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Antithrombin III (ATIII) replacement therapy in patients with sepsis and/or postsurgical complications: a controlled double-blind, randomized, multicenter study

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Abstract *Background:* ATIII is decreased in sepsis and/or shock and its baseline value correlates with mortality. The efficacy of ATIII therapy on mortality was assessed in a selected group of patients admitted to the intensive care unit (ICU) in a double-blind, randomized, multicenter study.
Methods: 120 patients admitted to the ICU with an ATIII concentration < 70 % were randomized to receive ATIII (total dose 24000 units) or placebo treatment for 5 days; 56 patients had septic shock.
Results: ATIII concentrations in the treated group remained constant throughout the treatment period (range 97–102 %). The Kaplan-Meier analysis showed no difference in overall survival between the two groups: 50 and 46 % for ATIII and placebo, respectively. Septic shock and hemodynamic support were unbalanced in the two groups at admission. Therefore the Cox analysis was carried out after adjusting for these two variables. Treatment with ATIII decreases the risk of death with an odds ratio (OR) of 0.56. Of the covariates analyzed, septic shock and the baseline multiple organ failure score were negatively associated with survival and plasma activity level was positively associated with survival with an OR of 0.97 for each 1 % increase in the ATIII plasma concentration at baseline.
Conclusions: The results of ATIII treatment in this population of patients suggests that replacement therapy reduces mortality in the subgroup of septic shock patients only.

Key words Acquired ATIII deficiency · ATIII replacement therapy · Septic shock

Introduction

ATIII is a glycoprotein synthesized in the liver and the most active physiological inhibitor of the serine proteases generated during blood coagulation (thrombin and FIXa, FXa, FXIa, FXIIa, plasmin, kallikrein) [1]. Its activity is increased 1000-fold by heparin and heparan sulphate. The concentration of ATIII in plasma is decreased in the conditions associated with disseminated intravascular coagulation (DIC), particularly in sepsis and shock [2–5]. Decreased plasma concentration of ATIII may be indicative of the role of DIC in the pathogenesis of multiple organ failure (MOF); it is a prognostic factor of poor outcome and correlates with survival [4, 6–11]. Two randomized studies addressed the use of ATIII concentrates in the treatment of DIC in sepsis and shock but did not include a placebo-control group. Blauhut et al. randomized 51 patients with shock of different etiology (sepsis, trauma, hepatic coma) to receive ATIII, heparin or ATIII + heparin. Time to normalization of platelet counts and of fibrinogen levels was shorter in the patients receiving ATIII, but no difference in survival was noted [5]. In a subsequent study in patients with traumatic shock, Vinazzer [11] reported a significant reduction in mortality in the patients treated with ATIII. Fourrier et al. [12] published the first randomized double-blind, placebo-controlled study in patients with septic shock. There was a trend toward improved survival rate in patients treated with ATIII compared to placebo. Lamy et al. [13] included in their meta-analysis two additional studies on the use of ATIII in severe sepsis (the German and the north-western European study) and documented a non-significant reduction in the 30-day mortality (22.9%) and an earlier discharge from the intensive care unit (ICU) of surviving patients. The objective of our study was to evaluate the effect of ATIII on survival in a selected group of patients requiring hemodynamic and/or respiratory support for whom a mortality higher than 50% is predicted according to the Acute Physiology and Chronic Health Evaluation II classification system of severity of disease [14].

Methods

Design

The study was randomized, double-blind, and placebo-controlled. The coordinator was responsible for the randomization procedure, the allocation of the codes, and the supply of the ATIII concentrate and the placebo. He was blind to the patient data. Randomization was balanced within each center by coded envelopes. The attending physicians, evaluating the clinical course, were blind to treatment allocation and to sequential measurements of ATIII levels. Bottles, syringes, and infusion sets were black and indentical. The analysis was carried out before the codes were broken. Informed consent was obtained according to the Good Clinical Practice rules.

