NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE/ARAŞTIRMA MAKALESİ

Arch Neuropsychiatry 2020;57:270–273
https://doi.org/10.29399/npa.25047

Efficacy and Tolerability of Interferon Gamma in Treatment of Friedreich's Ataxia: Retrospective Study

Friedreich Ataksisi Tedavisinde İnterferon Gama Etkinliği ve Tolerabilitesi: Retrospektif Çalışma

Mehmet Fatih YETKİN[1], **Murat GÜLTEKİN**[1]

[1]Department of Neurology, School of Medicine, Erciyes University, Kayseri, Turkey

ABSTRACT

Friedreich's Ataxia (FRDA) is the most common form of autosomal recessive ataxia. The disease primarily results from a GAA trinucleotide repeat expansion within the FXN gene in up to 97% of patients. The clinical presentation begins approximately between the ages of 5 and 15. The major clinical findings of FRDA are progressive extremity and gait ataxia. Although it is known that the disease is caused by low levels of functional protein in the target tissues, there is no effective treatment available for this pathology. However, significant improvements have been achieved in the research into pharmacological treatments for FRDA in recent years. Interferon-gamma (IFN-γ) has been shown to induce frataxin production in many cell types. In this study, the clinical features, tolerability, and the prognosis of individuals with FRDA to whom IFN-γ was administered in a university hospital were evaluated retrospectively and the results were discussed. To the best of our knowledge, this is the first study conducted in our country to evaluate the effect of IFN gamma on this patient group.

Keywords: Ataxia, interferon gamma, Friedreich's ataxia

ÖZ

Friedreich Ataksisi (FRDA) en yaygın otozomal resesif ataksidir. Hastalık, hastaların %97'sine yakınında FXN geninde GAA trinükleotid tekrar artışından kaynaklanır. Klinik prezentasyon yaklaşık 5 ile 15 yaşları arasında başlar. FRDA'nın başlıca klinik bulguları progresif ekstremite ve yürüyüş ataksisidir. Hastalığın hedef dokulardaki düşük fonksiyonel protein düzeylerinden kaynaklandığı bilinmesine rağmen, bu patoloji için etkili bir tedavi yoktur. Bununla birlikte, son yıllarda FRDA için farmakolojik tedavilerle ilgili araştırmalarda önemli gelişmeler sağlanmıştır. İnterferon-gama (IFN-γ)'nın birçok hücre tipinde frataksin üretimini indüklediği gösterilmiştir. Bu çalışmada bir üniversite hastanesinde IFN-γ uygulanan FRDA'lı bireylerin klinik özellikleri, toleransı ve prognozu retrospektif olarak değerlendirilmiş ve sonuçlar tartışılmıştır. Bildiğimiz kadarıyla bu çalışma ülkemizde IFN-γ'nın bu hasta grubu üzerindeki etkisini değerlendirmek için yapılan ilk çalışmadır.

Anahtar Kelimeler: Ataksi, interferon gama, Friedreich ataksisi

Cite this article as: Yetkin MF, Gültekin M. Efficacy and Tolerability of Interferon Gamma in Treatment of Friedreich's Ataxia: Retrospective Study. Arch Neuropsychiatry 2020; 57:270-273.

