Clazosentan (AXV-034343), a selective endothelin A receptor antagonist, in the prevention of cerebral vasospasm following severe aneurysmal subarachnoid hemorrhage: results of a randomized, double-blind, placebo-controlled, multicenter Phase IIa study

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Objective. The goal of this study was to investigate the safety and tolerability of the novel endothelin A (ET$_A$) receptor antagonist clazosentan in patients with subarachnoid hemorrhage (SAH) and its potential to reduce the incidence and severity of cerebral vasospasm following surgical clipping of the aneurysm.

Methods. This Phase IIa multicenter study had two parts: a double-blind, randomized Part A (some patients given clazosentan [0.2 mg/kg/hr] and others given placebo), in which statistical inference was performed, and an open-label Part B (patients with established vasospasm given clazosentan [0.4 mg/kg/hr for 12 hours followed by 0.2 mg/kg/hr]) for exploratory purposes only. Primary end points were the incidence and severity of angiographic vasospasm on Day 8 after SAH and the safety and tolerability of the drug.

Thirty-four patients (Hunt and Hess Grades III and IV and Fisher Grade $\geq 3$) were recruited and 32 (15 in the clazosentan group and 17 in the placebo group) were retained in the intent-to-treat population; 19 patients entered Part B. In Part A, treatment with clazosentan resulted in a reduced incidence of angiographically evident cerebral vasospasm (40% compared with 88% of patients, $p = 0.008$). In addition, the severity of vasospasm was reduced in the clazosentan group ($p = 0.012$). In Part B of the study, in 50% of assessable patients who were initially treated with placebo reversal of vasospasm was observed following the initiation of clazosentan therapy. The incidence of new infarctions was 15% in the clazosentan group and 44% in the placebo group ($p = 0.130$). There was no adverse event pattern indicating a specific organ toxicity of clazosentan.

Conclusions. This study indicates that clazosentan reduces the frequency and severity of cerebral vasospasm following severe aneurysmal SAH with the incidence and severity of adverse events comparable to that of placebo.

**Key Words** • aneurysm • clinical trial • subarachnoid hemorrhage • vasospasm • endothelin • clazosentan

Despite recent improvements in surgical and medical treatment, aneurysmal SAH remains a serious disease associated with high rates of mortality and morbidity. Delayed cerebral vasospasm leading to cerebral ischemia is one of the most serious complications to occur after aneurysmal SAH. The incidence of vasospasm confirmed on angiograms is as high as 70%, with symptomatic vasospasm occurring in 30% of patients and typically manifesting between 5 and 14 days after the bleeding event.

Progression to cerebral infarction occurs in 50% of symptomatic cases. At highest risk are patients who initially present with thick subarachnoid blood clots and a poor neurological condition. Because of these high morbidity and mortality rates, considerable research efforts have been directed at identifying the mechanism of cerebral vasospasm and underlying causative mediators.

Endothelin 1, a 21–amino acid peptide, is the most potent and persistent vasoconstrictive agent known to date whose activity is mediated by an increase in the intracellular concentration of calcium. The vasoconstrictive activity of ET$_1$ is primarily mediated via the ET$_A$ receptor, which is localized on vascular smooth-muscle cells. The production of ET$_1$ has been attributed to endothelial cells, smooth-muscle

