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BAY 58–2667, a soluble guanylate cyclase activator, improves cardiopulmonary haemodynamics in acute decompensated heart failure and has a favourable safety profile

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Background

BAY 58–2667 is a soluble guanylate cyclase (sGC) activator that acts independently of nitric oxide (NO) and haem. Data from preclinical studies show that BAY 58–2667 preferentially dilates diseased vessels, without the development of tolerance [1]. In healthy humans, this novel agent has a favourable safety profile and is well tolerated. We hypothesized that BAY 58–2667 would improve cardiopulmonary haemodynamics and be well tolerated in patients with acute decompensated heart failure (ADHF).

Materials and methods

This was a non-randomized, uncontrolled, unblinded, multicentre phase II study in patients with ADHF (pulmonary capillary wedge pressure [PCWP] ≥ 18 mmHg). After initial dose-finding studies (part A) using 50, 100, 200 and 400 μg/h, respectively, BAY 58–2667 was evaluated (part B) using a starting dose of 100 μg/h, which could be titrated after 2 h, 4 h and 6 h to doses between 50 μg/h and 400 μg/h, depending on the haemodynamic response. Haemodynamic parameters were measured by pulmonary artery catheter and impedance cardiography. Patients were categorized as responders if their PCWP decreased by ≥4 mmHg compared with baseline. Thirty-three patients were eligible for the safety evaluation and 30 for the haemodynamic evaluations (part B).

Results

Haemodynamic parameters at baseline were: PCWP, 25 mmHg; right atrial pressure (RAP), 13 mmHg; mean pulmonary artery pressure (PAPmean), 36 mmHg; systolic blood pressure (SBP), 119 mmHg; systemic vascular resistance (SVR), 1581 dyn · s · cm^{-5}; heart rate (HR), 76.7 beats per minute (bpm); and cardiac index, 2.1 L/min/m2. Final doses of BAY 58–2667 after 6 h of infusion were: 50 μg/h (n = 2); 200 μg/h (n = 12); and 400 μg/h (n = 16). Compared with baseline, a 6 h infusion of BAY 58–2667 reduced PCWP by 7.9 mmHg, RAP by 2.9 mmHg, PAPmean by 6.5 mmHg, SBP by 13.9 mmHg and SVR by 597 dyn · s · cm^{-5}, while increasing HR by 4.4 bpm and cardiac index by 0.82 L/min/m^2. The responder rate was 53% after 2 h, 83% after 4 h and 90% after 6 h. BAY 58–2667 was well tolerated. Of the 33 patients, six individuals reported 11 adverse events (AEs) of mild-to-moderate intensity and there was one serious AE. Three AEs were

related to the study drug (hypotension and sickness) and eight were not. There was no evidence of tachyphylaxis.

Conclusion

These first clinical results with BAY 58–2667 in patients with ADHF demonstrate the potential of this new therapeutic principle. In patients with ADHF, continuous parenteral administration of BAY 58–2667 was well tolerated and induced potent arterial and venous vasodilation, which resulted in significant reductions in cardiac pre- and after-load and an increase in cardiac index. These data also suggest that a pool of oxidized or haem-free sGC is present in human ADHF; these forms are preferentially activated by BAY 58–2667.

References

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