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Vascular Integrity

The key to treating sepsis and septic shock: matching treatment to causal pathophysiology

Adrenomed AG is translating the concept of precision medicine to acute care with a biomarker-guided antibody therapy for sepsis and septic shock.

With a mortality rate of 20–30% in developed countries, sepsis represents an enormous public health burden. Many survivors experience long-term morbidity and loss of quality of life. In the US, sepsis accounts for 30–50% of deaths among hospitalized patients, making it the number one cause of death in hospitals. The annual cost of treating septic patients in the US alone amounts to $24 billion. The burden of sepsis, on patients and healthcare providers, has become even more pronounced during the COVID-19 pandemic, as severe cases of COVID-19 present as viral sepsis.

Despite improvements in identifying and managing sepsis over the past 30 years, mortality remains troublingly high, and new approaches to improving patient outcomes are desperately needed. Previous attempts to develop new therapies for sepsis show that one-size-fits-all approaches are not successful. Sepsis is a multi-complex disease with different underlying pathophysiologies comparable to cancer, for which targeted biomarker- guided treatments have led to therapeutic breakthroughs.

Adrenomed AG, based in Hennigsdorf, Germany, is bringing precision medicine to the acute care setting with a pioneering biomarker-guided approach to sepsis. One of the hallmarks of sepsis is loss of integrity of the endothelial barrier separating the bloodstream from surrounding tissues, allowing fluid to leak into tissues and eventually leading to organ failure, shock and death[1]. To date, dysfunction of the endothelial barrier has been untreatable. Adrenomed has developed Adrecizumab (HAM8101; enibarcimab), a first-in-class non-blocking monoclonal antibody that binds to and functionally stabilizes the peptide hormone adrenomedullin (ADM), which has a crucial role in maintaining the endothelial barrier and its function.

Adrenomed is utilizing ADM as a biomarker to guide Adrecizumab treatment to patients with deteriorating endothelial barrier, while at the same time using another biomarker, dipeptidyl peptidase-3 (DDP3), to exclude patients whose cause of septic shock has a different pathophysiology. With this approach, Adrenomed is shifting sepsis treatment towards precision medicine, ensuring that patients get the right drug for their underlying disease mechanism.

Adrecizumab has completed clinical phase 1 and 2 trials, demonstrating a favorable safety profile[2] and the ability to systemically improve organ function and reduce mortality rates in septic shock patients, and is now poised for pivotal phase 2b/3 trials in septic shock. Beyond sepsis and septic shock, Adrecizumab has the potential to become a platform therapy applicable to a wide range of conditions, in which loss of endothelial barrier integrity plays a role, such as acute heart failure.

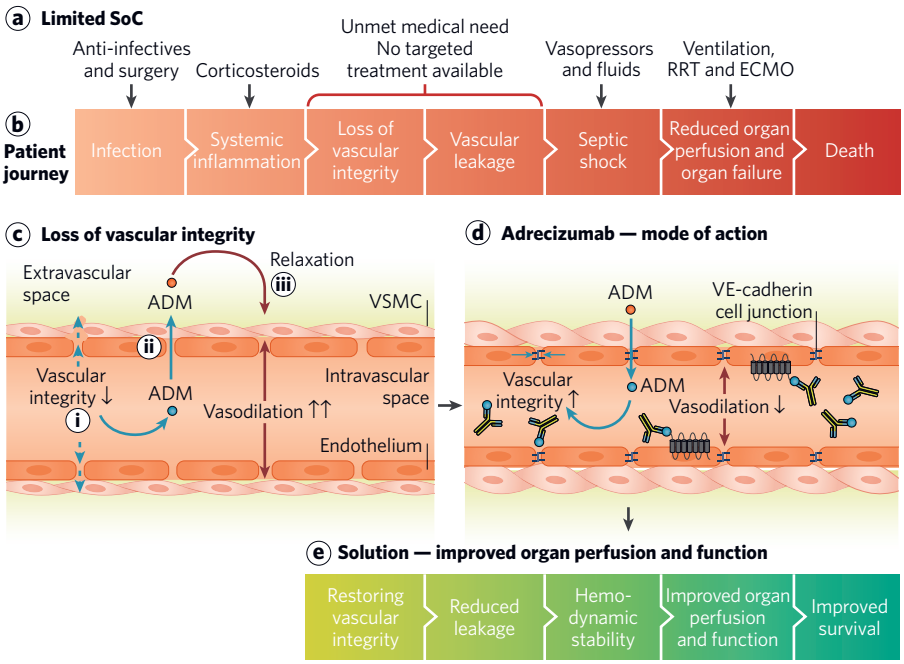

Fig. 1 | Adrecizumab modifying an important causal pathophysiology of sepsis. a. Standard of care for sepsis and septic shock does not address key pathophysiological process: the loss of vascular integrity. **b.** The patient journey in sepsis proceeds through a series of progressively more severe stages. **c.** Molecular pathophysiology in sepsis: i) Loss of vascular integrity, countermeasure increased ADM blood level; ii) ADM enters extravascular space; iii) leaked ADM causes vasodilation. **d.** Mechanism of action of Adrecizumab. ADM-Adrecizumab complexes remain in blood, and ADM retains the ability to restore vascular integrity. **e.** Adrecizumab restores vascular integrity, and improves downstream outcomes for patients. ADM, adrenomedullin; ECMO, extracorporeal membrane oxygenation; RTT, Renal Replacement Therapy; VE, vascular endothelial; VSMC, vascular smooth muscle cells.

