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

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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-macrophage 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. G-CSF was associated with a nonsignificant reduction in death and dependency in 2 small trials (n=46, n=46, respectively)._
odds ratio 0.21; 95% CI, 0 to 57.52)²,³ (Figure) and signifi-
cantly 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 pa-
tients 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 mecha-
nisms, 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 mobi-
lize 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
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(who are developing an EPO analogue); no monies received in
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whatsoever for the development of the protocol, and neither com-
pany had any influence over the initiation, planning or production of
the protocol.

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Key Words: colony-stimulating factors ■ recovery ■ stem cells ■ stroke
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