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# Interferon gamma may improve cardiac function in Friedreich's ataxia cardiomyopathy

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Freidreich's ataxia (FRDA) is an autosomal recessive hereditary disease with a prevalence of about 1 in 30,000, characterized by progressive neurologic impairment [1]. In addition, almost all patients have abnormal echocardiograms and more than 50% develop hypertrophic cardiomyopathy [2]. Survival in FRDA is determined by cardiac complications, and progressive decline of left ventricular function is a negative prognostic factor [2].

The FRDA phenotype results from mutations (commonly an expanded GAA repeat sequence) attenuating expression of the FXN gene encoding *frataxin*, a mitochondrial protein involved in iron metabolism [3]. Thus, in FRDA, the frataxin protein is normal, but its expression level is reduced, resulting in mitochondrial dysfunction which leads to attenuated oxidative phosphorylation, increased oxidative stress, iron accumulation and inflammation [4]. In the heart, the result is a variable mixture of increased ventricular mass, replacement fibrosis, impaired myocardial perfusion, increased troponin levels and systolic as well as diastolic dysfunction.

As yet there is no effective therapy for FRDA cardiomyopathy. However, small-scale trials of the antioxidant agents *co-enzyme* $Q_{10}$ and *idebenone* have reported modest beneficial effect on hypertrophy and systolic function [5]. Recently, *interferon gamma* (INFγ) was found to increase FXN gene expression in cells derived from FRDA patients, and to improve neurological function in FRDA mice [6]. Likewise, an open-label study of INFγ in children reported neurological improvement and minimal adverse reactions [7], and gene therapy restoring frataxin levels after the onset of heart failure in mice FRDA completely reversed the cardiomyopathy [8]. To the best of our knowledge, a possible therapeutic effect of INFγ on human FRDA cardiomyopathy has not been explored.

Here, we report the effect of INFγ therapy in a single patient suffering from severe FRDA cardiomyopathy. At baseline, our female patient was 18 years old with a BMI of 21.9. She was diagnosed with severe hypertrophic cardiomyopathy with preserved systolic but attenuated diastolic function at the age of 9, and severe FRDA at the age of 10 with GAA expansion to appr. 700 repeats in both alleles. During the last couple of years, she had experienced several hospital admissions for heart failure with preserved ejection fraction. She used metoprolol, disopyramide, ivabradine, ibedenone, ranitidine, esomeprazole, and fluoxetine on a regular basis. Because of her poor cardiac condition, experimental INFγ therapy was considered advisable despite the lack of research evidence in humans. The patient consented to the treatment plan, which complied with the Declaration of Helsinki; however, as the treatment was initiated for clinical reasons, not research purposes, no approbation was sought from the Regional Ethics Committee.

Treatment was initiated in October 2014. INFγ was administered as subcutaneous injections three times per week. Dosages were gradually increased from 10 μg up to 100 μg over two months; a further increment to 150 μg was instituted after 8 months of treatment. No other medication was initiated or altered during the INFγ treatment period.

Effect was monitored at predefined intervals (3, 6, 12, 24, 33 and 50 weeks after baseline). Echocardiography (Vivid 7, GE Healthcare, Buckinghamshire, UK) was performed by one investigator (VBW); markers of left ventricular hypertrophy (mean wall thickness), systolic function (shortening fraction) and diastolic function (mitral E/A flow, left ventricular untwist rate (2D strain Echopac® software version 113.1)) were independently assessed by another investigator (HB) who was masked for date of examination. Resting ECG recordings (Eli 350, Mortara Instruments, Milwaukee, WI, USA) were used to obtain

