

Research

Quality of life effects of antithrombin III in sepsis survivors: results from the KyberSept trial [ISRCTN22931023]

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Abstract

Introduction Treatment of sepsis is aimed at increasing both the duration and quality of survival. A long-term focus on quality of life (QoL) in clinical trial evaluations of sepsis care should be a priority.

Method QoL data were used to evaluate the effects of intravenous antithrombin III treatment for severe sepsis measured for up to 90 days during the follow-up phase of the KyberSept phase III clinical trial. A visual analog scale and a Karnofsky scale were used to measure physical, psychologic, and social QoL at regular intervals. Changes from baseline between placebo and antithrombin III groups were assessed using Wilcoxon statistical tests, with additional analyses by severity of illness and admitting diagnosis.

Results Among all sepsis survivors in the trial, there was a significant advantage on some attributes of QoL in the antithrombin III subgroup of patients who did not receive heparin as compared with the corresponding placebo group.

Discussion The present study represents the first attempt to evaluate patient QoL over a relatively long period in a large, randomized, placebo-controlled sepsis trial. Over a 90-day period, survivors of severe sepsis receiving antithrombin III experienced significant improvements as compared with placebo on several attributes of QoL. In conclusion, the present study demonstrated that clinical improvements over an extended time period with antithrombin III were complemented by improvements in QoL, particularly in social and psychologic functioning, in many patients.

Keywords antithrombin III, clinical trial, quality of life, sepsis

Introduction

In treating patients with severe sepsis, physicians are mainly concerned with biologic, physiologic, and clinical outcomes. Of those patients who survive to hospital discharge, little is known regarding their physical functioning (ability to conduct activities of daily life such as walking around), psychologic functioning (mental well-being), and social functioning (communication and relationships with others) after sepsis.

Because 'quality of life' (QoL) describes or characterizes what the patient has experienced as a result of sepsis care, it is a useful and important supplement to traditional physiologic or biologic measures of health status; that is, assessments of effectiveness need to include wider measures of benefits to patients, and particularly those that measure the impact from the patient's point of view. A relevant therapeutic benefit may also be in restoring the patient's ability to function on a daily basis, to socialize, and to be alert. In fact, a long-term focus on

QoL in clinical trial evaluations was among the recommendations of a recent sepsis international advisory group [1].

This report presents the results of an evaluation of QoL among sepsis survivors, done as part of the phase III multicenter KyberSept trial. To the best of our knowledge, limited information on the effects of sepsis treatment on QoL has been reported [2,3]. The report focuses on the effects of antithrombin (AT) III therapy related to physical, mental, and social functioning of patients who were randomly assigned to either high-dose intravenous treatment with Kybernin P® (Aventis Behring, Marburg, Germany; a plasma-derived AT III concentrate, 30,000 IU over 4 days) or placebo during up to 90 days of follow up. In the trial, overall survival tended to favor AT III over placebo after 90 days of follow up, although the differences were nominal. However, the AT III group that did not receive concomitant heparin exhibited a nominally statistically significant survival advantage over placebo at 90 days of follow-up. The purpose of this investigation was to establish whether these trends also held for the subjective effects of AT III in severe sepsis. It concludes that AT III treatment is effective in improving long-term patient QoL, and that future outcome research studies of severe sepsis should follow up patients throughout their hospital stay and after discharge.

Method

Quality of life instruments

There are a number of important conceptual and methodologic issues in assessing QoL in people who are critically ill, not least of which is the question of how it should be defined. Recent attempts to define QoL have resulted in the development of a functional definition that is measurable, evaluable over time, and readily applied to patients over a wide range of illness severity. Most attempts incorporate the domains of physical, psychologic/cognitive, and social functioning. Each of these domains can be measured in two dimensions: objective assessments of functioning or health status; and more subjective perceptions of general health. The patient's subjective experience translates that objective assessment into the actual QoL experienced. Thus, where the term 'QoL' is used in the present study, it refers to a composite of objective functional impairment and subjective perceptions and expectations. The instruments chosen for the study were designed to reflect this.

QoL gives information on what medical care has achieved for the patient, but severe sepsis is a difficult area in which to obtain such information. Normally, QoL data should be obtained directly from the patient. Unfortunately, patients hospitalized with severe sepsis may be unable to complete a QoL measure or it may be too burdensome. Rather than lose information on patients, the physician investigator was used as a proxy respondent.

Two instruments were used to cover the objective and subjective dimensions. The objective component in the study was measured using the Karnofsky performance scale. The

Table 1

Karnofsky performance scale: objective assessment of physical performance and dependency

Investigator assigned percentage	Features
100%	Normal; no complaints and no evidence of disease
90%	Able to carry on normal activities; minor signs or symptoms of disease
80%	Normal activities but with effort; some signs or symptoms of disease
70%	Cares for self, but is unable to carry on normal activities or to do active work
60%	Requires occasional assistance, but is able to care for most needs
50%	Requires considerable assistance and frequent medical care
40%	Disabled; requires special care and assistance
30%	Severely disabled; hospitalization is indicated but death is not imminent
20%	Hospitalization necessary, very sick, active supportive treatment necessary
10%	Moribund; fatal processes progressing rapidly

Karnofsky scale emphasizes physical performance and dependency; it is a descriptive, ordinal scale that ranges from 100 (good health) to 0 (dead). Trial investigators assigned percentages based on physical performance (Table 1). The Karnofsky scale is designed to assess independent functioning and appears to have substantial validity as an indicator of overall physical status. The validity and reliability of the scale have been shown in several populations [4–6].