Inclusion criteria

Patients were included in the study if they fulfilled the following criteria. (a) Admission to the ICU because of a requirement for respiratory and/or hemodynamic support. Sepsis is defined as the systemic response to infection; this systemic response is manifested by two or more of the following conditions as a result of infection: temperature > 38.5 °C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min, leukocytosis ($> 15\times10^9$/l) or leukopenia ($< 4 \times 10^9$/l) [15]. Septic shock is defined as sepsis-induced hypotension requiring vasoactive drugs for more than 24 h, persisting despite adequate fluid replacement along with the presence of hypoperfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status [15]. Postsurgical complications are defined as clinical conditions arising in the postoperative period and requiring respiratory and/or hemodynamic support. Respiratory support is defined as assisted or controlled ventilation for more than 24 h. Hemodynamic support is defined by the requirement for inotropic drugs (dopamine or dobutamine) (≥ 5 µg/kg per min) and/or vasoactive amines (epinephrine or norepinephrine). (b) Age 18–75 years. (c) ATIII activity < 70% (chromogenic method, Instrumentation Laboratory, Milan, Italy).

Exclusion criteria

Patients with the following conditions were excluded: multiple trauma, liver cirrhosis or acute liver failure, cancer in a terminal phase, immunodeficiency, leukemia, pregnancy, heparin therapy. Patients who received heparin prophylaxis were included. The prophylactic regimen in the three centers was subcutaneous unfractionated heparin 5000 units b.i.d.

Treatment

ATIII concentrate and placebo (albumin solution 50 g/l) were supplied by Immuno (Wien) in identical black bottles containing either 2000 units of ATIII or 2 g albumin in lyophilized form. The material was reconstituted with 40 ml of distilled water supplied by the manufacturer. A fixed dose of 4000 units of ATIII or 4 g albumin was injected as bolus in 30 min, followed by one bottle every 12 h for 5 days by a pump-driven syringe. These doses were calculated to reach and maintain a normal level [5]. Routine care was not specified by the protocol and was carried out according to the current practice in each center. Fresh frozen plasma (FFP) was infused in patients with bleeding and/or a prothrombin time ratio > 2; platelet concentrates (PC) were infused (1 unit/10 kg body weight) if the platelet count was $\leq 50 \times 10^9$/l because these patients were considered to be at high risk of bleeding.

Evaluation criteria

The Simplified Acute Physiology Score (SAPS) [16] was recorded for each patient at admission; the MOF score [17], modified as indicated in Table 1, was recorded at admission and daily thereafter for 7 days. The end-points were survival for 30 days and MOF score for 7 days. FFP and PC requirements were recorded daily.

Table 1 Modification of the MOF score (*PEEP* positive end-expiratory pressure, F_iO_2 fractional inspired oxygen, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *DIC* clinical conditions associated with laboratory evidence of fibrin generation and lysis (D-dimer), hypofibrinogenemia, thrombocytopenia)

	MOF score		
	1	2	3[a]
Lung			
PEEP (cmH_2O)	≤ 5	$> 5 - \leq 10$	> 10
	and	and/or	and/or
F_iO_2	≤ 0.4	$> 0.4 - \leq 0.6$	> 0.6
Heart			
Dopamine (μg/kg per min)	$\geq 4 - \leq 10$	> 10	Epinephrine or norepinephrine
Kidney			
Creatinine (mg/dl)	$\geq 2 - \leq 4$	> 4	Dialysis
Liver			
Bilirubin (mg/dl)	$\geq 3 - \leq 6$	$> 6 - \leq 10$	> 10
	or	or	or
AST–ALT (IU/ml)	$\geq 200 - \leq 300$	$> 300 - \leq 1000$	> 1000
	or		
Bilirubin + AST–ALT	$\geq 2 - \leq 3 + \geq 80 - \leq 200$		
Blood			
Platelets ($\times 10^9$/l)	≤ 50	≤ 20	DIC
	or	or	or
Leukocytes ($\times 10^9$/l)	≥ 30	≤ 2.5	≤ 1.0

[a] Score for failure of a specific organ

Table 2 Characteristics of the patients enrolled in the study ($n = 120$)

