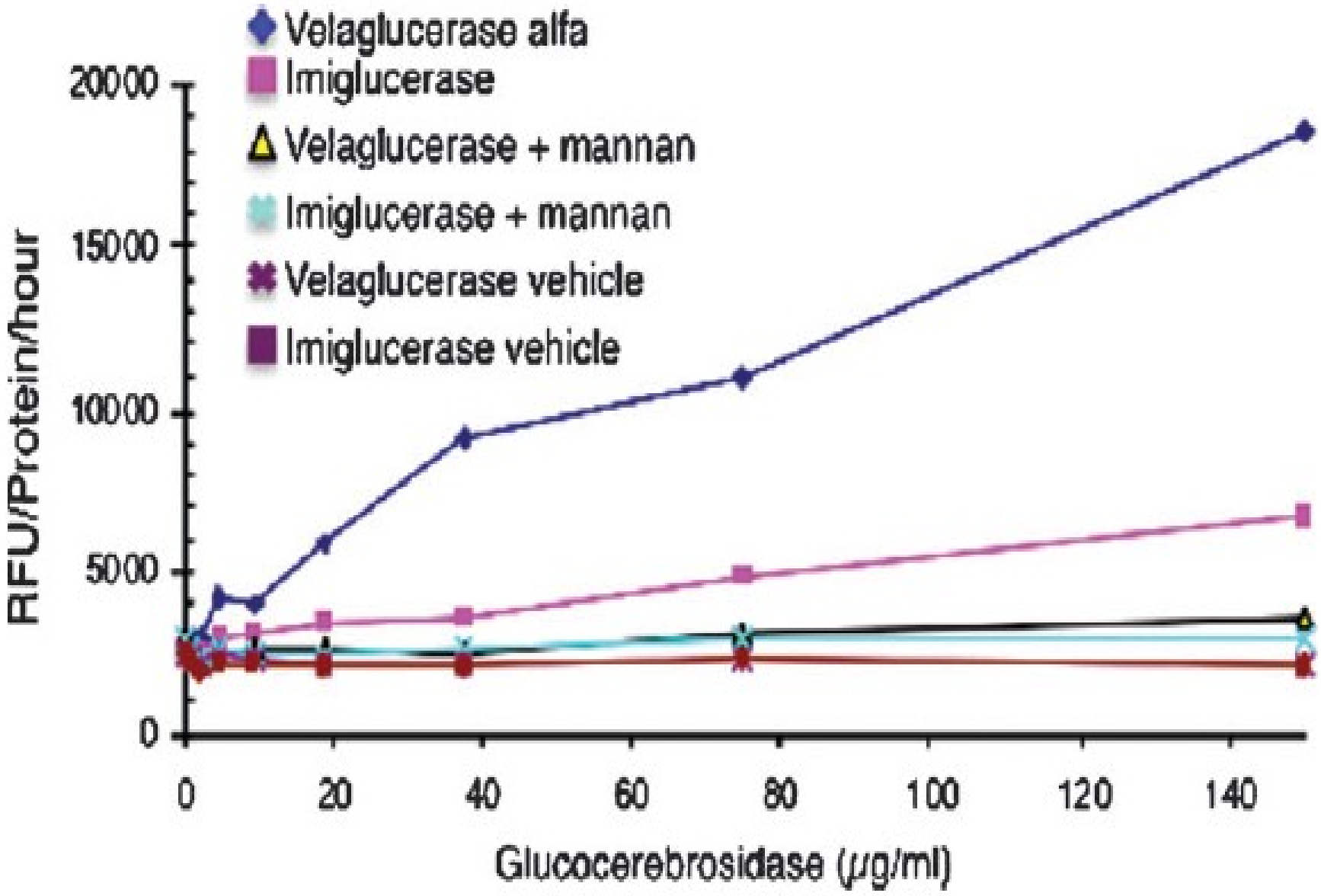
¿Es Velaglucerasa una opción en la enfermedad ósea de los pacientes con Enf de Gaucher tipo 1?

