A prospective randomized double-blind trial of antithrombin III concentrate in the treatment of multiple-organ dysfunction syndrome during hematopoietic stem cell transplantation

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ABSTRACT

Many of the complications of high-dose therapy with hematopoietic stem cells are caused by or lead to the multiple-organ dysfunction syndrome (MODS). In hematopoietic stem cell transplantation (HSCT), acquired antithrombin III (ATIII) deficiency is independently associated with MODS to the exclusion of transplant type, preparative regimen, and bacteremia. In experimental settings, replacement of ATIII can ameliorate the severity of MODS that develops in response to a variety of pathologic stimuli, suggesting that ATIII supplementation might improve the clinical course of MODS in patients undergoing HSCT. We performed a study to determine if ATIII can improve the morbidity of MODS in HSCT. Forty-nine patients undergoing HSCT, who developed pulmonary dysfunction (oxygen saturation of <90%), central nervous system dysfunction (drop of >4 points in the mini-mental status exam), or hepatic dysfunction (bilirubin >34 µmol/L [2.0 mg%], weight gain of >5% over baseline, and abdominal pain, possibly of hepatic origin) with a concomitant ATIII activity of <84% were double-blind randomized to receive ATIII concentrate, 70 units/kg within 24 hours of recognition of initial organ dysfunction followed by 50 units/kg 8, 16, 48, and 72 hours later, or albumin placebo. The group randomized to ATIII had a lower severity-of-illness score (15.7 ± 19.2 vs. 28.6 ± 25.2, p = 0.03), shorter duration of hospitalization (14.9 ± 16.7 vs. 25.7 ± 17.9 days, p = 0.03), and lower hospital charges ($138,700 ± $23,500 vs. $206,400 ± $34,000). ATIII concentrate was associated with improved morbidity of MODS in patients undergoing HSCT when given early in the evolution of the syndrome.

KEY WORDS

Hepatic veno-occlusive disease • Delerium • Idiopathic pneumonia syndrome • Systemic inflammatory response syndrome

INTRODUCTION

The multiple-organ dysfunction syndrome (MODS) is a recently defined clinical entity intended to describe the progressive functional deterioration of a variety of organ systems, which occurs after exposure to a wide spectrum of pathologic stimuli including infection, burns, and trauma [1]. MODS is currently understood to result from the systemic inflammatory response to these stimuli, which has escaped physiologic control [2]. This inflammatory response is mediated by a complex and incompletely understood interplay of cytokines, hemostatic factors, the complement cascade, lymphocytes, phagocytes, vascular endothelial cells, and probably other elements currently unrecognized [2,3]. At some point in its evolution, mediators of the inflammatory response begin to generate systemic reactions that are detrimental to the function of many organs, or the regulators of the inflammatory response suppress these mediators to the point of immune deficiency with resultant predisposition to infection and other adverse consequences of “immunologic dissonance.” While the precise mechanism of the generation of these harmful reactions is not well delineated, functional derangements in vascular endothelial cells are probably involved. MODS is responsible for the majority of deaths in the intensive care unit (ICU) patient popula-

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tion [4]. Even modest degrees of MODS correlate closely
with duration of hospitalization in patients who survive [4].
In survivors of illnesses or injuries requiring ICU care,
development of MODS significantly prolongs hospitalization
and increases costs of recovery to an average of 385,000
1996 dollars [4].

High-dose therapy and hematopoietic stem cell trans-
plantation (HSCT) is associated with a variety of complica-
tions that can result in progressive functional deterioration
of many organ systems and subsequent death. There are
similarities between the complications of transplantation
and MODS in other populations of critically ill patients.
These similarities have been used to postulate that the com-
plications seen in the two populations may be the result of
similar, if not identical, processes. One of the similarities is
an association with deficiencies of naturally occurring anti-
coagulants such as antithrombin III (ATIII) and protein C
[5–7]. The prognosis of MODS is proportional to the
degree of deficiency of these proteins [8–21]. In experimen-
tal models of MODS, generally using infection or endotoxin
as a stimulus, altering the hemostatic system to minimize
fibrin accumulation has prevented progressive organ dys-
function and mortality [22–36]. Administration of ATIII,
either before or after the inciting stimulus, can prevent the
fatal MODS that occurs in these models [29–35]. This
model has been applied to human subjects with some suc-
cess. When given to patients with bacteremia and dissemi-
nated intravascular coagulation, ATIII was associated with
a trend to lower mortality [37]. When given to patients suf-
fering multisystem trauma, ATIII use was associated with
lower plasma levels of neutrophil elastase, interleukin (IL)-
6, IL-8, and significantly fewer days in the ICU and on ven-
tilator support [38]. In none of the human or animal trials
was any adverse effect of ATIII detected. With this back-
ground, a study was designed to test the hypothesis that
ATIII supplementation would ameliorate the clinical mani-
festations of MODS from HSCT and that such improve-
ment would lower the overall cost of the HSCT procedure.

