Effect of Endothelin-Receptor Antagonists on Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage Remains Unclear

To the Editor:

With great interest I have read the recent meta-analysis on the effect of endothelin-receptor antagonists (ETRAs) in patients with aneurysmal subarachnoid hemorrhage.1 Because endothelin might have an important function in the pathogenesis of angiographic vasospasm, ETRAs are presently under intensive investigation in this group of patients. Recently, the results of a large double-blind, placebo-controlled Phase II study (Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage [CONSCIOUS-1]) investigating the effect of the ETRA clazosentan in patients with aneurysmal subarachnoid hemorrhage for the first time revealed a 65% relative risk reduction (95% CI, 47% to 78%) of angiographically demonstrated vasospasm in the group of patients treated with the highest dose of clazosentan (15 mg/h).2 This finding was impressive, because no other drug ever before was found to have such a spectacular effect on angiographic vasospasm. Therefore, it was even more surprising that no effect on the clinically more important predefined morbidity and mortality end point was observed. These recent findings more convincingly than ever suggest that no causal relation exists between angiographic vasospasm and clinical symptoms of delayed cerebral ischemia (DCI).

Dr. Kramer and Fletcher presented a meta-analysis on the effect of ETRAs in patients with aneurysmal subarachnoid hemorrhage.1 Three studies were included, enrolling 867 patients. It was concluded that ETRAs reduce radiographic vasospasm and DCI, but that there is currently no evidence that these drugs improve outcomes. The observation that ETRAs decrease the incidence of DCI was new, because none of the included individual studies showed a statistically significant effect on DCI. However, in my opinion, this conclusion might not be justified. In the largest study, the CONSCIOUS-1 study, DCI was documented as “clinical vasospasm” and defined as “locally defined vasospasm on DSA or transcranial Doppler associated with neurological worsening lasting for at least 2 hours.”3 In other words, patients were only documented to have this end point in the presence of vasospasm. Patients who were treated with clazosentan had a lower incidence of angiographic vasospasm and, as a result of the definition of “clinical vasospasm,” also had a lower incidence of that end point. Because it is well-known that patients with aneurysmal subarachnoid hemorrhage can also have symptoms of DCI in the absence of angiographic vasospasm, it could well be that in the group of patients treated with clazosentan, many patients had neurological worsening in the absence of vasospasm. I understand that Drs Kramer and Fletcher had no other data available for their meta-analysis than presented in the original study; however, their conclusion that ETRAs decrease the incidence of DCI might not be justified for the reason described previously here.

The issue is that clinical symptoms as a result of DCI are described in many different ways in the literature. Besides DCI, many other terms are used such as “delayed ischemic neurological deficit,” “secondary cerebral ischemia,” “vasospasm,” “clinical vasospasm,” “symptomatic vasospasm,” “vasospasm-related ischemia,” “symptomatic brain ischemia,” and “cerebral infarction.” The use of so many different terms is problematic, not only because often incomplete or no definitions are described of the terms used,3,4 but also because often various definitions are used for the same term. The use of different terms and definitions leads to confusion when defining end points in clinical trials and makes it difficult to compare the results of various studies. In meta-analyses, the combining of data from multiple studies becomes difficult when different definitions are used in the separate studies. However, because meta-analyses have more power than the results of individual randomized, controlled trials, it remains important that meta-analyses are undertaken in studies investigating DCI in patients with subarachnoid hemorrhage. As long as there is no uniform definition of DCI, in meta-analyses, special emphasis should be put on the definition of DCI within the individual trials, and the results of meta-analyses on DCI have to be interpreted with caution.

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