

Treatment of elevated C4a in patients with CFS using low doses of erythropoietin safely reduces symptoms and lowers C4a: a prospective clinical trial

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Objectives: Chronic Fatigue Syndrome (CFS) is a systemic illness associated with unexplained abnormalities in inflammatory responses, including innate immune system elements alpha interferon and pro-inflammatory cytokines (PIC). Little is known regarding the role of C4a, a powerful inflammatory anaphylatoxin produced by activation of the classical pathway of complement, as part of the innate immune response in CFS. Clinical data in over 1000 patients seen at one site documented the common occurrence of elevated C4a in CFS patients. Because use of low doses of erythropoietin (epo) safely lowered levels of C4a in other illnesses associated with elevated levels PIC, we hypothesized that (1) low doses of epo would lower symptoms and C4a safely in CFS patients; and that (2) lowered C4a would be associated with durable reduction of symptoms following cessation of therapy (3) reacquisition of symptoms would be associated with a repeat rise in levels of C4a.

Methods: 60 patients with CFS and C4a agreed to take low doses of epo in an off-label study. Symptoms were recorded before each dose of 8000 units of epo, given for 5 doses over 15 days, as was evaluation for adverse effects. C4a levels were drawn at the conclusion of the 5-dose regimen. Patients were classified as either non-responders or improved. Improved cases were observed for relapse in symptoms for 3 months. Improved patients were classified as relapsed or non-relapsed by symptoms. Repeat C4a levels were drawn in improved cases at three months.

Results: No adverse events occurred aside from soreness at the injection site in 10% of patients. 51 patients noted symptom reduction with epo; 9 did not. Of the improved patients, 34 relapsed; 17 were non-relapsed. C4a levels at entry showed differences: mean levels in non-responders were 19,500 (normal < 2830); responders 8200, with reduction to 11,300 and 3200 respectively. In the relapsed group, mean C4a rose to over 12,500 and in the non-relapsed group C4a was 3400.

Conclusions: Use of low dose epo in CFS patients in a short clinical trial safely lowered symptoms and improved levels of C4a in responders. Failure to lower C4a adequately or reacquisition of elevated C4a was associated with ongoing presence of symptoms. Maintenance of lowered C4a was associated with improved quality of life. A double blinded, placebo controlled trial is planned.

Treatment of CFS patients with elevated C4a using low dose erythropoietin corrects abnormalities in central nervous system metabolites and restores executive cognitive functioning.

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Objectives: Recent literature has supported the concept that erythropoietin (epo) is a neuroprotective agent for peripheral and central nervous system (CNS) that specifically prevents apoptosis of glial cells and improves capillary hypoperfusion in CNS.

Treatment of patients with Chronic Fatigue Syndrome (CFS) and elevated levels of the anaphylatoxin C4a, an inflammatory product of activation of the complement cascade, using epo lowers C4a and reduces neurocognitive symptoms. Magnetic resonance spectroscopy (MRS) can demonstrate levels of metabolites that are markers for CNS function. A prospective clinical trial was performed to assess (1) safety of epo in CFS patients and those with elevated C4a; (2) efficacy of epo to improve symptoms, reduce C4a and correct abnormalities in CNS metabolites; (3) provide data that supports a testable hypothesis of the inflammatory origin of systemic and CNS symptoms in CFS.

Methods: 35 patients with CFS provided informed consent for an IRB-approved study. Symptoms of executive cognitive function, C4a and MRS of 1 cubic cm areas of left and right frontal lobes and left and right hippocampus before and after treatment with 5 doses of 8000 units of epo given by the study physician over 2 weeks were compared to known controls. Symptoms were recorded at each visit, as were levels of C4a and a review of possible adverse effects.

Results: Symptoms of executive cognitive function were reduced in cases after treatment, though still higher than in controls. C4a was reduced beginning after the second dose of epo, achieving values equal to controls in 91% of cases. MRS-determined values of n-acetyl acetate; creatine; choline did not change in cases and equaled controls. Myoinositol was elevated in 20% of cases with reduction after epo in all to control values. Lactate was elevated in 77%, with reduction in all after epo to controls. Ratios of glutamate to glutamine were abnormal in 97% of cases, with reduction to controls achieved in 55%. No adverse effects of clotting, elevation of blood pressure or development of iron deficiency anemia occurred.

Conclusions: Use of low dose epo in CFS patients is safe and effective to improve symptoms, C4a and CNS markers of abnormal glial cell function (myoinositol); capillary hypoperfusion (lactate); and excitatory neurotransmission (glutamate/glutamine). These results suggest that the systemic inflammation in CFS caused by elevated C4a may be treated using epo and that the CNS correlates of cognitive dysfunction in CFS patients has an inflammatory basis. A double blinded, placebo controlled trial is planned.