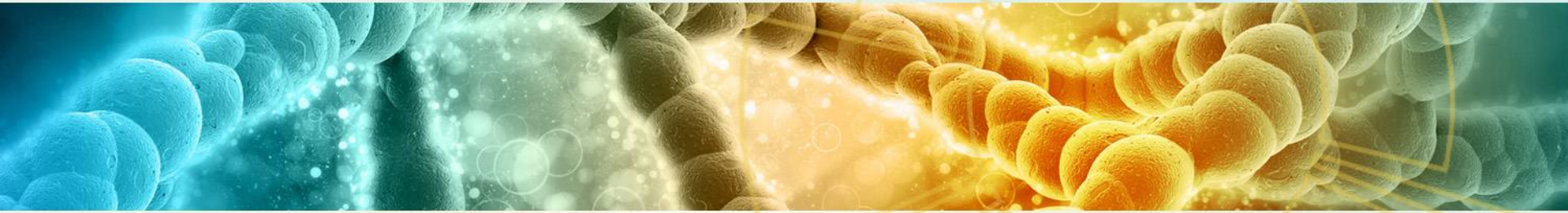

Réalisations marquantes du Centre de Référence de la Maladie de Fabry ces 20 dernières années

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Généo

maladies rares

European Reference Networks

Développement de l'enzymothérapie recombinante substitutive

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

CHRISTINE M. ENG, M.D., NATHALIE GUFFON, M.D., WILLIAM R. WILCOX, M.D., PH.D., DOMINIQUE P. GERMAIN, M.D., PH.D., PHILIP LEE, M.R.C.P., D.M., PH.D., STEVE WALDEK, M.B., B.CH., LOUIS CAPLAN, M.D., GABOR E. LINTHORST, M.D., AND ROBERT J. DESNICK, PH.D., M.D., FOR THE INTERNATIONAL COLLABORATIVE FABRY DISEASE STUDY GROUP

ABSTRACT

Background Fabry's disease, lysosomal α-galactosidase A deficiency, results from the progressive accumulation of globotriaosylceramide and related glycosphingolipids. Affected patients have microvascular disease of the kidneys, heart, and brain.

Methods We evaluated the safety and effectiveness of recombinant α-galactosidase A in a multicenter, randomized, placebo-controlled, double-blind study of 58 patients who were treated every 2 weeks for 20 weeks. Thereafter, all patients received recombinant α-galactosidase A in an open-label extension study. The primary efficacy end point was the percentage of patients in whom renal microvascular endothelial deposits of globotriaosylceramide were cleared (reduced to normal or near-normal levels). We also evaluated the histologic clearance of microvascular endothelial deposits of globotriaosylceramide in the endomyocardium and skin, as well as changes in the level of pain and the quality of life.

Results In the double-blind study, 20 of the 29 patients in the recombinant α-galactosidase A group (69 percent) had no microvascular endothelial deposits of globotriaosylceramide after 20 weeks, as compared with none of the 29 patients in the placebo group ($P<0.001$). Patients in the recombinant α-galactosidase A group also had decreased microvascular endothelial deposits of globotriaosylceramide in the skin ($P<0.001$) and heart ($P<0.001$). Plasma levels of globotriaosylceramide were directly correlated with clearance of the microvascular deposits. After six months of open-label therapy, all patients in the former placebo group and 98 percent of patients in the former recombinant α-galactosidase A group who had biopsies had clearance of microvascular endothelial deposits of globotriaosylceramide. Mild-to-moderate infusion reactions (i.e., rigors and fever) were more common in the recombinant α-galactosidase A group than in the placebo group.

Conclusions Recombinant α-galactosidase A replacement therapy cleared microvascular endothelial deposits of globotriaosylceramide from the kidneys, heart, and skin in patients with Fabry's disease, reversing the pathogenesis of the chief clinical manifestations of this disease. (N Engl J Med 2001;345:9-16.)

FABRY'S disease is an X-linked inborn error of glycosphingolipid catabolism due to deficient lysosomal α-galactosidase A activity.[1] In patients with the classic form of the disease, progressive accumulation of globotriaosylceramide and related glycosphingolipids in vascular endothelial lysosomes of the kidneys, heart, skin, and brain leads to the main disease manifestations. The clinical onset is in childhood and is characterized by severe acroparesthesias, angiokeratoma, corneal and lenticular opacities, and hypohidrosis. Over time, microvascular disease of the kidneys, heart, and brain progresses, leading to early death.[1] Treatment is limited to symptomatic management of pain and the end-stage complications of renal failure, cardiac disease, and strokes.