MATERIALS AND METHODS

Patients
All patients with malignant disease who were admitted
to the University of Nebraska Medical Center for HSCT
and not committed to other confounding clinical trials were
eligible to participate, except those for whom English was
not their first language and who had not completed an
eight grade education (to allow reliable use of the mini-
mental status examination; see below).

Informed consent and high-dose therapy regimens
The study was approved by the institutional review
board. Informed consent for organ dysfunction monitoring
and infusion of the study drug (if necessary) was obtained
before beginning the high-dose therapy regimen for HSCT.
The regimens used in this study have been previously
described [5,39,40].

Organ dysfunction
All patients were screened daily by one of two individu-
als for the development of central nervous system (CNS),
pulmonary, or hepatic dysfunction. These organ dysfunc-
tions were chosen because of previous demonstrations of
their contribution to MODS and subsequent mortality in
HSCT as well as their close correlation with ATIII levels
during HSCT [5]. For our analyses, organ dysfunction was
considered as an all or none phenomenon rather than a
spectrum of increasingly severe physiologic derangements,
an approach supported by our experience in previous
cohorts of patients undergoing HSCT [5]. Grading organ
dysfunction severity at the time of presentation on a four-
point scale of progressive severity added no value in predict-
ing subsequent organ dysfunction or mortality compared
with considering organ dysfunction and no organ dysfunc-
tion as dichotomous variables, similar to the experience
using two types of organ dysfunction definitions to predict
mortality in critically ill non–HSCT patients [41]. Organ
dysfunctions were defined as follows:

1) CNS—A drop in the score of the standardized mini-
mental status examination of ≥4 points from the pre-chemo-
therapy score. This score represents slightly more than two
standard deviations from the mean of the differences in
test/retest scores with this tool [42]. This definition has been
shown to have a specificity of 100% for delirium in subjects
with an education level of at least the eighth grade [43].

2) Pulmonary—Finger oximetry reading of SaO2 <90%
on two occasions on the same day separated by at least 2
hours.

3) Hepatic—A combination of bilirubin >2.0 mg%, a
weight gain of >5% over prechemotherapy weight, and
abdominal pain of possible hepatic origin. This definition
has a high degree of concordance with histologically defined
veno-occlusive disease from autopsy [44] and premortem
[45] liver tissue.

MODS

Patients with single-organ dysfunction (either pulmo-
nary, hepatic, or CNS) during HSCT who have a con-
comitant ATIII activity of <84% have been shown to have a
71.8% likelihood of progression to multiple-organ dysfunc-
tion in the following week [5]. Consequently, for the purpos-
es of this study, patients with single-organ dysfunction with a
concomitant ATIII activity of <84% of normal were defined
as having MODS.

Randomization

Patients with MODS were randomized to receive ATIII
concentrate (ATnativ, Baxter Healthcare, Glendale, CA) or
albumin placebo (5% human albumin, Baxter Healthcare).
The ATIII concentrate was given at a dose of 70 U/kg with-
in 24 hours of organ dysfunction detection, followed by 50
U/kg 8, 16, 48, and 72 hours later. The total dose of ATIII
concentrate was 270 U/kg, similar to the dose found effec-
tive in animal models [30,31,34] and human sepsis [37].
Albumin was given in a volume equal to the calculated vol-
ume of ATIII concentrate. Based on a recovery of 1.8%/U-
kg and a half-disappearance time of 12 hours 14 days after
beginning the high-dose therapy regimen for HSCT [46],
the study dose of ATIII concentrate was estimated to pro-
vide an increment of ~250% activity above pretreatment
levels after the third dose, levels similar to those achieved in
prior human studies found to be effective in shortening the
duration of disseminated intravascular coagulation due to sepsis [37]. The duration of therapy was chosen based on previously published evidence from animal [29,30,31,33,34] and human [37] studies, suggesting efficacy with 72 hours of therapy or less.

