Response to Letter Regarding Article, “Granulocyte Colony-Stimulating Factor in Patients With Acute Ischemic Stroke: Results of the AX200 for Ischemic Stroke Trial”

Taguchi et al\(^1\) have raised several points in critique of the AXIS 2 trial\(^2\) that are unsubstantiated and give a wrong impression on the preclinical data assembled on granulocyte colony-stimulating factor.

The authors have conducted 1 singular experiment with granulocyte colony-stimulating factor treatment in a severely immunodeficient mouse strain (CB17 scid) with a defect in V-D-J recombination and absence of all T and B cells.\(^3\) Although this observation has certainly been kept in mind, this is 1 experiment in a highly artificial model little characterized in experimental stroke that has not been repeated. And it reports unusual outcome parameters against at least 31 publications to date in mostly standard focal models in rodents with positive outcome and 1 with neutral outcome. The data set also contains data on permanent models.\(^4\)

The decision to test granulocyte colony-stimulating factor in a human trial was taken by a broad array of experts from different disciplines and was in no way based only on animal stroke studies but on (1) mechanisms of action, (2) impact on recovery, (3) evidence from disease models outside stroke, and (4) previous clinical data. We still think that this was one of the most substantiated decisions throughout stroke drug history.

The authors also state a well-known deleterious role of activated granulocytes and increased inflammation. Several articles that have examined inflammatory parameters report a significant decrease by granulocyte colony-stimulating factor treatment (eg, Sehara et al\(^5\)) and that neutrophilic granulocytes do not have a role in parenchymal damage in stroke (eg, Enzmann et al\(^6\)). We think that our notion on potential problems in using rodent stroke models as predictors of efficacy of drugs in the patient with stroke is therefore valid and necessary to stimulate rethinking the way to arrive at new stroke drugs in the future.

Disclosures

Drs Schneider and Schäbitz are inventors on patent applications claiming the use of granulocyte colony-stimulating factor for the treatment of stroke. Dr Schneider is an employee of SYGNIS Bioscience. The study was funded by SYGNIS Bioscience. Dr Ringelstein received fees and expenses from SYGNIS for his steering board work.

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