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Too Premature to Deny the Potential of Thrombomodulin Alfa in Idiopathic Pulmonary Fibrosis

To the Editor:

We read with much interest the recent work reported by Kondoh and colleagues regarding the effect of thrombomodulin alfa (TM-alfa) in patients with acute exacerbation of idiopathic pulmonary fibrosis (IPF) in a randomized, double-blind, placebo-controlled clinical trial (1). Surprisingly, the reported results contradict the clinical benefits shown by TM-alfa in previous open-label and nonrandomized clinical studies (2).
We congratulate the authors for their excellent work in successfully completing this randomized trial in IPF. The study, however, has serious limitations that argue against the author's conclusions about the potential of TM-alfa in IPF. The baselines of the TM-alfa and placebo groups were not matched. Patients treated with TM-alfa had advanced disease (stage IV) and a $Pa_{O_2}/F_{I_{O_2}}$ ratio of ⩽250, and used noninvasive respiratory support or supplemental oxygen almost twice as often as the patients receiving placebo. In addition, there were three times as many patients with worse high-resolution computed tomography findings in the TM-alfa arm than in the placebo group. Although subgroup stratification favored the placebo group, the small sample size together with the significant number of confounding factors mentioned above (stage, hypoxemia, respiratory support, and radiological findings) casts doubt on the results. The use of a multivariate model is the best statistical approach to correct the influence of multiple confounding factors (3). The authors mentioned the use of "a *post hoc* baseline adjustment analysis," but neither the specific statistical method used nor the data were reported. This information is critical to predict the potential of TM-alfa in future clinical trials. Another important drawback in this study is the concurrent use of corticosteroids with TM-alfa. The authors provided no rationale for the concurrent therapeutic approach. Corticosteroids may downregulate the expression of anticoagulant factors and cell-surface receptors that mediate the antiinflammatory activity of TM-alfa (4, 5). TM-alfa also inhibits epithelial–mesenchymal transition and apoptosis, two well-recognized pathogenic pathways of tissue fibrosis, through a receptor-mediated mechanism (6, 7). Therefore, a sequential therapeutic approach would have been ideal to maximize the beneficial effects of TM-alfa and to avoid the disadvantageous biological consequences of high-dose corticosteroids. Given these limitations, we believe it is too early to deny the potential of TM-alfa for the treatment of patients with IPF. ■

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Reply to Kobayashi *et al.*

From the Authors:

We thank Dr. Kobayashi and colleagues for their interest and insightful comments regarding our recent randomized trial (1). We agree that imbalances in some baseline factors could be a limitation of this study.

As described in our article, a *post hoc* baseline adjustment analysis in separate models was conducted, and it was confirmed that there was no change in the conclusion regarding survival. It is well known that *post hoc* analysis using multiple factors can have issues involving multiplicity and credibility, and may lead to contradictory conclusions simply owing to the play of chance (2). Therefore, the adjusted treatment differences from the *post hoc* analysis were not shown in our article.

Regarding the concurrent use of corticosteroids, as indicated by Dr. Kobayashi and colleagues, corticosteroids could possibly downregulate the expression of anticoagulant factors and cell-surface receptors that mediate the antiinflammatory activity of thrombomodulin alfa.

On the other hand, the use of corticosteroids for patients with acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is weakly recommended in the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement (3) and is considered a standard treatment in Japan, although clinical evidence has not been established through controlled studies. Indeed, corticosteroid therapy is used for most patients with AE-IPF in Japan. In addition, in all of the previous clinical studies that suggested the efficacy of thrombomodulin alfa in patients with AE-IPF and provided theoretical support for the implementation of our trial, thrombomodulin alfa was used concomitantly with corticosteroids (4–6). Given these circumstances, and taking ethical issues and the generalizability of the study results into consideration, all of the subjects in our trial were treated with corticosteroids concomitantly.

It should be noted that patients with AE-IPF were included in this study, and that the results of the study do not provide evidence regarding the usefulness of thrombomodulin alfa in patients with stable IPF. ■

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