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Colony Stimulating Factors (Blood Growth Factors) Are Promising but Unproven for Treating Stroke

Nikola Sprigg, MRCP; Philip M.W. Bath, MD

Colony stimulating factors (CSFs), also called hematopoietic growth factors, regulate bone marrow production of circulating blood cells. They have been shown to be neuroprotective in experimental stroke. Some CSFs also mobilize the release of bone marrow stem cells into the circulation; these could help brain repair processes after stroke. We systematically assessed the effects of CSFs on functional outcome and hematology measures in patients with recent stroke.

Search Strategy

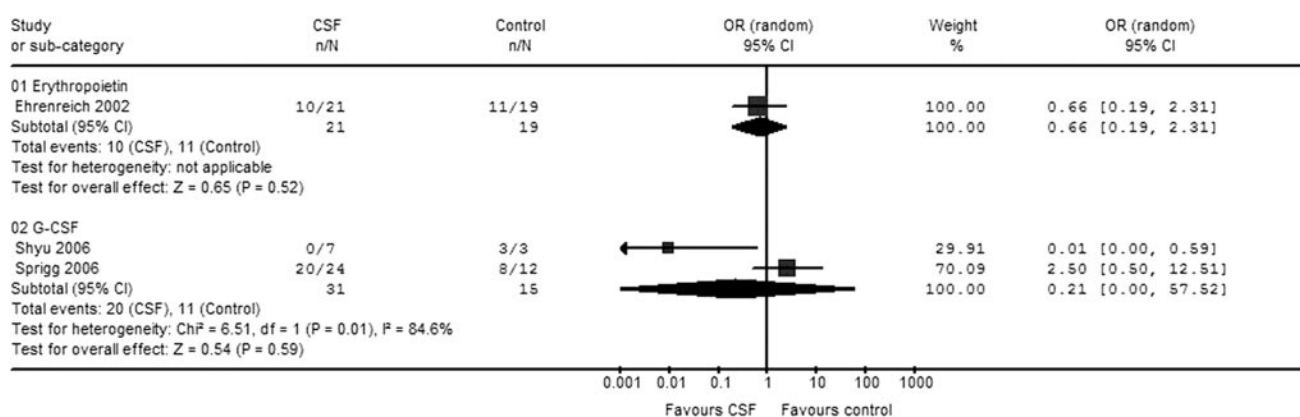
We searched the Cochrane Stroke Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and Science Citation Index. Principal investigators of trials were also contacted. Unconfounded randomized controlled trials recruiting patients with acute or subacute ischemic or hemorrhagic stroke were included. CSFs included stem cell factor, erythropoietin (EPO), granulocyte colony-stimulating factor (G-CSF), granulocyte-mac-

rophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF, CSF-1), and thrombopoietin, or analogues of these. The primary outcome was functional outcome (assessed as combined death or disability and dependency using scales such as the modified Rankin Scale or Barthel Index) at the end of the trial. Secondary outcomes included safety at the end of treatment (death, impairment, deterioration, extension or recurrence), death at the end of follow-up, and hematology measures. Data on measures by intention to treat were collected and analyzed using random-effects models.

Main Results

No large trials were identified. EPO therapy was associated with a nonsignificant reduction in death or dependency in 1 small trial (n=40 participants, odds ratio 0.66; 95% CI, 0.19 to 2.31; Figure) but had no significant effect on hematological measures.¹ G-CSF was associated with a nonsignificant reduction in death and dependency in 2 small trials (n=46,

Review: Colony stimulating factors (including erythropoietin, granulocyte colony stimulating factor and analogues) for stroke
 Comparison: 01 Colony stimulating factor (CSF)
 Outcome: 02 Functional outcome (death or dependency), end of trial



Forest-plot showing the effect of CSF on combined death or disability and dependency at end of trial.

