# Safety and Efficacy of Interferon γ in Friedreich's Ataxia

Friedreich's ataxia (FRDA) is the most frequent among the autosomal recessive ataxias, caused by an insufficient production of the mitochondrial protein frataxin and characterized by a number of sensorimotor deficits that, together with progressive heart failure, reduce life expectancy.[1] There is no approved cure for FRDA.[2]

We report here the results of an open-label clinical trial testing the safety and efficacy of recombinant human interferon γ (IFNγ)-1b (Imukin, Boheringer Ingelheim, Germany) in a group of 12 young FRDA patients treated for 6 months. The treatment was safe, with only 2 serious adverse effects, both spontaneously resolved, and 1 termination as a result of a refusal by the patient to continue the treatment despite resolution of the event. Otherwise the treatment was reasonably well tolerated with the occurrence of common adverse events known to be associated with IFNγ treatment.

Efficacy was measured by the Scale for the Assessment and Rating of Ataxia (SARA), by cardiac parameters, and by frataxin quantitation using a longitudinal design in which disease progression is monitored before and after therapy so that each patient is an effective control for him/herself.

In the 11 patients who completed the treatment, SARA scores increased an average of $2.7 \pm 0.7$ points from evaluation completed 6-12 months prior to medication start (Tpre) to treatment start (T0) (Fig. 1A,B). On the contrary, nonsignificant and slightly negative changes in the SARA score were measured during IFNγ treatment. The SARA score resumed a moderate uptrend after the discontinuation of the treatment. The progression of SARA was therefore completely halted during IFNγ treatment ($P = 0.013$), strongly suggesting efficacy. Blockade of SARA progression in the group was significant even when considering 3 poorly responding patients.

Among the cardiac parameters investigated, the end diastolic interventricular septal wall thickness and the Sokolow-Lyon index were reduced by the treatment (Fig. 1C,D). Both parameters rebounded 6 months after termination of the treatment.

Additional cardiac parameters and frataxin quantitation in peripheral blood mononuclear cells did not provide significant indications (see Supporting Information).

IFNγ promotes frataxin accumulation and improves motor performances in FRDA mice.[3] Two clinical phase II studies suggested possible clinical improvement in FRDA patients.[4,5] The successful use of IFNγ in the treatment of the cardiac manifestations of FRDA was also reported.[6] Recently, a large, multicenter study could not detect significant changes in the modified Friedreich Ataxia Rating Scale scores between IFNγ-dosed and placebo-dosed groups for 26 weeks. However, the high variability of the modified Friedreich Ataxia Rating Scale scores caused the study to be statistically underpowered. Moreover, the wrong timing in drug dosing caused transient side effects to interfere with the neurological assessments. Nevertheless, in the open-label extension of the study, the patients who received IFNγ for 52 weeks showed a more stable disease course compared to the natural history data.[7]

A relevant indication that emerges from our study, the previously mentioned study,[7] and from the numerous FRDA patients using IFNγ off label is the possible presence of nonresponders. A randomized withdrawal design is therefore best suited to increase the power of future clinical trials to definitively assess the efficacy of IFNγ treatment in FRDA.