INTRODUCTION

Friedrich's Ataxia (FRDA) is the most common form of autosomal recessive ataxia. The prevalence was set approximately to 1.7–4.7/100.000 (1). The disease results from a GAA trinucleotide repeat expansion within the FXN gene in 97% of patients while 3% have a GAA trinucleotide repeat in one allele and a point mutation or homozygous deletion in the other allele. These mutations lead to a frataxin deficiency (2, 3). The clinical presentation begins approximately between the ages of 5 and 15 years. The onset of the disease before the age of 20 is one of the prominent features (4). The major clinical findings of FRDA are progressive extremity and gait ataxia. In neurological examination, cerebellar disorders and pathological reflexes such as deep sensory impairment and positive Babinski sign can be observed. These findings are seen commonly within the early periods of treatment. Skeletal deformities can also be seen in patients (5). Although it is known that the disease is caused by low levels of functional protein in the target tissues, there is no effective treatment available for this pathology. In recent years, several treatment methods have been adopted to increase the transcription of frataxin (6–9). As there is no definite treatment available, care and rehabilitation are particularly important in the recovery of the patients. However, significant improvements have been achieved in the research into the pharmacological treatment of FRDA in recent years. Antioxidants, agents that increase frataxin production (histone deacetylase inhibitors and IFN-γ), and gene therapy are the treatment methods that have been studied in recent years (10). While pharmacological treatments are focused on the molecular pathophysiology of FRDA, studies testing symptomatic treatments have also been conducted. Bupropion and citalopram have been evaluated in FRDA, however, neurological and cardiac benefits were modest (10, 11). Amantadine was also evaluated

Correspondence Address: Mehmet Fatih Yetkin, Department of Neurology, School of Medicine, Erciyes University, Kayseri, Turkey • **E-mail:** mfyetkin@erciyes.edu.tr
Received: 23.01.2020, **Accepted:** 10.07.2020, **Available Online Date:** 21.09.2020

in a double-blind cross-over study, however, no significant effect was observed in patients with FRDA (12). IFN-γ is a natural cytokine with an effect on iron metabolism and the immune system (9). A study showed that IFN-γ can increase frataxin production significantly in many cell types. In subsequent studies, it was reported as well tolerated and safe (13). In this study, clinical features, tolerability, and the prognosis of patients with FRDA to whom IFN-γ was administered in a university hospital were evaluated retrospectively and the results were discussed. To the best of our knowledge, this is the first study made conducted in our country to evaluate the effect of IFN gamma on this patient group.

METHOD

Ethics Committee approval was obtained from the Faculty of Medicine Erciyes University (Meeting Date of the Ethics committee: 25.12.209, Decision Number: 2019/882). All patients were between the ages of 25–40 and they had expanded GAA repeat (patients with point mutation were excluded). All of the participants were ambulatory patients and treated with subcutaneous IFN-γ 3 times a week. The exclusion criteria were set as refusing treatment, having an unstable clinical condition due to a chronic disease, having liver disease, being pregnant, or in the lactation period.

Our study is a retrospective study and the demographic data, duration of the disease, initial symptoms, clinical findings, comorbidities, prognosis, and treatment-related side effects have been evaluated. The complete blood count and biochemical tests of the patients were evaluated before and after the treatment. The neurological status of the patients was assessed before and after treatment at 3 and 6 months using the Scale for the Assessment and Rating of Ataxia (SARA). This scale had been assessed previously in terms of validity and reliability (14). The data were analyzed with IBM SPSS V23. The comparison of baseline, third, and sixth-month SARA scores was performed with the Friedman test. The significance level was taken as $p<0.05$.

RESULTS

The mean age of the 14 patients included in our study was 29.64±6.046 and 10 of them were female. The time since the onset of symptoms was 11.50±5.110 years and the time since diagnosis was 9.43±4.398. The first symptom was gait ataxia in all patients. All of the patients were evaluated in terms of cardiomyopathy. However, none of them were observed to have it. It was reported that 7 patients had scoliosis and 3 had diabetes. The mean IFN-γ treatment period was 7.21±1.105 months. Eleven of the patients had been also receiving idebenone therapy. The SARA tests before and after the treatment of the patients were evaluated using the Wilcoxon Sum Rank test. Even though a significant difference was observed in the SARA gait scale between the periods before and after 3 months of treatment (P=0.025), no significant difference was observed in terms of the stance, sitting, speech disturbance, finger chase, nose-finger, fast alternating hand movements, and heel-shin slide tests (P values=0.083, 1.000, 0.157, 0.157, 1.000, 1.000, 1.000, 1.000, respectively). Significant improvements in terms of gait and stance were reported after 6 months of treatment (P values=0.018 and 0.014 respectively). No significant difference was observed in terms of the sitting, speech disturbance, finger chase, nose-finger, fast alternating hand movements, and heel-shin slide tests (P values=1.000, 0.317, 0.157, 1.000, 0.157 and 1.000 respectively) (Table 1). Ten patients were reported to show drug-induced flu-like reactions. Of these patients, 1 showed severe, 2 showed moderate and 7 showed mild reactions. The liver enzymes were elevated up to 10% of the upper limit in 1 patient. While all of the patients were followed up after 3 months, it was observed that the treatment was discontinued in 2 patients due to drug ineffectiveness and patient incompatibility in the follow-up at 6 months.

