Consensus conference on Allogenic Hematopoietic Stem Cell (AHSCT) versus Orthotopic Live transplantation (OLT) as enzyme replacement therapy in Mitochondrial Neuro-Gastro-Intestinal Encephalomyopathy (MNGIE)

Carlo Casali e Consorzio ItaMNGIE

Dip SBMC - Roma Sapienza – Roma

Objectives: To describe the results of a Consensus Conference on Enzyme replacement theraphy in Mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE). MNGIE is a rare autosomal recessive mitochondrial disease caused by mutations of TYMP gene (with a markedly reduced TP activity) which is known to result in nucleoside accumulation and related mtDNA damage. The phenotype is characterized by gastrointestinal and neurological manifestations with an unavoidable fatal outcome. The ideal treatment is based on TP replacement, which has been first achieved with allogenic hematopoietic stem cell transplantation (AHSCT), which is associated to a very high mortality. Thus, other tissue sources of TP have been investigated. We have recently characterized TP in human liver and demonstrated that TYMP transcript is endogenously synthesized and expressed in comparable amounts to that detectable in the bone marrow. This in turns pointed to orthotopic liver transplantation (OLT) as an alternative to AHSCT. So far 2 MNGIE patients have received worldwide, one in the US and one in Italy, with encouraging results both in terms of biochemical correction and outcome. In view of the availability of such a novel approach to treatment of MNGIE, an international consensus conference was convened in Innsbruck on February 2016 to discuss the clinical and laboratory criteria which should be met in order to select patients for either procedure.

doi:10.1093/brain/aww226 BRAIN 2015: 138; 2847–2858 | 2847

BRAIN
A JOURNAL OF NEUROLOGY

Allogeneic haematopoietic stem cell transplantation for mitochondrial neurogastrointestinal encephalomyopathy

Joerg P. Halter,[1,*] W. Michael M. Schüpbach,[2,3,*] Hanna Mandel,[4] Carlo Casali,[5] Kim Orchard,[6] Matthew Collin,[7] David Valcarcel,[8] Attilio Rovelli,[9] Massimiliano Filosto,[10] Maria T. Dotti,[11] Giuseppe Marotta,[12] Guillem Pintos,[13] Pere Barba,[8] Anna Accarino,[8] Christelle Ferra,[14] Isabel Illa,[15] Yves Beguin,[16] Jaap A. Bakker,[17] Jaap J. Boelens,[18] Irenaeus F. M. de Coo,[19] Keith Fay,[20] Carolyn M. Sue,[21] David Nachbaur,[22] Heinz Zoller,[22] Claudia Sobreira,[23] Belinda Pinto Simoes,[24] Simon R. Hammans,[25] David Savage,[26] Ramon Martí,[8,27] Patrick F. Chinnery,[7] Ronit Elhasid,[28] Alois Gratwohl[1,#] and Michio Hirano[29,#]

unrelated donors ($n = 15$) in 15 institutions worldwide were analysed for outcome and its associated factors. Overall, 9 of 24 patients (37.5%) were alive at last follow-up with a median follow-up of these surviving patients of 1430 days. Deaths were

neurogastrointestinal encephalomyopathy in the long term. Allogeneic haematopoietic stem cell transplantation should be considered for selected patients with an optimal donor.

Liver as a Source for Thymidine Phosphorylase Replacement in Mitochondrial Neurogastrointestinal Encephalomyopathy

Elisa Boschetti[1,2], Roberto D'Alessandro[3], Francesca Bianco[1], Valerio Carelli[2], Giovanna Cenacchi[2], Antonio D. Pinna[1], Massimo Del Gaudio[1], Rita Rinaldi[4], Vincenzo Stanghellini[1], Loris Pironi[1], Kerry Rhoden[1], Vitaliano Tugnoli[2], Carlo Casali[5], Roberto De Giorgio[1]*