The complexity of sepsis

Sepsis is a complex disorder or syndrome that presents as a cluster of symptoms and biological changes driven by diverse underlying processes, rather than a single disease with a clear-cut aetiology. Sepsis begins with an infection—bacterial, viral or fungal—that initiates a systemic inflammatory response. This, in turn, drives loss of vascular integrity that causes vascular leakage, which results in a drop in blood pressure (and in severe cases septic shock) and reduced organ perfusion that can cause organs to fail. When multiple organs fail at once, the patient is at high risk of dying[3] (Fig. 1 (a)).

Contemporary treatment of sepsis follows this patient journey. The first step is usually to try to control the infection with anti-infectives or surgery, followed by symptom management through fluid and vasopressor administration to restore blood pressure. If and when organs begin to fail, patients receive supportive care, including mechanical ventilation, renal replacement therapy and extracorporeal membrane oxygenation[4] (Fig. 1 (a)).

Missing from this treatment package is any intervention that targets the underlying pathophysiological processes driving sepsis. These include the loss of endothelial barrier function caused by the dysregulated inflammatory response and indicated by elevated blood ADM levels, as well as disturbance of the renin-angiotensin systems (RAS) caused by elevated levels of DDP3.

ADM: key regulator of the endothelial barrier

Adrenomed's goal is to fill the gap in patient treatment further downstream of inflammation with Adrecizumab, the first sepsis therapy candidate to target an important causal pathophysiology of the condition—loss of vascular integrity and endothelial barrier function—rather than merely offering symptomatic or supportive relief.

ADM is a free-circulating 52-amino-acid peptide belonging to the calcitonin gene-related peptide family. Originally thought to function principally as a vasodilator, ADM has since been found to have a variety of biological effects, and is a key regulator of the endothelial barrier and vascular tone. ADM has also emerged as an important player in the sepsis response. Many of the known mediators implicated in the pathophysiology of sepsis, such as cytokines and hypoxia, increase ADM production. In addition, levels of circulating ADM are elevated in sepsis, reflecting the body's repair response to loss of vascular integrity and reduced endothelial barrier function. Elevated ADM levels also correlate with disease severity, need for vasopressors, onset of shock and mortality[5,6].

These findings might suggest that ADM is bad news for sepsis, and that blocking its effects might prove therapeutic. The biology of ADM has, however, proved more complicated, with different effects that simultaneously exacerbate and ameliorate sepsis. It all depends on where ADM is acting.

As a small peptide, ADM can easily leave the bloodstream by crossing the endothelial barrier and entering the extravascular space, where it affects vascular smooth muscle cells and regulates vascular tone by promoting vasodilation—an unwelcome effect in the context of sepsis as it contributes to increased hypotension and organ damage. ADM that remains in the bloodstream, however, has a different effect, one that helps mitigate sepsis: promoting stability of the endothelial barrier by restoring the tight junctions between endothelial cells that ordinarily regulate molecule transport and leakage.

In health, levels of ADM in the bloodstream and extravascular space are in equilibrium so that endothelial barrier integrity is maintained and blood pressure remains normal. In sepsis, more ADM is produced to counteract loss of endothelial barrier function, but as the endothelial barrier becomes more permeable as a result of systemic immune dysregulation, more ADM enters the extravascular space in a dangerous cycle that can contribute to shock and organ failure (Fig. 1 (c)).

Adrecizumab: precision medicine for acute care

Adrecizumab binds to ADM inside of the blood vessel, but does not block its action. Instead, Adrecizumab sequesters ADM in the bloodstream, as the ADM-antibody complex is too large to cross the endothelial barrier. In addition, the complex with Adrecizumab increases the half-life of ADM, which ordinarily is about 20 minutes, in a dose-dependent manner. The half-life extending benefits of Adrecizumab are thought to result from the antibody binding to the N-terminal part of ADM, where proteolytic degradation occurs. This specific binding of ADM through its N-terminal domain, which is not required for ADM to bind to its receptor, is also key to maintaining the functionality of ADM signalling once ADM is in a complex with Adrecizumab[7,8].