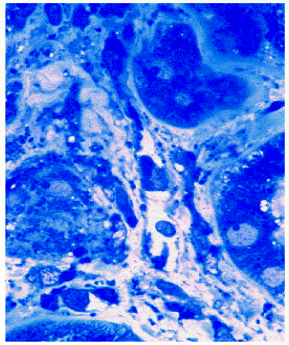
Early trials demonstrated the feasibility of enzyme replacement to correct the metabolic defect in Fabry's disease.[2-4] A phase 1 trial demonstrated reductions of globotriaosylceramide in the liver and in urinary sediment with a single dose of recombinant α-galactosidase A.[5] A phase 1 and 2 open-label dose-escalation study of replacement therapy with recombinant α-galactosidase A in 15 male patients with classic Fabry's disease demonstrated that repeated administration (a total of five infusions) was safe and effective in clearing plasma globotriaosylceramide and microvascular endothelial deposits of globotriaosylceramide from target tissues.[6] Plasma and tissue clearance of globotriaosylceramide was observed for all dose regimens, and the effect was most pronounced at higher doses. Therefore, we evaluated the safety and efficacy of recombinant α-galactosidase A replacement therapy in Fabry's disease in a multicenter, randomized, double-blind, placebo-controlled trial and subsequent open-label study.

METHODS

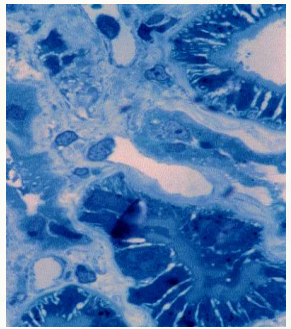
Patients

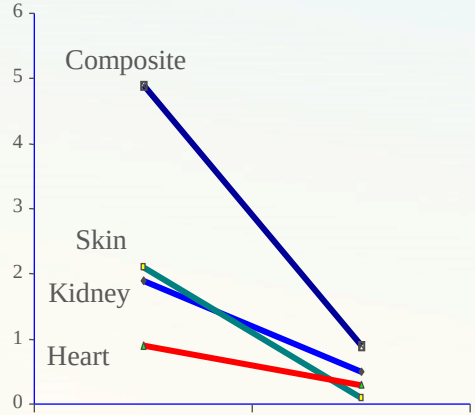
Eligible patients had an enzymatically confirmed diagnosis of classic Fabry's disease, had a level of activity of α-galactosidase A of less

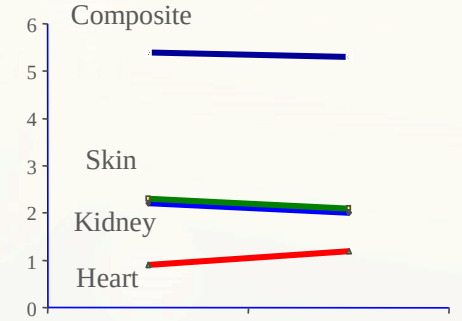
From the Mount Sinai School of Medicine, New York (C.M.E., R.J.D.); Hôpital Edouard Herriot, Lyons, France (N.G.); Cedars–Sinai Burns and Allen Research Institute, UCLA School of Medicine, Los Angeles (W.R.W.); Hôpital Européen Georges Pompidou, Paris (D.P.G.); University College London Hospitals, London (P.L.); Hope Hospital, Salford, Manchester, United Kingdom (S.W.); Beth Israel Deaconess Medical Center, Boston (L.C.); and Academisch Medisch Centrum, Amsterdam (G.E.L.). Address reprint requests to Dr. Desnick at the Department of Human Genetics, Box 1498, Mount Sinai School of Medicine, Fifth Ave. at 100th St., New York, NY 10029, or at rjd.fabry@msum.edu.



