Significance of adrenomedullin and the role of adrecizumab in sepsis

To the Editor,

In sepsis, there is damage to vascular integrity i.e., the vascular endothelium as a result of which there is vasodilation, edema, hypotension, and organ failure, which leads to significant morbidity and mortality. Once vascular endothelium is breached, there is a distributive shock, which eventually requires vasoconstrictors if not addressed on time and managed appropriately.

Adrenomedullin (ADM) is a free-circulating peptide hormone, which is responsible for the regulation of vascular tone and stabilization of the endothelial barrier. Adrenomedullin (ADM) is a free-circulating, 52-amino acid peptide hormone belonging to the calcitonin gene–related peptide family. ADM helps in the regulation of vascular integrity and vasodilatation. Studies have shown that in patients with septic shock there is increased levels of bioactive ADM, which has served as a prognostic marker in defining the severity of shock and also mortality. [1,2] ADM is produced by endothelial cells, vascular smooth muscle cells (VSMCs), monocytes, renal parenchymal cells, and macrophages. Situations such as inflammation, hypoxia, oxidative stress, and surgery are commonly encountered in clinical situations when ADM levels are elevated in the blood. In experimental studies, ADM administration has been shown to be effective in certain models of endotoxemia and lung, liver, and kidney injury.[3] ADM has a short half-life (22 min); therefore, it has to be administered as a continuous infusion till clinically important endpoints are achieved based on clinician's discretion. One important concern is deleterious effects on hemodynamics with ADM infusion, which is undesirable. ADM has been referred to as a double-edged sword because in health it maintains vascular tone but when administered intravenously in septic patients, it leads to vasodilatation and a compensatory increase in heart rate, which is detrimental. Unfavorable issues are seen when ADM is used in higher doses.[4] Thereafter, clinicians investigated molecules that could modulate or antagonize ADM, which led to the development of adrecizumab (ADZ).

ADZ or HAM 8101 (name during experimental phase) is a humanized targeted therapy directed against the N-terminus of ADM. ADZ is a non-neutralizing, anti-ADM antibody that binds to excessive ADM in sepsis.[5] It is produced for clinical use using Chinese hamster ovary cells. ADZ inhibits increased circulating levels of ADM due to sepsis, protects the endothelial barrier, and decreases interstitial vasodilatory effects mediated via ADM. It binds to the circulating ADM released due to sepsis, stimulates ADM's beneficial effects such as maintaining the endothelial barrier, preventing

capillary leak syndrome, and also decreasing interstitial vasodilatory effects produced in sepsis. When administered systemically as a single dose of 2 mg/kg, ADZ did not increase heart rate or lead to vasodilatation like ADM.

Geven *et al*. enrolled 48 healthy patients in two randomized, double-blind, placebo-controlled phase I studies to investigate the safety, tolerability, and pharmacokinetics (PK)/pharmacodynamics of ADZ in humans and a second study involving experimental human endotoxemia. In these studies, subjects received a placebo or one of three doses of ADZ. In the second study, a bolus of 1 ng/kg endotoxin was followed by an infusion of 1 ng/kg/h endotoxin for 3 h to induce systemic inflammation. The medication under investigation was started as an infusion 1 h after the bolus dose of endotoxin. Authors found that ADZ was tolerated well in subjects, in the absence and presence of systemic inflammation.[6] However, a further research in the form of adequately-powered randomized controlled trials are awaited, which are already ongoing, most importantly the phase II randomized control trial (RCT) by Geven *et al*. i.e., the AdrenOSS-2 trial which is a randomized, double-blind, placebo-controlled, biomarker-guided, proof-of-concept, and dose-finding clinical trial in patients with early septic shock and high concentration of circulating ADM involving 300 patients (https://clinicaltrials.gov/ct2/show/NCT03085758).[7] ADZ has a longer half-life of 15 days; thus, a single loading dose is enough in indicated patients once a decision has been made to administer. However, the allowable, safe dose that can be administered in humans has not been declared yet.

In conclusion, ADZ therapy appears to be a novel, targeted, biomarker-guided intervention in septic patients in an attempt to prevent organ dysfunction, morbidity, and reduced length of stay, but the verdict is not out yet.

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Conflicts of interest
There are no conflicts of interest.

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