Safety and efficacy of Interferon gamma in Friedreich ataxia, using clinical and paraclinical indicators of disease

A. Martinuzzi1, M. Vavla1, G. D’Angelo1, F. Arrigoni1, N. Toschi, D. Peruzzo1, S. Gandossini1, A. Russo1, E. Diella, R. Salati1, P. Scarpazza1, R. Luffarelli1, S. Fortuni1, I. Condà1, R. Testi2

1: Dipartimento di Conegliano-Piece di Soligo e Bosisio Parini - IRCCS E. Medea
2: Biomedicine and Prevention - Rome Tor Vergata - Roma

Flow chart of the trial protocol

**Introduzione**

Friedreich’s ataxia (FRDA) is the most frequent ataxia among the autosomal recessively inherited ataxias, with a prevalence of 1 in 30,000-50,000 people. It is caused by a GAA triplet expansion in the first intron of FXN gene, leading to a deficit in frataxin. FRDA is a primary degenerative disorder affecting the degeneration of the sensory neurons of spinal ganglia (DRG) and of glutamatergic neurons of the dentate nucleus of the cerebrum. Progressive cardiomyopathy is also a cardinal feature. There is still no cure for FRDA. Significant evidence has supported the possible use of recombinant interferon gamma (rIFNg) as a therapeutic in FRDA. It was observed that DRG sensory neurons produce and respond to rIFNg in an autocrine fashion. In an initial study, it was shown that rIFNg promotes the accumulation of frataxin in FRDA-derived cells in vitro and in the DRG neurons of YG8R mice in vivo, resulting in their improved motor performances. This study was followed by two clinical Phase II studies that demonstrated a good safety profile and possible clinical improvement in FRDA patients. More recently, a larger and randomized clinical trial could not measure significant benefits over a 6-months placebo-controlled treatment period, while detecting a slower than expected disease progression in FRDA patients during the 1 year open-label extension of the study. A major issue when measuring efficacy in clinical trials for FRDA is the generally poor sensitivity of the clinical scales used to quantitate disease status, given the individual variability and the slow progression of the disease. The use of objective instrumental measurements in addition of a pre- and post-treatment observation points to clearly define natural disease progression and focusing on younger subjects in whom disease progression is faster, could circumvent this problem.

**Metodi**

Patients were dosed with recombinant human IFNg 1b (IMUKIN ®), 100 mg, 3 times/week for the first 2 weeks (Dose 1) and with 200 mg, 3 times/week (Dose 2) for the following 4 weeks. Patients were assessed with the Scale for Assessing and Rating Ataxia (SARA) 6 months before starting the trial (T-6), at the start of the trial (T0), after 3 months of treatment (T3), at the end of the trial (T6) and 6 months after trial termination (T12). They went through ECG, EchoCG and Optical coherence tomography (OCT) evaluations at T0, T5, T12, and after MRI scans at T-6, T0, T6 and T12. Patients filled out the self-assessment questionnaires WHO DAS 2.0, for disability assessment, and SF36 on perceived quality of life, at T0, T3, T6 and T12. Blood samples for frataxin quantitation were processed at T0, T6 and T12. The task fMRI protocol was a standard block design finger tapping task, involving both hands, as previously described. The fMRI data for the motor task were preprocessed combining multiple tools (FSL, ANTs, SPM). Statistical analysis. All variables and biomarkers were analyzed using multivariate linear mixed models which modeled timepoints as a repeated within-subject factor and a Toeplitz unstructured estimate of the covariance matrix.

**Risultati**

The treatment was generally well tolerated with mainly minor adverse events immediately following the drug assumption. The results observed in the SARA score revealed no ECG, EchoCG changes and the MRI responses are shown in the figures show above. The structural and functional evaluation of the heart through echocardiography and electrocardiography showed some significant differences in measurements taken at the various time points during IFNg treatment. Interventricular septum thickness decreased after treatment and showed a sharp rebound after treatment discontinuation. fMRI analysis clearly points towards a reorganization of different sensory-motor networks during and after the treatment. An enhanced activation of the motor cortex during dominant hand movements was detected by fMRI at the end of the treatment compared to T0. A negative correlation between the enhanced motor cortex activation and the progression of the SARA score was detected between T0 and T6, suggesting that the fMRI modifications we observed during both hand movements corresponded to a more generalized clinical improvement. No changes were observed in PBMC frataxin content.

**Conclusioni**

The study shows the feasibility of a novel design that increases the power by allowing a case by case evaluation of treatment compared to natural progression and indicates which paraclinical measures can be sensible to change in the short time of a typical RCT (six months). The open design of the study prevents the conclusive identification of IFNg as an effective therapy for Friedreich ataxia, but gives clear indications that the molecule deserves more attention especially in consideration of the negative results of a recently completed RCT that showed several methodological problems possibly overshadowing a clinical benefit.

**Bibliografia**


