Discussion to: Prospective randomized controlled trial of the safety and feasibility of a novel mesenchymal precursor cell therapy in hypoplastic left heart syndrome

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Dr. Michael Ma (Palo Alto, CA):

Okay. All right. So, I'll try not to waste time. I'll speak louder. I thought that was a great presentation. Thank you for providing the manuscript in advance for us to review. Congratulations to you and your group. You have always been blazing the path for trying to recruit the hypoplastic ventricle to achieve two ventricle circulation. I've a few questions for you. One is the slight differences that you may or may not have seen in the population of received MPCs. If you were to project this out and you mentioned in your paper that this might be the way to power an inadequate number, do you think that this is at all potentially compounded by differences in the way the patients receive their staged recruitment i.e., were there differences in the shunt size you used to try to grow
the ventricle? Were there differences in how well you supercharged the Glenn at the time of recruitment? That's one question. And the other question would be, for those of us that are very impatient to see this stem cell therapy work for these patients, what are the next steps, do you think, for your analysis? Are you going to be looking at the actual myocardium to see what the stem cell therapy is doing? Are you going to be sampling their blood to see if there's any paracrine effect, as you mentioned, as a mechanism of action for the therapy?

Ms. Rachel Wittenberg (Boston, MA):

Thank you for your comments and for the questions. Certainly, there are factors in the LV recruitment procedures that may impact the degree of pulmonary and left ventricular blood flow, and thus the degree of ventricular expansion. In patients under consideration for biventricular conversion at our center, the 5mm RV to PA conduit, if performed at the time of stage 1 palliation, is typically left in place to achieve the super-Glenn physiology, so there shouldn't be a lot of variability in our patients between the two treatment groups with regard to the blood flow. In terms of the other factors, such as EFE resection, mitral valve repair, ASD fenestration, we would hope that these would balance out in randomization, although with a cohort of 19 patients, this would be more challenging. Our overall message is that while we hope this would balance out in randomization, we need a larger trial powered to detect efficacy in order to both rigorously determine efficacy and also balance out these differences in physiology.

With regard to the second question of sampling the LV and determining the fate of the MPCs, I think there are a couple of next steps. Certainly, an LV biopsy would be helpful in terms of understanding the fate of the MPCs. We know that in most trials, tracking of these cells showed that a relatively large proportion undergo apoptosis within days to weeks after administration. Unfortunately, I think there are sort of feasible and logistical constraints to performing LV biopsy in these patients that might make this a more suitable approach for the animal model, at least at this time. Other concerns with the LV biopsy approach would be knowing exactly where to biopsy, given the cells may stay relatively localized to the injection site, as well as knowing how deep within the endocardium it would be necessary to biopsy. Other imaging modalities may help to understand the fate of the cells. There are none currently in clinical use, but it would be helpful to have a non-invasive modality to track these cells. Thank you.

Dr. Ma:

So sorry, just to respect everybody's time in terms of presentations, we're just going to allow for one question/comment right now.

Dr. Mino Cabrana (Charleston, SC):
Mino Cabrana, Charleston, South Carolina. Quick question. What's the highest Glenn pressure you tolerate at stage 2 to promote maximal LV recruitment? Thank you.

Unidentified Speaker 1:

I can answer that. So generally speaking, we want to make sure that the left atrial pressure is low enough that we don't end up with pulmonary vascular disease, so we follow this by echocardiogram. If the gradient across the atrial-septal defect gets any higher than 8, we're going to the cath lab to balloon-dilate and open up the atrial septum. It's a pretty easy and quick fix to get us back to a baseline status. If we septate between the antegrade flow and the Glenn, we tend not to see the pulsatile Glenn, which can sometimes occur with the super Glenn and with the antegrade blood flow. But we're paying very close attention to the Glenn pressures. With the right management, you'll usually have Glenn pressures in the mid-teens and not very high. Great. Thank you. Thank you, Rachel.

Ms. Wittenberg:

Thank you.