

PHYSICIAN'S GUIDE: SPECIAL CONSIDERATIONS IN THE OFF-LABEL USE OF ERYTHROPOIETIN

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 (rev. 3/09)

One of the agents proposed for development as a potential treatment in FA is erythropoietin, an agent currently approved for other uses. In considering off-label uses of erythropoietin, all of the same guidelines concerning selection of patients, response monitoring and safety as in our more general **Physicians' guide for off-label Drug Use in Friedreich ataxia** should be followed. However, there are special considerations in rationale, safety, and dosing that any physician considering use of erythropoietin must understand.

Rationale for use of erythropoietin- Erythropoietin is a hormone made in the kidneys and released into the blood, where it circulates to reach the bone marrow. There, it controls production of red blood cells. The pharmaceutical form of erythropoietin is made using molecular biological approaches, then reconstituted into an appropriate vehicle for injection. It is approved for increasing red blood cell counts in people with a variety of forms of anemia (such as anemia associated with renal disease and anemia following chemotherapy).

The proposed use of erythropoietin in FA derives from findings in cell culture showing that erythropoietin can increase levels of frataxin when administered to cultured cells derived from FA patients. The effect has been identified in several cell types (compiled from 2 studies), none of them neuronal. The magnitude of the effect is modest, with increases in frataxin levels that are roughly 50% over baseline. Although small, this increase could conceivably translate into some degree of clinical benefit if it occurred in patients in the correct tissues.

Based on these studies, erythropoietin has been given in an initial open label trial to 11 FA patients. In the first reported study, these patients received erythropoietin for 8 weeks (5000 U SQ, three times per week). In 8 of 10 patients, frataxin levels in lymphocytes increased (although in only 6 was it greater than 25%). Five of 11 patients were clinically improved by an ataxia rating scale. The second study followed these same patients over the course of 6 months (2000 U SQ, three times per week). At the 6 month point, 5 of 8 retained their increase in frataxin level. Clinically, patients also improved mildly, though the improvement did not correlate with frataxin level, and the correlation between clinical improvement and the different scales used to assess neurologic function varied among scales. Thus the data from open labels trials suggest that there may be a possibility that erythropoietin can be useful in FA.

Dosing of erythropoietin. There have been no dose-finding trials with erythropoietin in FA. The dose chosen for the reported studies was a single dose in each case. Thus the ideal dose for producing benefit and for minimizing side effects is unclear. Furthermore, how readily erythropoietin penetrates the central nervous system at any of these doses is unknown.

Risk associated with erythropoietin therapy. Erythropoietin therapy can be dangerous. The two most common serious side effects are hypertension and an increase in red blood cell count beyond the normal range. The latter places individuals at a higher risk of stroke or myocardial infarction due to increases in blood viscosity. In the 6 month trial of erythropoietin in FA, 4 of eight patients required phlebotomy to control red blood cell count.

Because of the cardiac dysfunction associated with FA, phlebotomy is a nontrivial procedure. This increases the risk of erythropoietin in FA beyond that of other disorders.

Recent studies have also suggested that erythropoietin can increase the risk of cancer in people and that it can increase the damage associated with stroke. These studies are controversial, and there is no reason that patients with FA should be more susceptible to these side effects.

Based on these risks, safety monitoring for erythropoietin use should include, at a minimum, weekly CBC counts and blood pressure checks. In addition, should phlebotomy be necessary, it will most likely require admission to a care unit experienced in this procedure.

Monitoring of effects: If individuals choose to pursue off-label use of erythropoietin, efficacy monitoring can be the same as is performed for all other FA studies. There is no clinically available test for monitoring frataxin levels in any tissue. Also, if erythropoietin does raise frataxin levels in patients, the degree and time course of benefit are unknown. It is possible that the benefit could be immediate or be delayed by weeks to months. In addition, it could simply slow disease progression. Thus, the early clinical response of patients may be of modest benefit in determining whether the therapy is effective, particularly given the absence of published natural history data on FA.

References:

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