IxCELL-DCM: rejuvenation for cardiac regenerative therapy?

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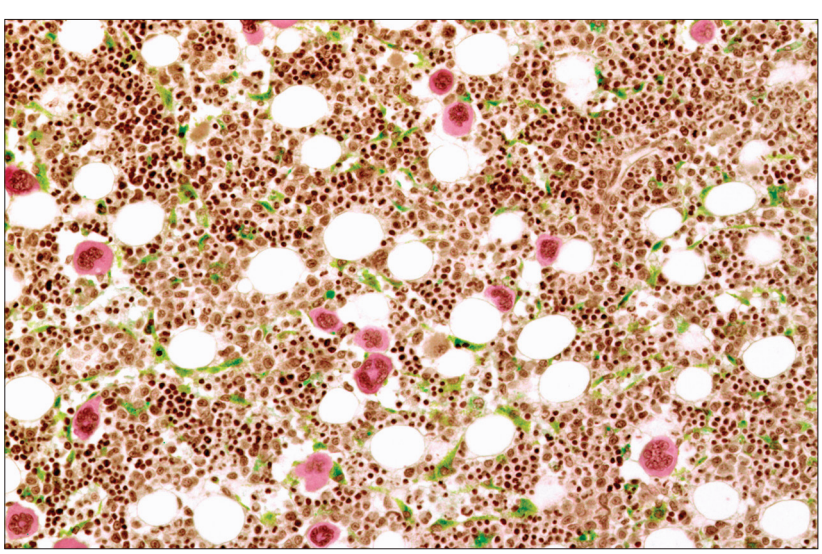
The possibility of tissue rejuvenation through regenerative therapies has generated great excitement among both the scientific community and the public, especially for conditions with perceived irreversible tissue loss such as myocardial injury. Groundbreaking approaches have experimentally identified reparative capacity in the human heart,[1,2] suggesting that if this process could be harnessed, the treatment of conditions such as acute myocardial infarction and chronic congestive heart failure might be revolutionised.

A series of studies first presented a decade ago showed that administration of various selected and unselected bone marrow preparations were associated with improvement, albeit relatively modest, in left ventricular function. Individually not powered to detect improvements in cardiac events, in aggregate, these studies suggest that, despite the rather modest improvement in left ventricular function, a reduction in clinical events might be attained if adequately powered clinical trials could be done.[3,4]

Nonetheless, the field has generated some scepticism for several reasons including individual, poorly conducted and reported studies, and discordant findings among trials, including several National Institutes of Health-sponsored trials, one of which showed no benefit of unselected bone marrow cells on a series of surrogate markers in congestive heart failure.[5]

In *The Lancet*, Amit Patel and colleagues[6] present the results of the IxCELL-DCM trial, a randomised, rigorously conducted double-blind study comparing intramyocardial injection of Ixmyelocel-T with intramyocardial placebo injections. Ixmyelocel-T is an expanded multicellular therapeutic product produced from a patient's own bone marrow by selectively expanding bone marrow mononuclear cells for 2 weeks. The expanded cell product enriched for mesenchymal and macrophage lineages might enhance potency. In the per-protocol population encompassing all patients with adequate intramyocardial delivery of the investigational product (defined as at least 50% of the prepared product), the authors showed an improvement in the prespecified composite primary endpoint of total deaths, cardiovascular admissions to hospital, and outpatient visits requiring treatment for congestive heart failure. The results were robust for a variety of analyses, including analysis of a modified intention-to-treat population of all patients receiving any injections, conventional Kaplan-Meier analysis, total mortality (eight in the placebo group *vs* four in the Ixmyelocel-T group), and number of serious adverse events, which all favoured patients given Ixmyelocel-T. Importantly, the improved clinical outcome was noted despite only marginal changes in left ventricular functional parameters. These results substantiate the aggregate findings of previous studies.

Nevertheless, the modest size of IxCELL-DCM affects several aspects of trial interpretation. First, the population analysed included only those who received therapy, and an intention-to-treat analysis was not the predefined analysis population; thus, the results do not capture three deaths and nine patients who were removed from all of the analysis populations due to inadequate cell product or adverse events. It is unlikely that a trial of this design would meet regulatory requirements for approval. Second, the primary endpoint could have been driven by two patients receiving placebo who each experienced five and seven admissions, to hospital for congestive heart failure, a limitation of an analysis dependent on total number of events. The consistency of trends among the modified intention-to-treat and Kaplan-Meier analyses are reassuring in this regard, and novel approaches to clinical endpoint trials such as this are urgently needed if outcome studies are



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Light micrograph of bone marrow

to be reasonably sized.[7] Finally, IxCELL-DCM showed a 37% reduction in total clinical events (risk ratio 0·63 [95% CI 0·42–0·97]; p=0·0344), an effect size that is uncommon for most medical interventions. Although this could represent the effect of a groundbreaking therapy, it might not be prudent to expect replication of this magnitude of effect in future studies.

The accomplishments of the IxCELL-DCM investigators and study teams should be acknowledged—for the first time, a clinical trial has shown that administration of a cellular therapeutic results in an improvement in cardiac outcomes based on a prespecified analysis. These results reflect the maturing nature of this field and should invigorate and stimulate interest and research in cardiovascular regenerative treatments. As with the findings of previous meta-analyses,[3,4] there seems to be a disconnect between improved clinical outcome and the rather marginal recovery of left ventricular function. In view of the established safety of this therapeutic approach, we now anxiously await the results of a series of clinical endpoint trials including the BAMI trial (NCT01569178),[8] a mortality trial enrolling 3000 patients post acute myocardial infarction throughout the European Union; the CHART-1 trial (NCT01768702), which successfully enrolled 240 high-risk patients with advanced congestive heart failure;[9] and the DREAM-HF (NCT02032004) study, with a target enrolment of more than 600 high-risk patients with congestive heart failure.[10] The results of these trials will provide much-needed information about the potential effectiveness, over and above surrogate endpoints of cardiac function, of various cell-based approaches to conditions characterised by loss of myocardial tissue and performance.

For the field to progress, the completion and reporting of these trials is absolutely essential. In this regard, Baxalta's decision to stop enrolment in the phase 3 RENEW trial,[11] despite robust results in early phase trials,[12] and the recent change in sample size of the DREAM-HF trial from more than 1700 to 600 patients are concerning,[10] because the power of a trial is driven predominantly by the anticipated effect size, not by the absolute number of events. The IxCELL-DCM study serves as a reminder of the power of a trial run to completion, and should rejuvenate interest in and commitment to developing regenerative approaches to the treatment of patients with highly limiting cardiovascular conditions.

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