Postsurgical patients ($n = 92$)	
Sepsis	84
Nonsepsis	8
Acute hemorrhagic pancreatitis	2
Acute cardiac–respiratory insufficiency	1
Acute respiratory insufficiency	1
Multiple organ dysfunction	2
Hemorrhagic shock	2
Nonsurgical patients ($n = 28$)	
Sepsis	16
Bronchopneumonia	12
Chronic renal failure	1
Salmonella typhi	1
Hemorrhagic pancreatitis	1
Mediastinitis	1
Nonsepsis	12
Acute pancreatitis	4
Mesenteric ischemia	1
Hemorrhagic shock	2
Acute respiratory insufficiency	2
Cardiogenic shock	3

Statistical methods

The sample size (60 patients treated with ATIII vs 60 controls) was calculated to detect a 50% reduction in expected mortality in the placebo group (60%) with a two-sided α error of 0.05 and a β error of 0.10. Continuous data were compared with analysis of variance and the *t*-test. For qualitative comparisons the chi-square test and Fisher's exact test were used. Two-way analysis of variance was used to investigate the effect of treatment and center and their interaction on the continuous variables. The Mantel–Haenszel test was used to study the effect of treatment on the qualitative variables and homogeneity of the effect in the different centers. In order to compare changes in MOF score in the two treatment groups, after adjusting for the baseline value, analysis of variance with repeated measures was used with the MOF baseline value as a covariate. Mortality rates were compared by Kaplan–Meier survival curves and the log-rank test. The cox model was used to investigate variables associated with survival after adjusting for the unbalance, at baseline, of the variables influencing the prognosis. Differences were considered to be significant when $p < 0.05$.

The trial was not planned to evaluate prospectively the subgroup of patients with septic shock; this subgroup was the object of a post hoc analysis.

Results

A total of 120 consecutive patients were enrolled from January 1991 to November 1994 in three ICUs: 92 because of postsurgical and 28 because of nonsurgical complications (Table 2). Of these, 100 patients (49 in the ATIII group and 51 in the placebo group) were septic (84 postsurgery) and 56 were in septic shock. The infectious agents were identified in 93 patients by culture of blood, urine, and bronchial aspirate and were similarly distributed in the two groups: Gram-positive, 46 (*Staphylococcus aureus, Staphylococcus epidermidis);* Gram-negative, 44 (*Pseudomonas aeruginosa, Serratia, Acinetobacter, Enterobacter, Klebsiella pneumoniae, Escherichia coli*); fungi, 34 (*Candida albicans, Aspergillus);* cytomegalovirus, 1.

Four patients received therapy for less than 24 h: 1 patient in the placebo group was transferred to another hospital after the bolus infusion and was considered not evaluable; 3 patients with septic shock (2 ATIII and 1 placebo) died within 24 h. Therefore, 119 patients

Table 3 Distribution of patients according to their characteristics at inclusion in each center. Values are mean ± SD

Parameters	Placebo (%)	ATIII (%)	*p*
Number of patients	60	60	
Age	62.2 ± 12.2	58.6 ± 13.8	NS
Male/female	41 (68)/19 (32)	42 (70)/18 (30)	NS
SAPS	16.5 ± 5.5	15.6 ± 4.4	NS
MOF score	4.8 ± 2.3	5.6 ± 2.5	0.08
Surgery	45 (75.0)	47 (78.3)	NS
Surgery with sepsis	41 (68.3)	43 (71.6)	NS
Sepsis	51 (85.0)	49 (81.7)	NS
Septic shock	23 (38.9)	33 (55.0)	0.08
Respiratory support	48 (81.6)	51 (85.0)	NS
Hemodynamic support	42 (70.0)	53 (88.3)	0.04
Hemorrhages	6 (10)	5 (8.3)	NS
ATIII %	52.9 ± 14.5	52.8 ± 15.5	NS

