Angiotensin II for Vasodilatory Shock

Guest: Dr. Michael McCurdy

Key Article

- *Khanna A, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017. The ATHOS Investigators.*

Background

- Vasodilatory shock is the most common form of shock
- Vasopressors are used when IVFs alone fail to restore MAP
- Currently, only 2 classes of vasopressors are available: catecholamines (i.e, norepinephrine) and vasopressin
- During hypotension, however, a 3rd system is engaged – the renin-angiotensin-aldosterone system
- A recent pilot study by authors demonstrated that angiotensin II added to catecholamines increased MAP in patients with vasodilatory shock

Objective

- To determine whether the addition of angiotensin II to background vasopressors would improve blood pressure in patients with catecholamine-resistant vasodilatory shock.

Methods

- International, randomized, double-blind, placebo-controlled trial
- Designed in collaboration with sponsor – La Jolla Pharmaceutical Company
- Patients
    - 18 years or older
    - Vasodilatory shock despite IVF resuscitation (at least 25 ml/kg over previous 24 hours) AND administration of high-dose vasopressors
        - Vasodilatory shock defined as a cardiac index of 2.3 L/min/m^2 or an ScvO2 > 70% coupled with CVP of more than 8 mm Hg with a MAP between 55 to 70 mm Hg
        - High-dose vasopressors as more than 0.2 mcg/kg of norepinephrine or equivalent dose of another vasopressor
    - For at least 6 hours but no longer than 48 hours
    - Excluded: burns, ACS, bronchospasm, active bleeding, abdominal aortic aneurysm, liver failure, mesenteric ischemia, ANC < 1000 cells/m^3, or those on VA ECMO
- Assigned 1:1 ratio to receive angiotensin II or placebo

- Clinical Regimen
    - Baseline MAP established as mean of 3 measurements
    - Angiotensin II infusion started at a rate of 20 ng/kg/min and adjusted during first 3 hours to increase MAP to 75 mm Hg
        - Doses of standard vasopressors held constant and could not be increased
        - Maximum rate of study drug allowed during first 3 hours was 200 ng/kg/min
    - After 3 hours and 15 min, study drug or placebo and other vasopressors adjusted to maintain MAP between 65 mm Hg and 75 mm Hg
    - After 48 hours, study infusion was discontinued according to tapering protocol
- Primary endpoint: response with respect to MAP at hour 3 (response defined as MAP of 75 mm Hg or higher or increase of at least 10 mm Hg from baseline without increase in standard vasopressors)
- Secondary endpoints: changes in cardiovascular SOFA score between baseline measurement and hour 48; serious adverse events, all adverse events, and all-cause mortality at day 7 and day 28

Results

- 344 patients enrolled: 23 did not receive angiotensin II or placebo; study regimen initiated in **321 patients** (164 in angiotensin II group and 158 in placebo)
- Sepsis most common cause of vasodilatory shock (80.7%)
- Efficacy Outcomes
    - More patients in the angiotensin II group met the criteria for primary end point of response with MAP at hour 3 (69.9% vs. 23.4%, $p<0.001$; OR 7.95, CI 4.76 to 13.3)
    - During first 3 hours, angiotensin II group had significantly greater increase in MAP than placebo (12.5 mm Hg vs. 2.9 mm Hg, $p<0.001$)
    - During the first 48 hours, mean doses of background vasopressors were consistently less than in the angiotensin II group
    - At 48 hours, improvement in the cardiovascular SOFA score was significantly greater in the angiotensin II group than placebo (-1.75 vs. -1.28, $p=0.01$)
- Safety
    - Adverse events of any grade occurred in 87.1% of angiotensin II group and 91.8% of placebo group
- Mortality
    - No patient died during initial period of adjustment of dose of angiotensin II or placebo
    - All-cause mortality at day 7 occurred in 28.8% of angiotensin II group and 34.8% of placebo (hazard ratio 0.78; CI 0.53 to 1.16, $p=0.22$)
    - All-cause mortality at day 28 occurred in 46% of patients in the angiotensin II group and 53.8% of placebo (hazard ratio 0.78, CI 0.57 to 1.07, $p=0.12$)

Limitations

- Phase 3 manufacturer sponsored trial
- Small sample size
- Primary endpoint was MAP response at 3 hours – patient centered outcome?
- Not powered to detect mortality difference
- Further study required to investigate clinically meaningful outcome

Take Home Message

- Angiotensin II increased MAP and reduced doses of cathecholamines in patients with fluid/vasopressor refractory vasodilatory shock.
- This therapy may be beneficial pending additional confirmatory studies.