

# Stem-Cell Therapy Following Large Acute Myocardial Infarction

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In just a few years, research into the use of stem cells for treating patients with acute myocardial infarction has become a reality in Spain. Since the first safety studies we have moved on to the design of randomized trials to determine whether this therapy works. To understand why the paper by Suárez de Lezo et al<sup>1</sup> deserves to be discussed in an editorial, the short history of cell therapy in patients with acute myocardial infarction needs to be told.

The first stem cell therapy experiments in this area were performed some five years ago with the main aim of determining whether such an approach was safe, and whether this new therapeutic possibility was feasible.<sup>2-7</sup> All were small studies without controls. As it remains to this day, two ways of using these cells were contemplated: their intracoronary injection, or the stimulation of their proliferation in the bone marrow through the use of growth factors. The latter substances, which are in daily hematological use, increase spectacularly the number of stem cells the bone marrow produces. This in turn promotes their mobilization into the blood stream, which theoretically they then leave in order to colonize damaged tissues. Once the absence of important secondary effects and the feasibility of such treatment was confirmed, efficacy studies were undertaken using surrogate endpoints (generally the development of remodeling in the post-infarction left ventricle). In this second phase, experimental designs now contemplated control groups, but work did not go beyond comparing the two routes of administering these cells (mentioned above). At this point the number of types of stem cell used was increased, although all came from the bone marrow subpopulations.<sup>8</sup> These comparative studies raised the first doubts regarding the mechanism of action of these stem cells. It was found that after the intracoronary infusion of stem cells they did indeed settle in the myocardium, and that the more stem cells added, the more myocardium that became

colonized.<sup>9</sup> Curiously, it was also observed that the use of some bone marrow subpopulations, such as CD133+, was associated with a risk of re-stenosis greater than might be expected after angioplasty with a naked stent in patients who had suffered a recent infarction. Similarly, re-stenosis was seen more often than expected when growth factors were administered before stem cell intracoronary injection.<sup>10</sup> However, the discrepancy in the results obtained has been notable: while some studies report this therapy to have a positive effect on ventricular function, others have reported it to have none.<sup>8</sup> In summary, the only stem cells (whether administered as an intracoronary injection or via stimulation with growth factors) currently used in the treatment of acute myocardial infarction are of bone marrow origin, and their efficacy remains questionable.

## What Information Does the Article of Suárez de Lezo et al Provide Beyond That Which Is Already Known?

In their paper, Suárez de Lezo et al show they have a profound knowledge of and expertise in cardiac hemodynamics, in particular overall and regional left ventricular function. This is enviable in these times of lost respect for catheterization methods. This profoundly interesting paper highlights a number of other outstanding features.

Firstly, the design of the work is novel. Never before have the three treatment strategies discussed (intracoronary injection without stimulation with granulocyte colony stimulating factor [G-CSF], treatment with G-CSF alone, and conventional treatment [control]) been compared.

Secondly, the increase in the ejection fraction seen in the members of the intracoronary treatment group is the largest recorded to date, in fact doubling the benefits previously recorded. In agreement with the authors, this could be explained by the fact that all these patients presented with an extensive anterior infarction and a notable deterioration of their left ventricular function – greater in absolute terms than patients in other randomized studies. The BOOST<sup>11</sup> and REPAIR-AMI<sup>12</sup> studies both showed that the greater the deterioration of ventricular function, the greater the benefit of such intracoronary treatment. In addition, the overall number of stem cells administered was greater than in earlier studies, especially in terms of the CD34+ subpopulation. It is also important to note, however, that the small

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sample size limits the extrapolation of the study's findings, and that the time window allowed for angiographically estimating baseline ventricular function (between 3 and 12 days) is perhaps rather wide. As the authors themselves point out, during this time the ejection fraction could have naturally become significantly modified.

Thirdly, the results obtained for the patients who received G-CSF alone are quite disappointing and question the efficacy of this procedure. The pharmacological mobilization of bone marrow stem cells with G-CSF is an attractive alternative since it is non-invasive and simple. However, the neutral results of Suárez de Lezo et al. agree with those obtained by other authors in randomized, double-blind, placebo-controlled clinical trials of the efficacy of G-CSF,<sup>13-15</sup> in which studies the patients also showed no differences in the size of infarction, left ventricular ejection fraction, or ventricular volume. There are several possible explanations for these results. It may be that the G-CSF was not administered at the most appropriate time, thus leading to an inadequate recruitment of cells. Indeed, in those studies that report this treatment to be beneficial, G-CSF was administered immediately after the infarction, while in those that report neutral results treatment began later.<sup>8</sup> It is also possible that the cells mobilized may have been inactive populations, or that these studies failed to fix adequate objectives. Finally, it may simply be that this treatment is ineffective. The failure to achieve benefits in the present study, however, is unlikely to be due to the dose of G-CSF used since it was higher than in all other studies to date involving patients with myocardial infarction (treatment was prolonged for 10 days).

Fourthly, all the patients were treated with a rapamycin-eluting stent, with no increase in the risk of re-stenosis or associated thrombotic problems.

Finally, and probably most importantly, Spain forms part of the vanguard with respect to this kind of treatment, and the number of clinical research groups working in this area is growing rapidly. This coincides with the trend highlighting the need to undertake mid-sized, controlled, randomized clinical trials to confirm the safety of these strategies, and to answer mechanistic questions regarding their efficacy, eg, on choosing the best cell type, on dose, on the repetition of treatment, on the association with bone marrow stimulating factors or factors that stimulate proliferation at the target tissue, on the administration method, and on timing, etc.<sup>16</sup> Clearly, preclinical research in models very similar to the human clinical situation are required to learn more in these areas—particularly with respect to the best types of cell to be used in each situation (if indeed these exist).<sup>17</sup> At this moment in the development of stem cell therapy for the repair of the myocardium, the work of Suárez de Lezo et al<sup>1</sup> invites objective optimism.

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