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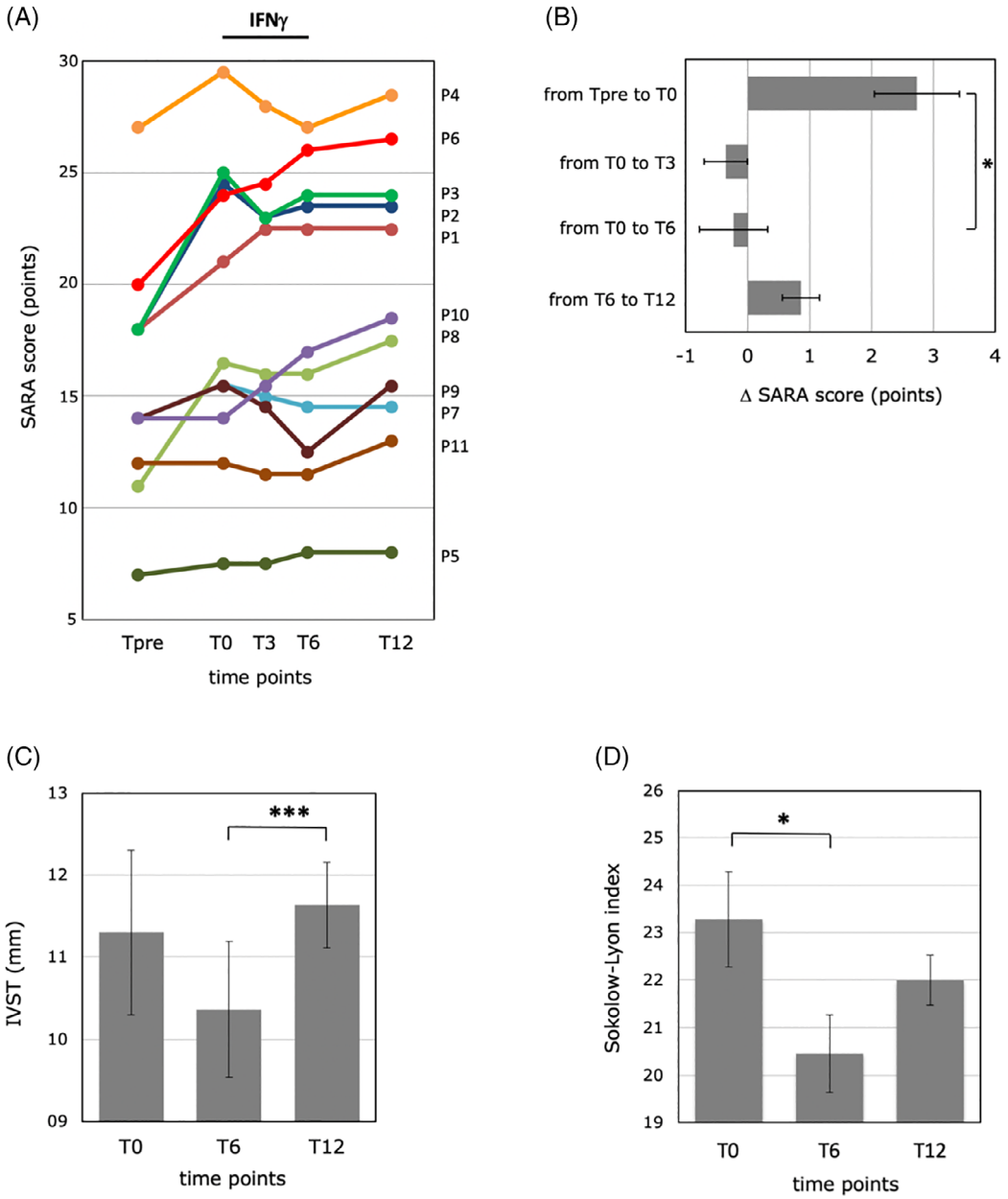


**FIG. 1.** Scale for the Assessment and Rating of Ataxia (SARA) scores were acquired 6 to 12 months (average 6.8 months) before the start of the interferon γ (IFNγ) treatment (Tpre), before the start of the treatment (T0), after 3 (T3) and 6 months of treatment (T6), and 6 months after the termination of the treatment (T12). (**A**) SARA scores of each of the 11 patients who terminated the study. (**B**) Mean ± standard error of SARA score changes of the study group. A significant SARA score change occurred between Tpre and T0 ($P = 0.002$), whereas the SARA score did not change during the treatment, from T0 to T3 ($P = 1$) or from T0 to T6 ($P = 1$) and after the discontinuation of the treatment from T6 to T12 ($P = 0.57$). *SARA score progression from Tpre (normalized at 6 months) to T0 differed significantly from SARA score progression from T0 to T6 ($P = 0.013$). (**C**) Echocardiographic measure of the interventricular septal wall thickness (IVST) at T0, T6, and T12. The *y* axis indicates the mean ± standard error of the mean of IVST in the study group. A trend toward reduction of IVST was detected during the treatment (T0 vs. T6, $P = 0.47$), whereas a significant rebound of the IVST (***) was detected after termination of the treatment (T6 vs. T12, $P = 0.003$). (**D**) The Sokolow-Lyon index measured by electrocardiography (SV1 + RV5) at T0, T6, and T12. The *y* axis indicates the mean ± standard error of the mean of Sokolow-Lyon index in the study group. *A significant decrease of the index was detected during treatment (T0 vs. T6, $P = 0.036$), with a rebounding trend at T12. Superimposable results were obtained when the index was calculated as SV1 + RV6 (not shown).


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## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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## Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

M.V.: 1B, 1C, 3A, 3B
M.G.D.A.: 1B, 3A, 3B
F.A.: 3A, 3B
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Nothing to report.