Efficacy of ulinastatin (human urinary trypsin inhibitor) in severe sepsis

THE RECENT ADVANCEMENT IN UNDERSTANDING SEPSIS: A FUTURISTIC APPROACH

Sepsis is a leading global healthcare issue and continues to be a significant cause of death from infection. Early recognition and diagnosis of sepsis is important to prevent septic shock, which is associated with unacceptably high rate of mortality and also long-term morbidity for many who survive.1 Recent advancements and increased awareness have led to a better understanding of sepsis along with improved outcomes.2 In 2017, the World Health Assembly and WHO made sepsis a global health priority and adopted a resolution to improve the prevention, diagnosis, and management of sepsis. In 2016, a new definition of sepsis (Sepsis-3) was developed wherein it was defined as infection with organ dysfunction by using the Sequential Organ Failure Assessment (SOFA) score.2

SOFA is a simple system of routinely assessed parameters used in daily clinical practice to identify dysfunction or failure of the key organs as a result of sepsis (box 1). Regardless of the initial values, an increase in the SOFA scores during the first 48 h in the ICU predicts a mortality rate of at least 50%.3

SEPSIS AS A PREVENTABLE PUBLIC HEALTH PROBLEM: A PARADIGM SHIFT

Earlier, sepsis was solely viewed as a problem of individual patient treated in emergency departments and ICUs. However, it is now addressed as a public health issue with population- and systems-based solutions. Prevention of sepsis can be conceptualized using the familiar model of primary, secondary, and tertiary prevention as given in figure 1.4

Box 1: Clinical parameters assessed in SOFA score

- Altered level of consciousness, defined as a Glasgow Coma Scale score ≤ 13
- Systolic blood pressure ≤ 100 mmHg
- Respiratory rate ≥ 22 rpm.


Primary prevention4

- It refers to the prevention of infection or the sepsis event (i.e., onset of life-threatening organ dysfunction)
- This includes nationwide vaccine campaigns and outbreak management; hospital-wide policies on invasive medical devices, skin care, sterile techniques, hand hygiene, and quarantine; clinic-based surveillance and quarantine practices in high-risk specialty clinics such as those treating patients with cystic fibrosis; and individualized infection prophylaxis among those with immune compromise.

Secondary prevention4

- It has existing familiar foundations in clinical initiatives underscoring early recognition and treatment to prevent infections. Sepsis has its “golden hours” where treatment with antibiotics is much more effective in reducing mortality
- Instituting early sepsis care, with public awareness campaigns highlighting early recognition, call-ahead triage or early treatment by emergency medical services providers, and hospital-wide sepsis rapid response teams.
Tertiary prevention
- It refers to in-hospital and post-hospital treatment to mitigate the long-term consequences of sepsis
- It involves measures to limit the downstream effects of sepsis, optimizing the post-sepsis health trajectory
- This trajectory includes sepsis recurrence, long-term mortality, and long-term morbidity across domains of psychological, cognitive, and physical function.

THE COMPLEX PATHOGENESIS OF SEPSIS

The pathogenesis of sepsis is complex and is posited to be initiated by the interaction between pathogen-associated molecular patterns and recognition receptors on host immune cells which give rise to series of pro-inflammatory mechanisms. It includes synthesis and release of cytokines and complement, chemotaxis and activation of neutrophils, and initiation of coagulation which have widespread effects on other cells including inflammatory cells, immune response, endocrine and autonomic nervous systems, and vascular endothelium. They together aim at limiting spread or eliminating the infecting pathogen. Many of the intermediaries in the systemic inflammatory processes are serine proteases. These include trypsin, thrombin, chymotrypsin, kallikrein, plasmin, neutrophil elastase, cathepsin, neutrophil protease-3, and coagulation factors IXa, Xa, XIXa, and XIa. Proteases besides their potent proteolytic activity also have an important role in regulation of inflammation through inter- and intracellular signaling pathways. To counter-regulate the effect of these proteases, several protease inhibitors are produced by the liver in the presence of inflammation; these include acute phase reactants such as α1-antitrypsin and proteins of the inter-α-inhibitor family.5

AN INSIGHT INTO THE THERAPEUTIC UTILITY OF ULINASTATIN IN SEPSIS

Urinary trypsin inhibitor (UTI) is an important protease inhibitor found in human blood and urine; it is also referred as ulinastatin or bikunin. It is an acidic glycoprotein (molecular weight 30 kDa) and Kunitz-type serine protease inhibitor composed of 143 amino acid residues and includes two Kunitz-type domains. It is cleaved from the larger inter-α-trypsin inhibitor molecule by neutrophil elastase in the presence of inflammation. UTI is found to have many physiologic effects, including the inhibition of neutrophil elastase, trypsin, α-chymotrypsin, plasmin, and cathepsin G. Trypsin inhibitors act to suppress the proteolytic action of trypsin on a variety of tissues and exert a localized anti-inflammatory effect. Thus, making it a reasonable therapeutic choice in an array of acute inflammatory disorders, including acute pancreatitis,
systemic inflammatory reaction syndrome, circulatory insufficiency, Stevens-Johnson syndrome, Toxic epidermal necrolysis (TEN), disseminated intravascular coagulation (DIC) and multiple organ failure.5,6