Table 1. SARA scores before and after treatment

Age	B.T. Gait	B.T. Stance	B.T. Sitting	B.T. Speech disturbance	B.T. Finger chase	B.T. Nose-finger test	B.T. Alternating hand movements	B.T. Heel-shin slide	6th Month Gait	6th Month Stance	6th Month Sitting	6th Month Speech disturbance	6th Month Finger chase	6th Month Nose-finger test	6th Month Alternating hand movements	6th Month Heel-shin slide
27	4	1	0	2	1	2	1.5	1.5	3	0	0	2	1	2	1.5	1.5
27	5	2	0	3	2.5	2	2	2.5	4	2	0	2	2.5	2	2	2.5
34	8	5	0	2	2	2	2	2	8	4	0	2	1.5	2	2	2
31	5	4	0	2	2	2	2	2	-	-	-	-	-	-	-	-
29	3	2	0	2	1	1	2	1.5	2	2	0	2	1	1	2	1.5
31	6	4	0	3	2	2.5	2	2	5	3	0	3	2	2.5	2	2
21	3	2	0	2	1	1	1.5	1.5	3	2	0	2	1	1	1	1.5
21	7	5	1	3	3	3	3	3	6	5	1	3	3	3	3	3
30	4	3	0	2	1	1	2	2	4	3	0	2	1	1	2	2
28	3	3	0	2	1	1	2	1.5	3	3	0	2	1	1	1.5	1.5
32	3	3	0	2	1.5	1.5	1	1.5	3	1	0	2	1	1.5	1	1.5
20	4	2	0	2	1	1	1	1.5	3	1	0	2	1	2	1	1.5
41	8	5	0	2	2	2	2	2	-	-	-	-	-	-	-	-
33	3	3	0	2	1.5	1.5	1	2	2	2	0	2	1.5	1.5	1	2

B.T.; Before treatment, SARA; Scale for the assessment and rating of ataxia

DISCUSSION

To our best knowledge, this is the first study conducted in our country to evaluate the effect of IFN gamma on FRDA. Improvement was observed in the SARA gait scores of the patients in the third month after the initiation of IFN-γ for FRDA. Although there was no change in the SARA stance scale by the third month, improvements were observed in the sixth month. No significant change was observed in the other SARA parameters despite the treatment.