* See Appendix for a complete list of study participants.
cells, neurons, astrocytes, and monocytes. Several lines of evidence implicate ET1 in the pathophysiology of cerebral vasospasm after SAH. 1) Levels of ET1 are increased in the CSF and plasma of patients with SAH in close correlation with the development of vasospasm.\textsuperscript{13,14} 2) Delayed vasospasm can be experimentally evoked by intracisternal administration of ET1.\textsuperscript{14} 3) Endothelin 1 causes histological changes that resemble delayed SAH-associated vasospasm.\textsuperscript{14} 4) Thrombin and oxyhemoglobin, which are present in high concentrations in the CSF after SAH, can increase vasospasm-related reduced CBF.\textsuperscript{25} Clazosentan (also known as Ro 61-1790, VML 588, and AXV-034343) binds to the ET\textsubscript{A} receptor subtype with a much higher affinity than that seen with the ET\textsubscript{B} receptor subtypes (K\textsubscript{i} 0.6 ± 0.3 nM and 1930 ± 340 nM, respectively).\textsuperscript{14} Clazosentan was designed to be a parenteral drug capable of preventing or reversing cerebral vasospasm in patients with SAH. Proof of this concept has been experimentally provided using a double-hemorrhage canine SAH model;\textsuperscript{14} however, the clinical use of clazosentan has been limited to healthy volunteers in whom it was well tolerated at doses up to 0.8 mg/kg/hr (unpublished data). The primary objectives of the present Phase IIa, multicenter, double-blind, placebo-controlled randomized study in patients with aneurysmal SAH were to assess the safety and tolerability of clazosentan and determine its efficacy in reducing the incidence and severity of angiographically evident vasospasm.

**Clinical Material and Methods**

**Study Population**

Patients included in this study were selected from patients with aneurysmal SAH who were admitted to five neurosurgical centers in Germany, each of which received approval from its local ethics review committee. Informed consent was obtained from a legal representative of each patient before enrollment. The target population included patients with severe aneurysmal SAH (Grade III or IV according to the Hunt and Hess classification\textsuperscript{a} and Grade ≥ 3 according to the Fisher scale\textsuperscript{31,11}). Patients with intracerebral or intraventricular hemorrhage were only included if thick subarachnoid clots were present in addition to the intracerebral hemorrhage. Additional inclusion criteria were: 1) male or female patient 18 to 65 years of age; 2) diagnosis of SAH made using CT scanning and a saccular aneurysm confirmed by digital subtraction angiography; 3) surgical clipping of the aneurysm performed within 48 hours after SAH; and 4) initiation of the study medication immediately after surgery. The main exclusion criteria were: 1) rupture of a fusiform, traumatic, or mycotic aneurysm; 2) vasospasm present at the time of the screening angiogram; 3) occurrence of a warning hemorrhage; 4) endovascular treatment of the aneurysm; 5) pregnancy (confirmed by a serum human chorionic gonadotropin pregnancy test) or breast feeding; and 6) treatment by investigational drugs within 30 days before screening. Patients could be withdrawn from the study at any time. If patients chose to withdraw from the trial, infusion of the study medication and all related observations were stopped. If patients were withdrawn because they experienced adverse events, they were followed and relevant information was collected until the adverse event resolved or until 30 days after termination of the infusion. Data from these patients were included in the analysis. We continued to enroll patients in the study until at least 32 were available for the efficacy evaluation (that is, patients in whom both baseline and follow-up angiograms had been obtained).

**Study Design**

The study was divided into two parts. Part A followed a multicenter, double-blind, randomized, placebo-controlled parallel-group design on which statistical inference was performed. Patients received a continuous intravenous infusion of clazosentan (0.2 mg/kg/hr) or placebo for up to 14 days postrupture starting within 48 hours after onset of the SAH and after surgical clipping of the aneurysm. In addition, all patients received standard medical, pharmacological, and surgical management of the SAH and delayed ischemia. Administration of the calcium antagonist nimodipine was left to the individual investigator’s discretion. Angiographic assessments were performed preoperatively and at post-SAH Day 8 (± 1 day) to evaluate the occurrence of cerebral vasospasm, or at any time prior to this if the patient began to experience clinical or TCD changes suggestive of vasospasm. If vasospasm was not confirmed at that time, the angiogram was repeated at Day 8 (± 1 day) after aneurysm rupture according to the study protocol. If a patient whose Day 8 angiogram proved to be nondiagnostic later demonstrated clinical or TCD signs of vasospasm, other confirmatory angiograms could be obtained at the discretion of the investigator. If one of these angiograms demonstrated cerebral vasospasm the patient could be entered into the exploratory open-label Part B of the study. In Part B, the placebo or clazosentan infusion was stopped and triple-H therapy (hemodilution, hypervolemia, and hypertension) was initiated. Following stabilization of mean arterial blood pressure and central venous pressure for 2 hours, clazosentan was administered at a dose of 0.4 mg/kg/hr for 12 hours and thereafter continued at a dose of 0.2 mg/kg/hr until post-SAH Day 14. Additional angiograms could be obtained during Part B to evaluate the reversal of angiographic vasospasm; these were left to the discretion of the investigator. Patients who were not entered into Part B remained in the double-blind Part A of the study and continued to take the assigned medication. Clazosentan doses were selected based on the results of the Phase I study of the drug.