Previously performed multivariate analyses considering transplant type (alloge nic, autologous bone marrow, and autologous peripheral blood stem cell), type of preparative regimen, presence of positive blood culture, and AT III level have shown that only the AT III level was a consistent independent association of organ dysfunction during transplantation [5]. Because transplant type, treatment regimen (and, by inference, disease type), and bacteremia were not independent risk factors for organ dysfunction in this population, no attempt to stratify for these variables was made in this study.

With no prior experimental experience available, the degree of change in the major outcomes of the study expected from ATIII supplementation was unknown. Consequently, accurate prediction of sample size necessary to establish a statistically significant difference between the two groups could not be precisely estimated. The factors ultimately governing the final number of subjects to be accrued were the number that would reasonably be required to show a trend to different outcomes between the two groups, the frequency with which organ dysfunction was seen in this single institution, and the amount of funding available to carry out the study. The number of 25 subjects in each arm was determined before beginning the study to meet these limitations.

Randomization was accomplished using a computer-generated list of random numbers. An unblinded research pharmacist reconstituted the requisite volume of study drug and provided it to the ward personnel in unmarked containers.

**Post-randomization monitoring**

After randomization, daily monitoring for organ dysfunction continued until hospital dismissal or death. Criteria for dismissal from the hospital were standardized before the beginning of this trial and included neutrophil recovery of >500/mm³, absence of fever or active infection, minimum oral intake of 1000 mL of fluid and 1000 kcal, controlled GVHD of grade less than II, ability to ambulate, and need for no more than one daily transfusion of red blood cells or platelets [47]. Decision for hospital dismissal was made without knowledge of study treatment allocation. The severity-of-illness score was calculated after study completion by summing the number of organ dysfunctions (0–3) on each day of hospitalization from the point of randomization until dismissal or death. Thus, for example, a patient with CNS dysfunction on 6 days, pulmonary dysfunction on 3 days, both CNS and pulmonary dysfunction on 4 days, and no organ dysfunction for the remaining 7 days of hospitalization would have a severity-of-illness score of 17. The rationale of this approach is based on the observation that there is a direct relationship between the number of organ dysfunctions per unit time and mortality in critically ill non–HSCT patients [48], suggesting that patients with more organ dysfunctions per unit time were at greater risk of dying than those with fewer organ dysfunctions. Consequently, this measurement of severity of illness encompasses more than simply the duration of hospitalization. If the MODS or its therapy predisposed to early death, this calculation would be expected to be falsely indicative of a good outcome. In the absence of a higher mortality rate, a lower severity-of-illness score would be indicative of less severe MODS.

**Statistical analysis**

Data are expressed as the mean ± SEM. Wilcoxon’s rank sum test assessed the difference in duration of hospitalization, hospital charges, and severity-of-illness scores between the two groups. The Fisher’s exact test was used to look at the differences in the mortality distribution of the study groups. A p value <0.05 was considered significant.

**RESULTS**

A total of 197 patients were approached to give informed written consent. Eight patients declined to give such consent, one patient had not completed an eighth grade education and so was disqualified, and two patients had committed to participate in another clinical trial. The demographics, diseases, preparative regimens, and types of HSCT performed for the remaining 186 patients entered into the study are outlined in Table 1. All 186 patients were evaluable.

**Significance of the definitions of organ dysfunction and MODS**

Organ dysfunction was detected in 54 patients. Of this group, 25 died during hospitalization (mortality 46.3%). The mortality rate was 0% in the remaining 132 patients who did not meet our criteria for organ dysfunction (p < 0.0001).