FRDA is an inherited, neurodegenerative disease without any current approved treatment. Therapeutic strategies and the knowledge of disease have, in recent years, been expanding rapidly, offering new opportunities for the treatment of disease. Advances in the mechanisms of the disease have evolved into the clinical trial of potential therapies. The homogeneity of the study populations involved in the clinical trials and the use of technologically-advanced measurements will improve the capacity to test promising treatments. These may offer a promising direction in terms of the future treatment of FRDA (10). The IFN-γ -1b injection is used for chronic granulomatous diseases and malignant osteopetrosis. IFN-γ regulates almost all stages of inflammation and the immune response mimics the effect of interferon-gamma naturally occurring in the body. It affects the mediation, activation, and differentiation of T cells, B cells, macrophages, and NK cells. It is a cytokine that plays a role in the immune response and iron metabolism. IFN-γ has been shown to stimulate frataxin production by enhancing FXN gene transcription both in human and animal models of FRDA (15). The most significant side effects of IFN-γ are flu-like symptoms. The drug's tolerability and potential clinical efficacy have been demonstrated in a small, open-ended study observing children with FRDA to whom IFN-γ was administered via subcutaneous injections for 12 weeks (16). It was observed in our study that 10 out of 14 patients showed drug-induced flu-like reactions. Of these patients, 1 showed severe, 2 showed moderate and 7 showed mild reactions. The liver enzymes elevated up to 10% of the upper limit in 1 patient. No other side effects were observed. Its safety was evaluated mostly as good in our study. In another double-blind multicenter placebo-controlled study evaluating the efficacy and reliability of IFN-γ, the clinical status of the patients was evaluated using the modified Friedreich Ataxia Rating Scale (FRDARS) and no difference was observed after 6 months. Unlike this study, we found that there were improvements in the SARA gait scale of the patients in the third month after the treatment for FRDA. Although there was no change in the SARA stance scale in the third month, improvements were observed in the sixth month in our study. Another study has reported that IFN-γ was well tolerated and no serious side effects were seen. There was a partial improvement in the FRDARS scores, similar to our study (13). In this study, a statistically significant relationship has not been observed between the frataxin protein levels and FRDARS. A recent double-blind, placebo-controlled study evaluated the efficacy and safety of IFN-γ in the treatment of FRDA by using the modified Friedreich Ataxia Rating Scale (mFARS) for 6 months. There was no significant change in the mFARS scores after six months. However, over the open-label period of the study, the absolute values of mFARS were better than those from parallel natural history studies. Also, the rate of progression was observed as slightly slower than expected over this short period (17). Likewise, we observed no significant improvement in SARA stance scale by the third month, improvements were observed in the sixth month. It can be concluded that longer studies might show a modest benefit of IFN-γ in FRDA.

In our study, the clinical findings of the response to interferon treatment were evaluated with SARA which is also widely used by previous clinical trials (18, 19). It has been shown that SARA shows results similar to FARS (18, 20, 21). Additionally, SARA has the distinct advantage of being a more compact scale, and because of simpler training (22).

There some limitations of this study. First of all, the retrospective design of the study makes it difficult to evaluate the response to treatment. In addition, measuring frataxin levels could use an objective scale to evaluate response to treatment. Also, a longer follow-up time with more participants could provide more information in the evaluation of treatment.

In conclusion, this study revealed that interferon is a well-tolerated and partially effective treatment option in the treatment of FRDA. Further studies are needed to better determine the long term results.

An earlier version of this study was presented at 54th National Neurology Congress, Antalya, Turkey, 1–5 December 2018 (p.1061).

Ethics Committee Approval: Ethics Committee approval was obtained from the Faculty of Medicine Erciyes University (Meeting Date of the Ethics committee: 25.12.2009, Decision Number: 2019/882).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - MFY, MG; Design - MFY, MG; Supervision - MFY, MG; Resource - MFY; Materials - MFY; Data Collection and/or Processing - MFY; Analysis and/or Interpretation - MFY, MG; Literature Search - MFY, MG; Writing - MFY; Critical Reviews - MFY, MG.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: In this study, interferon gamma treatment have been provided by the Republic of Turkey Ministry of Health with off-label approval individually to each patient.

Bu çalışmanın daha önceki bir versiyonu 54. Ulusal Nöroloji Kongresi, Antalya, Türkiye, 1-5 Aralık 2018'de sunulmuştur (s.1061).

Etik Komite Onayı: Etik Kurul onayı Erciyes Üniversitesi Tıp Fakültesi'nden alınmıştır (Etik Kurul Toplantı Tarihi: 25.12.2009, Karar Numarası: 2019/882).

Hasta Onamı: Tüm katılımcılardan yazılı bilgilendirilmiş onam alınmıştır.

Hakem Değerlendirmesi: Dış Bağımsız.

Yazar Katkıları: Fikir- MFY, MG; Tasarım- MFY, MG; Denetleme- MFY, MG; Kaynaklar- MFY; Malzemeler- MFY; Veri Toplanması ve/veya İşlemesi- MFY; Analiz ve/veya Yorum- MFY, MG; Literatür Taraması- MFY, MG; Makale Yazımı- MFY; Eleştirel İnceleme- MFY, MG.