were included in the analysis. The distribution of the patients in the two arms of the study according to their characteristics at inclusion, was well balanced except for septic shock [ATIII 33 patients (55%); placebo 23 patients (39%); $p = 0.08$] and for the baseline MOF score (ATIII 5.6 vs placebo 4.8; $p = 0.08$) (Table 3). As a consequence, more patients in the ATIII group required hemodynamic support (ATIII 53, placebo 42; $p = 0.04$). The patients in the septic shock subgroup were well balanced according to the hemodynamic profile (arterial pressure, heart rate, central venous pressure, pulmonary wedge pressure, systemic vascular resistance index, cardiac index) and the doses of dopamine, dobutamine, or epinephrine. SAPS and ATIII baseline values were unbalanced in the patients enrolled in the three centers (Table 4). Mean time to treatment after admission to the ICU (ATIII 5.1 ± 7 days, placebo 4.9 ± 6 days), number of days in the ICU (ATIII 12.8 ± 9, placebo 14.5 ± 9.9), and mortality in the ICU (29 patients in each group) were not different.

Significant bleeding, requiring packed red blood cells and platelet concentrates, occurred in 11 patients (6 placebo, 5 ATIII: gastrointestinal tract 6, hemoptysis 2, surgical wound or venous catheter insertion points 3). Plasma and platelet replacement therapy was no different in the two groups. The ATIII plasma concentration in the treated group remained constant throughout the treatment period (mean ± SD: 102 ± 9 vs placebo 56.8 ± 4%), indicating that the plasma infusion did not affect the ATIII level (Fig. 1). On average 1.58 ± 0.99 units/kg of ATIII were required to increase the plasma concentration by 1%. The MOF score, adjusted for its baseline value, showed a significant change with time ($p < 0.001$) but not with treatment ($p = 0.26$). There was no significant interaction between treatment and time ($p = 0.36$); in fact both arms showed changes in the MOF score with time (Fig. 2). The weight of platelet and leukocyte values in the calculation of the MOF score was less than 10%; when these parameters were excluded again no significant difference was observed between the two groups (data not shown).

Overall survival was no different in the two arms: at day 30, 30 patients in the ATIII group (50%) and 27 patients in the placebo group (46%) were alive (Fig. 3). Because of the unbalanced distribution of patients needing hemodynamic support and with septic shock and of the MOF scores in the two groups at admission, the influence of various variables on survival was analyzed. Only septic shock ($p < 0.0001$) and hemodynamic support ($p < 0.0001$) were negatively associated with survival (Table 5): 77% of the patients with septic shock died versus 32% of the patients without shock. The 75th percentile for survival time was 5 days for septic shock and 22 days for nonseptic shock. The Cox regression analysis was carried out to determine the net weight of treatment after adjusting for septic shock and hemodynamic support. The model includes treatment, baseline

Table 4 Distribution of the patients according to their characteristics at inclusion in each center. Values are mean ± SD and numbers

Parameters	Center 1		Center 2		Center 3		*p* values[a]		
	Placebo	ATIII	Placebo	ATIII	Placebo	ATIII	Center	Treatment	Center × treatment
Number of patients	20	20	20	20	20	20			
Age (years)	64 ± 10	62 ± 11	61 ± 10	60 ± 9	61 ± 16	55 ± 16	NS	NS	NS
Male/female	14/6	13/7	11/9	13/7	15/5	16/4	NS	NS	NS
SAPS	19.6 ± 5.6	15.9 ± 4.2	16.4 ± 5.2	16.2 ± 4.4	13.3 ± 3.8	14.8 ± 4.7	0.003	NS	0.045
MOF score	5.05 ± 2.4	6.16 ± 2.1	3.95 ± 2.2	5.25 ± 3.1	5.63 ± 2.1	5.85 ± 2.1	0.07	0.046	NS
Surgery	15	13	11	14	18	20	NS	NS	NS
Sepsis	18	20	16	16	16	13	NS	NS	NS
Septic shock	10	16	7	13	6	4	NS	NS	NS
Respiratory support	20	20	9	12	19	19	NS	NS	NS
Hemodynamic support	11	16	11	15	19	20	NS	NS	NS
ATIII %	48 ± 14	49 ± 14	55 ± 11	47 ± 15	56 ± 17	62 ± 13	0.004	NS	NS

