Randomised Trial of Clazosentan, an Endothelin Receptor Antagonist, in Patients with Aneurysmal Subarachnoid Hemorrhage Undergoing Surgical Clipping (CONSCIOUS-2)

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Abstract We report here results of a randomized, double-blind, placebo-controlled study (http://www.ClinicalTrials.gov, NCT00558311) that investigated the effect of clazosentan (5 mg/h, $n=768$) or placebo ($n=389$) administered for up to 14 days in patients with aneurysmal subarachnoid hemorrhage (SAH) repaired by surgical clipping. The primary endpoint was a composite of all-cause mortality, new cerebral infarction or delayed ischemic neurological deficit due to vasospasm, and rescue therapy for vasospasm. The main secondary endpoint was the Glasgow Outcome Scale Extended (GOSE), which was dichotomized. Twenty-one percent of clazosentan- compared to 25% of placebo-treated patients met the primary endpoint (relative risk reduction [RRR] [95% CI]: 17% [−4% to 33%]; $p=0.10$). Poor outcome (GOSE score ≤ 4) occurred in 29% of clazosentan- and 25% of placebo-treated patients (RRR: −18% [−45% to 4%]; $p=0.10$). In prespecified subgroups, mortality/vasospasm-related morbidity was reduced in clazosentan-treated patients by 33% (8–51%) in poor WFNS (World Federation of Neurological Surgeons) grade (≥III) and 25% (5–41%) in patients with diffuse, thick SAH. Lung complications, anemia and hypotension occurred more frequently with clazosentan. Mortality (week 12) was 6% in both groups. The results showed that clazosentan nonsignificantly decreased mortality/vasospasm-related morbidity and nonsignificantly increased poor functional outcome in patients with aneurysmal SAH undergoing surgical clipping.

Keywords Aneurysmal subarachnoid hemorrhage Clazosentan • Surgical clipping • CONSCIOUS-2

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Introduction

About 40% of patients with aneurysmal subarachnoid hemorrhage (SAH) die, and many of the survivors have permanent cognitive and neurological impairment [1, 13]. Morbidity is associated with increasing age, worse clinical grade on admission and delayed complications, principally delayed ischemic neurological deterioration (DIND). Cerebral angiographic vasospasm is highly associated with DIND and has been an important target for prevention and treatment to improve outcome [3, 4]. Unfortunately, current management for vasospasm and DIND is not effective and is expensive. It

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includes prophylactic nimodipine and rescue therapy with induced hypertension and intra-arterial infusion of vasodilators and angioplasty [5, 7, 14].

Clazosentan is an endothelin A receptor antagonist that has demonstrated significant efficacy against angiographic vasospasm [10, 15]. In a phase 2b study, clazosentan produced a dose-dependent reduction in moderate/severe angiographic vasospasm, amounting to a 65% relative risk reduction (RRR) with the highest dose (15 mg/h) [10]. The current phase 3 study, CONSCIOUS-2, was designed based on the results of the phase 2b study to enrich for patients at risk for vasospasm-related morbidity and targeted patients undergoing surgical clipping.

Methods

This randomized, placebo-controlled, double-blind clinical trial included patients aged 18–75 years with aneurysmal SAH who had the ruptured aneurysm repaired by surgical clipping. Patients had at least diffuse SAH and were World Federation of Neurological Surgeons (WFNS) grade I–IV. Written informed consent was obtained according to local laws, and the trial was registered with http://www.ClinicalTrials.gov (NCT00558311). Additional information on the rationale, study design and methodology is published [11, 12].

Patients were recruited from 102 sites in 27 countries and were assigned (2:1) to receive 5 mg/h clazosentan (Actelion Pharmaceuticals Ltd., Allschwil, Switzerland) or placebo within 56 h of SAH. Clazosentan or placebo was administered intravenously for up to 14 days after SAH. The primary endpoint was vasospasm-related morbidity and all-cause mortality within 6 weeks of SAH, defined by at least one of the following: death; vasospasm-related cerebral infarction (where vasospasm was the primary cause or a relevant contributing factor); DIND due to vasospasm (where vasospasm was the primary cause or a relevant contributing factor); or neurological signs or symptoms, in the presence of a positive angiogram, leading to rescue therapy. DIND was defined as a decrease of ≥2 points on the modified Glasgow coma scale (mGCS) or an increase of ≥2 points on the abbreviated NIHSS (National Institute of Health Stroke Scale) lasting for at least 2 h. Rescue therapy included initiation or increase in dose of an intravenous vasopressor with or without fluid therapy or intra-arterial vasodilator or balloon angioplasty. The main secondary outcome was the Glasgow Outcome Scale Extended (GOSE) 12 weeks after SAH.

