Antithrombin III in patients with severe sepsis

A randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis

Abstract Objectives: To evaluate the safety and potential efficacy of antithrombin III (AT III) in reducing mortality in patients with severe sepsis.

Design: Prospective, randomized, placebo-controlled, double-blind, phase II, multicenter, multinational clinical trial.

Setting: Seven academic medical center intensive care units (ICU) in Belgium, Denmark, the Netherlands, Norway and Sweden.

Patients: 42 patients with severe sepsis who received standard supportive care and antimicrobial therapy, in addition to the administration of AT III or placebo.

Interventions: Patients received either an intravenous loading dose of 3000 IU AT III followed by a maintenance dose of 1500 IU every 12 h for 5 days or equivalent amounts of placebo.

Measurements and results: All patients were evaluated for safety and for 30-day all-cause mortality.

Conclusions: The administration of AT III was safe and well-tolerated. It was followed by a 39% reduction in 30-day all-cause mortality (NS). The reduction in mortality was accompanied by a considerably shorter stay in the ICU. Patients treated with AT III exhibited a better performance in overall severity of illness and organ failure scores (Acute Physiology and Chronic Health Evaluation II, multiple organ failure, organ system failure), which was noticeable soon after initiation of treatment. Patients treated with AT III demonstrated a better resolution of pre-existing organ failures and a lower incidence of new organ failures during the observation period. A meta-analysis comprising this and two other double-blind, placebo-controlled trials with AT III with a total of 122 patients suffering from severe sepsis confirms the positive trend. The results of the meta-analysis demonstrate a 22.9% reduction in 30-day all-cause mortality in patients treated with AT III. Although still too small to be confirmative, the meta-analysis clearly points to the fact that a sufficiently powered phase III trial is warranted to prove whether AT III has a beneficial role in the treatment of severe sepsis.

Key words Antithrombin III · Sepsis · Multiorgan failure · Clinical trial · Meta-analysis
Introduction

Sepsis describes a constellation of maladaptive responses to infection often including hypotension and organ failure [1]. Despite major advances in antimicrobial therapy, surgical techniques, and intensive care, there has been little improvement in morbidity and mortality due to sepsis during the past 30 years. The average mortality from severe sepsis remains at approximately 35–45%, and the incidence of sepsis continues to increase [2, 3].

For quite a long time, our understanding of the pathophysiology of sepsis was clearly focused on endotoxin and proinflammatory cytokines. Large randomized placebo-controlled trials in patients with sepsis, however, failed to demonstrate the clinical benefit of a specific blockade of endotoxin, tumor necrosis factor-alpha (TNF α) or interleukin-1 (IL-1) β alone [3–9].

It is now appreciated that many signs and symptoms of sepsis are not the direct effects of cytokines but are transmitted through other mediator systems [10, 11]. The septic process progresses to malperfusion and organ failure, the unbalanced – and cytokine-mediated – activation of the coagulation system comes into play [12–16].

Antithrombin III (AT III) is an important physiological regulator of blood coagulation as it inhibits the clotting process at various levels. Its inhibitory profile includes the intrinsic (F Xla, F IXa), extrinsic (tissue factor bound F VIIa), and common pathway (F Xa, thrombin) of coagulation [17]. AT III is a single-chain glycoprotein which is produced by the liver. It belongs to the SERPIN (serine protease inhibitor) superfamily. The AT III molecule contains two main functional domains: a reactive site domain binding to the target proteases and a heparin-binding domain. The inactivation of target proteases (e.g., thrombin) occurs through a stoichiometric complex formation between AT III and the enzyme. This reaction is then accelerated several hundred times by complex formation with heparin.

In healthy individuals, its half-life ranges from 18 to 27 h but may be markedly reduced in patients with severe sepsis [18], even in the absence of clinically manifest defibrinating disseminated intravascular coagulation [19]. The acute consumption of the molecule during the process of coagulation, its increased leakage from the intravascular compartment, and the proteolytic inactivation by elastase are the pathophysiologic mechanisms responsible for the acquired AT III deficiency in these patients [20, 21].

The decrease in AT III is related to outcome, and levels are significantly lower in nonsurvivors than in survivors [18]. A decrease in AT III levels below 50% was demonstrated to be a good prognostic predictor of subsequent death with a sensitivity of 96% and a specificity of 76% [15].

The first administration of AT III in patients with sepsis was reported in 1978 [22]. Subsequently, many other clinical studies were published. Yet, despite the fact that the therapeutic administration of AT III was generally found to be beneficial, the open, and in some cases nonrandomized, design of the trials limited the level of evidence for demonstration of treatment efficacy.

In the present study, the safety and potential efficacy of AT III in reducing mortality in patients with severe sepsis was assessed in a randomized, double-blind, placebo-controlled, multinational setting. The study comprised 42 patients suffering from severe sepsis. The primary endpoint was comparison of 30-day all-cause mortality for AT III relative to placebo. Seven academic medical centers in Northern and Western Europe participated in this trial. The study protocol was approved by the ethical review committee at each participating center, and informed consent for participation was obtained for all patients (either from the patients themselves or from relatives, if a patient was not able to give informed consent due to the severity of the sepsis) prior to the performance of any study-related procedures.

In order to base the evaluation on a larger number of patients, a meta-analysis comprising 122 patients was also made. The analysis combines the results of the present study with those of two other double-blind, placebo-controlled clinical trials with AT III in patients with severe sepsis. The results of both these trials were presented recently [23, 24].

Patients and methods

Study design and treatment

The study was designed as a phase II pilot trial not aiming at statistical significance for the main criterion. It consisted of three phases: screening, treatment, and follow-up. During the screening phase, patient eligibility was determined, informed consent was obtained, and patients were randomly assigned to receive either AT III (Kybergen P Centeon Pharma GmbH, Marburg, Germany) or placebo. During the treatment phase, all patients received an intravenous loading dose of either AT III 3000 IU or an equivalent volume of placebo, administered over approximately 1 h. Subsequently, AT III (1500 IU) or placebo was infused every 12 h for 5 days. Thus, the cumulative dose of AT III was 18000 IU. Decisions regarding the use of antimicrobial agents, intravenous fluids, cardiovascular and respiratory support, and surgical intervention were made by each patient's attending physician and were not dictated by the study protocol. After completion of the 5-day treatment phase, patients were followed-up for the remainder of 30 days.

Patient selection

Patients with a diagnosis of sepsis were enrolled if they fulfilled the following criteria within a 6- to 8-h time window prior to initiation of treatment with the study medication: (a) clinical evidence of sepsis...