Çıkar Çatışması: Yazarlar çıkar çatışması olmadığını beyan etmişlerdir.

Finansal Destek: Bu çalışmada interferon gama tedavisi, Türkiye Cumhuriyeti Sağlık Bakanlığı tarafından her hastaya ayrı ayrı endikasyon dışı onay ile sağlanmıştır.

REFERENCES

1. Klockgether T. Ataxias. Parkinsonism Relat Disord 2007;13:S391–S394. [Crossref]
2. Campuzano V, Montermini L, Molto MD, Pianese L, Cossée M, Cavalcanti F, Monros E, Rodius F, Duclos F, Monticelli A, Zara F, Canizares J, Koutnikova H, Bidichandani SI, Gellera C, Brice A, Trouillas P, De Michele G, Filla A, De Frutos R, Palau F, Patel PI, Di Donato S, Mandel JL, Cocozza S, Koenig M, Pandolfo M. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 1996;271:1423–1427. [Crossref]
3. Cossée M, Dürr A, Schmitt M, Dahl N, Trouillas P, Allinson P, Kostrzewa M, Nivelon-Chevallier A, Gustavson KH, Kohlschütter A, Mandel JL, Brice A, Koenig M, Cavalcanti F, Tammaro A, De Michele G, Filla A, Cocozza S, Labuda M, Montermini L, Poirier J, Pandolfo M. Friedreich's ataxia: point mutations and clinical presentation of compound heterozygotes. Ann Neurol 1999;45:200–206. [Crossref]
4. Harding A, Zilkha K. 'Pseudo-dominant' inheritance in Friedreich's ataxia. J Med Genet 1981;18:285–287. [Crossref]
5. Boz PB, Koc F, Kocatürk Sel S, Güzel Aİ, Kasap H. Determination of Genotypic and Phenotypic Characteristics of Friedreich's Ataxia and Autosomal

