Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING
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Angiotensin II acetate (Giapreza) for vasopressor resistant hypotension due to distributive shock

NIHRIO ID	11178	**NICE ID**	9931
Developer/Company	La Jolla Pharmaceutical Company	**UKPS ID**	Not available

Licensing and market availability plans	The company submitted a Marketing Authorisation Application to the EMA in June 2018, with a final licence and UK launch expected in late/end 2019.

SUMMARY

Angiotensin II acetate is in clinical development for the treatment of catecholamine and/or vasopressin resistant hypotension due to distributive shock. Shock is a critical condition in which blood pressure drops so low that the brain, kidneys and other vital organs cannot receive enough blood flow to function properly. Distributive shock is the most common type of shock that is most commonly caused by bacterial or fungal infection (septic shock) or allergic reaction (anaphylactic shock). Severe shock is usually treated with drugs called catecholamines or vasopressin. Shock that does not respond to treatment with these drugs is resistant shock.

This medicinal product is a formulation of synthetic angiotensin II administered by intravenous infusion. Angiotensin II is a naturally occurring hormone that regulates blood pressure by attaching to the angiotensin II type 1 receptor, causing the blood vessels to narrow, increasing sodium and water retention and increasing aldosterone and vasopressin release, all of which increase blood pressure. If licensed, angiotensin II acetate may provide a treatment option for people with refractory shock who do not have any other treatment options.

PROPOSED INDICATION

Vasopressor therapy (catecholamines and/or vasopressin) resistant hypotension due to distributive shock[1]

TECHNOLOGY

DESCRIPTION

Angiotensin II acetate (Giapreza, LJPC-501) is proprietary formulation of synthetic human angiotensin II. Angiotensin II is the major bioactive component of the renin-angiotensin-aldosterone system (RAAS system), one of the body's central regulators of blood pressure. The RAAS system along with the arginine-vasopressin system and the sympathetic nervous system make up the three major counter-regulatory systems the human body utilizes to manage blood pressure. Angiotensin II is a naturally occurring peptide hormone that regulates blood pressure through activation of the angiotensin II type 1 receptor (AT1R). Through the AT1R, angiotensin II induces peripheral vasoconstriction, increases sodium and water retention, aldosterone release, and vasopressin release leading to increase in blood pressure.[1]

Angiotensin II acetate is currently in development for the treatment of patients with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy (catecholamines and/or vasopressin).[1] In the phase III trial (ATHOS-3, NCT02338843), angiotensin II acetate is administered intravenously at a starting dose of 20ng/kg/min which may escalate up to 200ng/kg/min to achieve a mean arterial pressure (MAP) of 75mmHg or higher. If a MAP of 75mmHg is achieved, study drug will be titrated to maintain the MAP between 75 and 84 mmHg until the 3-hour time point on Day 1, i.e., 3 hours from the initiation of study drug. Pre-specified dose titration and withdrawal guidelines based on MAP through 48 hours. Continued use for up to 7 days is permitted per pre-specified dose guidelines.[2,3]

INNOVATION AND/OR ADVANTAGES

Shock is a critical condition in which blood pressure drops so low that the brain, kidneys and other vital organs do not receive enough blood flow to function properly.[5] Traditionally, catecholamines and vasopressin have been used to achieve an acceptable mean arterial pressure (MAP). However these therapies introduce the risk of adverse events including peripheral and splanchnic ischemia, dysrhythmias, and organ dysfunction. Additionally no vasopressin to date has been shown to improve mortality outcomes.[4] Hence, there is a need for treatment options for critically ill hypotensive patients who do not adequately respond to available therapies (catecholamines and vasopressin).[5] Angiotensin II has been shown in clinical trials to increase blood pressure in patients with hypotension and has recently been approved by the US Food and Drug Administration.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Angiotensin II acetate does not currently have Marketing Authorisation in the EU for any indication.[6]

Angiotensin II acetate is in currently in preregistration stage in the EMA for the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.[7]

Angiotensin II acetate is in phase II development for the treatment of hypotension associated with distributive or vasodilatory shock in paediatric patients.[8]

Angiotensin II acetate received a Priority Review and was approved for use in the USA by the FDA on 21 December 2017.[5, 9]

PATIENT GROUP

DISEASE BACKGROUND

Shock is defined as a state of cellular and tissue hypoxia due to reduced oxygen delivery and/or increased oxygen, consumption or inadequate oxygen utilization. Shock can be classified into four categories: distributive (or vasodilatory), hypovolemic, cardiogenic and obstructive.[10] Distributive shock (DS) is the most common form of shock and is characterised by vasodilation and low systemic vascular resistance.[10, 11] Common causes of DS in the emergency department are sepsis (due to bacteremia or fungemia) or anaphylaxis.[10, 12]

There is no universal consensus definition of resistant shock. However, a reasonable definition of refractory shock has been reported as an inadequate response to high-dose vasopressor therapy (defined as ≥ 0.5 µg/kg/min norepinephrine-equivalent dose). The main pathophysiological feature of refractory shock is the impairment of vascular response to catecholamine stimulation and uncontrolled pathologic vasodilation (vasoplegia) occurring because of changes in receptor signaling, metabolic derangements, and depletion of endogenous vasoactive hormones such as cortisol, vasopressin and angiotensin II.[11]

Mortality rates are high in those with refractory DS, varying between 37% and 66% depending on the definition used.[4] There is no consistent relationship between norepinephrine-equivalent dose (used to compare total vasopressor dose among patients) and short term mortality in patients with DS, implying that outcomes are generally poor once refractory DS develops despite vasopressor dose.[11] Additionally, at higher doses, catecholamines are strongly associated with mortality and may have toxic effects that contribute substantially to morbidity and may be an independent predictor of mortality.[4]