1 Department of Surgical and Medical Sciences, University of Bologna, Bologna, Italy, 2 Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy, 3 Institute of Neurological Sciences, University of Bologna, Bologna, Italy, 4 Neurology Unit, St. Orsola-Malpighi Hospital, Bologna, Italy, 5 Department of Medico-Surgical Sciences and Biotechnologies, University 'La Sapienza', Rome, Italy

Abstract

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive mitochondrial disease associated with mutations in the nuclear *TYMP* gene. As a result, the thymidine phosphorylase (TP) enzyme activity is markedly reduced leading to toxic accumulation of thymidine and therefore altered mitochondrial DNA. MNGIE is characterized by severe gastrointestinal dysmotility, neurological impairment, reduced life expectancy and poor quality of life. There are limited therapeutic options for MNGIE. In the attempt to restore TP activity, allogenic hematopoietic stem cell transplantation has been used as cellular source of TP. The results of this approach on ~20 MNGIE patients showed gastrointestinal and neurological improvement, although the 5-year mortality rate is about 70%. In this study we tested whether the liver may serve as an alternative source of TP. We investigated 11 patients (7M; 35–55 years) who underwent hepatic resection for focal disorders. Margins of normal liver tissue were processed to identify, quantify and localize the TP protein by Western Blot, ELISA, and immunohistochemistry, and to evaluate *TYMP* mRNA expression by qPCR. Western Blot identified TP in liver with a TP/GAPDH ratio of 0.9±0.5. ELISA estimated TP content as 0.5±0.07 ng/μg of total protein. TP was identified in both nuclei and cytoplasm of hepatocytes and sinusoidal lining cells. Finally, *TYMP* mRNA was expressed in the liver. Overall, our study demonstrates that the liver is an important source of TP. Orthotopic liver transplantation may be considered as a therapeutic alternative for MNGIE patients.

Citation: Boschetti E, D'Alessandro R, Bianco F, Carelli V, Cenacchi G, et al. (2014) Liver as a Source for Thymidine Phosphorylase Replacement in Mitochondrial Neurogastrointestinal Encephalomyopathy. PLoS ONE 9(5): e96692. doi:10.1371/journal.pone.0096692

Editor: Paul A. Cobine, Auburn University, United States of America

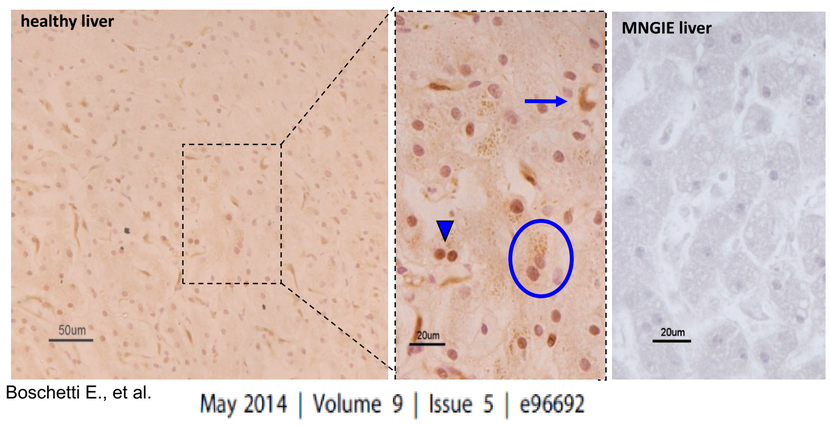
Received January 15, 2014; **Accepted** April 10, 2014; **Published** May 6, 2014

Funding: This work was partly supported by grants from the Italian Ministry of Health (Ricerca Finalizzata 2009 RF2009) and funds from University of Bologna (R. De G.). R. De G., V. T. and E. B. were the recipients of grants from "Fondazione Del Monte di Bologna e Ravenna", Bologna, Italy. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: roberto.degiorgio@unibo.it

TP in healthy liver



Boschetti E., et al. May 2014 | Volume 9 | Issue 5 | e96692

TP nuclei = blue triangle
TP sinusoidal lining cell = blue arrow
TP cytoplasm = blue circle

Case history - VMA, M, 25 anni

Genitori consanguinei (figli di cugini).