[a] Two-way ANOVA or Mantel-Haenszel statistic. Effects tested by two-way ANOVA were center, treatment, and the interaction center × treatment. Effects tested by the Mantel-Haenszel statistic were treatment and the homogeneity of treatment effect in the centers

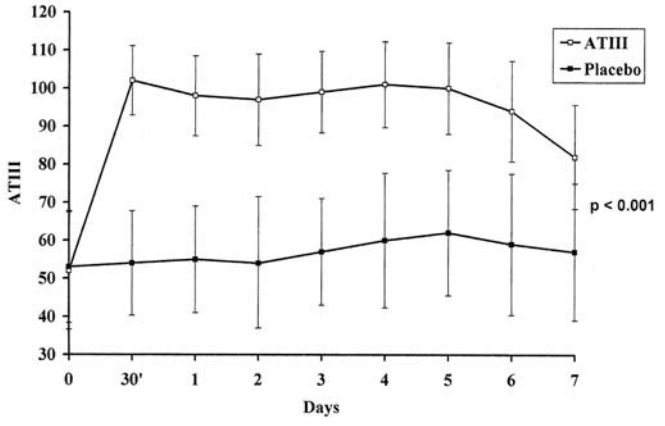

Fig. 1 ATIII plasma level throughout the treatment period (mean values ± SE). On average, 1.58 ± 0.99 units/kg of ATIII were required to increase the plasma concentration by 1 %

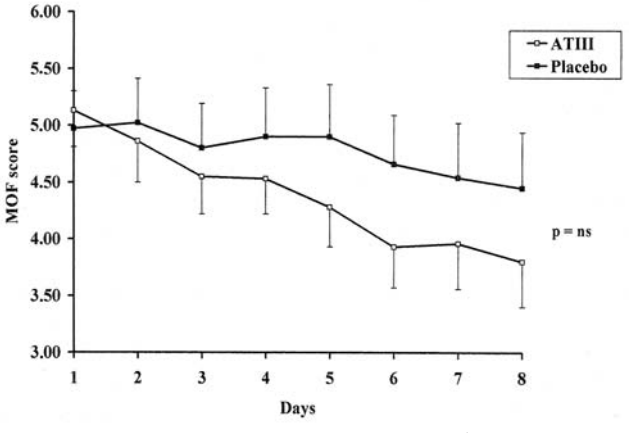

Fig. 2 MOF variations in the surviving patients (ATIII 45, placebo 43) at day 7 adjusted to the baseline score; intention-to-treat analysis (mean values ± SE). No significant difference between ATIII and placebo. ATIII: $F = 1.28$; $p = 0.26$. Days: $F = 5.21$; $p < 0.0001$. Interaction ATIII × days: $F = 1.06$; $p = 0.36$

values of MOF, SAPS, and ATIII, hemodynamic support, center, days from admission, sepsis, septic shock, and age (Table 6).

Treatment with ATIII decreases the risk of death ($p = 0.03$). Plasma ATIII level was positively and independently associated with survival with an OR of 0.97 ($p = 0.004$) for each 1 % increase in the basal ATIII value. Septic shock ($p < 0.0001$), baseline MOF score ($p = 0.02$), and center ($p = 0.01$) were also associated with increased risk of death. As the two arms had an unbalanced distribution of patients with septic shock, its interaction with treatment was tested in the model and was significantly associated with survival (χ^2 without interaction = 45.33; χ^2 model with interaction = 47.7; $p < 0.0001$). After stratification of the patients for septic shock, a net effect of treatment was evident with a reduction of risk of death ($p = 0.01$). In the patients with septic shock, a significant effect of ATIII treatment on survival was also shown by the Kaplan–Meier analysis [$p = 0.04$: at day 30, the probability of survival in the ATIII group was 30 % (95 % CI 17–43) vs placebo 13 % (95 % CI 0–26) with a reduction in mortality of 30 %; Fig. 3]. When survival as a whole, not truncated at day 30, was considered, only the baseline level of ATIII [OR 0.98; 95 % confidence interval (CI) 0.97–0.99; $p < 0.05$), septic shock (OR 3.42; 95 % CI 1.69–8.86; $p < 0.001$], and center (OR 1.53; $p < 0.05$) were associated with survival. No side effects related to ATIII treatment were observed. The laboratory data, indicating DIC, were initially positive in all the patients with septic shock or severe sepsis in both treatment groups; subsequently the relevant tests have not been carried out systematically. Therefore the effects of ATIII treatment cannot be evaluated.

