Developing Granulocyte-Colony Stimulating Factor for the Treatment of Stroke: Current Status of Clinical Trials

To the Editor:

The review of Solaroglu et al1 on granulocyte-colony stimulating factor (G-CSF) as novel neuroprotectant is important, and the fact that it comes from a group not involved in primary research in this field illustrates the growing attention of the general stroke community to hematopoietic factors for the treatment of stroke. However, we believe that the readers of Stroke would also be highly interested in recent clinical developments in this field, which are not mentioned in the article. We have, therefore, summarized the currently ongoing G-CSF trials in stroke.

Preclinical studies clearly demonstrated activity of G-CSF in the acute as well as in the chronic stroke situation and suggest therapeutic potential in both settings. The powerful multimodal interference of G-CSF with acute ischemic pathophysiology (see review)2 combined with a substantial time window of opportunity3 (Schneider et al, unpublished data, 2006) are the foundation for a multicenter acute stroke trial we have initiated (AXIS, phase IIa).4 Here, G-CSF is administered in escalating doses from a total of 30 μg/kg per bodyweight cumulated over 3 days to 180 μg/kg per bodyweight over 3 days. Dosing is initiated by an IV bolus followed by continuous G-CSF infusion within 12 hours of stroke onset. The primary goal is to establish safety in this population of cerebrovascular patients. Second, potential hints for efficacy regarding lesion growth on MRI and neurological outcome at 3 months may also be detected. Results are expected this year. Feasibility of escalating subcutaneous doses of G-CSF (1 to 10 μg/kg per bodyweight within a 12-hour time window) in acute ischemic stroke is currently assessed in the RAIS study (Dr Bogdahn, personal communication, 2005). Attributable to the fact that this study design includes no control, group indications of potential efficacy will however be quite limited.

Apart from G-CSF’s activity in acute stroke, recent preclinical studies demonstrated the strong trophic activity of this factor in the recovery phase after stroke. In these studies, treatment was delayed for days after onset of the stroke.5,6 (Schneider et al, unpublished data, 2006). G-CSF demonstrated a direct neurogenic6 and angiogenic7 effect in the brain, questioning the widely favored perception that a mobilization of bone marrow–derived stem cells, G-CSF’s primary function in the hematopoietic system, could be the sole or even the most important mechanism for its delayed functioning. Although there are still a number of question marks regarding the optimal trial design and end points for stroke recovery studies in humans, G-CSF is currently being studied in a chronic stroke pilot trial. This study (STEMS) investigates the effects of subcutaneous G-CSF (escalating doses from 1 to 10 μg/kg per bodyweight) on CD34 count, safety and on neurological outcome within the time window of 1 to 4 weeks poststroke.8

Finally, a recently published trial from Taiwan examined G-CSF in acute and chronic stroke patients for safety and efficacy.9 Here, the time window ranged up to 1 week after stroke onset with 50% of patients being treated 24 hours after stroke with 15 μg/kg per bodyweight G-CSF SC for 5 days. Several functional neurological outcome parameters were measured, including National Institutes of Health Stroke Scale (NIHSS) and Barthel Index. This study was certainly too small (7 patients G-CSF treated, 3 placebo), and too heterogeneous in infarct parameters to allow any conclusions regarding efficacy; it demonstrated, however, for the first time feasibility and probable safety of G-CSF in the human-stroke situation. Excellent tolerability was recently also shown in patients with myocardial infarctions treated with G-CSF (REVIVAL-2 trial)10 which should encourage ongoing research in this interesting and novel field of stroke therapy.

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References

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