Patient management guidelines were followed by the investigators [11]. Clinical and imaging data were evaluated by a blinded, centralised critical events committee. Prespecified subgroups that were analysed were WFNS grade, clot size, age and gender.

Sample size calculations were done, and analysis was done in accordance with the intention-to-treat principle [12]. Treatment effect was tested by logistic regression adjusted for WFNS (I, II, >II) with the Wald chi-square test used to determine treatment effect.

Results

There were 1,157 patients randomised and 1,147 treated (placebo $n=383$; clazosentan $n=764$). Patient demographics were consistent with those of the SAH population. Vasospasm-related morbidity and all-cause mortality occurred in 161/764 (21%) of patients treated with clazosentan and 97/383 (25%) of patients treated with placebo (RRR: 17%, 95% CI: −4% to 33%; $p=0.10$ [logistic regression with WFNS as covariate]; Fig. 1a). This was mainly affected by reduction in rescue therapy from 16% of placebo- to 11% of clazosentan-treated patients (RRR: 36%, 95% CI: 14–53%; Fig. 1b). There was no significant difference between treatment groups in poor outcome (GOSE ≤ 4) at week 12 in the all-treated dataset; poor outcome was reported in 224 (29%) patients receiving clazosentan and 95 (25%) patients receiving placebo (RRR: −18%, 95% CI: −45% to 4%; $p=0.10$ [logistic regression with WFNS as covariate]; Fig. 2).

In the planned subgroup analyses, clazosentan reduced the primary endpoint in patients with poor WFNS grade (≥III) (RRR: 33%, 95% CI: 8–51%; RRR for grade I–II 9%, 95% CI: −21% to 32%) or diffuse, thick SAH (RRR: 25%, 95% CI: 5–41%; RRR for diffuse thin, local thick or local thin SAH 11%, 95% CI: −40% to 43%). The GOSE was not significantly affected by clazosentan in these subgroups.

In terms of adverse effects, there were more lung complications, anaemia, and hypotension in patients treated with clazosentan. Mortality was 6% in placebo and clazosentan groups.

Discussion

We found that 5 mg/h clazosentan for up to 14 days after aneurysmal SAH was associated with a nonsignificant 17% relative reduction in mortality or vasospasm-related morbidity. This was due largely to reduced rescue therapy in the clazosentan group. On the other hand, clazosentan was associated with a nonsignificant 18% increase in poor outcome 12 weeks after SAH. In prespecified subgroups, there was a greater RRR with clazosentan in patients with poor WFNS grade or diffuse, thick SAH. Again, however, the GOSE was not significantly affected. We expected, based on results of phase 2 studies, that since clazosentan significantly reduces angiographic vasospasm, there would be a significant reduction in vasospasm-related morbidity and an improvement in clinical outcome [10, 15].

