Angiotensin II Brings More Questions Than Answers

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ABSTRACT

The approval of synthetic human angiotensin II (Giapreza, LaJolla Pharmaceuticals) by the FDA in December 2017 provides clinicians with a new tool in the treatment of distributive shock. Angiotensin II (ATII) was approved based on the results of the ATHOS-3 trial. In this trial, patients who received angiotensin II were more likely to achieve a mean arterial pressure of 75 mmHg or an increase in mean arterial pressure of 10 mmHg above that seen in patients who received a placebo. However, the results of ATHOS-3 also highlighted important concerns about thrombotic and infectious complications associated with ATII. Given that the cost of medication acquisition is approximately $1,500 per vial, practitioners must also decide how to implement ATII into practice in the most cost-effective manner. This commentary examines the current controversies surrounding both the safety and efficacy of ATII.

Keywords: shock, sepsis, hemodynamics, medication safety, angiotensin II, ATII

INTRODUCTION

Current pharmacotherapy options for hemodynamic support in patients with septic shock remain surprisingly limited. Classes of agents include catecholamines (norepinephrine, epinephrine, phenylephrine, dopamine) and vasopressin; corticosteroids may also be administered to improve blood pressure. The Surviving Sepsis Campaign guidelines recommend norepinephrine as the first agent to be initiated for vasopressor support in patients with septic shock following adequate fluid resuscitation. For patients already receiving norepinephrine, vasopressin at a dose of up to 0.03 units/minute or epinephrine may be added. In patients with hemodynamic instability despite adequate fluid resuscitation and vasopressor support, hydrocortisone at a dose of 200 mg/day may be initiated.[1] The approval of ATII by the FDA in December 2017 provides intensive care unit (ICU) clinicians with a new tool to combat hemodynamic instability. At the time of writing, the price for one vial of Giapreza, containing 2.5 mg of ATII, is $1,500.[2]

CLINICAL TRIALS

ATII gained approval based on results of the Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3) trial.[3] In this trial, patients with vasodilatory shock who received at least 25 mL/kg of fluid and required vasopressor support with at least 0.2 mcg/kg/min of norepinephrine equivalents were randomized to ATII (n = 163) or placebo (n = 158). Of note, over 95% of all patients were receiving norepinephrine and

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approximately 70% of all patients were receiving vasopressin prior to the initiation of study medication. The primary endpoint of the study was an increase in mean arterial pressure (MAP) at the end of three hours of at least 10 mmHg, or to 75 mmHg without an increase in baseline vasopressor dosing. After three hours, the study drug or other baseline vasopressors were adjusted to keep the MAP between 65 and 75 mgHg. Patients who received ATII were significantly more likely to achieve a MAP of 75 mmHg or greater after three hours of study drug infusion (69.9% vs. 23.4%; $P < 0.001$). Although statistical significance was not assessed, patients receiving ATII had lower mean dosing requirements for baseline vasopressors over the first 48 hours following study drug initiation. Reduction in the cardiovascular Sequential Organ Failure Assessment (SOFA) score after 48 hours following study drug initiation was significantly greater in patients who received ATII (–1.75 vs. –1.28; $P = 0.01$). However, total SOFA score changes were similar (ATII = 1.05 vs. placebo = 1.04; $P = 0.49$), meaning that the use of ATII did not yield better overall organ function than the placebo did. There was no difference in seven-day mortality (29% vs. 35%; $P = 0.22$) or 28-day mortality (46% vs. 54%; $P = 0.12$) among patients who received ATII compared to placebo.[3]

Since the publication of the ATHOS-3 trial, the results of two subgroup analyses have been reported. In an abstract presented at the 2018 Society of Critical Care Medicine's Annual Congress in San Antonio, Texas, administration of ATII was associated with lower 28-day mortality (51.8% vs. 70.4%; $P = 0.037$) in patients with an APACHE II score greater than 30.[4] Patients in the subgroup analyses were extremely ill. APACHE II predicts inpatient mortality, and a score of 30 correlates to an expected mortality rate of approximately 70%.[5] Although this was a prespecified subgroup analysis, the significant finding is unexpected given that the study was underpowered to detect this outcome, and the finding should be seen as hypothesis-generating only.[6]

