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Nicotinamide in Friedreich's ataxia: useful or not?

David R Lynch and Kenneth H Fischbeck

Division of Neurology and Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA (DRL) Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA (KHF)

David R Lynch: lynchd@mail.med.upenn.edu

Friedreich's ataxia is an autosomal recessive neurodegenerative disorder caused by mutations in the frataxin gene (*FXN*), leading to progressive ataxia, cardiomyopathy, scoliosis, and various other clinical features.¹ Most patients have GAA repeat expansions in intron 1 of *FXN*, leading to decreased concentrations of frataxin protein and downstream mitochondrial dysfunction. The GAA repeats lead to gene silencing through heterochromatin formation, and decreased transcription of *FXN* mRNA. The coding region of the mRNA and the amino acid sequence of the protein are normal, but the amount of protein produced is reduced; as a result, reversal of the epigenetic changes (such as histone deacetylation) represents a potential therapeutic strategy in Friedreich's ataxia. Inhibitors of histone deacetylase (HDAC) have been reported to increase frataxin concentrations in cell culture and in animal models of Friedreich's ataxia.^{2,3}

In an open-label, dose-escalation study reported in *The Lancet*, Vincenzo Libri and colleagues⁴ note an increase in *FXN* mRNA expression and frataxin protein concentration in peripheral blood mononuclear cells in patients given nicotinamide, a drug that has HDAC inhibitor activity when given at high concentrations. Ten adult patients with Friedreich's ataxia from the UK were given single doses (phase 1) and repeated daily doses of 2–8 g oral nicotinamide for 5 days (phase 2) and 8 weeks (phase 3). In phase 1, a single dose of up to 8 g (about 200 times higher than the typical recommended daily allowance for nicotinamide as a vitamin [B3])⁵ led to an increase in frataxin concentration in peripheral blood mononuclear cells, and this effect increased with increasing dose ($p=0.0004$). In phases 2 and 3, repeated daily dosing at 3.5–6 g resulted in a sustained and significant ($p<0.0001$) upregulation of frataxin expression, which was associated with changes in chromatin structure (a significant reduction methylation at amino acid position 9 of the histone H3 tail and a non-significant increase in H3 acetylation at the *FXN* locus). The investigators did not report any significant improvements in neurological measures, as assessed by the scale for the assessment and rating of ataxia and the spinocerebellar ataxia functional index.

These results are of interest for several reasons. First, although nicotinamide has several potential mechanisms of action, these data match the effects of nicotinamide and other

HDAC inhibitors seen in model systems, both in the increase in frataxin concentration over the course of several hours, and in the estimated induction of frataxin expression by 1.5 to 2.0 times (corresponding to nicotinamide doses of 3.8–7.5 g).^{2,3} Libri and colleagues' findings substantiate the existence of epigenetic mechanisms in patients with Friedreich's ataxia like those seen in model systems, as well as raising the possibility of therapeutic interventions based on the manipulation of such mechanisms. The increase in *FXN* mRNA expression was fairly small, but within a range that could affect clinical outcome in Friedreich's ataxia on the basis of an association between frataxin concentrations and disease severity.⁶ Thus, the estimated increase in frataxin mRNA and protein reported with nicotinamide could be clinically meaningful if the drug is provided at the right time, for a sufficient duration, and to the appropriate tissues.

Nevertheless, the evidence for nicotinamide in Friedreich's ataxia is incomplete. Although even a small increase in frataxin concentration might be clinically meaningful, how long the effect of nicotinamide on frataxin expression could be maintained is unclear. The biological effect lasted for 2 months in Libri and colleagues' study—a short time in the life of a patient with Friedreich's ataxia. Additionally, the effects on frataxin noted by the investigators were assessed in peripheral blood mononuclear cells, which are not functionally affected in Friedreich's ataxia. Although nicotinamide crosses the blood–brain barrier, Libri and colleagues' study does not address whether nicotinamide increases the amount of frataxin in the nervous system and other affected tissues; it would have been useful to have measured drug concentrations and biological effects in disease-relevant tissues such as the dorsal root ganglia and heart. Finally, restoration of frataxin concentrations must occur while the nervous system is still responsive to increases in frataxin. No effects on ataxia were noted in the study; whether this finding was caused by an inability of patients to respond or by the short duration of the study is not yet known. Longer studies will be needed to answer this question.

Although nicotinamide was used at doses that are much higher than the recommended daily allowance for vitamin B3, it was still reasonably well tolerated, with minor to moderate side-effects such as nausea (100% during phases 2 and 3 combined) and vomiting (50%). These adverse effects could be limiting for long-term treatment. Thus, in view of the fairly small changes in *FXN* expression and frataxin concentration, the absence of a demonstrated clinical effect, and the unknown risks of long-term use, we need to look for a clinically meaningful benefit in randomised controlled studies of longer duration to determine whether nicotinamide is effective for Friedreich's ataxia.

Unlike other targeted drugs currently under development for Friedreich's ataxia,^{7,8} nicotinamide is widely available, and patients and carers might be tempted to start using it for treatment. Although the data from Libri and colleagues' study⁴ show the potential for epigenetic-based treatments in Friedreich's ataxia, such approaches are not yet ready for widespread application in this disorder.

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