**Randomization and Blinding**

Randomization of eligible patients to the treatment groups followed a 1:1 ratio. To maintain the study blind, the investigator or other staff member was not allowed to witness the preparation of study medication by the pharmacist.

**Clinical and Laboratory Assessments**

All angiograms (see Study Design) were evaluated locally for patient management decisions only. The assessment of clazosentan’s efficacy in preventing and reversing vasospasm was performed centrally by two blinded neuroradiologists who compared data from baseline and follow-up examinations. The presence and severity of vasospasm were defined by categorizing changes in arterial diameters as follows: none (0–33% reduction in arterial diameter),
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moderate (34–66% reduction in arterial diameter), and severe (67–100% reduction in arterial diameter). Computerized tomography scans were obtained for the diagnosis and grading of SAH, and on post-SAH Day 14 to assess the number and sizes of the ischemic lesions. The incidence of vasospasm-associated infarctions was assessed by comparing hypodensities present on the Day 14 CT scan with the appearance of the preoperative CT scan. Transcranial Doppler measurements of mean flow velocities were performed bilaterally in the MCA and ICA. The Lindegaard index (ratio between flow velocities in the MCA and ICA) was calculated daily until the end of the study period. The mGCS was used to evaluate the patient daily through Day 14 post-SAH and the NIHSS was used at baseline and at Day 14 post-SAH. A GOS score was recorded on post-SAH Day 14.

Safety assessments consisted of monitoring and recording of adverse events, serious adverse events, and regular central and peripheral hemodynamic measurements (cardiopulmonary parameters; heart rate; and systolic, diastolic, and mean arterial blood pressure). In addition, routine hematological, biochemical, urinalysis, and coagulation measurements, as well as 12-lead electrocardiographic studies were assessed locally at both screening and study completion, and every 48 hours during the infusion period.

End Points of the Study

The primary end points of the study were to assess the safety and tolerability of clazosentan in patients with aneurysmal SAH and to evaluate whether its administration following surgical aneurysm clipping can reduce the incidence and/or severity of angiographic vasospasm. Secondary end points included the effect of clazosentan on ischemic deficits, as documented by CT scanning, and its peripheral and cardiopulmonary hemodynamic effects. An exploratory tertiary objective was to assess the effect of clazosentan on the reversal of angiographically confirmed vasospasm.

Statistical Analysis

The population used for the safety analysis included all randomized patients in whom administration of the study medication was initiated. The ITT population, which was the population used for the efficacy analyses, included all randomized patients who received study medication and had at least one efficacy measurement. A primary efficacy analysis was conducted to compare the incidence of vasospasm in the two treatment groups by performing the two-sided Fisher exact test, and the distribution of the severity scores of vasospasm was determined using the Wilcoxon rank-sum exact test.

Two-sided probability values were compared with the predefined 0.05 significance threshold. Multiplicity of testing was not planned to be taken into account. Additionally, conservative analyses of the primary efficacy variables were defined and performed post hoc; in those analyses missing angiogram data due to premature death were replaced by “severe vasospasm.”

This Phase IIa study was not powered to be confirmatory and sample size estimation was not based on statistical considerations. With the planned number of patients (16 in each treatment group) the study allowed us to detect a statistically significant (type I error < 0.05 [two-sided], Fisher exact test) reduction in the incidence of vasospasm from the expected 50% in the placebo group to 10% in the active treatment group with a 58% power.

For the analysis of secondary end points missing data were imputed by carrying forward the last available observation. All computations were done with the aid of SAS software (version 8; SAS Institute, Inc., Cary, NC).