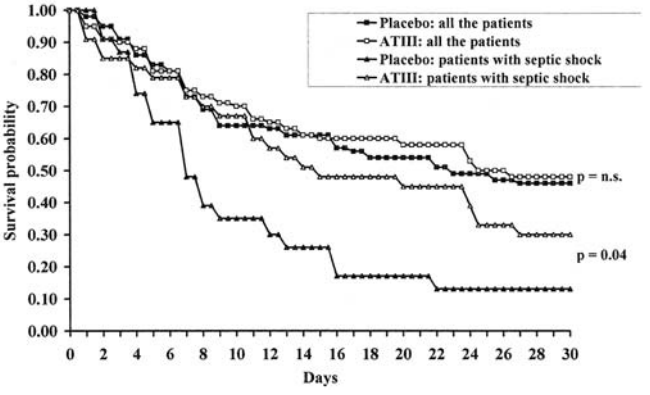

Fig. 3 Survival curves for all the patients and for patients with septic shock according to the intention-to-treat analysis (Kaplan–Meier). Number of patients in total group: at day 0, ATIII 60, placebo 59; at day 30, ATIII 30, placebo 27. No difference between ATIII and placebo. Number of patients with septic shock: at day 0, ATIII 33, placebo 23; at day 30, ATIII 10, placebo 3. The survival advantage in the patients with septic shock treated with ATIII is significant ($p = 0.04$)

Discussion

Available data on the use of ATIII concentrates in patients with DIC and acquired ATIII deficiency are inconclusive [18]. The studies included small numbers of patients in different and often very critical conditions and referred mainly to the modifications in laboratory parameters. Only two randomized studies already referred to [5, 12], in patients requiring admission to the ICU were reported, but neither included a placebo arm. In the study of Fourrier et al. [12] 35 patients with septic shock were enrolled: 18 received ATIII 90–120 U/kg per day for 5 days; an ATIII level of 175–200 % was

Table 5 Influence of various variables on survival at day 30 (Kaplan–Meier) in the different subgroups of patients

Variables	No. (%) of deaths		p (log rank test) adjusted for strata of treatment
	Placebo	ATIII	
Center			
1	10 (50)	10 (50)	0.47
2	11 (55)	13 (65)	
3	11 (58)	8 (40)	
Sepsis			
No	4 (45)	4 (36)	0.21
Yes	28 (56)	27 (55)	
Septic shock			
No	12 (33)	8 (30)	< 0.0001
Yes	20 (87)	23 (70)	
Surgery			
No	8 (53)	6 (46)	0.89
Yes	24 (55)	25 (53)	
Hemorrhages			
No	29 (55)	27 (49)	0.31
Yes	3 (50)	4 (80)	
Hemodynamic support			
No	3 (17)	2 (22)	< 0.0001
Yes	29 (71)	29 (57)	

Table 6 Cox regression analysis (stepwise): significant variables

Variables included	Odds ratio	95% confidence interval
All the patients		
Treatment	0.54	0.31–0.91
Baseline ATIII	0.97[a]	0.95–0.99
Baseline MOF	1.15	1.02–1.30
Center	1.61	1.15–2.24
Septic shock	3.33	1.77–6.29
Patients without septic shock		
Baseline MOF	1.26	1.04–1.53
Patients with septic shock		
Treatment	0.43	0.23–0.83
Baseline ATIII	0.97[a]	0.95–0.99
Center	1.53	0.99–2.36

The model includes: treatment, baseline MOF, SAPS, and ATIII, hemodynamic support, center, days since admission, sepsis, septic shock, age.

