Response by Imamura et al. regarding the article "Update of acute and long-term tolvaptan therapy"

To the Editor,

We express our great appreciation for the critical comments from Tanaka et al. to our review article updating tolvaptan therapy. First, we would like to reply about long-term tolvaptan therapy briefly. We totally agree with prioritizing clinical endpoints rather than surrogate markers when investigating the long-term impact of any therapy for heart failure. We do not claim that long-term efficacy of tolvaptan has been established, but there is a huge discrepancy between our clinical experience and the EVEREST result [1]. Therefore, we try to explain where differences lie by referring to relatively small-size studies that have shown the long-term advantage of tolvaptan in improving clinical outcomes. We have not drawn any definite conclusion for this issue but would like to propose a working hypothesis in our current manuscript. Large-scale additional data for long-term treatment of tolvaptan are warranted in the future as they have suggested.

However, the argument of Tanaka et al. largely focused on short-term tolvaptan therapy, and they appear to have questioned our interpretation of evidence. Our discussion is mostly based on our recent meta-analysis [2]. The meta-analysis consisted of not only placebo-controlled ones but also open-labeled studies as far as they were conducted in a randomized fashion. Such an inclusion policy would not reduce the strength of the meta-analysis, because the well-known robust aquaresis of this drug usually makes a double-blind protocol less significant. We do not consider that we have mixed heterogeneous levels of studies in the meta-analysis. Tanaka et al. recommend emphasizing SECRET of CHF [3] and TACTICS-HF [4] as larger-scale data, but the sample sizes of these two studies were not so large (~100 patients per arm), and about the same as the AQUAMARINE study [5]. We equally included these studies in the meta-analysis, and never ignored them.

On the other hand, we agree with their assertion about the study endpoint. Previous trials of tolvaptan adopted changes in urine volume or body weight as a primary endpoint, whereas recent trials on acute heart failure were more focused on the improvement in symptoms. The trend has been apparent since the ASCEND-HF trial [6]. In this sense, TACTICS-HF and SECRET of CHF were designed in a contemporary manner that set the improvement of dyspnea at day 1 as a primary endpoint. Improvement in dyspnea within 1 day was somewhat a tough choice for a primary endpoint, but the decision might be due to the demand for shortening length of hospital stay. The average in-hospital length for heart failure patients is already short (i.e. 5 days) in the USA. Nevertheless, if addition of tolvaptan improved major symptoms within 24 h, hospital stay might be expected to be so short that made this drug cost-effective. Disappointingly, both studies failed to show the efficacy at day 1, but showed that tolvaptan treatment for 3 days significantly improved dyspnea. Moreover, our meta-analysis including both studies revealed that tolvaptan improved dyspnea even at day 1 with comparable heterogeneity among the trials [2]. We believe that we have appropriately interpreted study results on the short-term tolvaptan therapy, and the efficacy of tolvaptan on acute decompensated heart failure, if patients do not respond well to conventional diuretics, has already been established. Accordingly, it is also plausible that tolvaptan therapy is assigned to class IIa/A in the recent Japanese clinical practice guideline for acute heart failure [7].

In our recent review article [8], we might have covered too many issues to be explained in detail. We apologize if insufficient description creates misunderstanding among readers, and we sincerely hope that this reply helps better comprehension of our opinion.

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