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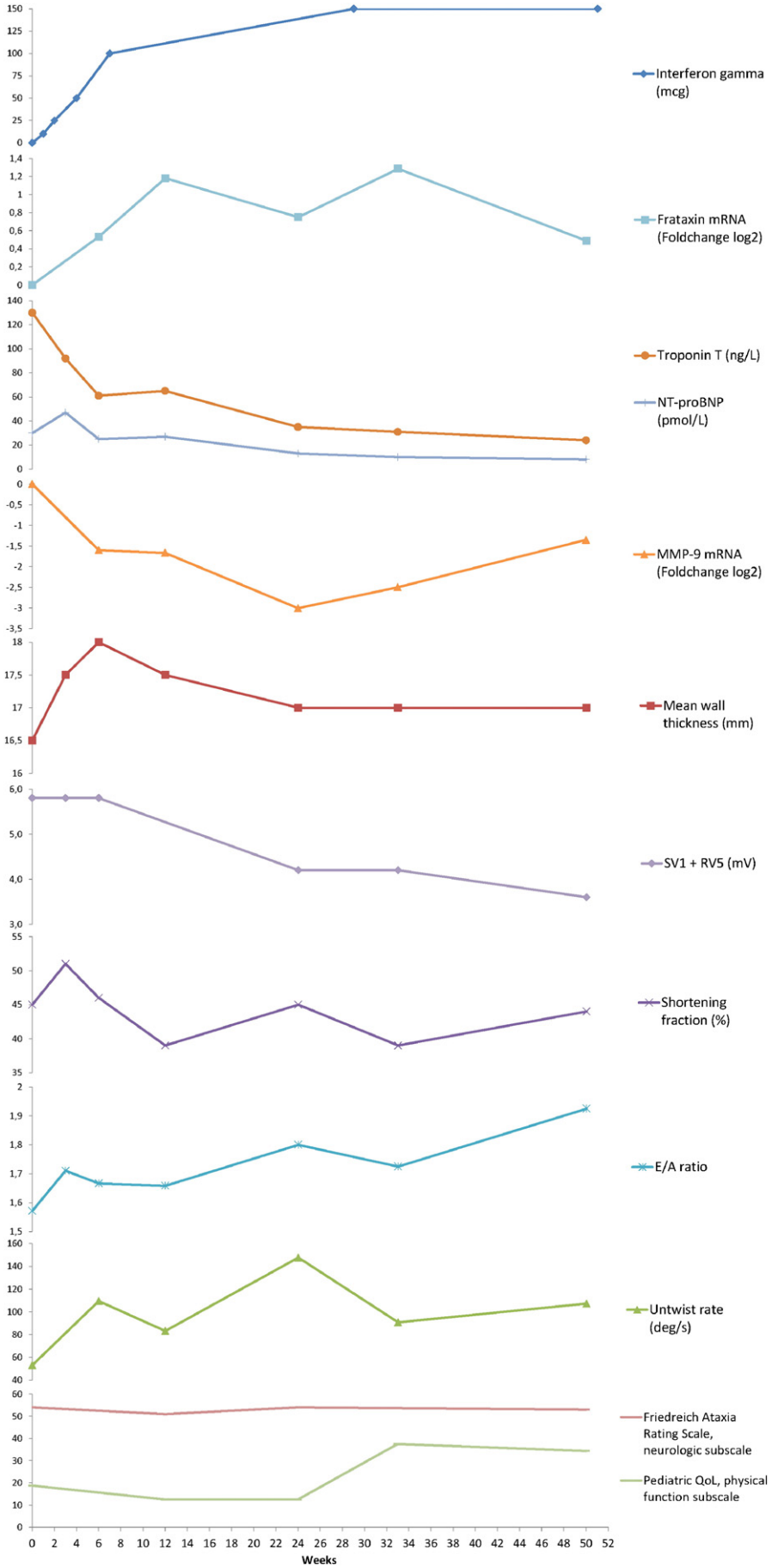


**Fig. 1.** One patient with Friedreich's ataxia hypertrophic cardiomyopathy treated with interferon gamma: dosages, biochemical markers, echocardiographic markers, ECG markers and clinical variables during the one year treatment period.

the Sokolow index (S in $V_1$ + R in $V_5$). Ambulant 48-hour ECG recordings (Medilog AR4(+), Schiller, Baar, Switzerland) were checked for arrhythmias. Troponin T and NT-proBNP were assayed by routine laboratory methods. Whole blood mRNA of frataxin and matrix metalloproteinase 9 (MMP-9, a marker of cardiac remodelling) [9] were assayed by real-time quantitative polymerase chain reaction (7900 HT Real-Time PCR System, Applied Biosystems, Foster City, CA, USA); frataxin expression levels were normalized to those of the housekeeping gene peptidylproplyl isomerase B. Again, masking for date of examination was ensured. Neurological impairments were assessed by the same investigator (SP) using the Friedreich Ataxia Rating Scale (FARS) [10]. Quality of life was charted by a questionnaire.

During the course of INFγ treatment, levels of troponin T and NT-proBNP as well as the Sokolow index decreased, whereas frataxin levels, markers of diastolic function (E/A ratio, untwist rate), markers of cardiac remodelling (MMP-9) and quality of life tended to improve (Fig. 1). Shortening fraction, wall thickness and FARS score remained largely unaltered.

Apart from the prescheduled visits, the patient was hospitalized for one day 8 weeks after treatment initiation due to chest pain, nausea and general malaise. She was slightly dehydrated, and improved spontaneously after rehydration therapy. There were no other serious adverse events during the treatment period; in particular, repeated resting and ambulant ECG did not reveal any pro-arrhythmic tendency.

In conclusion, INFγ treatment seemed to attenuate cardiomyocyte damage and improve diastolic function in our patient. No serious side effects were registered. Thus, INFγ treatment might be a promising therapy option for FRDA hypertrophic cardiomyopathy, which is otherwise characterized by progressive decline of cardiac function and a poor long-term outcome [2]. A cardiomyocyte protective effect might be an argument for early therapy initiation in an attempt to prevent irreversible tissue damage. It is possible that the observed reduction of troponin T levels in our patient is due to fibrosis progression and actually a worsening of the cardiomyopathy. However, this seems unlikely in light of the concomitant improvement of echocardiographic markers and NT-proBNP levels.

Results from a case report must be interpreted with great caution; ideally, a randomized controlled trial should be undertaken in order to assess the effects and safety of INFγ treatment in FRDA cardiomyopathy. In our patient, cardiac MRI and myocardial biopsy might have provided additional information about treatment effects.

## Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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