LETTER TO THE EDITOR

Response to Letter from Dickerson and Slade

To the Editor:

Thank you for allowing us to respond to the comments from Dickerson and Slade pertaining to our article “A Multicenter Randomized Controlled Clinical Trial Evaluating the Use of Dehydrated Human Amnion/Chorion Membrane Allografts and Multilayer Compression Therapy vs. Multilayer Compression Therapy Alone in the Treatment of Venous Leg Ulcers.”

We agree with Dickerson and Slade that there is serious need for new treatments to manage venous leg ulcers (VLUs) and feel that this initial study of dehydrated human amnion/chorion membrane (dHACM), which delivers human extracellular matrix components, essential growth factors, and specialized mediating cytokines to wounds, represents an exciting opportunity towards this goal.

In our study, patients in both groups received multilayer compression therapy which is the current standard of care for venous leg ulcers. As Dickerson and Slade pointed out, the response rate to this standard treatment varies widely. This broad range of response further suggests the need for new and innovative treatments and was the basis for the current study.

Regarding the comments related to study inclusion criteria, we agree that that “rapid healers” as the authors describe them should be excluded during the screening period. Procedurally during the study, patients showing rapid healing defined as >20% wound reduction during the run-in period were not eligible to continue to the treatment phase. There were three patients who met this healing threshold and were no longer eligible for study inclusion after the run-in period. It was an oversight on our part to not include this in the paper. In regard to excluding wounds receiving continuous multilayer compression for over 1 year, we did not want very old wounds to be a part of the trial because there are likely to be a variety of issues with such wounds that might need addressing. As this was a controlled trial seeking to determine effect sizes of endpoints under controlled conditions, and the comparator group received only multilayer compression, the investigators felt it would not be appropriate to include a group of patients known to have already failed over 1 year of treatment with multilayer compression. The minimum eligible wound size was 2 cm². There was a typographical error in the clinicaltrials.gov submission regarding the smallest wound area (eligibility) that was not caught as the protocol went through some changes; we sincerely apologize for this and corrections have been made.

In our study, a surrogate endpoint of 40% wound closure at 4 weeks was utilized and results were compared between those that received dHACM in addition to multilayer compression therapy and those receiving multilayer compression therapy alone. Dickerson and Slade voiced concern over our use of a surrogate endpoint rather than the Food and Drug Administration (FDA)-recognized endpoint of 100% reepithelialization. While we acknowledge that the validation for surrogate endpoints (to date) could be much better and certainly has limitations that the authors and other wound care researchers acknowledge, and this discussion should be an exhortation to the field to do better, the authors should also be aware that wound care trials using a single clinically meaningful endpoint—complete wound healing—also have limitations. For example, ascertaining that a wound really is closed initially is not as easy as it sounds. Moreover, looking at a wound 2 weeks later does not tell us much about the robustness of healing as much as the behavior of the subject, which can substantially influence whether the wound stays closed. Indeed, evaluating a new treatment with only the endpoint of 100% reepithelialization may result in throwing the baby out with the bathwater. Over the past 15 years, there have been no new drugs approved by the FDA for the treatment of chronic wounds. Although there are many reasons a potential wound care treatment agent may fail in a Phase 2/Phase 3 study, an inability to reach the FDA-accepted endpoint of “complete wound closure” is one of the most common reasons of failure. Failure to consider intermediate outcomes dismisses the potential value of wound size reduction and other symptomatic improvements. It should also be noted that FDA guidance does recognize that partial wound closure might “indicate relevant biologic activity and guide subsequent study design.” It is known that running controlled clinical trials is very expensive; using a surrogate endpoint, we can gain information about the new therapeutic intervention in a shorter time, thus not exposing patients to potentially nonhelpful treatments for longer periods of time. The information learned in a less expensive study using a surrogate endpoint may help us design those much more expensive trials in which we need to demonstrate the only hard endpoint we have in wound care: complete wound healing.

Dickerson and Slade went on to extrapolate our results to determine a complete healing rate at 12 weeks, although they only performed the calculation for one arm of the study which we feel is misleading. Had they done the calculation for both arms of the study, the results would have yielded an estimated complete healing rate of 43% and 22% for dHACM and controls, respectively. We feel that a nearly 50% difference in estimated healing rates between treatment and control arms is still quite a respectable result, which is supportive of the use of dHACM.

The list of “problems” the authors have articulated about our trial (bias, wound measurement technique, etc.) is fallacious. Conducting tightly controlled trials (even for 12 weeks) does not tell us anything about how the therapeutic intervention might perform in “the real world” and is a major criticism of all randomized controlled trials (RCTs). Use of visual analog scale (VAS) for pain and measuring wound area using a ruler have been long-accepted means of measuring...
endpoints in both uncontrolled and controlled trials in wound care, and for the authors to dismiss them out of hand is capricious. Likewise, we are confident that Dickerson and Slade are knowledgeable that blinding treatments in nondrug or biological wound care studies can be extremely difficult. It is quite common for patients to drop out for a variety of reasons, including their feeling that whatever treatment they are receiving is not doing them any good. Losing only about 5% of patients in these kinds of trials is actually quite reasonable. Most importantly, when there is clear evidence of a difference between two groups as was evidenced in this trial, bias in the form of the issues raised by Dickerson and Slade becomes less of a concern than if the differences had been more marginal.

Overall, we do not feel there is real merit to the concerns voiced by Dickerson and Slade. This study represents the first report on the use of dHACM for the treatment of VLUs. The use of the surrogate endpoint allowed us to determine if further studies are warranted. The study strengths and weaknesses were clearly articulated in the publication and the authors are fully aware that this work does not represent the final say regarding the use of dHACM for the treatment of VLU. Additional studies are currently under way to further elucidate our position.

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Conflicts of Interest: Dr. Serena has provided consultative services to MiMedx and has been a speaker on their behalf. Dr. Carter has provided consultative services to MiMedx. All other authors have no potential conflicts to disclose.

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