**Table 1. Characteristics of the population monitored for organ dysfunction**

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>Cyclophosphamide, total-body irradiation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>34</td>
<td>6</td>
</tr>
<tr>
<td>Acute myelogenous leukemia</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>68</td>
<td>51</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
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<td>3</td>
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<tr>
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<td>11</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>68</td>
<td>12</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>99</td>
<td>68</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>186</td>
<td>186</td>
</tr>
<tr>
<td>Transplant type</td>
<td>Carmustine, etoposide, cyclophosphamide</td>
<td>186</td>
</tr>
<tr>
<td>Allogeneic, related</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Allogeneic, unrelated</td>
<td>18</td>
<td>47</td>
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<tr>
<td>Autologous</td>
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<td>99</td>
</tr>
<tr>
<td>bone marrow</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>peripheral blood</td>
<td>5</td>
<td>186</td>
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<tr>
<td>Total</td>
<td>186</td>
<td>186</td>
</tr>
<tr>
<td>Preparative regimens</td>
<td>Carmustine, etoposide, cyclophosphamide</td>
<td>186</td>
</tr>
<tr>
<td>Cyclophosphamide, thiopeta</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Cyclophosphamide, thiopeta, hydroxyurea</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Carmustine, etoposide, cyclophosphamide</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Busulfan, cyclophosphamide</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Cyclophosphamide, total-body irradiation</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Cyclophosphamide, etoposide, total-body irradiation</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>186</td>
<td>186</td>
</tr>
</tbody>
</table>
MODS was diagnosed by the presence of an ATIII activity of <84% in 49 of these 54 patients. That our definition of MODS (single-organ dysfunction with a low ATIII level) was truly indicative of a high risk of multiple-organ dysfunction is illustrated by the observation that progression to a second- or third-organ dysfunction occurred in 29 of these patients (16 of the 25 patients randomized to placebo, 13 of the 24 patients randomized to ATIII), compared with zero of the five patients with single-organ dysfunction but without a low ATIII level (Fisher’s exact test, \( p = 0.017 \)). The significance of progression from single- to multiple-organ dysfunction is evident in the observation that of the 20 MODS patients who did not progress to second-organ dysfunction, only three died; 10 of the 19 who progressed to second- and all 10 of those who progressed to third-organ dysfunctions died (Fisher’s exact test, \( p < 0.001 \)). This also confirms the observation in non–HSCT patients that mortality is related to the absolute number of organ dysfunctions that occur during HSCT. In addition to predicting mortality, MODS was a strong indicator of in-hospital morbidity. Patients with MODS, but dismissed from the hospital alive, had longer (37.5 ± 19.5 days vs. 15.7 ± 9.6 days, \( p = 0.0001 \)) hospitalizations than those who did not develop MODS.

The severity-of-illness score in the 23 randomized patients who died was 35.3 ± 24.4 compared with 10.7 ± 14.5 in the patients who were dismissed alive (Wilcoxon’s rank sum test, \( p = 0.0003 \)), confirming that mortality was related to the duration and the absolute number of organ dysfunctions.

**Results of randomization**

ATIII levels were <84% in 49 (90.7%) of the 54 patients who developed organ dysfunction (mean ATIII level = 65.1 ± 3.1%); these patients were randomized and received a complete course of the study drug. One patient was randomized and received the first dose of the study drug based on an erroneous laboratory report. No further study drug was given and this patient was not included in our analysis. The mean weight of the randomized patients was 76 kg, making the mean total dose of ATIII concentrate 20,520 U/patient. The diagnoses and types of HSCT procedures performed on the patients who came to randomization are listed in Table 2. There were no significant differences between the treatment groups with respect to these parameters. Although all patients with MODS during unrelated allogeneic transplants who developed organ dysfunction were randomized to receive the placebo, analysis of outcomes of these patients showed no difference in their severity-of-illness score, hospital length of stay, or hospital charges compared with the related allogeneic transplant patients (severity-of-illness score, 28.2 ± 12.8 vs. 28.7 ± 27.1; length of hospital stay, 40.0 ± 8.0 vs. 41.7 ± 19.7 days; and hospital charges, $233,863 ± $159,448 vs. $201,140 ± $173,789). Consequently, any differences between the outcomes of the ATIII and placebo groups were not due to inordinately adverse outcomes of the unrelated allogeneic transplant patients in the placebo group.

The pattern of clinical progression from single- through multiple-organ dysfunction after randomization is outlined in Table 3. Of the 24 patients randomized to ATIII, 13 (54%) progressed to other organ dysfunctions compared with 16 (64%) of 25 patients randomized to placebo (\( p = \text{NS} \)). In the ATIII treatment group, 12 presented with CNS dysfunction, six of whom progressed to other organ dysfunctions; 10 presented with pulmonary dysfunction, six of whom progressed to other organ dysfunctions; and two presented with hepatic dysfunction, one of whom progressed to other organ dysfunctions. In the group randomized to placebo, 10 presented with CNS dysfunction, six of whom progressed to other organ dysfunctions; nine presented with pulmonary dysfunction, six of whom progressed to other organ dysfunctions; and six presented with hepatic dysfunction, four of whom progressed to other organ dysfunctions.