Gb_3 Clearance from Renal Peri-Tubular Capillaries







Thérapie Enzymatique Substitutive

Am. J. Hum. Genet. 75:65–74, 2004

Long-Term Safety and Efficacy of Enzyme Replacement Therapy for Fabry Disease

William R. Wilcox,[1,2,*] Maryam Banikazemi,[3,*] Nathalie Guffon,[4] Stephen Waldek,[5] Philip Lee,[6] Gabor E. Linthorst,[7] Robert J. Desnick,[3] and Dominique P. Germain,[8] for the International Fabry Disease Study Group

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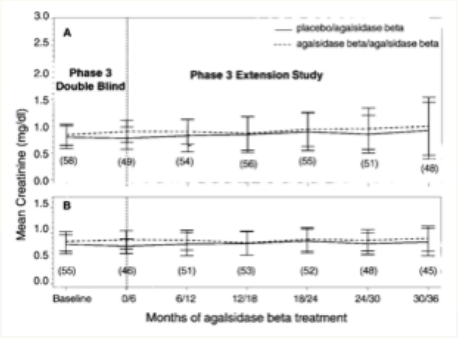

Sustained, Long-Term Renal Stabilization After 54 Months of Agalsidase β Therapy in Patients with Fabry Disease

Dominique P. Germain,[*] Stephen Waldek,[†] Maryam Banikazemi,[‡] David A. Bushinsky,[§] Joel Charrow, Robert J. Desnick,[‖] Philip Lee,[¶] Thomas Loew,[**] Anouk C. Vedder,[††] Rekha Abichandani,[‡‡] William R. Wilcox,[§§] and Nathalie Guffon[‖‖]

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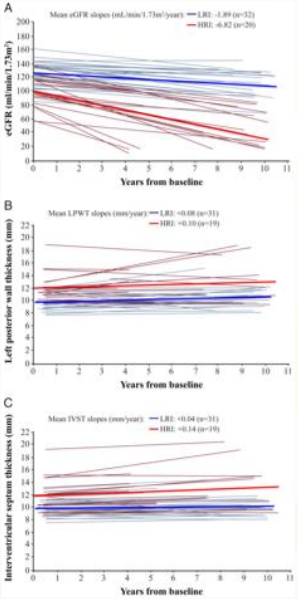
ORIGINAL ARTICLE

Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease

Dominique P Germain,[1] Joel Charrow,[2] Robert J Desnick,[3] Nathalie Guffon,[4] Judy Kempf,[5] Robin H Lachmann,[6] Roberta Lemay,[5] Gabor E Linthorst,[7] Seymour Packman,[8] C Ronald Scott,[9] Stephen Waldek,[10] David G Warnock,[11] Neal J Weinreb,[12] William R Wilcox[13]



Successful reinstitution of agalsidase beta therapy in Fabry disease patients with previous IgE-antibody or skin-test reactivity to the recombinant enzyme

David Bodensteiner, MD[1], C. Ronald Scott, MD[2], Katherine B. Sims, MD[3], Gillian M. Shepherd, MD[4], Rebecca D. Cintron, MD[5], and Dominique P. Germain, MD, PhD[6]

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ORIGINAL ARTICLE

CLINICAL GENETICS WILEY

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]

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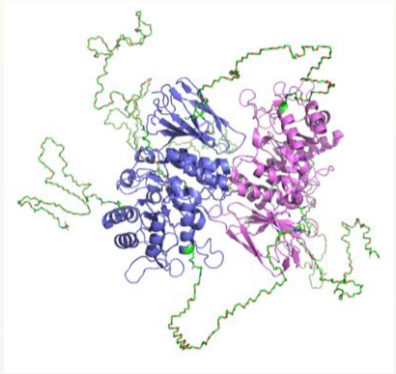
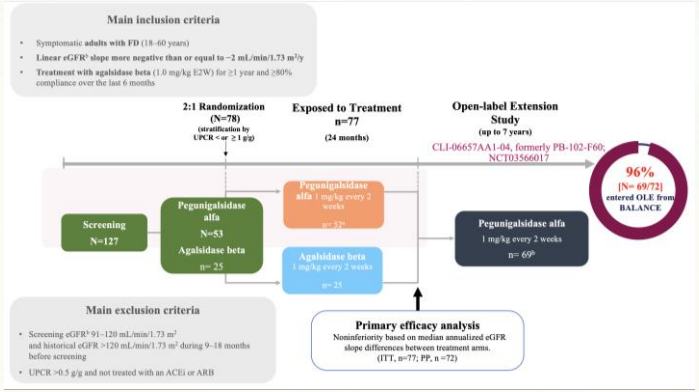
MGM Reports

