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# Authors' reply to "Cell therapy in dilated cardiomyopathy: back to the right scientific track?"

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Bias is a bad companion for scientific endeavors. In reading our review of cell therapy trials in animal models of dilated cardiomyopathy, Marin-Neto points to the diversity of animal species, methods of inducing the cardiomyopathy, cell types, techniques of injecting the cells and methods for the evaluation of the effects as weaknesses of the pre-clinical experimental approach and concludes that "no wonder that the reported results have been so variable". If anything, all the results have been consistent in the animal models, and in contrast to what the author of the comment says, "the ultimate goals of these studies, i.e., to achieve cardioprotective effects and/or to regenerate components of the diseased heart" have clearly shown a beneficial cardiac effect and therefore do not "remain quite elusive".

Granted that the usual policy of scientific journals not to publish negative results may in itself introduce some bias into the subject; however, a careful review of the literature points to a large body of evidence showing a positive effect of cell therapy in the various experimental models of dilated cardiomyopathy. That animal models of human disease cannot faithfully reproduce the complexity and subtleties of the pathology seen in patients has been recognized by the medical and scientific community for many decades. This only adds value to the fact that different animal models have been used, ranging from mice to dogs, in the experimental setting, and justifies the need for safety and feasibility trials in well-selected patients.

We agree with Marin-Neto that "the current scenario in human investigation of cell therapy for non-ischemic dilated cardiomyopathy is full of uncertainties". Clinical research in this area has been restricted to phase I-II trials, basically concerned with the safety and feasibility of the procedure. Therefore, it is logical and expected that the scenario should still be uncertain. The clinical

research roadmap requires safety studies before efficacy can be tested. In the still small number of safety clinical trials performed in dilated cardiomyopathy patients, even a smaller number have been restricted only to patients with cardiomyopathy of non-ischemic origin. In all but one two-case report (1), where balloon inflation for intracoronary delivery of cells was used, the procedure has been performed safely either by intracoronary or direct intramyocardial delivery in nearly 100 patients. This number is quite small if compared to the more than 1500 patients with cardiomyopathy of ischemic origin to whom cell therapy has already been applied, also without adverse effects related to the procedure. At any rate, the lack of events related to the immediate cell therapy procedure does not preclude that long-term adverse effects may manifest. This again is an inherent risk of any new therapy, but since the first cardiomyopathy patients were treated with cell therapy a little more than a decade ago, it is reasonable to assume that safety is warranted for at least the first decade.

Surprisingly, in his next to last paragraph Marin-Neto tries to analyze the results of the clinical trials performed. Since all of these trials were admittedly not designed to test for efficacy his comments are unjustified. The conclusions from all of the trials is that the procedure seems to be safe and that larger, randomized trials should be performed to test for efficacy of this new therapy. But it is also unquestionable that if some favorable results had not been observed in these small trials, larger trials would not be pursued. So what the authors of the trials did was to report the small improvements in objective and subjective variables measured during the studies and that Marin-Neto took out of context. Changes in pharmacological therapies during the course of a clinical study are undesirable but are necessary for the benefit of the patient; these changes can increase or

decrease the number of medications or doses, negatively or positively affecting the results of the new therapy being tested. That is the reason why well-designed randomized, placebo-controlled trials are needed for efficacy tests; randomization takes care of balancing the effects of the ethically required need to adjust pharmacologic therapy. It is also quite disturbing that an experienced clinical researcher may think that two imaging methods with strikingly different sensitivities should yield the same results.

As stated by the consensus of the task force of the European Society of Cardiology concerning the clinical investigation of the use of autologous adult stem cells for repair of the heart (2), back in 2006, safety of the procedure is the primary concern in considering if future clinical trials should be undertaken. Along with other very pertinent considerations, this group of distinguished clinical and interventional cardiologists and cardiac surgeons have

pointed out the many reasons that justify going ahead with well-designed clinical trials to test the efficacy of cell therapies in cardiac diseases. We highly recommend the reading of this insightful consensus.

In conclusion, we firmly believe that animal studies have provided convincing evidence that human studies should be carried out. We, and others, have performed the necessary safety studies and the indication of a potential benefit to the patients has encouraged us to pursue the efficacy trial that is currently underway (3). We hope to announce the results of this trial in the coming months. This study will provide solid scientific evidence for the incorporation or not of intracoronary bone marrow-derived mononuclear cell delivery into dilated cardiomyopathy patients. Following the long and winding road from bench to bedside is the only way science can bring progress to medicine.

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