The outcome of therapy is summarized in Table 4. The duration of first-, second-, and third-organ dysfunctions tended to be shorter in patients randomized to ATIII, but differences in durations of individual organ dysfunctions did not reach statistical significance. However, when the clinical effect of the aggregate of these changes was considered, patients receiving ATIII fared better than those receiving placebo. Patients randomized to ATIII had a lower mean severity-of-illness score (15.7 ± 19.2 vs. 25.7 ± 17.9, \( p = 0.03 \)) and a

<table>
<thead>
<tr>
<th>Table 2. Characteristics of the patients randomized to treatment with antithrombin III or placebo</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Total</td>
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<tr>
<td><strong>Transplant type</strong></td>
</tr>
<tr>
<td>Allogeneic, related</td>
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<td>Allogeneic, unrelated</td>
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<tr>
<td>Autologous</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td><strong>Source of stem cells</strong></td>
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<tr>
<td>Bone marrow</td>
</tr>
<tr>
<td>Peripheral blood</td>
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<tr>
<td>Total</td>
</tr>
<tr>
<td><strong>Underlying disease</strong></td>
</tr>
<tr>
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<td>Cyclophosphamide, etoposide, total-body irradiation</td>
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<tr>
<td>Total</td>
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</table>
shorter hospitalization (14.9 ± 16.7 vs. 25.7 ± 17.9 days, p = 0.03) after randomization than did those randomized to placebo. This improvement translated to a tendency toward lower hospital charges for the ATIII group ($138,700 ± $23,500 vs. $206,400 ± $34,000, p = 0.06). There was a lower mortality rate in the group randomized to ATIII (39% [9/23] vs. 56% [14/25]), but the difference did not reach statistical significance (p = 0.19).

**DISCUSSION**

MODS has been recognized as the leading cause of death among critically ill or injured patients [4], including patients undergoing HSCT [5]. Our data confirmed the unfavorable clinical course of MODS in HSCT and supported the validity of the use of simple clinical measurements to define the disorder and estimate outcomes. Patients meeting the criteria for single-organ dysfunction had a mortality rate approaching 50%, suggesting the presence of significant physiologic derangement at the time of presentation, despite the often mild deviation from normal organ function parameters at that time. Patients who developed no organ dysfunction by these criteria did not die. Approximately one-half of the patients presenting with pulmonary, CNS, or hepatic dysfunction, by our definitions, progressed to second- or third-organ dysfunctions. An ATIII level ≤84% combined with the presence of single-organ dysfunction further improved the predictive value of progression to multiple-organ dysfunctions. In this prospective study, the rate of development of subsequent organ dysfunction in untreated patients with single-organ dysfunction and a low ATIII level was 64%, very similar to the 70.5% predictive value previously reported for this combination [5]. The development of second- and third-organ dysfunctions was an ominous occurrence, with mortality reaching 100% among those who developed CNS, hepatic, and pulmonary dysfunction. Not only was the development of organ dysfunction an important determinant of mortality, but the duration of organ dysfunction was also important. When the number of organ dysfunctions per day was combined with the number of days of hospitalization, the resultant severity-of-illness score associated strongly with mortality. In addition to its relationship to death, the severity of MODS had other clinically relevant features. Patients who developed nonfatal MODS had greater morbidity than did similar patients who did not develop MODS, which likely translated into increased suffering, longer hospitalization, and higher financial costs. This was observed in both HSCT patients and in populations with other severe illnesses [4,5]. Consequently, mortality is not the only clinically relevant goal of proposed therapies for this syndrome. An effective therapy should lower the duration and cost of hospitalization and lower the severity-of-illness score without increasing mortality. Unfortunately, to date no specific therapy has been identified. The only therapy available for MODS is the elimination (where possible) of its inciting stimuli and the provision of supportive care until dysfunctional organs regain full activity.

