Physicians' guide for off-label Drug Use in Friedreich ataxia

Prepared by: Friedreich's Ataxia Compassionate Care Group (Jennifer Farmer, MS, CGC; Paul Konanz; David Lynch, MD, PhD; Susan Perlman, MD), Collaborative Clinical Research Network in Friedreich's Ataxia (3/09)

The development of agents for treatment of Friedreich ataxia (FA) has been very rapid. There are agents in development directed to improving neurologic function, increasing levels of the deficient protein frataxin, and ameliorating the abnormalities of mitochondrial function found in FA. Most of these agents are novel drugs not currently available in the United States or most other countries. For example, the one agent currently in Phase 3 trials in the US and Europe, (idebenone) has been developed in that manner. However, some of the other agents proposed for use in FA are existing drugs already marketed for other indications. *For all of these agents (whether available in the US or not) the primary method for determining efficacy, defining side effects, and determining the relative balance of risks and benefits in systematic clinical trials is essential*. The physicians in the Collaborative Clinical Research Network for Friedreich ataxia adhere to this belief.

Off-Label Use: In some situations though, off-label use of available medications may be reasonable to consider. Off-label use is the administration, for an initially unintended indication, of an agent available for another approved indication. An example would be the use of Topomax for headache, or the use of steroids for a variety of immunologic disorders. In these situations, the off-label use has grown over time through individual reports of potential efficacy of the agent followed by larger case series.

Off-label use can be smaller in scope and less well documented when the drug has never been used for a given purpose before. This is not a research situation but a decision between a prescribing physician and a receptive patient.
Still, it should adhere to certain principles.

- The drug must be administered safely. This requires a systematic clinical monitoring for adverse effects.
- The drug must have a reasonable chance of being helpful to the patient, and particularly have a low risk/benefit ratio. If the patient does not show some benefit after starting, then the drug usually should be discontinued. This requires specific methods for monitoring.
- Off-label use should not compromise systematic attempts at clinical trials.

Individual physicians may be approached for off-label use by FA patients. In such situations, each physician must decide how to proceed. In most cases the risk / benefit ratio for off-label use of a medication will be unknown for FA patients in general and for that specific FA patient. If an individual physician decides to proceed with off-label use of an agent, we have developed the following guidelines for assessment of response, general safety (not including potential side effects specific to the drug being used), and general criteria for potential candidates (those not likely to be eligible for clinical trials).

Criteria for severe FA: At present clinical trials in FA are being directed at patients whose disease is not completely disabling, but the exact criteria for inclusion in a trial vary from

study to study. Those not likely to be eligible for clinical trials are individuals who are at a later or more advanced stage, which is roughly defined as loss of ambulation and requiring assistance with transfers, unable to use hands to a significant degree, severe diabetes, speech dysfunction severe enough that they have difficulty being understood, hearing loss, vision loss to visual acuity worse than 20/70, and/or progressive cardiomyopathy.

Measures of response: FA is typically monitored by neurologic exams (FARS) or by performance based measures. The measures available to typical clinicians include nine hole peg boards, vision testing (visual acuity) and low contrast vision testing. Speech tests include "PATA", Boston Aphasia exam (oral and motor components), intelligibility, length of a sentence, and ability to count on a single breath.
There are also subjective measures: fatigue, activities of daily living and quality of life scales that can be helpful in monitoring patients.

Safety: In monitoring FA, it is essential to obtain cardiac as well as general safety measures. These would include EKG, echocardiogram, CBC, complete metabolic panel, and blood sugar. For monitoring typical off-label use, one would expect that ECG and basic laboratory tests should be done at initiation and periodically throughout the administration of the agents. The frequency would depend on the exact properties of the off-label agent. An echocardiogram should be done within 6 months of the initiation of the agents.

SPECIFIC OFF-LABEL GUIDES:
EPO (Erythropoietin): Patient Guide / Physician's Guide