IMIGLUCERASA



VELAGLUCERASA





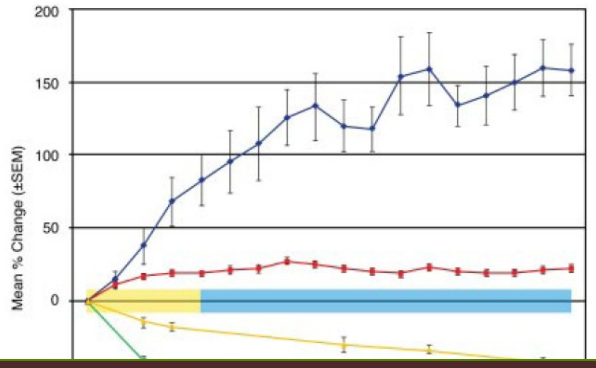
Brumshtein B, et al. Glycobiology 2010; 20: 24–32

blood

2010 115: 4651-4656
Prepublished online March 18, 2010;
doi:10.1182/blood-2010-02-268649

Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experier

Ari Zimran, Gheo
Kiran Bhirangi, G



LA VELAGLUCERASA ES SEGURA Y ALTAMENTE EF
EL CONTROL DE LAS MANIFESTACIONES HEMATOLÓGICAS Y REVERTIR LAS VISCEROMEGA

ELSEVIER

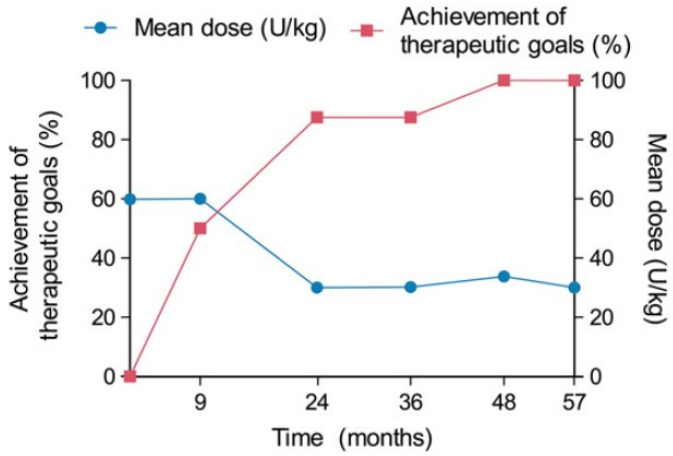
Contents lists available at ScienceDirect

Blood Cells, Molecules, and Diseases

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

Early achievement and maintenance of the therapeutic goals using velaglucerase alfa in type 1 Gaucher disease

D. Elstein [a,*], G.M. Cohn [b], N. Wang [b], M. Djordjevic [c], C. Brutaru [d], A. Zimran [a]



Enzyme replacement therapy with velaglucerase alfa in Gaucher

Safety and efficacy of velaglucerase alfa in Gaucher disease type 1

Velaglucerase alfa enzyme replacement therapy compared with imiglucerase in patients with Gaucher disease

Hadhami Ben Turkia,[1] Derlis E. Gonzalez,[2] Norman W. Barton,[3] Ari Zimran,[4] Madhulika Kabra,[5] Elena A. Lukina,[6] Pilar Giraldo,[7] Isaac Kisinovsky,[8] Ashish Bavdekar,[9] Marie-Françoise Ben Dridi,[1] Neerja Gupta,[5] Priya S. Kishnani,[10] Sureshkumar E.K.,[11] Nan Wang,[3] Eric Crombez,[3] Kiran Bhirangi,[3] and Atul Mehta[12]*