The results of this study suggest that the clinical course of MODS can be favorably altered with active therapy directed at the acquired ATIII deficiency. Patients given ATIII concentrate early in the evolution of MODS recovered faster and with a lower aggregate severity of illness than did patients given placebo. In addition to improved overall morbidity, ATIII therapy was associated with a trend of decreased recovery costs. In this study, the ATIII concentrate was provided without charge; thus, the reported hospital charges did not reflect the use of ATIII concentrate. However, if one factors in the cost of the ATIII concentrate (current average wholesale price of $60/U), the mean cost of therapy in this study would have been $12,312 per patient. This compares favorably with the mean difference in hospital charges of $67,700 per patient between those receiving

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**Table 3. Organ dysfunction outcomes of treatment in patients treated with antithrombin and placebo**

<table>
<thead>
<tr>
<th>ATIII (n=24)</th>
<th>Placebo (n=25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>3.5 (1.0, 63.0)</td>
<td>8 (0, 66.0)</td>
</tr>
<tr>
<td>1st Organ dysfunction</td>
<td>5.0 (1.0, 56.0)</td>
<td>18.5 (1.0, 50.0)</td>
</tr>
<tr>
<td>2nd Organ dysfunction</td>
<td>16.0 (1.0, 34.0)</td>
<td>28.5 (8.0, 51.0)</td>
</tr>
<tr>
<td>3rd Organ dysfunction</td>
<td>5.5 (1.0, 77.0)</td>
<td>27.0 (3.0, 66.0)</td>
</tr>
<tr>
<td>Severity-of-illness score</td>
<td>7.5 (1.0, 62.0)</td>
<td>21.0 (3.0, 66.0)</td>
</tr>
<tr>
<td>Hospital length of stay (days post-randomization)</td>
<td>96.1 (25.0, 46.5)</td>
<td>118.0 (51.0, 630.3)</td>
</tr>
</tbody>
</table>

*Results are reported as medians, with minimum and maximum values in parentheses.
ATIII and those receiving placebo. Because ATIII therapy decreased morbidity of organ dysfunction and because organ dysfunction often leads to death, ATIII therapy might also improve the mortality of HSCT. The mortality rate was lower in the ATIII-treated group, but the difference was not statistically significant ($p = 0.19$), although the study was not designed to test this hypothesis. Data suggest that the evaluation of the effect of ATIII on MODS mortality requires a study randomizing 200–250 patients between active therapy and placebo. Because $\sim 25\%$ of all transplant patients develop complications leading to MODS, such a study would require a population of $\sim 1000$ transplant patients. And because $\sim 20,000$ transplants are performed annually in the United States, this type of study seems feasible.

In our study, treatment with ATIII resulted in a lower frequency of progression from single- to multiple-organ dysfunction ($54\%$ progression in the ATIII group vs. $64\%$ in the placebo group) and a shorter duration of first-, second-, and third-organ dysfunctions. However, none of these differences reached statistical significance. The aggregate severity of all organ dysfunctions, as attested to by the severity-of-illness scores, was significantly improved with the use of ATIII, suggesting that individual organ dysfunctions were affected by this intervention as well. Perhaps, as with mortality considerations, the lack of statistically significant differences might be related to the small sample size used in this study. It is also reasonable to assume that organ dysfunctions detected, according to the definitions used in this study, were present several days before their diagnosis, but that our tools were too crude to detect them. Further research into methods of detecting clinically significant organ dysfunction may allow earlier intervention, possibly with better clinical outcomes, including improvement in frequency of progression from single- to multiple-organ dysfunction and duration of single-organ dysfunction. Additionally, higher doses of ATIII concentrate, dosing the concentrate to achieve a threshold level of plasma activity, or longer duration of ATIII supplementation may further improve outcomes. These issues should be addressed in subsequent clinical trials.