[a] For each 1% increase in ATIII plasma concentration at baseline

achieved and maintained. The laboratory data indicative of DIC reverted to normal in the patients surviving at day 10; in the intent-to-treat analysis the reduction of mortality in the ATIII versus the placebo arm was 18% ($p = 0.6$). Lamy and co-workers reported similar results in the meta-analysis of three studies (Fourrier, German and north-western European studies): a trend toward a 30-day reduction in mortality of 22.9% [13].

In our study the inclusion criteria were selected to include a population of critically ill patients with a mortality higher than 50% [14]. Approximately 10% of the patients admitted to the ICU in Italy fulfill these criteria [19]. The number of eligible patients accepted in our ICUs in the study period correspond to the number of patients actually enrolled after the due exclusions. The ATIII dose was empirically fixed, from previously published clinical studies, and was sufficient to maintain the ATIII plasma concentration at 100% throughout the treatment period [2, 10, 11]. It should be noted that subsequent experimental [20, 21] and clinical [22] studies stressed the importance of high-dose ATIII to maintain a supranormal level. In the univariate analysis there was no difference in survival between the ATIII and the placebo arm; only septic shock and hemodynamic support had a significant negative effect. Septic shock also emerged as a powerful factor for survival in the multivariate analysis. The distribution of patients with septic shock and requiring hemodynamic support was unbalanced, insofar they were more numerous in the ATIII arm. Therefore, the Cox regression model was used to evaluate the net effect of ATIII treatment on day-30 mortality.

When considering the separate effects of septic shock, baseline MOF score, and plasma ATIII levels on survival, ATIII treatment reduces by almost 50% the risk of death at day 30 in the entire population of patients. However, because a significant interaction was observed in the effects of treatment and septic shock on survival, we further stratified the patients according to the presence or absence of septic shock. In the group of patients with septic shock, the survival advantage of ATIII replacement therapy at day 30 was even greater (57%) and it was also statistically significant when tested by the Kaplan-Meier approach. At variance, no significant effect of treatment was observed in patients without septic shock. In this group of patients the efficacy of ATIII replacement cannot be ruled out as the overall mortality was low (32%) and a greater number of patients may be necessary to prove a survival advantage; baseline MOF score was associated with survival advantage while baseline level of ATIII had no predictive value. In two prospective studies in patients with DIC [4] and in patients with chemotherapy-induced neutropenia [23], the ATIII baseline level was a strong predictor of outcome. In the latter study an ATIII level lower than 70% at the onset of fever predicted a lethal outcome with a sensitivity and a specificity of 85%. In both studies low baseline values of ATIII correlated with high mortality. In agreement with these reports, in our study the multivariate analysis confirmed that the ATIII baseline value is a powerful risk factor, particularly in patients with septic shock in whom severity of the clinical condition (indicated by the MOF score) is not significant (Table 6). Mortality in the patients in septic shock in the placebo arm was 87% at day 30, significantly higher than that reported by Fourrier et al. [12].

In a recent survey in Italy carried out in 96 ICUs, which included 2815 critically ill patients classified according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) classification for sepsis, mortality in the patients with septic shock was 81.1% [19]. Therefore, the mortality in the placebo group is in line with that generally observed in the ICU in Italy. Treatment with ATIII did not significantly modify the MOF score. In fact, the variations were related only to time with no significant difference between the two arms, although a tendency toward an improvement in the MOF score with the active treatment was observed. The center was also predictive of outcome (OR 1.61). The mean values of the ATIII concentration and of the SAP scores at presentation differed in the three centers. The criteria of referral to each hospital may explain this difference. Our study confirms that the low baseline value of ATIII is a strong risk factor for death. The reduction of death in a study population including a large number of patients with septic shock suggests this particular indication for treatment, although it should be confirmed in a properly planned study.

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