Granulocyte colony-stimulating factor

In the background section of their abstract, Woei-Cherng Shyu and associates[1] state that because granulocyte colony-stimulating factor (G-CSF) has anti-inflammatory and neuroprotective properties and the capacity to mobilize stem cells, it has the potential to be used in treatment of stroke. However, there are limited data about the effects of G-CSF on hemostasis.[2,3] It has been suggested that G-CSF may induce a hypercoagulable state, possibly by increasing levels of endothelial markers and thrombin generation or by stimulating tissue factor.[4,5] A few reported cases of acute arterial thrombosis in patients receiving G-CSF support the hypothesis of induction of a transient hypercoagulable state.[6,7] In addition, acute arterial thrombosis in healthy donors, possibly related to G-CSF, has been reported.[2] A transient hypercoagulable state related to G-CSF may be important for thrombophilic, atherosclerotic or immobilized patients.

Therefore, whenever G-CSF is administered, the patient should be followed carefully.

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DOI:10.1503/cmaj.1060064

Having reviewed the baseline functional stroke scale scores reported by Woei-Cherng Shyu and associates,[1] I cannot share the excitement displayed by Cesar Borlongan and David Hess in their accompanying commentary.[2] The methodologic limitations of such a small phase 1 study are addressed in the commentary, but I have an additional concern: the 3 patients in the control group were significantly more impaired at the outset than the 7 patients who were randomly assigned to receive the treatment. It is well recognized that presenting impairment, as measured with scales such as the European Stroke Scale (ESS), the ESS Motor Subscale and the Barthel Index, is a strong predictor of ultimate outcome for stroke patients,[3–5] regardless of treatment. It is therefore crucial to recognize that patients presenting with the greatest of impairments are likely to improve least; conversely, those with milder impairments are more likely to improve more rapidly and more completely.[6,7]

Thus, it is not surprising that the 7 patients who were treated (who on average had more than 10% better stroke scale scores at recruitment) ultimately fared better than the 3 patients in the control group.

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DOI:10.1503/cmaj.1060067

[Drs. Shyu, Lin and Li respond:]

Following the guidelines on using G-CSF for stem cell mobilization,[1] we carefully adjusted the dose of G-CSF (15 μg/kg) for up to 5 days to avoid the leukocyte numbers rising above 70×10^9/L (in fact, the leukocyte count for all patients was below 61.3×10^9/L). In addition, we also prescribed moderate hydration and antiplatelet medicine, as suggested by LeBlanc and colleagues,[2] to minimize hyperosmolarity and hypercoagulability. During the clinical course of G-CSF treatment, there were no abnormal findings for biochemistry, bleeding time, coagulation time or C-reactive protein. Therefore, we conclude that no patient receiving G-

CSF therapy experienced a thrombotic complication. We agree that more factors need to be monitored when using G-CSF treatment for thrombophilic, atherosclerotic and immobilized patients. Given that thrombotic complications possibly induced by G-CSF have been reported, strict selection of patients, adequate hydration and appropriate dosage of G-CSF are needed in the treatment of individual stroke patients.

In our trial, the mean baseline score on the National Institutes of Health Stroke Scale was 12.0 (standard deviation [SD] 4.3) for patients treated with G-CSF and 12.0 (SD 2.6) for the control group. However, for the other scales, some of the individual scores for patients who received G-CSF were higher than those of the controls at the time of recruitment; as a result, the means for the EES, ESS Motor Subscale and Barthel Index were higher for patients in the treatment group. If these outliers are removed, the average scores at recruitment were similar between the treatment and control groups. Similarly, at the 12-month follow-up, scores for the G-CSF-treated patients (excluding those with higher scores at the time of recruitment) remained higher than those of controls. Therefore, although there was some bias in the initial selection of patients, we conclude that G-CSF could be an important treatment for acute stroke.

We emphasize that more randomized, double-blind, placebo-controlled trials are needed to confirm the preliminary findings that we have reported.[3]

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DOI:10.1503/cmaj.1060131

[Drs. Borlongan and Hess respond:]

Although we welcome the clinical trial by Woei-Cherng Shyu and associates[1] and the European clinical trials cited in our commentary,[2] we reiterate that critical assessment of these trials is warranted. As we pointed out,[2] given the small number of patients in the study by Shyu and associates, and the variable onset of treatment, conclusions about the efficacy of this treatment cannot be drawn. Nonetheless, this is the first demonstration of feasibility and safety of G-CSF in human stroke patients. In view of the limited therapeutic window for thrombolytic therapy with tissue plasminogen activator, the feasibility and safety of administering G-CSF between 1 and 7 days after stroke is a significant clinical advance.

Julian Harriss argues that at the outset, the patients assigned to receive the treatment had on average "more than 10% better stroke scale scores" than the patients who received the placebo. Shyu and associates[1] noted that there were no statistically significant differences at baseline between the 2 groups of patients, who were randomly assigned to the treatment conditions. We confirmed, through our own statistical analysis, that there were no significant differences between the groups at baseline for the 4 stroke scales used. Closer examination of the baseline scores (see Table 2 in the article by Shyu and associates[1]) reveals that for 3 of the 4 stroke scales (National Institutes of Health Stroke Scale, ESS, ESS Motor Subscale), the patients with the worst scores were in the G-CSF group; for the Barthel Index, 3 of the patients with the second-worst score were in that group.

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DOI:10.1503/cmaj.1060118

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