Another subgroup analysis examined patients with acute kidney injury who were receiving renal replacement therapy (RRT) at the time of randomization.[7] Placebo medication was administered to 60 patients and ATII was administered to 45 patients. Receipt of ATII was associated with a lower 28-day mortality compared to placebo (30% vs. 53%; $P = 0.012$). The median baseline APACHE II score in this study was 32; there was likely significant patient crossover between this subgroup analysis and the subgroup analysis described previously. Further, the placebo group had a higher norepinephrine dose (0.46 vs. 0.36 mcg/kg/min; $P = 0.019$), a higher Model for End-Stage Liver Disease score (predictive of 3-month mortality in patients with liver disease), and a higher angiotensin I/II ratio (healthy individuals have an angiotensin I/II ratio of

0.5). Contrary to the prior subgroup analysis, this was a post-hoc analysis, and the results should likewise be viewed as hypothesis-generating.[6,7]

It is recommended to start ATII at a dose of 20 nanograms (ng)/kg/min. The medication can be titrated every five minutes to achieve hemodynamic goals. Dosing should not exceed 80 ng/kg/min during the first three hours of therapy. Subsequent dosing should not exceed 40 ng/kg/min.[8] In the ATHOS-3 trial, patients with a baseline MAP below 59 mmHg were initiated on an ATII dose of 80 ng/kg/min. Two patients in ATHOS-3 required ATII doses in excess of 80 ng/kg/min; however, the median dose of ATII at 30 minutes was 10 ng/kg/min.[3]

There are some encouraging takeaways from the ATHOS-3 trial. As opposed to both catecholamines and vasopressin, ATII is part of the renin–angiotensin-aldosterone system and exerts its effects by direct vasoconstriction. The results of ATHOS-3 indicate that ATII may be effective in providing hemodynamic support in patients already receiving norepinephrine and vasopressin, validating its unique mechanism of action.[3] In addition, a chest X-ray consistent with the diagnosis of acute respiratory distress syndrome (ARDS) was significantly associated with attainment of a MAP of 75 mmHg or greater after three hours of study drug infusion (OR 2.03; $P = 0.03$). An explanation for this finding is that approximately 90% of human angiotensin converting enzyme (ACE) is located in lung tissues; perfusion to this tissue is limited in ARDS and endogenous production of ATII often is lacking.[9] As a result, ATII may be particularly effective at restoring hemodynamic stability in patients with ARDS.

ADVERSE EFFECTS

There are several concerns regarding the ATHOS-3 trial. Principle among them is the risk of thrombosis, which is noted as a warning in the package insert. Although the published ATHOS-3 results did not denote a difference in rates of symptomatic venous thromboembolism (VTE) between treatment groups, the package insert indicates that patients who received ATII had a significantly greater incidence of VTE (12.5% vs. 5%; $P = 0.015$).[8] Further, data obtained from the manufacturer show that antithrombotic medications administered prior to, or concomitantly with, the initiation of the study drug were significantly greater in patients receiving ATII compared to placebo (87.1% vs. 72.2%; $P < 0.001$). Thus, the high prevalence of VTE among patients receiving ATII is of even greater concern given that more of these patients were also administered some form of anticoagulation. ATII has been recognized as a mediator of thrombosis in hypertensive patients, as evidenced by a lower incidence of thrombotic events in patients treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers.[10] In rat models, ATII has also been recognized to have pro-thrombotic effects although the precise mechanism behind the pro-coagulant activity is not well understood.[11] The manufacturer states that patients receiving Giapreza should receive concurrent VTE prophylaxis.[8]

ATHOS-3 reported no difference in the proportion of patients who experienced an infection or infestation (not defined in study documents) during the study (ATII = 30 [18.4%] patients vs. placebo = 21 [13.3%] patients; $P = 0.21$).[3] However, there were patients who experienced more than one infection or infestation. Consequently, the total number of events of infection or infestation was significantly different. More events occurred in the ATII cohort compared to the placebo cohort (60 events vs. 35 events, respectively; $P = 0.029$).[3] Moreover, the package labeling denotes a higher rate of fungal infection in patients who received ATII compared to placebo (6% vs. 1%; $P = 0.035$).[8] Recent data have associated the use of ACE inhibitors with an increased risk of sepsis.[12] Also, laboratory data have shown that ACE knockout mice were more susceptible to bacterial infection and that overexpression of ACE in mice led to an increased resistance to infection.[13] Thus, it is possible that ATII infusions led to downregulation of ACE expression in the ATII cohort, leading to an increased risk of infection.