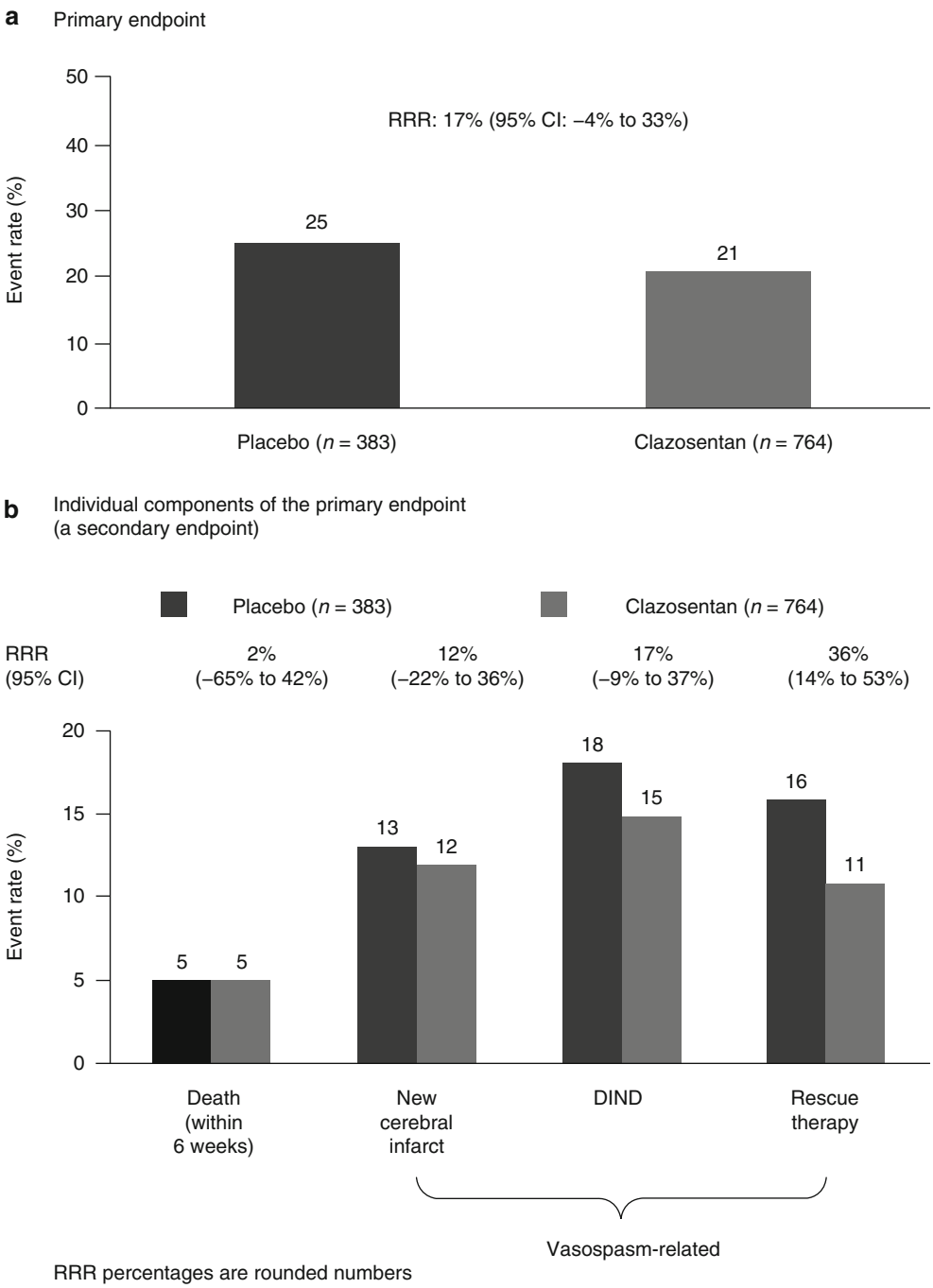

Fig. 1 Event rate (%) for all-cause mortality and vasospasm-related morbidity at 6 weeks (all treated, endpoint substituted; the primary endpoint) (**a**) and for each of the individual components of the primary composite endpoint (alltreated, endpoint substituted; planned analysis, secondary endpoint) (**b**). *RRR* relative risk reduction, *CI* confidence interval, *DIND* delayed ischemic neurological deficit

Conclusion

Explanations for the lack of significant effect of clazosentan on outcome include the possibility that off-target effects of the drug counterbalanced therapeutic benefit. There was a higher frequency of hypotension and lung complications in the clazosentan group, although the exact contribution of these effects to poor outcome remains to be defined. Rescue therapy was used more frequently in the placebo group and could improve outcome in that group to the same extent that clazosentan did, which could obscure treatment effect. Another theory is that the lack of improvement was because processes other than vasospasm contribute to DIND and poor outcome, and these are not improved by preventing angiographic vasospasm [8]. There are robust data showing that clazosentan decreases angiographic vasospasm [10]. However, other processes, such as microthromboembolism, microcirculatory dysfunction, cortical spreading ischemia and delayed neuronal injury have been postulated to contribute to DIND and outcome and may not be prevented by clazosentan [3, 6, 9, 16]. The GOSE was not developed as an outcome measure for SAH and may not be sensitive or appropriate for measuring outcome after SAH. Finally, the severity of the initial hemorrhage is an important