Dominant Spinocerebellar Ataxia Types 1, 2, 3, and 6. Nöro Psikiyatri Arş 2016;53:115–119. [Crossref]
6. Boesch S, Nachbauer W, Mariotti C, Sacca F, Filla A, Klockgether T, Klopstock T, Schöls L, Jacobi H, Büchner B, vom Hagen JM, Nanetti L, Manicom K. Safety and tolerability of carbamylated erythropoietin in Friedreich's ataxia. Mov Disord 2014;29:935–939. [Crossref]
7. Libri V, Yandim C, Athanasopoulos S, Loyse N, Natisvili T, Law PP, Chan PK, Mohammad T, Mauri M, Tam KT, Leiper J, Piper S, Ramesh A, Parkinson MH, Huson L, Giunti P, Festenstein R. Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study. Lancet 2014;384:504–513. [Crossref]
8. Mariotti C, Nachbauer W, Panzeri M, Poewe W, Taroni F, Boesch S. Erythropoietin in F riedreich ataxia. J Neurochem 2013;126:80–87. [Crossref]
9. Pandolfo M, Arpa J, Delatycki MB, Le Quan Sang KH, Mariotti C, Munnich A, Sanz-Gallego I, Tai G, Tarnopolsky MA, Taroni F, Spino M, Tricta F. Deferiprone in F riedreich ataxia: A 6-Month randomized controlled trial. Ann Neurol 2014;76:509–521. [Crossref]
10. Aranca TV, Jones TM, Shaw JD, Staffetti JS, Ashizawa T, Kuo SH, Fogel BL, Wilmot GR, Perlman SL, Onyike CU, Ying SH, Zesiewicz TA. Emerging therapies in Friedreich's ataxia. Neurodegenerat Dis Manage 2016;6:49–65. [Crossref]
11. Rohr A, Eichler K, Hafezi-Moghadam N. Citalopram, a selective serotonin reuptake inhibitor, improves symptoms of Friedreich's ataxia. Pharmacopsychiatry 1999;32:113–114. [Crossref]
12. Filla A, De Michele G, Orefice G, Santorelli F, Trombetta L, Banfi S, Squitieri F, Napolitano G, Puma D, Campanella G. A double-blind cross-over trial of amantadine hydrochloride in Friedreich's ataxia. Can J Neurol Sci 1993;20:52–55. [Crossref]
13. Marcotulli C, Fortuni S, Arcuri G, Tomassini B, Leonardi L, Pierelli F, Testi R, Casali C. GIFT-1, a phase IIa clinical trial to test the safety and efficacy of IFNgamma administration in FRDA patients. Neurol Sci 2016;37:361–364. [Crossref]
14. Salcı Y, Fil A, Keklicek H, Çetin B, Armutlu K, Dolgun A, Tuncer A, Karabudak R. Validity and reliability of the International Cooperative Ataxia Rating Scale (ICARS) and the Scale for the Assessment and Rating of Ataxia (SARA) in multiple sclerosis patients with ataxia. Mult Scler Relat Dis 2017;18:135–140. [Crossref]
15. Tomassini B, Arcuri G, Fortuni S, Sandi C, Ezzatizadeh V, Casali C, Condo I, Malisan F, Al-Mahdawi S, Pook M, Testi R. Interferon gamma upregulates frataxin and corrects the functional deficits in a Friedreich ataxia model. Hum Mol Genet 2012;21:2855–2861. [Crossref]
16. Seyer L, Greeley N, Foerster D, Strawser C, Gelbard S, Dong Y, Schadt K, Cotticelli M, Brocht A, Farmer J, Wilson RB, Lynch DR. Open-label pilot study of interferon gamma-1b in Friedreich ataxia. Acta Neurol Scand 2015;132:7–15. [Crossref]
17. Lynch DR, Hauser L, McCormick A, Wells M, Dong YN, McCormack S, Schadt K, Perlman S, Subramony SH, Mathews KD, Brocht A, Ball J, Perdok R, Grahn A, Vescio T, Sherman JW, Farmer JM. Randomized, double-blind, placebo-controlled study of interferon-γ 1b in Friedreich Ataxia. Ann Clin Transl Neurol 2019;6:546–553. [Crossref]
18. Reetz K, Dogan I, Hilgers RD, Giunti P, Mariotti C, Durr A, Boesch S, Klopstock T, de Rivera FJR, Schöls L, Klockgether T, Bürk K, Rai M, Pandolfo M, Schulz JB, EFACTS Study Group. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study. Lancet Neurol 2016;15:1346–1354. [Crossref]
19. Borel S, Gatignol P, Smail M, Monin ML, Ewenczyk C, Bouccara D, Durr A. Oral mobility reflects rate of progression in advanced Friedreich's ataxia. Ann Clin Transl Neurol 2019;6:1888–1892. [Crossref]
20. Patel M, Isaacs CJ, Seyer L, Brigatti K, Gelbard S, Strawser C, Foerster D, Shinnick J, Schadt K, Yiu EM, Delatycki MB, Perlman S, Wilmot GR, Zesiewicz T, Mathews K, Gomez CM, Yoon G, Subramony SH, Brocht A, Farmer J, Lynch DR. Progression of Friedreich ataxia: quantitative characterization over 5 years. Ann Clin Transl Neurol 2016;3:684–694. [Crossref]
21. Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, Parkinson MH, Sweeney MG, Mariotti C, Panzeri M, Nanetti L, Arpa J, Sanz-Gallego I, Durr A, Charles P, Boesch S, Nachbauer W, Klopstock T, Karin I, Depondt C, vom Hagen JM, Schols L, Giordano IA, Klockgether T, Burk K, Pandolfo M, Schulz JB. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol 2015;14:174–182. [Crossref]
22. Pandolfo M. Rating scales for rare neurological diseases: What are we learning from Friedreich ataxia? Neurol Genet 2019;5:e380. [Crossref]