Results

Study Population

Patients were recruited between October 2002 and April 2003 from four centers (no patients were enrolled at the fifth center). Of the 40 patients screened, 34 fulfilled the inclusion criteria, were enrolled (16 assigned to be given clazosentan and 18 given placebo; Fig. 1), and constituted the population for the test of clazosentan’s safety. Thirty-two of these patients were included in the analysis of the primary efficacy end point (the ITT population: 15 patients in the clazosentan group and 17 in the placebo group). Two patients (one in the clazosentan group and one in the placebo group) died soon after randomization; they had to be excluded from the ITT population because of missing efficacy assessments, but were included in the post hoc analyses. Nineteen patients (seven in the clazosentan group and 12 in the placebo group during Part A) entered Part B of the study. For 15 of these patients (seven in the clazosentan group and eight in the placebo group during Part A), an additional follow-up angiogram was available for further evaluation of whether clazosentan is capable of reversing established vasospasm (one patient in the active group entered Part B and was later rated centrally as having a reduction in arterial diameter to less than 33% of baseline and was thus categorized as having no vasospasm).

Demographically, the patients who were randomized to the clazosentan and placebo groups were well matched. In these two groups, the majority of randomized patients was female—69 and 61%, respectively—and the median age was 45 and 50 years, respectively. Smoking habits and alcohol consumption were equally distributed; 47% of all patients were active smokers. The study groups were also comparable with respect to medical (except arterial hypertension, which was present in 13% of patients in the clazosentan group and 33% of patients in the placebo group) and surgical histories as well as the results of physical, neuroimaging, and laboratory examinations, surgical procedures, and concomitant medication usage. Only a few patients (one in the clazosentan group and three in the placebo group) were treated with nimodipine.

Efficacy of Treatment

A review of angiograms showed that six (40%) of 15 patients in the clazosentan group had cerebral vasospasm compared with 15 (88%) of 17 patients in the placebo group (p = 0.008, two-sided Fisher exact test; relative risk reduction 55%; Fig. 2A). In addition, the distribution of the severity scores was different between the two treatment groups with less pronounced vasospasm in the clazosentan group (p = 0.012, two-sided Wilcoxon rank-sum test; Fig. 2B). At follow up, four patients treated with clazosentan demonstrated no sign of vasospasm at all and some had basal cere-
bral arteries that were even wider than baseline measurements (Fig. 3). All patients in the placebo group demonstrated at least some constriction of their basal cerebral arteries.

The robustness of these results, which demonstrated marked improvements in the incidence and severity of vasospasm with clazosentan therapy, was essentially confirmed in a conservative post hoc analysis, that is, an analysis in which missing data were replaced by data representing the worst possible scenario. In the post hoc analysis of the primary efficacy parameter, angiographic evidence of cerebral vasospasm was found in nine (56%) of 16 patients in the clazosentan group and in 16 (89%) of 18 patients in the placebo group (p = 0.052, two-sided Fisher exact test; relative risk reduction 37%). The distribution of vasospasm severity scores between the clazosentan and placebo groups was seven (44%) of 16 and two (11%) of 18 for cases with no vasospasm, four (25%) of 16 and six (33%) of 18 for cases of moderate vasospasm, and five (31%) of 16 and 10 (56%) of 18 for cases of severe vasospasm (p = 0.061, two-sided Wilcoxon rank-sum test).

The TCD measurements performed during Part A of the study yielded median Lindegaard indices of 1.8 and 2.4 for patients randomized to the clazosentan and placebo groups, respectively. The median change in these indices from baseline to the last available value was markedly lower in the clazosentan group than in the placebo group (0.60 compared with 1.85).