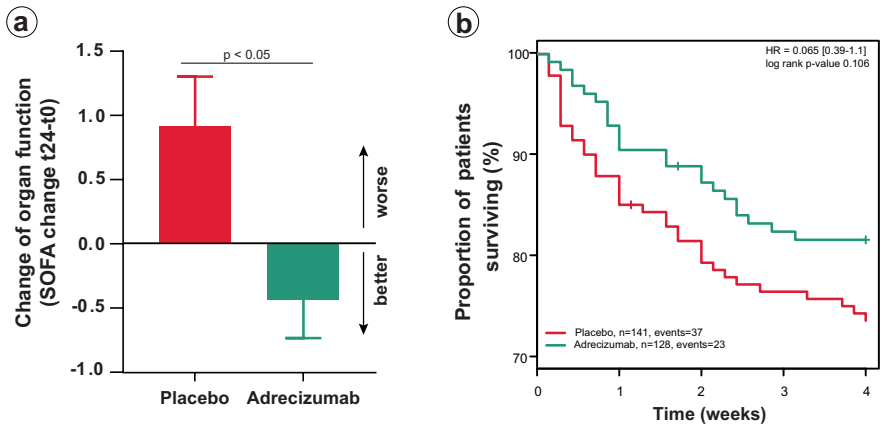

Fig. 2 | Results from the AdrenOSS-2 trial. a. SOFA scores 24h post-treatment showed that organ function in patients receiving placebo worsened, but significantly improved in patients receiving Adrecizumab ($p<0.05$). **b.** Survival 28 days post-treatment is improved by Adrecizumab treatment compared with placebo. (Shown is the prespecified subset of intention-to-treat with DPP3 <70 ng/ml; Hazard Ratio=0.65 [0.39–1.1].)

By preventing ADM from leaving the bloodstream and enhancing its half-life, Adrecizumab increases the concentration of functional ADM within the lumen of blood vessels where it has the effect of promoting stability of the endothelial barrier (Fig. 1 (d)).

In conducted clinical studies a single intravenous administration of Adrecizumab led to a dose-dependent increase in plasma ADM concentration within minutes, an effect that has been seen in all species investigated to date. Adrecizumab's half-life of approximately 15 days in healthy subjects allows for administration of a single dose in treating sepsis and septic shock[2], covering the critical first week after onset of the disease.

Dysregulation of endothelial barrier integrity, which Adrecizumab counteracts, is at the core of many cases of sepsis and septic shock, but not all; in some, plasma elevation of DDP3 also is a driver for mortality. Previous clinical trials of sepsis therapies have typically recruited patients with diverse aetiologies for sepsis, and did not distinguish between those experiencing dysregulation of endothelial barrier function and DPP3 pathways, which may mask benefits that accrue only to a subset of patients exhibiting particular pathological processes.

Adrenomed's biomarker-guided, precision medicine approach means that treatment is matched to underlying pathophysiology to be disease modifying: patients with sepsis/septic shock who show elevated levels of plasma ADM can receive Adrecizumab, while those whose show high levels of DDP3, and who are therefore less likely to benefit from Adrecizumab, will not. To rapidly identify these groups of patients, the biomarkers bio-ADM and DPP3 can be tested with SphingoTec's commercially available Nexus IB10 point-of-care platform within 20 minutes.

The phase 2 AdrenOSS-2 trial has demonstrated the benefits of this biomarker-guided approach. In AdrenOSS-2, which recruited 301 patients across 24 active European sites, septic shock patients with elevated ADM (>70 pg/ml) received Adrecizumab at either 4 mg/kg or 2 mg/kg, or placebo. The antibody was well tolerated and showed a favorable safety profile, thereby reaching its primary objective. Analyses of both Adrecizumab dose groups were combined, and AdrenOSS-2 included a prespecified analysis by exclusion of patients with elevated DPP3 (>70 ng/ml), which removed 32 patients from the final analysis.

For patients with ADM >70 pg/ml and DPP3 <70 ng/ml, Adrecizumab led to rapid and sustained improvement in organ function measured by the clinical-validated SOFA (Sequential Organ Failure Assessment) score, and reduced mortality at 28 days from 26% to 18% (Fig. 2 (b)).

Building on the lessons learned in the AdrenOSS-2 trial, Adrenomed is now planning a pivotal phase 2b/3 trial program, ENCOURAGE, which will use refined inclusion/exclusion criteria and explore the benefits of earlier intervention, with separate trials for sepsis and septic shock. The ENCOURAGE trials will form the basis for marketing applications for the treatment of sepsis and septic shock. More than 50% of septic shock patients treated within the intensive care unit would be eligible for the biomarker-guided treatment with Adrecizumab.

Backed by decades of experience in sepsis diagnostics, Adrenomed is dedicated to pioneering precision medicine for acute care. Adrenomed welcomes discussions with potential investors or partners who are interested in joining in the development and commercialization of Adrecizumab in sepsis and septic shock to benefit millions of patients.

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