Another concern with ATII is that it can promote tachycardia through the modulation of baroreceptor control of heart rate.[14] Although rates of tachycardia in ATHOS-3 were higher among patients receiving ATII, there were no differences in rates of atrial fibrillation (13.5% vs. 13.3%) or ventricular arrhythmia (4.3% vs. 5.1%).[3] These findings suggest that ATII may be a safe agent to use in patients with or at high risk for tachyarrhythmia.

While the rate of delirium was higher in patients who received ATII (5.5% vs. 0.6%), the relevance of this finding is questionable given that the overall delirium rate of 3.1% in the study is much lower than what has been described in other critically ill cohorts.[3,15] In phase 2 data, ATII was demonstrated as having a higher rate of hypertension (defined as MAP greater than 85 mmHg) than placebo (20% vs. 0%).[16] However, in ATHOS-3 there was no difference in the rate of MAP greater than 85 mmHg between ATII and placebo (5.5% vs. 5.7%; $P = 1.00$).[3] This calls the hypertensive risk associated with ATII into question; hypertensive events were likely a result of either patient hyper-response to ATII or aggressive dosing of ATII by starting at 40 ng/kg/min.

The adverse effects associated with ATII in ATHOS-3 occurred during a short period of drug use. The pre-defined duration of therapy for the study drug was a maximum of seven days. There were 77 (47.2%) patients who received ATII for a period greater than 51 hours and only 13 patients who received ATII for greater than 72 hours. Thus, the incidence of adverse events for longer durations of therapy is unknown.

PLACE IN THERAPY

Patients receiving hydrocortisone at doses of 500 mg and above were excluded from the ATHOS-3 trial; however, the results of the trial do not describe the number of patients receiving hydrocortisone at doses of 200 mg/day, which is commonly referred to as "stress dose steroids." Stress dose steroids are often used in septic shock and have consistently been shown to reduce the duration of shock in clinical trials.[17-20] Further evidence suggests that in patients with septic shock who are receiving high doses of catecholamines, stress dose steroids may result in lower mortality.[20] Given that ATII has not been shown to reduce the duration of shock or mortality, stress dose steroids should be initiated prior to or concomitantly with ATII.

The results of ATHOS-3 raise questions regarding how to best integrate ATII into practice, especially concerning when to initiate ATII relative to other vasoactive agents. The ATHOS-3 investigators defined a norepinephrine equivalent dose of

0.2 mcg/kg/min as "high dose vasopressor therapy" and used this definition in the study inclusion criteria.[3] However, this is not a consensus definition. In other studies, a norepinephrine dose exceeding 0.5 mcg/kg/min for more than one hour, or a dose greater than 1 mcg/kg/min for any duration, has been suggested as a definition of refractory shock.[21,22] In ATHOS-3, a baseline norepinephrine-equivalent dose of ≥ 0.5 mcg/kg/min was an independent predictor of failure to meet the primary outcome of the study (OR, 0.4; CI, 0.21–0.77).[3] While the addition of ATII at a norepinephrine-equivalent dose below 0.5 mcg/kg/min frequently resulted in the achievement of a MAP ≥ 75 mm Hg at three hours after study drug initiation, this finding suggests that similar effects may have been seen by increasing the doses of other vasopressors. It is also important to remember that in ATHOS-3, 30% of patients who received ATII did not achieve the primary outcome.

The price of ATII is another important consideration and a potential limitation to its use. At $1,500 per vial (2.5 mg), the cost significantly exceeds that of other comparative therapies such as vasopressin and methylene blue. Given that the use of ATII has not been demonstrated to reduce ICU length of stay, duration of mechanical ventilation, or mortality, the cost-effectiveness of its use should be questioned.

CONCLUSION

ATII provides clinicians with another tool to increase blood pressure in patients with distributive shock. It may even be particularly effective at improving blood pressure in patients with Acute Respiratory Distress Syndrome (ARDS). The adverse effect profile of ATII is a cause for concern, and additional data are needed to more fully understand the implications of the adverse events associated with this agent. Finally, the high cost of ATII will likely prohibit routine use. Until more data are available, it seems prudent to reserve the use of ATII to patients with distributive shock refractory to high-dose vasopressor therapy and stress dose corticosteroids. The dose of vasopressors that defines refractory therapy is controversial, but a reasonable threshold suggested by the authors of this commentary is a norepinephrine equivalent dose greater than 0.5 mcg/kg/min for one hour or a dose of 1 mcg/kg/hour for any duration.

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