Letter to the Editor

Intramyocardial bone marrow-derived cells for ischemic heart disease: Is the benefit clinically relevant?

The effectiveness of intramyocardial bone marrow-derived cells in ischemic heart disease has been addressed by several studies and meta-analyses, but the results are still conflicting, particularly as regards the effectiveness in patients unsuitable for revascularization [1]. In this disease condition, the effectiveness of this intervention can be viewed from two different perspectives. The first focuses on the demonstration of a significant improvement in left ventricular function. The second gives instead priority to the magnitude of this improvement and therefore tries to establish whether or not the benefit is clinically relevant (upon the condition that the benefit itself is statistically significant).

Since this second perspective requires to set a threshold for differentiating between relevant and irrelevant benefits, pre-defined superiority margins are helpful for this purpose. In fact, on the one hand these margins are readily available from randomized controlled trials (in which they are used to predict the expected magnitude of the incremental benefit and to calculate an appropriate sample size [2]); on the other, they represent an estimate of the threshold differentiating clinically relevant benefits from irrelevant ones.

To interpret the benefits found in comparative clinical trials, equivalence testing is increasingly being used [3–5], and the approach based on confidence intervals (CIs) is particularly suitable for this purpose. In this context, we carried out a statistical equivalence analysis to re-examine the series of 6 randomized studies included in the meta-analysis by Tian et al. [1].

Our equivalence test was focused on the end-point of improvement in the left ventricular ejection fraction (LVEF) (namely: change from baseline to the end of study) and analyzed the comparison between patients receiving bone-marrow derived cells and controls given placebo. The available evidence was interpreted according to CI-based equivalence testing. The end-point was expressed as weighted mean difference as described by Tian et al. [1]. The pre-specified equivalence margin (expressed according to the end-point of LVEF improvement) was set at ±6%. Although we tried to derive the information on this pre-specified margin from the 6 randomized trials included in the analysis, this could not be made because all included trials adopted primary endpoints other than LVEF improvement. We therefore retrieved the 6% margin from a very recent randomized trial [6], in which however the administration of intramyocardial bone marrow cells was for patients suitable for revascularization (and not for patients unsuitable for this intervention as those included in the present analysis).

Our results are shown in Fig. 1 (data from 6 studies, 428 patients). According to the 6% threshold for a clinically relevant benefit, intramyocardial infusion proved to be equivalent to placebo (Fig. 1), thus providing the proof of no effectiveness for this intervention. It should be noted that, in Fig. 1, the 90%CI for the pooled mean difference tested the “traditional” 5% alpha level, while the 95%CI (i.e. the interval originally published by Tian and co-workers [1]) tested a more restrictive alpha level of 2.5%. Interestingly enough, these results at the same time indicated a statistically significant improvement in LVEF.

Should priority be given to statistical significance or to clinical relevance? Cases where an improvement is statistically significant

Fig. 1. Forest plot and equivalence testing for meta-analytical values of mean difference in LVEF improvement between patients with ischemic heart disease receiving intramyocardial bone marrow cells and controls. The pooled mean difference, obtained from Tian’s meta-analysis [1], was 3.76% (90%CI: 2.45%–5.07%; 95%CI: 2.20%–5.32%). The equivalence test is based on the area comprised between the two vertical dashed lines, that reflect the pre-determined equivalence margins (from −6% to +6%). Each horizontal bar indicates the two-sided CI ([1], two-sided 90%CI [2]; two-sided 95%CI) for the pooled mean difference. The criterion for demonstrating equivalence is when both extremes of the CI remain within the two vertical dashed lines. Since Tian and co-workers did not report the 90%CI for the pooled mean difference, we recomputed this interval from the study-specific outcomes by using the OMA software (Open Meta-Analyst version 4.16.12, Tufts University, U.S.) according to the random effect model.

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but lacks clinical relevance have already been pointed out [7]; as suggested by Ahn et al. [7], if the margins are reasonable, when a result shows at the same time superiority and equivalence priority should be given to equivalence rather than to superiority. Also in the case of intramyocardial bone marrow cells, therefore, the controversy should not be based on the dichotomy “improvement” vs “no improvement” in left ventricular function, but on the dichotomy “presence” vs “absence” of a clinically relevant benefit.

Finally, the main limitation of the approach described herein is that the role of margins is still fraught with some uncertainties. For example, it is often postulated that equivalence and non-inferiority margins differ from superiority ones, but this assumption does not seem to have any specific basis [2]. On the other hand, margins are recognized to intrinsically have a certain degree of arbitrariness [2].

References


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