Enzyme replacement therapy for Gaucher disease (GD) has been available since 1991. This study compared the efficacy and safety of velaglucerase alfa with imiglucerase, the previous standard of care. A 9-month, global, randomized, double-blind, non-inferiority study compared velaglucerase alfa with imiglucerase (60 U/kg every other week) in treatment-naïve patients aged 3–73 years with anemia and either thrombocytopenia or organomegaly. The primary endpoint was the difference between groups in mean change from baseline to 9 months in hemoglobin concentration. 35 patients were randomized: 34 received study drug (intent-to-treat: 17 per arm), 20 were splenectomized. Baseline characteristics were similar in the two groups. The per-protocol population included 15 patients per arm. The mean treatment difference for hemoglobin concentration from baseline to 9 months (velaglucerase alfa minus imiglucerase) was 0.14 and 0.16 g/dL in the intent-to-treat and per-protocol populations, respectively. The lower bound of the 97.5% one-sided confidence interval in both populations lay within the pre-defined non-inferiority margin of −1.0 g/dL, confirming that velaglucerase alfa is non-inferior to imiglucerase. There were no statistically significant differences in the secondary endpoints. Most adverse events were mild to moderate. No patient receiving velaglucerase alfa developed antibodies to either drug, whereas four patients (23.5%) receiving imiglucerase developed IgG antibodies to imiglucerase, which were cross-reactive with velaglucerase alfa in one patient. This study demonstrates the efficacy and safety of velaglucerase alfa compared with imiglucerase in adult and pediatric patients with GD clinically characterized as Type 1. Differences in immunogenicity were also observed. Am. J. Hematol. 88:179–184, 2013.

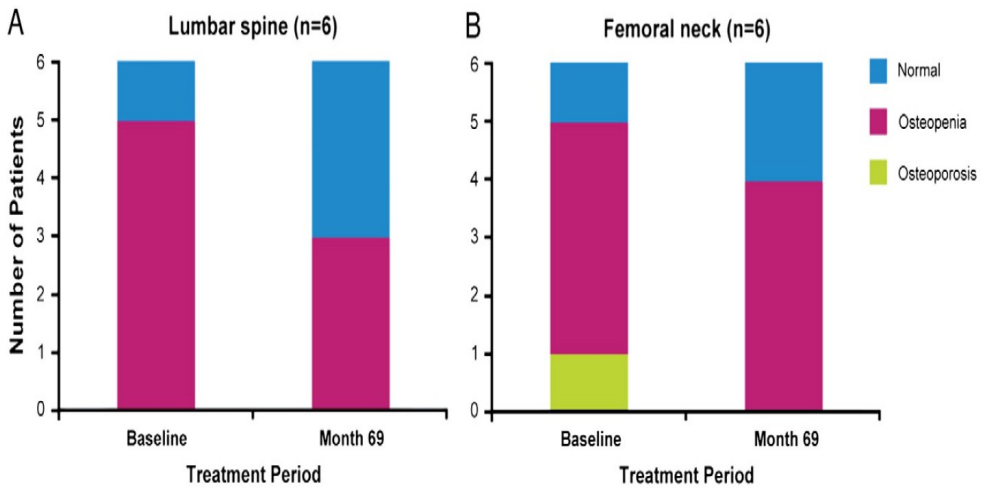
Contents lists available at ScienceDirect

