Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage: Is Angiographic Vasospasm an Epiphenomenon?

To the Editor:

We would like to congratulate the Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1) investigators with the completion of this large phase IIb study, investigating the effect of the endothelin receptor A antagonist clazosentan in patients with aneurysmal hemorrhage. We have a few comments.

First, the CONSCIOUS-1 study has angiographic vasospasm as a primary end point. Although we understand this from a pathophysiological point of view, namely that angiographic vasospasm is caused by endothelin release and might be counteracted by an endothelin receptor A antagonist, we are concerned that angiographic vasospasm is used as a surrogate marker for delayed cerebral ischemia. We realize that there is a widely held assumption that delayed cerebral ischemia is caused by vasospasm, and that this assumption is based on several studies that found a strong association between radiologically confirmed spasm and clinical signs of delayed cerebral ischemia, but an association is not a causal relation.

In a recent large and thorough review (by the first author of the CONSCIOUS-1 study), investigating the relation between vasospasm and cerebral infarction after aneurysmal subarachnoid hemorrhage, it was concluded “that the data linking angiographic vasospasm to cerebral infarction and to outcome are somewhat weak. Not enough evidence is available to prove that angiographic vasospasm in itself could be used as a surrogate marker to monitor disease progression and efficacy of intervention.”

Second, this randomized, double-blind, placebo-controlled study lacks an intention-to-treat analysis. Efficacy is only analyzed in the ‘all-treated set’ and ‘per-protocol set’. In the highest treatment dose of clazosentan (15 mg/h) a highly significant and impressive 65% relative risk reduction of angiographic vasospasm was observed, but without effect on the clinically more important predefined morbidity and mortality end point. These results add to an accumulating body of clinical data, and more convincingly than ever suggest that no causal relation exists between angiographic vasospasm and delayed cerebral ischemia. Because no effect was observed on the predefined secondary morbidity and mortality outcome, it is therefore surprising that it was decided to perform a phase III study to investigate the effects of clazosentan in this group of patients.

Finally, we disagree that for the planned phase III study vasospasm-related outcome measures will be used in order to reduce sample size, and to use the extended Glasgow Outcome Scale as a secondary instead of primary end point. The authors state that first more sensitive and validated clinical outcome scales should be developed. However, use of clazosentan will not be justified in patients with aneurysmal subarachnoid hemorrhage based on a phase III trial if such a study was not sufficiently powered to detect differences on a clinically important outcome scale.

Disclosures

None.

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