An analysis of CT scans demonstrated that fewer patients in the clazosentan group experienced new infarctions compared with patients in the placebo group (p = 0.130, two-sided Fisher exact test; relative risk reduction 65%, 95% CI 41–91%; Fig. 4). Moreover, although all patients treated with clazosentan displayed only lacunar infarctions, most
patients receiving placebo were characterized by territorial infarctions. In a conservative post hoc analysis (missing data imputed with the maximum of new infarctions occurring during the study), the difference between the treatment groups with respect to the incidence of new infarctions was numerically less marked but still apparent (clazosentan group 31%, placebo group 50%; p = 0.315, two-sided Fisher exact test; relative risk reduction 38%, 95% CI 48–74%). Median and mean changes in mGCS scores from baseline to the last available value were identical in both treatment groups. The total NIHSS score was notably different between baseline and the end of study; however, there were no apparent differences in changes from baseline between the treatment groups. The median GOS score at the end of the study was 3 in both treatment groups. This was most likely influenced by the fact that approximately half of the patients were sedated.

During Part B, additional follow-up angiograms were obtained after a median time interval of 2 days following crossover to open-label treatment with clazosentan. Figure 5 shows angiograms obtained in a patient who initially received placebo and experienced diffuse moderate vasospasm on post-SAH Day 8. Two days after the patient began clazosentan therapy, follow-up angiograms revealed complete reversal of the vasospasm. An evaluation of all follow-up angiograms for changes in vasospasm severity revealed that four (50%) of eight assessable patients who initially received placebo exhibited a reversal of vasospasm following treatment with clazosentan (Fig. 6A). Moreover, none of the patients initially receiving placebo demonstrated a worsening of their vasospasm. In contrast, none of the patients who initially received clazosentan at 0.2 mg/kg/hr profited from an increase in the dosage to 0.4 mg/kg/hr (followed by a return to 0.2 mg/kg/hr after 12 hours; Fig. 6B). Instead, the
severity of the vasospasm remained unchanged in five patients and worsened in two patients.

**Safety and Tolerability**

The overall median duration of the study medication infusion was 12.5 days (range 1–14 days), and this was identical in the two treatment groups. Most of the 28 patients (22 [79%]) who received clazosentan treatment in Part A or Part B were exposed to clazosentan for at least 120 hours at an infusion rate of 0.2 mg/kg/hr.

Overall, the rates, nature, and severity of adverse events were comparable between the two treatment groups. No adverse event pattern indicated a specific organ toxicity of clazosentan (Table 1). Note the incidence of arterial hypotension was not greater in clazosentan-treated patients (one patient in the clazosentan group and two patients in the placebo group). A trend for a lower incidence of neurological disorders (for example, cerebral infarctions) in the clazosentan group was observed (25% in the clazosentan group compared with 44% in the placebo group).

Six patients died (three in each group) during the course of the study. Progression of the disease was considered to be the main cause of death in each case. In the clazosentan group the patients suffered from intracranial hemorrhage and acute respiratory distress syndrome, multiple brain infarcts, or left-sided MCA thrombosis and increased intracranial pressure. In the placebo group the patients with fatal outcomes suffered from cerebral infarction or increased intracranial pressure.

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**Fig. 5.** Anteroposterior views of right ICA angiograms demonstrating the reversal of moderate cerebral vasospasm within 2 days after crossover from treatment with placebo to clazosentan. A: Angiogram obtained on the day of SAH from a ruptured ACoA aneurysm (arrow). B: Angiogram obtained on post-SAH Day 8 revealing diffuse moderate vasospasm after an initial treatment with placebo. C: Angiogram obtained on post-SAH Day 10 demonstrating complete reversal of vasospasm 2 days after initiation of clazosentan treatment.

**Fig. 6.** Individual analysis of severity of vasospasm observed on angiograms before and after initiation of Part B for patients initially receiving placebo (A) or clazosentan (B). Initially eight of these patients were in the placebo group and seven in the clazosentan group. The median time until a follow-up angiogram was obtained was 2 days. Each line represents one patient.
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**Discussion**

