Granulocyte Colony-Stimulating Factor and Granulocyte-Macrophage Colony-Stimulating Factor Double-Edged Swords*

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Two studies in this issue of the Journal report the effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) to promote coronary neovascularization; both were stopped early because of ominous results. In the report by Zbinden et al. (1), GM-CSF (10 μg/kg/day given subcutaneously for two weeks) was administered to patients with stable angina before undergoing percutaneous coronary intervention. Within 12 days of treatment, two of seven treated patients developed an acute occlusion of a coronary artery (1). In the study by Hill et al. (2), 2 of 16 patients with refractory angina treated with G-CSF (10 μg/kg/day given subcutaneously for five days) suffered an acute myocardial infarction, which was fatal in one patient (2).

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The ability to stimulate neovascularization is an attractive goal for patients with a number of serious ischemic syndromes, such as refractory and stable angina, acute myocardial infarction, critical limb ischemia, and claudication. However, measuring treatment effects and detecting unintended complications has been difficult. Early therapeutic angiogenesis trials used agents that primarily stimulated angiogenesis (the growth of new capillaries from pre-existing ones). They demonstrated excellent safety but only modest efficacy, prompting a shift in focus to agents that stimulate arteriogenesis (growth of larger, more mature vessels) (3,4).

In the race to develop more effective neovascularization, G-CSF and GM-CSF were attractive candidates because they appeared in animal models to stimulate arteriogenesis directly. In addition, they increased circulating progenitor cells, which themselves may cause neovascularization in ischemic tissues by directly incorporating or by stimulating cytokines. Moreover, these drugs already were approved for use in large numbers of patients undergoing chemotherapy for malignancies and for use in increasing circulating progenitor cells in transplant donors.

We now have four published trials in which G-CSF/GM-CSF alone or in combination with local delivery of progenitor cells was given to promote neovascularization in patients with atherosclerosis (1,2,5,6). Preclinical trials and these initial clinical studies suggest that G-CSF and GM-CSF are more effective when used in combination with the local delivery of progenitor cells than when they are used alone. Hill et al. (2) and Kang et al. (5) demonstrated no significant benefit of G-CSF alone in patients with refractory angina and acute and chronic myocardial infarction, respectively (2,5). In two other reports, Zbinden et al. (1) and Seiler et al. (6) reported an improvement in coronary flow index in patients with stable angina treated with GM-CSF alone, but these findings are confounded by the small sample size and the lack of improvement when the treated and placebo groups are compared directly (1,6). The strongest indication for benefit comes from the Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial, in which a significant improvement in left ventricular function, myocardial perfusion, and treadmill times was found in patients who received intracoronary delivery of progenitor cells after the administration of G-CSF (5).

Unfortunately, three of these four early trials were stopped early because of significant safety concerns. In addition to the apparent increase in acute coronary syndromes in the two trials reported in this issue of the Journal, Kang et al. (5) reported a marked increase in in-stent restenosis in patients with acute myocardial infarction who received G-CSF after percutaneous coronary intervention. The mechanism for these complications is not clear, but G-CSF and GM-CSF both have proinflammatory and procoagulant effects, in addition to their potent arteriogenic actions (7).

Researchers have used G-CSF and GM-CSF extensively to stimulate circulating progenitor cells both for patients serving as donors and those with underlying malignancy in lieu of more complex harvesting from the bone marrow (8–10). Some concern exists about safety in these patients also, including a number of case reports of acute myocardial infarction, unstable angina, and stroke in patients with and

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without a history of previous myocardial infarction (10). An "ad-hoc" workshop convened with investigators in the field recommended the creation of an international cytokine-mobilized peripheral blood stem cell donor registry to monitor the short- and long-term effects of the procedure (8). Some controversy also exists regarding the optimal dose, with one recommendation to not exceed 8.8 μg/kg/day, but both the dose and time course remain controversial (8–10). Of note, all of the angiogenesis trials with excessive complications have used 10 μg/kg/day for as long as two weeks. No cases of acute coronary syndrome have been reported in three ongoing clinical trials using lower doses of G-CSF, based on personal communication with the trial investigators.

It is not surprising that these safety concerns were not detected during preclinical testing. Infrequent complications can be nearly impossible to predict from large animal studies, in part because of natural biological differences and in part due to the enormous costs of testing therapies in large numbers of animals with complex protocols (sometimes exceeding the cost of human treatments). As a result, many treatments go to market with limited, necessarily imperfect animal model data.

In the case of GM-CSF, we may have been lucky because the scientific community published their results, allowing the rapid identification of a potential problem. It might be a fluke or it might only occur at higher doses, but we have been alerted to the issue by honest clinical investigators.

The challenge for clinical investigators is to establish, perhaps with the help of the Food and Drug Administration, a worldwide system for monitoring the safety of these new therapies. Many serious complications occur infrequently; without a coordinated clinical reporting system, their detection will occur randomly and late. Cardiovascular investigators have been incredibly successful in collaboratively developing enormous clinical studies. We now should support a collaborative cardiovascular safety database where investigators report therapeutic complications and the safety of new therapies can be monitored across multiple studies.

On the basis of the reports in this Journal, in addition to previous reports, it seems prudent to restrict ongoing trials using G-CSF or GM-CSF to patients with no other therapeutic options, such as those with refractory angina or critical limb ischemia. Using a lower dose may be safer but needs confirmation. Additionally, we need to know more about the safety of G-CSF/GM-CSF in normal donors and patients with malignancy, especially those with coronary atherosclerosis. Finally, the recommendation for the international registry for growth factor therapy proposed previously should be implemented. These trials remind us again of the delicate balance involved in the natural process of vascular growth. For those without the option of revascularization, therapeutic angiogenesis or arteriogenesis remain attractive-yet-elusive goals.

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REFERENCES