CLINICAL NEED AND BURDEN OF DISEASE

Using the definition of refractory shock described in the above section, observational studies suggest that 6-7% of critically ill patients may develop refractory shock.[11] The prevalence of refractory DS in the UK could not be found. However, prevalence statistics regarding the most common causes of DS, sepsis and anaphylactic shock. There are approximately 250,000 cases of sepsis and 46,000 deaths per year in the UK due to sepsis.[13] According to Allergy UK, the prevalence of anaphylaxis type reactions is approximately 1 in 1000 of the general population. The overall case fatality ratio (proportion of anaphylaxis that is fatal) is estimated at 1-5.5 fatal episodes from anaphylaxis per million of the population annually.[14]

In 2016-17, there was 377 admissions and 635 finished consultant episodes (FCEs) for septic shock (ICD10: R57.2), 1,769 admissions and 1,922 FCEs for anaphylactic shock due to adverse food reaction (ICD10: T78.0) and 2,324 admissions and 2,701 FCEs for unspecified anaphylactic shock (ICD10: T78.2).[15]

Hospital mortality rates vary greatly according to the definition of refractory shock used however they general exceed 50%.[11]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Management of shock involves correcting the triggering cause and restoring adequate organ perfusion by using fluid resuscitation (an initial fluid bolus of 250-500ml) and vasoactive medication with the ultimate aim of achieving adequate tissue perfusion.[11, 12] This can be achieved by targeting a mean arterial pressure of greater than 65 mmHg, which is the approximate critical perfusion pressure for both the heart and kidneys. The pressor choice and additional medications will vary depending on the suspected etiology of distributive shock.[12] Rescue therapies are available, however none of these therapies have been conclusively shown to reduce mortality after the onset of refractory shock.[11]

CURRENT TREATMENT OPTIONS

Treatment of DS:[11]

- *First line:*
  - Catecholamines – e.g. norepinephrine, epinephrine
- *Second line:*
  - Vasopressin – for patients with inadequate response to catecholamine

Cause specific treatments:

- *Septic shock:*[16]
  - Intravenous antibiotics
- *Anaphylactic shock:*[17]
  - Adrenaline auto-injectors – e.g. EpiPen, Jext, Emerade
  - Antihistamines
  - Steroids

PLACE OF TECHNOLOGY

If licensed, angiotensin II acetate will offer a treatment option for patients with hypotension due to DS who are refractory to treatment with catecholamines and vasopressin. These patients currently have no approved treatment options.[5]

CLINICAL TRIAL INFORMATION

Trial	**ATHOS-3, NCT02338843, EudraCT-2015-002448-15; angiotensin II acetate vs placebo; phase III**
Sponsor	La Jolla Pharmaceutical Company
Status	Published
Source of Information	Publication[18, 19], trial registry[2,3]
Location	EU (including UK), USA, Canada and other countries
Design	Randomised, placebo-controlled, quadruple masked, parallel assignment

Participants	n=344; aged 18 years and older; catecholamine-resistant hypotension; clinical features of high-output shock; progression despite catecholamine
Schedule	Participants were randomised to receive either 2.5mg/ml intravenous angiotensin or intravenous placebo (0.9% sodium chloride solution)
Follow-up	3 hours following start of infusion
Primary Outcomes	An Increased MAP, defined as Achievement of a Day 1 MAP at 3 Hours Following the Initiation of Study Drug, of ≥ 75 mmHg OR a 10 mmHg Increase in Baseline MAP [Time Frame: Hour 3]
Secondary Outcomes	• To compare change in Sequential Organ Failure Assessment (SOFA) scores with LJPC-501 infusion, versus placebo • To establish the safety and tolerability of LJPC-501 and compare to placebo in patients with CRH • To compare change in heart rate with LJPC-501 infusion, versus placebo • To compare change in catecholamine dosing with LJPC-501 infusion, versus placebo • To compare mortality with LJPC-501 infusion, versus placebo.
Key Results	A total of 344 patients were assigned to one of the two regimens; 321 received a study intervention (163 received angiotensin II, and 158 received placebo) and were included in the analysis. The primary end point (response with respect to mean arterial pressure at hour 3 after the start of infusion, with response defined as an increase from baseline of at least 10 mm Hg or an increase to at least 75 mm Hg without an increase in the dose of background vasopressors) was reached by more patients in the angiotensin II group (114 of 163 patients, 69.9%) than in the placebo group (37 of 158 patients, 23.4%) (odds ratio, 7.95; 95% confidence interval [CI], 4.76 to 13.3; P<0.001). At 48 hours, the mean improvement in the cardiovascular Sequential Organ Failure Assessment (SOFA) score (scores range from 0 to 4, with higher scores indicating more severe dysfunction) was greater in the angiotensin II group than in the placebo group (-1.75 vs. -1.28, P=0.01).[19]
Adverse effects (AEs)	Serious adverse events were reported in 60.7% of the patients in the angiotensin II group and in 67.1% in the placebo group. Death by day 28 occurred in 75 of 163 patients (46%) in the angiotensin II group and in 85 of 158 patients (54%) in the placebo group (hazard ratio, 0.78; 95% CI, 0.57 to 1.07; P=0.12).[19]
Expected reporting date	-

ESTIMATED COST

The cost of angiotensin II acetate is not yet known.

ADDITIONAL INFORMATION

La Jolla Pharmaceutical Company did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning;

allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified

OTHER GUIDANCE

- Surviving Sepsis Campaign Group. *Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012.* 2012[20]

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