The present study is the first to demonstrate significant efficacy for a compound aimed at the pharmacological prevention of cerebral vasospasm without affecting peripheral hemodynamics. This multicenter, placebo-controlled, double-blind randomized study showed that the novel ET_1_ receptor antagonist clazosentan significantly decreases the incidence and severity of angiographically confirmed cerebral vasospasm following severe aneurysmal SAH. This effect was associated with a clear reduction in the number of new cerebral infarcts observed on CT scans. Moreover, the exploratory open-label Part B of this study indicated that clazosentan may be capable of not only preventing but also reversing already established angiographic cerebral vasospasm. Treatment with clazosentan was safe and well tolerated. The incidences of death, adverse event, severe adverse event, and premature discontinuation of therapy were similar to those observed with placebo. Endothelin 1 is the most powerful vasoconstrictor and inducer of long-lasting hypertension, with a potency 10 times that of angiotensin II. It causes prolonged, powerful arterial constriction that is slow in onset and resistant to washout in vitro. Endothelin 1 acts by means of two different receptor subtypes: ET_1_ and ET_2_. Whereas the ET_1_ receptor is expressed on vascular smooth muscle cells and mediates the vasoconstrictive effect of ET1, the ET_2_ receptor is mainly expressed on endothelial cells and mediates the endothelium-dependent vasodilative action of ET1. Based on their putative role as the main mediator of cerebral vasospasm, ET receptors have become a primary target for its pharmacological prevention following aneurysmal SAH. A dual ET receptor antagonist, TAK-044, was assessed for its efficacy in the prevention of vasospasm in a multicenter, randomized placebo-controlled investigation. That study failed to show any significant difference in the frequency of beneficial effects between the TAK-044-treated and placebo-controlled groups. The probable explanation for this negative result is the unselective inhibition of the ET_1_ and ET_2_ receptor subtypes by TAK-044, in which the beneficial, antivasoconstrictive effect obtained with ET_1_ receptor blockade may be offset by a simultaneous blockade of nitric oxide generation via ET_2_ receptor inhibition.

Clazosentan belongs to a new generation of specific ET receptor antagonists, which is characterized by a higher affinity for the ET_1_ receptor than for the ET_2_ receptor. Its affinity constant values for the ET_1_ and the ET_2_ receptor subtypes are 9.5 and 6.4, respectively, thereby conferring a three orders of magnitude (~1000-fold) selectivity for the ET_1_ receptor subtype. Consequently, in contrast to previous ET receptor antagonists, clazosentan exerts a selective and potent inhibition of the ET_1_–mediated vasoconstrictive effects of ET1 without interfering with its endothelium-dependent vasodilative action. In vivo, clazosentan has been shown to prevent and reverse cerebral vasospasm in a canine double-hemorrhage SAH model following systemic administration. In the same experiments, clazosentan demonstrated a 10-fold higher potency than bosentan, a dual ET receptor antagonist, in reversing cerebral vasospasm.

In the context of these preclinical studies, the concentration of clazosentan was also measured in the CSF to address the issue of penetration of clazosentan into the CNS compartment. At the maximal efficacious dose for the reversal of vasospasm observed on angiography (3 mg/kg administered intravenously as a bolus, followed by an infusion of the same dose per hour over a 2-hour period), a concentration of 160 nM was measured in CSF. These data indicate that the drug reaches the smooth-muscle cell layer of cerebral blood vessels in order to block the actions mediated by the abluminal ET_1_ receptor in response to ET1 binding. Given the high potency of clazosentan to bind to the ET_1_ receptor, this concentration is certainly sufficient to explain the observed effects on cerebral blood vessels.

In addition to the placebo-controlled, double-blind Part A of the study we also performed an exploratory, open-label Part B in which patients with angiographically verified cerebral vasospasm could be treated with clazosentan at doses up to 0.4 mg/kg/hr to assess the efficacy of clazosentan in the reversal of established vasospasm. It was not surprising that patients in whom treatment with clazosentan initially failed did not benefit from an additional increase in the dose. In contrast, 50% of assessable patients who initially had received placebo exhibited a significant and permanent reversal of their angiographically verified cerebral vasospasm, as documented by a follow-up angiography study after a median time of 2 days. Certainly, this observation cannot be simply explained by the natural history of chronic cerebral vasospasm, which has been shown to persist for up to 14 days after SAH. If this observation holds true, clazosentan may prove to be more potent in the reversal of cerebral vasospasm than any other pharmacological strategy suggested to date, such as papaverine, sodium nitroprusside, or verapamil. Nevertheless, the results of the Part B study also confirm the general notion that the pathogenesis of cerebral vasospasm is complex and multifactorial, and that ET1 may play a central role in mediating arterial vasoconstriction following SAH.

