

How to pursue EPO in MS

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With surprise we read the paper, published recently in the Multiple Sclerosis Journal, *High-dose erythropoietin in patients with progressive multiple sclerosis: A randomized, placebo-controlled, phase 2 trial*,¹ reporting overall negative results. Since our small proof-of-concept trial² and subsequent studies³⁻⁵ showed beneficial effects of erythropoietin (EPO) in multiple sclerosis (MS), an analysis of potential reasons for this discrepancy is mandatory:

1. Only a single (!) patient here received the EPO dose, and the treatment as planned. Most patients had considerably lower doses with unclear dose distribution over time.
2. In contrast to the Schreiber study,¹ patients in our trial and all following compassionate use approaches were instructed to train compromised functions hard during EPO treatment and thereafter to generate and preserve beneficial outcome.^{2,6} We consider the remarkable EPO doping effect as the “best possible field study.” No sportsman would dope and stop training: EPO strongly supports motor and cognitive functions—but all functions follow the principle “use it or lose it”.^{2,6}
3. Critical is the assessment of just a single baseline performance to judge individual improvement under EPO. Due to considerable fluctuations in chronic progressive MS patients, the mean of several independent measurements over days or weeks should be used as a more valid baseline for any target outcome (motor performance, cognition).^{2,6}
4. Astonishing are the many blood-lettings here (36× in 16 EPO patients; up to 6×/patient) despite reduction of the per-protocol dose. In our trial, in all visits where patients received EPO (total = 116), only five blood-lettings were necessary (three in one patient, one in two patients). There are several potential explanations. (1) We strictly forbid iron substitution (also informing treating physicians), making use of the “iron-block” to prevent an increase in red blood cells. No information on iron substitution boosting hematopoiesis or blood values is given here. (2) An underlying inflammation

reduces the hematopoietic efficacy of EPO. Stronger inflammation in our patients may explain the lower erythropoietic EPO effect. (3) We excluded additional pro-hematopoietic factors: smoking (here only heavy smokers) and women on contraceptives (here allowed). (4) Finally, our patients were asked to drink plenty of water to avoid a hematocrit rise due to exsiccosis rather than hematopoiesis. Some increases here may have been “pseudo-increases” in patients with bladder dysfunction who tend to avoid fluid intake.^{2,6}

5. We started with three high doses of prednisolone (3 × 1 g iv) and two EPO applications over 3 days, followed by 12 weeks weekly and then 12 weeks biweekly EPO treatment, with no premature termination of EPO in any patient.^{2,6}

We hope that the Schreiber study¹ will not discourage clinical researchers from continuing to explore EPO in MS and that our letter may help explaining the unfortunate negative outcome. For future studies, we suggest to select patients with ongoing inflammation. The initial response to EPO regarding hematopoiesis may even serve as an indicator² leading to early exclusion of strong responders. Blood lettings for iron depletion in patients preceding EPO treatment might be considered as alternative.³ Individually tailored treatment and follow-up² are needed to make EPO a successful MS therapy. EPO will never be a “laissez-faire” drug,⁶ therefore challenging for routine care, but in the absence of any other effective treatment definitely worthwhile pursuing.

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