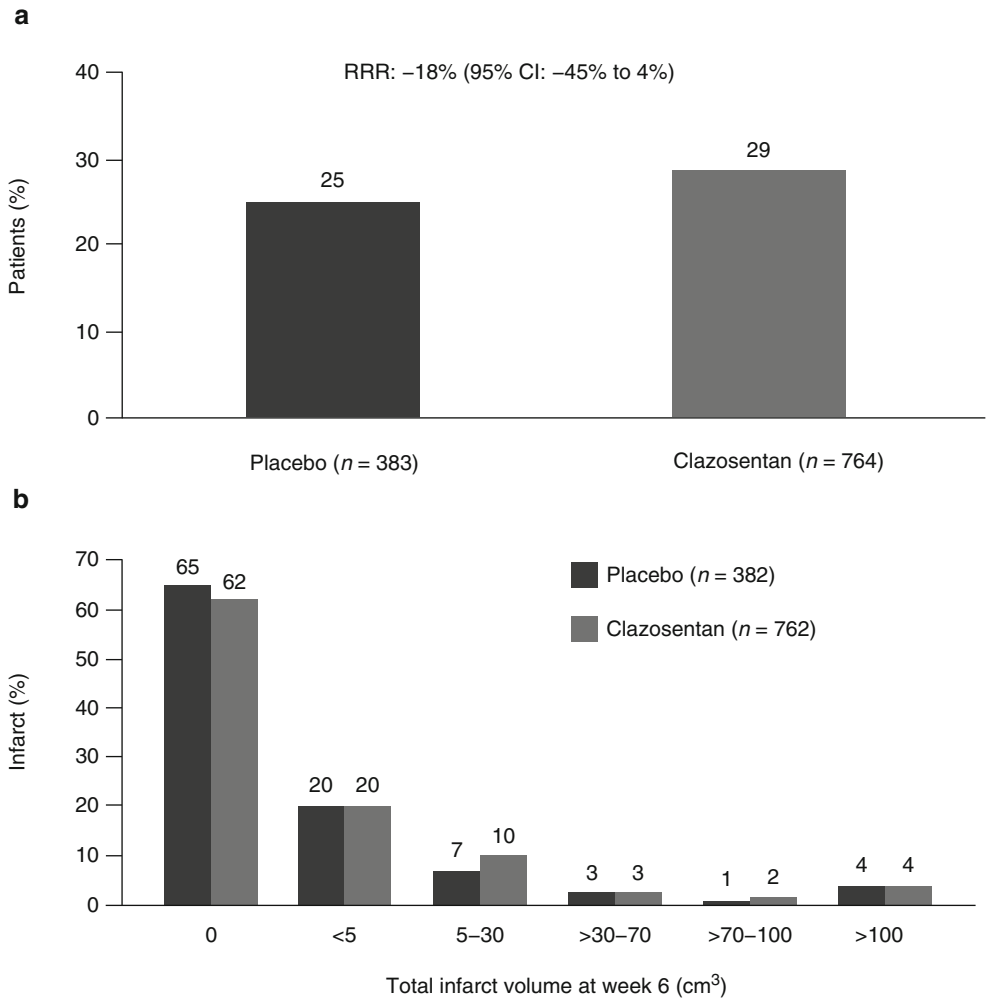

Fig. 2 Key secondary endpoints. Patients (%) with poor outcome (GOSE ≤ 4) at week 12 (dichotomized GOSE, all treated, endpoint substituted) (**a**) and total infarct volume of new/worsened infarcts (all causes) at week 6 (all treated, endpoint substituted) (**b**)

determinant of clinical outcome and may overwhelm the contribution of other processes in some settings and patient populations [2, 9].

Additional studies of clazosentan have been conducted, including a study similar to CONSCIOUS-2 but in patients with aneurysmal SAH undergoing endovascular coiling to repair the ruptured aneurysm. The results of this study are awaited.

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Conflicts of Interest RLM receives grant support from the Physicians Services Incorporated Foundation and is a stockholder of Edge Therapeutics. RLM, RTH, EK, SAM, AMo, AR, PV, IW, and NK are consultants for Actelion Pharmaceuticals. SAM is a consultant for Edge Theraputics. RLM is Chief Scientific Officer of Edge Theraputics. EK has been on advisory boards for Roche Diagnostics, and is a stockholder in NeMoDevices. AMo has been a consultant for Micrus Endovascular and Covidien. PV is a consultant for Aesculap. IW is a consultant for Boston Scientific, ev3, and BALT, and receives a departmental grant from Boston Scientific. DB, AF, AMa, and SR are employees and stockholders of Actelion Pharmaceuticals.

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