The assessment of symptomatic vasospasm was limited by the fact that a majority of patients were sedated, making the mGCS not interpretable. Given the paucity of effective treatments for life-threatening vasospasm following aneurysmal SAH, the results of this study are very encouraging. Because of the limited number of patients, the absence of patients with a Fisher grade equal to or lower than 3 and a Hunt and Hess Grade V, and the rather high incidence of angiographically verified vasospasm in the placebo group, however, the observed

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**TABLE 1**

Summary of treatment-emergent adverse events by organ class during part A of the study*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clazosentan Group (16 patients)</th>
<th>Placebo Group (18 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>infection</td>
<td>8 (50.0)</td>
<td>9 (50.0)</td>
</tr>
<tr>
<td>CNS</td>
<td>4 (25.0)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>blood</td>
<td>3 (18.8)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>hepatobiliary</td>
<td>3 (18.8)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>vascular</td>
<td>2 (12.5)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>metabolic</td>
<td>3 (18.8)</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>cardiac</td>
<td>2 (12.5)</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>respiratory</td>
<td>2 (12.5)</td>
<td>1 (5.6)</td>
</tr>
</tbody>
</table>

* Organ classes in which greater than 10% of patients experienced an adverse effect are listed.
benefits of clazosentan cannot be simply generalized for a larger SAH population and need to be confirmed in further studies. Similarly, future studies will also have to address the effect of clazosentan on clinical outcome parameters of these patients, and not only on the surrogate marker “angiographically verified vasospasm,” because an improvement in this vasospasm does not necessarily translate into an improved outcome.

Conclusions

In this study, clazosentan showed a clinically relevant and statistically significant reduction in the frequency and severity of vasospasm compared with placebo. The incidence and severity of adverse events observed with clazosentan were comparable to those associated with placebo and there was no adverse event pattern indicating a specific organ toxicity of clazosentan. Clazosentan had no impact on central and peripheral hemodynamics and particularly not with regard to systemic hypotension. The results support a further evaluation of the drug in larger clinical trials.

Appendix

Participants in the Study

Department of Neurosurgery, University Hospital Mannheim, Faculty for Clinical Medicine of the University of Heidelberg, Mannheim, Germany (Study Center). Dr. H. H. Capelle, Dr. M. Barth, Dr. J. Tuettenberg, Dr. J. Woitzik, Dr. C. Thomé, Dr. E. Muench, Dr. F. Fiedler, Dr. P. Vajkoczy, Prof. L. Schilling, and Prof. P. Schmidek (Principal Investigator).

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Department of Neurosurgery, Justus Liebig University, Giessen, Germany. Dr. S. Kästner, Dr. W. Deinsberger, and Prof. D. K. Boeker.

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IST GmbH, Mannheim, Germany. Dr. B. Ullrich, Dr. B. Junginger, Dr. D. Messinger, Dr. S. Schaefer, Dr. R. van der Does.

Authors of This Report

All authors participated in the development of the study and in the collection and interpretation of the data. All had access to all data and final responsibility for the decision to submit this paper for publication. Drs. Vajkoczy and Meyer drafted the paper, a process to which all authors contributed. Dr. Weidauer was responsible for the central review and interpretation of the angiograms.

Disclosure

Axovon, Ltd., and Actelion, Ltd., funded this study as part of their program for the clinical development of clazosentan. Professor Peter Schmieck is a consultant to Actelion, Ltd.; he received payments to attend meetings related to the trial and financial compensation for travel expenses and speaking engagements. Dr. Volker Breu is an employee of Actelion, Ltd.

Acknowledgments

Drs. Vajkoczy and Meyer contributed equally to this study. We thank Drs. Saadia Khalil-Ahmed, David Jacobs, Charlotte Keywood, and Markus G. Lang for their help and support in conducting the study. We appreciate the assistance given by Drs. Edgar A. Mueller and Christian Schweiger in the preparation of the manuscript.

References


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