Nessuna familiarità di rilievo (ipoacusia e diabete nei nonni, in età avanzata).

Fino ai 19-20 anni vita normale, eccetto un episodio di subocclusione intestinale da bambino, trattato con lassativi.

Dai 19 anni:

- Artriti ricorrenti
- Diarrea cronica con diagnosi di IBD
- Parziale risposta a cicli di t. steroidea e salazopirina

Dal maggio 2014 peggioramento della motilità intestinale con episodi di subocclusione e calo ponderale (BMI 13,4)

Inizio alimentazione parenterale

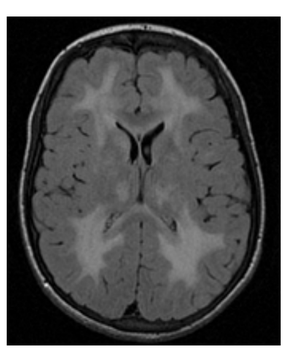
EON: sostanzialmente negativo (ROT deboli, Romberg +/-)

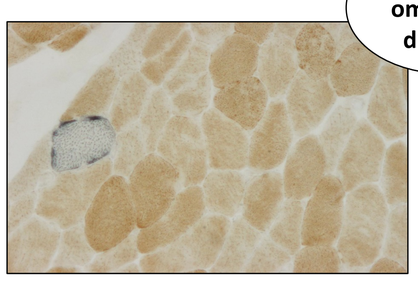
EMG: polineuropatia demielinizzante (VC ≈ 20-25 m/s)

RM encefalo: compatibile con MNGIE

BX Muscolo: COX negative; del mult mtDNA

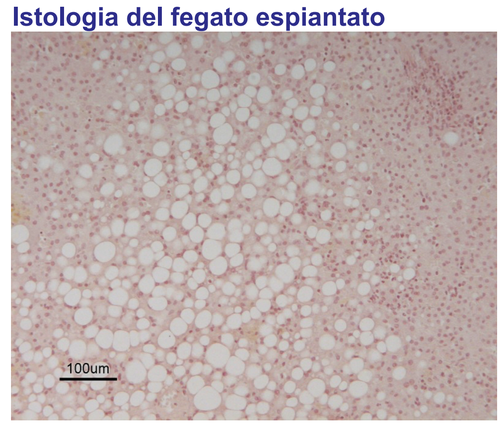
Dosaggio TP: 4 (vn> 252)

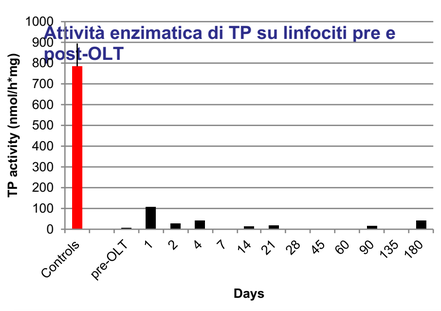


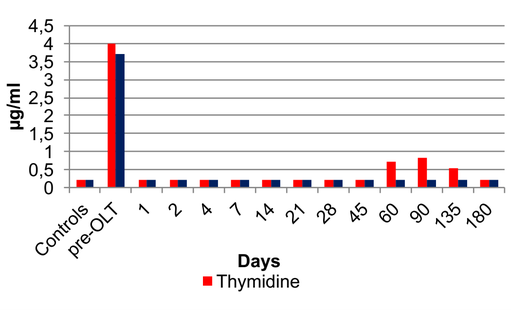


mutazione omozigote di *TYMP*

Istologia del fegato espiantato







- HSCT meglio tollerata nella popolazione pediatrica e da donatori familiari HLA compatibili
- Fegato frequentemente coinvolto in MNGIE (evoluzione cirrotica?)

The Consensus Conference recommended:

AHSCT: for pediatric patients
HLA-matched family donors available.

OLT : for adult patients
signs of substancial liver damage

Transiently benetifing therapuetic options as well as future direct gene replacement could also be considered, while selecting best suitable tratments in individual patients

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