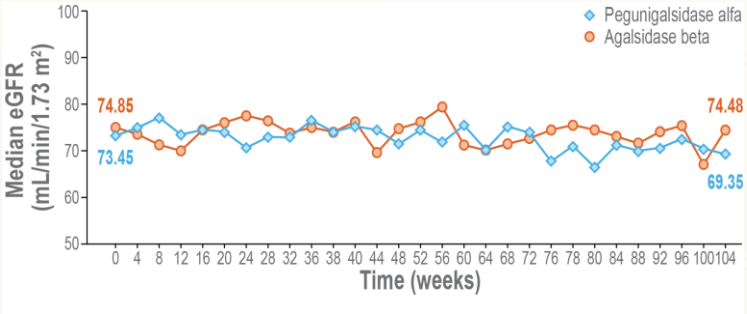
The effect of enzyme replacement therapy on clinical outcomes in male patients with Fabry disease: A systematic literature review by a European panel of experts

Dominique P. Germain[a,*], Perry M. Elliott[b], Bruno Falissard[c], Victor V. Fomin[d], Max J. Hilz[e], Ana Jovanovic[f], Ilkka Kantola[g], Aleš Linhart[r], Renzo Mignani[i], Mehdi Namdar[j], Albina Nowak[k], João-Paulo Oliveira[l], Maurizio Pieroni[m], Miguel Viana-Baptista[n], Christoph Wanner[o], Marco Spada[p]

Thérapies enzymatiques substitutives







Original research

Head-to-head trial of pegunigalsidase alfa versus agalsidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year randomised phase III BALANCE study

Eric L Wallace,[1] Ozlem Goker-Alpan,[2] William R Wilcox,[3] Myrl Holida,[4] John Bernat,[4] Nicola Longo,[5] Aleš Linhart,[6] Derralynn A Hughes,[7] Robert J Hopkin,[8] Camilla Tøndel,[9,10] Mirjam Langeveld,[11] Pilar Giraldo,[12,13] Antonio Pisani,[14] Dominique Paul Germain,[15] Ankit Mehta,[16] Patrick B Deegan,[17] Maria Judit Molnar,[18] Damara Ortiz,[19] Ana Jovanovic,[20] Michael Muriello,[21] Bruce A Barshop,[22] Virginia Kimonis,[23] Bojan Vujkovac,[24] Albina Nowak,[25] Tarekegn Geberhiwot,[26] Ilkka Kantola,[27] Jasmine Knoll,[28] Stephen Waldek,[29] Khan Nedd,[30] Amel Karaa,[31] Einat Brill-Almon,[32] Sari Alon,[33] Raul Chertkoff,[32] Rossana Rocco,[34] Anat Sakov,[35] David G Warnock[1]

Pegunigalsidase alfa: a novel, pegylated recombinant alpha-galactosidase enzyme for the treatment of Fabry disease

Dominique P. Germain[1,2]* and Ales Linhart[2]

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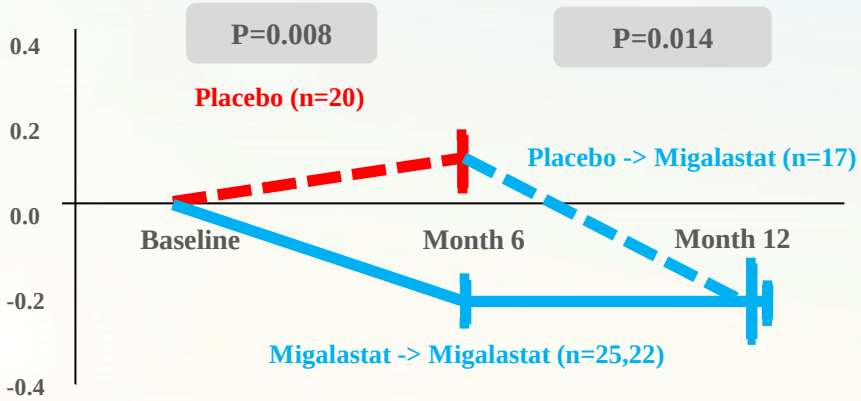
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat

D.P. Germain, D.A. Hughes, K. Nicholls, D.G. Bichet, R. Giugliani, W.R. Wilcox, C. Feliciani, S.P. Shankar, F. Ezgu, H. Amartino, D. Bratkovic, U. Feldt-Rasmussen, K. Nedd, U. Sharaf El Din, C.M. Lourenco, M. Banikazemi, J. Charrow, M. Dasouki, D. Finegold, P. Giraldo, O. Goker-Alpan, N. Longo, C.R. Scott, R. Torra, A. Tuffaha, A. Jovanovic, S. Waldek, S. Packman, E. Ludington, C. Viereck, J. Kirk, J. Yu, E. Benjamin, F. Johnson, D.J. Lockhart, N. Skuban, J. Castelli, J. Barth, C. Barlow, and R. Schiffmann