The possibility of other explanations for the better outcomes observed in the ATIII-treated group should be carefully considered. All unrelated allogeneic transplant patients treated in this study were randomized to receive placebo. However, the outcomes of these patients were similar to those undergoing related allogeneic transplantation, suggesting that inordinately worse outcomes in the unrelated allogeneic transplant patients is unlikely to explain the differences in outcomes between the ATIII and placebo groups. The absolute numbers of autologous transplant patients was higher in the group randomized to ATIII, while the number of allogeneic transplant patients was higher in the group randomized to placebo. This imbalance may account for some of the differences between the outcomes of the two groups. Data are insufficient to prove or disprove this hypothesis. However, previous analyses have shown that while the frequency and type of organ dysfunction varies with type of transplant (allogeneic, autologous bone marrow, autologous peripheral stem cell), treatment regimen, and disease type, these are not independent risk factors for development of organ dysfunction during transplantation [5]. These analyses have shown the only consistent independent associate of organ dysfunction is the ATIII level during the transplant course. This is consistent with the hypothesis that the inflammatory response is responsible for the generation of much of the organ dysfunction seen during transplantation, that ATIII is actively involved in the pathogenesis of this response, that the ATIII level is a marker of the severity of the inflammatory response, and that, while certain transplant-specific variables (type of transplant or preparative regimen) result in higher frequencies of complications, they do so by inducing a more robust inflammatory response. This suggests that differences between treatment and control arms in the areas of transplant type, treatment regimen, and bacteremia might not be relevant to differences in outcomes, except insofar as they induce a stronger inflammatory response as manifested by lower ATIII values. Potential contributions of these variable outcomes should be considered in any future trial of ATIII or other proposed therapy of MODS during HSCT by limiting studies to patients with transplant-specific variables associated with a high likelihood of inflammation-associated organ dysfunctions.

The mechanism of action of ATIII concentrate is unknown. Serine proteases are activated during the administration of chemotherapy [49–51] and the genesis of the inflammatory reaction [6–7]. The serine protease thrombin can convert fibrinogen to fibrin monomer, levels of which predict development and fatal outcome of MODS in non-HSCT patients [52]. Additionally, thrombin has effects on vascular endothelial cells that are of major importance in the inflammatory process [53]. Thrombin causes these cells to secrete plasminogen activator inhibitor-1 [54], an inhibitor of fibrinolysis found in high concentrations in patients with hepatic dysfunction during HSCT [55]. Thrombin also induces the expression of P-selectin, facilitating polymorphonuclear leukocyte adhesion to endothelial cells and their subsequent degranulation [56,57]. Neutrophil degranulation releases elastase and proteinase 3, serine proteases that can mediate endothelial cell death by apoptosis [58] when they become procoagulant [59] and cause further activation of coagulation in a potentially self-propagating manner. Thrombin stimulates production of transforming growth factor beta [60], a predictor of pulmonary and hepatic dysfunction in HSCT patients [61].

When activated, another serine protease, factor XII, can generate bradykinin by activating prekallikrein and its subsequent cleavage of high-molecular-weight kininogen [62]. Bradykinin can produce many of the observed cellular and physiologic effects associated with inflammation [63], including increases in vascular permeability (part of the clinical syndrome of hepatic veno-occlusive disease) [43,44]. In addition to generation of bradykinin, plasma kallikrein can induce a variety of other inflammatory reactions that can lead to organ dysfunction. Specific inhibition of plasma kallikrein can prevent inflammation-induced pulmonary dysfunction in experimental settings [64]. Factor XII can also activate the complement cascade via the classical pathway, generating biologically active substances that are involved in the inflammatory reaction [62]. Inhibiting complement activation can prevent inflammation-induced pulmonary dysfunction in experimental inflammation [65]. ATIII as an inhibitor of serine proteases could be active at these and other interfaces of the coagula-
tion and inflammatory systems, especially if present in supra-
physiologic levels, and could favorably alter their contribu-
tion to the intensity of the systemic inflammatory response as
one of its mechanisms of action. ATIII may also alter
cytokine expression during inflammation through unknown
mechanisms. When given to patients after multisystem trau-
ma, ATIII resulted in lower levels of IL-6 and IL-8 [38].

The notion that modulators of the coagulation cascade
can favorably affect the outcomes of inflammation is not lim-
ited to ATIII. In experimental settings, outcomes of inflam-
mation due to sepsis or trauma can be improved by modula-
tion of the hemostatic system by protein C [11,24], throm-
bolomodulin [23], heparin [26], inhibitors of tissue factor [22],
and recombinant tissue plasminogen activator [27,28]. Similar
alterations in the hemostatic system using heparin or re-
combinant tissue plasminogen activator have been report-
red to be helpful in preventing and treating hepatic veno-
occlusive disease, one of the manifestations of MODS during
HSCT [66–70]. The link between the coagulation and inflam-
matory systems may prove to be an important focus of
therapy in HSCT and other disease processes. Perhaps fur-
ther study will open the door to ways of providing patients
with MODS more than nonspecific supportive therapy to
prevent subsequent complications and death.

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