Use of ulinastatin in sepsis

- Serum levels of ulinastatin decrease in patients with sepsis, with the lower levels being found in patients with severe sepsis and septic shock
- A reduction in the systemic inflammatory response and organ dysfunction due to sepsis has been observed in subjects treated with ulinastatin
- Clinical studies have shown a trend towards reduced mortality and duration of hospitalization with ulinastatin in severe sepsis.5

Clinical rationale for the use of ulinastatin in severe sepsis

Effect of ulinastatin on 28-day all-cause mortality in a double-blind trial in patients with severe sepsis in a specific patient population.5

METHODS

A randomized double-blind, placebo-controlled trial was conducted in the intensive care units (ICUs) of seven tertiary care hospitals in India.

Critically-ill adult patients were enrolled into this trial between September 2009 and June 2010. Inclusion and exclusion criteria for the trial are given in table 1.

After obtaining written informed consent, patients were randomized in a 1:1 ratio to receive ulinastatin or placebo in addition to standard care. Subjects were randomized using a computer-generated sequence was used to ensure balance between treatments. Randomized patients received an intravenous infusion of either 200,000 IU ulinastatin or identical placebo dissolved in 250 mL of 0.9% saline given intravenously over 1 h every 12 h for 5 days in a double-blind evaluation. For patients with fluid restriction, 100 mL of 0.9% saline was used. Infusion was interrupted for 1 day, if there was evidence of hepatotoxicity (LFTs ≥ 3 times baseline levels).

In addition to the study medications, patients also received antibiotics, intravenous fluids, enteral or parenteral nutrition, transfusion of blood and blood products, and supportive care for organ dysfunction including mechanical or non-invasive ventilation, vasopressors (noradrenaline, adrenaline, dopamine, or vasopressin), or dialysis as per the standard treatment protocols followed in each ICU. The study did not impose restrictions on concomitant medications.

Baseline characteristics including demographics, pre-existing conditions, organ dysfunction, infection, and hematologic and other laboratory tests were assessed within the 24 h prior to infusion of the first dose of study medication. Blood samples were also obtained on the day of discharge. Patients were followed up till 28 days after the start of treatment. The primary end-point for this study was 28-day all-cause mortality. Secondary end-points included onset of new organ failure, duration of vasopressor use, ventilator-free days till day 28, and length of hospital stay.

Statistical analysis

Forward stepwise multiple logistic regression analysis was used for assessment of the primary end-point. Other categorical data were compared between the treatment groups by Pearson’s Chi-squared test or Fisher’s exact test, as appropriate. The unpaired t test was used for continuous variables and the Mann–Whitney test for ordinal data like the APACHE II score.

RESULTS

At baseline, the ulinastatin and placebo groups were similar with respect to demographic characteristics, cause of sepsis, number of organs affected, pattern
of organ dysfunction, and need for vasopressors or mechanical ventilation.

Outcomes

- There was a significant difference in the 28-day mortality, (the primary end-point of this study), between the ulinastatin (N = 4) and placebo group (N = 12) (Figure 2)
- On stepwise multiple logistic regression, treatment with ulinastatin was found to produce a statistically significant decrease in risk of death (odds ratio 0.26, 95% confidence limits 0.07–0.95; p = 0.042)
- Cause of death in the ulinastatin group and the placebo group is depicted in figure 3 respectively
- Among the secondary end-points, onset of new organ failure was seen in significantly fewer patients in the ulinastatin group (p = 0.003), duration of ventilator free days was significantly more in the ulinastatin group (p = 0.019), and length of hospital stay was significantly less in the ulinastatin group (p = 0.001).

Thus, intravenous administration of ulinastatin in patients with severe sepsis, when started within 48 h of organ dysfunction, resulted in a reduction in 28-day all-cause mortality in the modified intention-to-treat analysis.

CONCLUSION

Sepsis is a leading cause of critical illness and hospital mortality. Early recognition and intervention are essential for the survival of patients with this syndrome.

Ulinastatin is a potent multivalent serine protease inhibitor having therapeutic potentials in treating sepsis, and the most life-threatening complication of critically ill population owing to its potent immunomodulatory properties.

REFERENCES