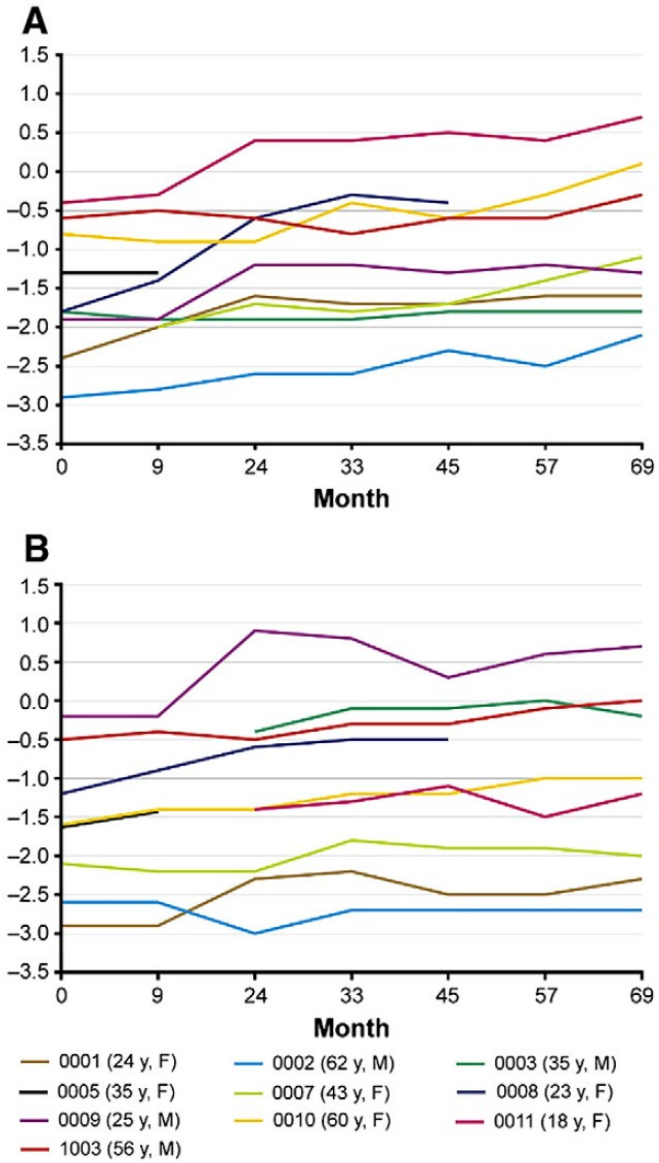
Blood Cells, Molecules, and Diseases

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

Significant and continuous improvement in bone mineral density among type 1 Gaucher disease patients treated with velaglucerase alfa: 69-month experience, including dose reduction

Deborah Elstein [a,*], A. Joseph Foldes [b], David Zahrieh [c], Gabriel M. Cohn [c], Maja Djordjevic [d], Costin Brutaru [e], Ari Zimran [a]