Germain et al. Orphanet Journal of Rare Diseases 2012, 7:91
http://www.ojrd.com/content/7/1/91

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Safety and pharmacodynamic effects of a pharmacological chaperone on α-galactosidase A activity and globotriaosylceramide clearance in Fabry disease: report from two phase 2 clinical studies

Dominique P Germain[1*†], Roberto Giugliani[2†], Derralynn A Hughes[3], Atul Mehta[3], Kathy Nicholls[4], ..aura Barisoni[5], Charles J Jennette[6], Alexander Bragat[7], Jeff Castel[7], Sheela Sitaraman[7], David J Lockhart[7] and Pol F Boudes[7]

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ARTICLE Genetics inMedicine

Efficacy of the pharmacologic chaperone migalastat in a subset of male patients with the classic phenotype of Fabry disease and migalastat-amenable variants: data from the phase 3 randomized, multicenter, double-blind clinical trial and extension study

Dominique P. Germain, MD, PhD[1], Kathy Nicholls, MD[2], Roberto Giugliani, MD, PhD[3], Daniel G. Bichet, MD[4], Derralynn A. Hughes, MD, PhD[5], Laura M. Barisoni, MD[6], Robert B. Colvin, MD[7], J. Charles Jennette, MD[8], Nina Skuban, MD[9], Jeffrey P. Castelli, PhD[9], Elfrida Benjamin, PhD[9], Jay A. Barth, MD[9] and Christopher Viereck, PhD[9]

Contributions à l'étude de la maladie de Fabry

Non-invasive evaluation of arterial involvement in patients affected with Fabry disease

Pierre Boutouyrie, Stéphane Laurent, Brigitte Laloux, Olivier Lidove, Jean-Pierre Grunfeld, Dominique P Germain

BMC Medical Genetics

BioMed Central

Research article

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Patients affected with Fabry disease have an increased incidence of progressive hearing loss and sudden deafness: an investigation of twenty-two hemizygous male patients

Dominique P Germain*[1], Paul Avan[2], Augustin Chassaing[1] and Pierre Bonfils[3]

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CLINICAL GENETICS
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Letter to the Editor

Osteopenia and osteoporosis: previously unrecognized manifestations of Fabry disease

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CLINICAL GENETICS
doi: 10.1111/cge.12613

Original Article

X-chromosome inactivation in female patients with Fabry disease

L. Echevarria[a,b], K. Benistan[b], A. Toussaint[c], O. Dubourg[d], A.A. Hagege[e], D. Eladari[f], F. Jabbour[g], C. Beldjord[c], P. De Mazancourt[g] and D.P. Germain[a,b,g]

Echevarria L., Benistan K., Toussaint A., Dubourg O., Hagege A.A., Eladari D., Jabbour F., Beldjord C., De Mazancourt P., Germain D.P.
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Fabry disease (FD) is an X-linked genetic disorder caused by the deficient

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REVIEW

CLINICAL GENETICS WILEY

Challenging the traditional approach for interpreting genetic variants: Lessons from Fabry disease

Dominique P. Germain[1,2] | Thierry Levade[3,4] | Eric Hachulla[5] | Bertrand Knebelmann[6] | Didier Lacombe[7,8] | Vanessa Leguy Seguin[9] | Karine Nguyen[10] | Esther Noël[11] | Jean-Pierre Rabès[2,12]

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REVIEW ARTICLE

Molecular Genetics & Genomic Medicine WILEY

The benefits and challenges of family genetic testing in rare genetic diseases—lessons from Fabry disease

Dominique P. Germain[1,2,3,4] | Sergey Moiseev[5] | Fernando Suárez-Obando[6] | Faisal Al Ismaili[7] | Huda Al Khawaja[8] | Gheona Altarescu[9] | Fellype C. Barreto[10] | Farid Haddoum[11] | Fatemeh Hadipour[12] | Irina Maksimova[13] | Mirelle Kramis[14] | Sheela Nampoothiri[15] | Khanh Ngoc Nguyen[16] | Dau-Ming Niu[17,18] | Juan Politei[19] | Long-Sun Ro[20] | Dung Vu Chi[16] | Nan Chen[21] | Sergey Kutsev[22]