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odds ratio 0.21; 95% CI, 0 to 57.52)^{2,3} (Figure) and significantly elevated white cell count in 3 trials (n=91, weighted mean difference 27.56; 95% CI, 17.56 to 37.56).²⁻⁴

Further randomized controlled trials of CSFs are underway or recently completed; these include 1 with EPO⁵ and 2 with G-CSF.^{6,7} No trials of stem cell factor, GM-CSF, M-CSF, thrombopoietin, were identified.

Discussion

It is apparent that at least 2 paradigms are being studied with CSF in the treatment of stroke. First, CSFs such as EPO and G-CSF are neuroprotective in animal models of acute stroke, and this potential mechanism is under investigation in patients with acute stroke.^{1,5,6} Second, stem cell mobilizing CSFs (as with stem cell factor, G-CSF, and GM-CSF) could contribute to brain repair through neurogenic-related mechanisms, again as has been seen in experimental models of stroke; 3 trials have investigated this approach, with a further trial ongoing.⁷

Implications for Future Research

Further studies need to address mechanisms by which CSFs might work; for example, preclinical studies suggest that CSF could be neuroprotective whereas those factors which mobilize endogenous stem cells could enhance neurogenesis. Understanding potential mechanisms of action will help investigators decide when to administer treatment for testing in phase III trials: for example, during the hyperacute or subacute phases of stroke. Whether CSFs aid recovery in chronic stroke also needs to be addressed.

Conclusion

No large trials of EPO, G-CSF or other CSFs have been performed, and it is too early to know whether CSFs improve functional outcome.

Disclosures

The authors are running an independent phase II trial of G-CSF funded by a UK charity, The Stroke Association. P.B. has acted as a consultant to Axaron (who are developing G-CSF) and Lundbeck (who are developing an EPO analogue); no monies received in consultancy fees from Axaron or Lundbeck were used in any way whatsoever for the development of the protocol, and neither company had any influence over the initiation, planning or production of the protocol.

References

- Ehrenreich H, Hasselblatt M, Dembowski C, Cepek L, Lewczuk P, Stiefel M, Rustenbeck HH, Breiter N, Jacob S, Knerlich F, Bohn M, Poser W, Ruther E, Kochen M, Gefeller O, Gleiter C, Wessel TC, De Ryck M, Itri L, Prange H, Cerami A, Brines M, Siren AL. Erythropoietin therapy for acute stroke is both safe and beneficial. *Molecular Medicine*. 2002;8:495-505.
- Shyu WC, Lin SZ, Yang HI, Tzeng YS, Pang CY, Yen PS, Li H. Functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated cells. *Circulation*. 2004;110:1847-1854.
- Sprigg N, Bath P, Zhao L, Willmot M, Gray LJ, Walker M, Dennis MS, Russel N. Granulocyte-colony stimulating factor mobilizes bone marrow stem cells in patients with sub-acute ischaemic stroke: The Stem cell Trial of recovery EnhanceMent after Stroke (STEMS) pilot randomized controlled trial. *Stroke*. 2006;37:2979-2983.
- Zhang J, Deng M, Zhang Y, Sui W, Wang L, Sun A, Song H, Lu M, Fan D. A short-term assessment of recombinant human granulocyte-stimulating factor (rhg-csf) in treatment of acute cerebral infarction. *Cerebrovascular Diseases*. 2006;21(suppl 4):143. Abstract.
- Ehrenreich H. The Multicenter-Erythropoietin-Stroke trial. Available at: http://www.epo-study.de/index_eng.html. Accessed August 2006.
- Axaron Bioscience A. Treatment with ax200 for acute ischemic stroke. Available at: <http://clinicaltrials.gov>. Accessed August 2006.
- Bath PMW. Stem cell Trial of recovery EnhanceMent after Stroke 2 (STEMS2): pilot randomised placebo-controlled trial of granulocyte-colony stimulating factor in mobilising bone marrow stem cells in sub-acute stroke. Available at: <http://www.controlled-trials.com/ISRCTN63336619>. Accessed November 2006.

KEY WORDS: colony-stimulating factors ■ recovery ■ stem cells ■ stroke