SIN BIFOSFONATOS

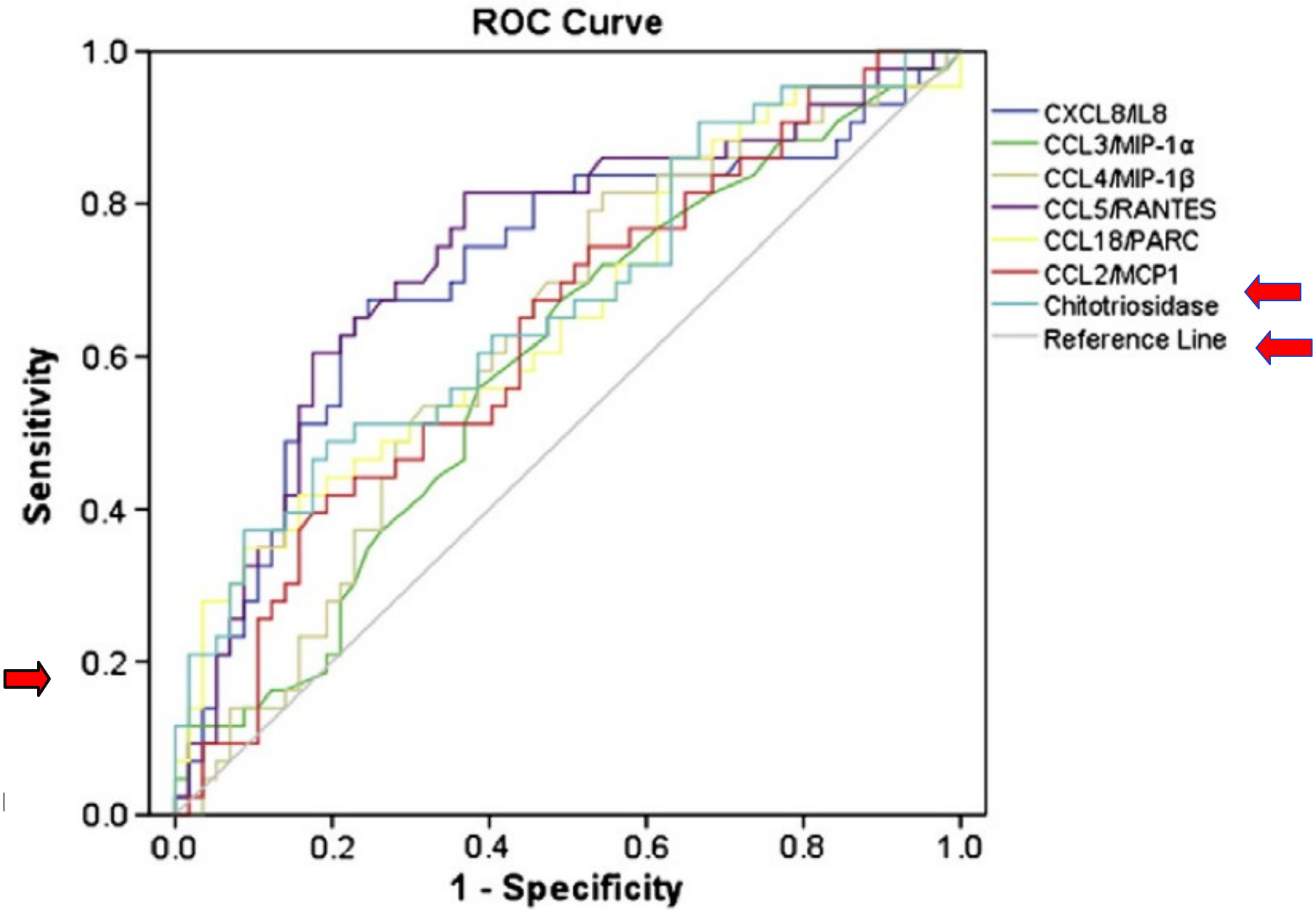
GRADOS DE AFECTACIÓN
(desde un punto de vista Radiológico)

Wenstrup RJ et al. BJR 2002.

GRADOS DE AFECTACIÓN CLÍNICA

GRADOS DE AFECTACIÓN CLÍNICA

GRADOS DE AFECTACIÓN CLÍNICA


ROC Curve
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
CXCL8/IL8
CCL3/MIP-1α
CCL4/MIP-1β
CCL5/RANTES
CCL18/PARC
CCL2/MCP1
Chitotriosidase
Reference Line

IMIGLUCERASA ES EL TRATAMIENTO DE ELECCIÓN EN LA AFECTACIÓN ÓSEA DE LA ENF. DE GAUCHER

VELAGLUCERASA ES SEGURA Y **EFICAZ** EN

- EL TRATAMIENTO DE LA AFECTACIÓN ÓSEA GENERALIZADA Y
- MUY PROBABLEMENTE TAMBIÉN LO SEA EN LAS MANIFESTACIONES LOCALES

DEBEN DISEÑARSE ESTUDIOS QUE DEMUESTREN LA UTILIDAD DE VELAGLUCERASA EN LA PREVENCIÓN Y TRATAMIENTO DE LA **NECROSIS AVASCULAR**; A SER POSIBLE EN PACIENTES REFRACTARIOS A IMIGLUCERASA

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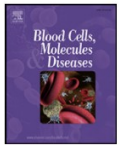

Taliglucerase alfa leads to favorable bone marrow responses in patients with type I Gaucher disease