The subjective component of the trial was measured with multiple items using a visual analog scale [7]. A visual analog scale is a line with defined end-points on which investigators indicate a patient's health state. Thus, the investigator placed a mark along a 100 mm line that best described his or her assessment of the patient with the domain in question. There were six domains (Table 2). The scales ranged from 0 (worst health status) to 100 (best health status). The visual analog scale has been used in several studies of QoL [8–10]. Reliability estimates for visual analog scaling items range from 0.40 to 0.95 [11], and these estimates compare favorably with those for other scales [12,13].

The six domains of the first visual analog scale and the Karnofsky score are hereafter referred to as 'attributes'.

The clinical trial

The KyberSept trial was a large, international, phase III clinical trial that enrolled 2314 patients who were evaluable for efficacy

Table 2**Visual analog scale: subjective assessment of physical performance and dependency**

Domain	Definition
Mobility	How would you rate this patient's mobility today?
Physical activity	How would you rate this patient's physical activity today?
Communications/speech	How would you rate this patient's communication/speech today?
Alertness	How would you rate this patient's level of alertness today?
Energy	How would you rate this patient's energy level today?
Overall quality of life	How would you rate this patient's overall quality of life today?

and safety in a randomized, double-blind, placebo-controlled design in order to determine the role of high-dose AT III in patients with severe sepsis. Patients randomly assigned to the AT III group received a total of 30,000 IU plasma-derived AT III (Kybernin P[®]) administered as a loading dose of 6000 IU given over 30 min, followed by a continuous infusion of 6000 IU/day for 4 days. The study protocol permitted investigators to prescribe unfractionated or low-molecular-weight heparin for venous thrombosis prophylaxis ($\leq 10,000$ IU/day subcutaneous) and heparin flushes for vascular catheter patency (≤ 2 IU/kg body weight per hour intravenous).

In the trial, the all-cause mortality rate at 28 days was almost identical between the placebo group and the group that received AT III (38.7% versus 39.9%; not significant). At the 90-day time point, the AT III group had a nominally lower mortality than did the placebo group (46.4% versus 48.5%). Among the 680 patients in the trial who did not receive heparin concomitantly, there was a statistically significant difference between the AT III and placebo groups. In this subgroup, mortality at 90 days in the AT III subgroup was 44.9%, versus 52.5% in the placebo subgroup ($P_{\text{nominal}} = 0.03$). A complete description of that study and results are reported elsewhere [14].

Outcomes

The Karnofsky scale and visual analog scales were both administered by physician investigators when patients enrolled in the trial (referred to as 'baseline'); during the trial at 28 days, 56 days and 90 days after enrollment; and at discharge from the hospital (if it occurred other than at one of those three intervals). For example, if a patient survived and was discharged at day 60, there would be four assessments (i.e. baseline and days 28, 56, and 60). The primary outcome was change in attribute scores until 90 days after patients were assigned to either treatment or placebo. For this analysis, two

patient populations were used. The smaller population was the group remaining in the hospital 90 days from baseline – the 'in-hospital survivors'. The larger population comprised all survivors at 90 days, or at the time point closest to 90 days. This group is labeled the 'all-survivors' group. It includes the in-hospital group. In cases in which there was no patient response at 90 days because they had been discharged, the data from the last assessment but before 90 days were used. This method is equivalent to using the last observation carried forward.

The last observation carried forward method uses the last observed value for that case, and it therefore assumes that the outcome remains constant at the last observed value after discharge. Otherwise stated, it is assumed that QoL in sepsis patients is stable on average for the short time period between discharge and 90 days. It is not possible to conclude firmly that the change in QoL between discharge and 90 days was small and unbiased. However, the fact that the hospital discharge curve between AT III and placebo was almost identical provides evidence that the comparison between treatment groups should be unbiased. Moreover, the physician investigator, the patient, and the family were blinded to the treatment assignment (placebo versus AT III) throughout the duration of the clinical trial.

The secondary outcome was change in the attribute scores at 28, 56, and 90 days after assignment to treatment or placebo. That outcome measure was used in order to compare relative changes between AT III and placebo groups at the 28-day, 56-day, and 90-day assessments.

Analysis*Patient characteristics*

Mean, standard deviation, and range values (for age) and percentages for relevant patient characteristics (at enrollment and administration of heparin) are reported. The overall trial population is presented, as well as the all-survivors and the in-hospital survivors groups. The other variables used were Simplified Acute Physiology Score (SAPS) II [15] (a measure of severity of illness), admitting diagnosis, and concomitant use of heparin. In the SAPS II system, a score-to-risk transformation developed by Le Gall *et al.* [16] for sepsis patients was used. The risk intervals were identical to the SAPS II strata defined in the trial.

Changes in quality of life between baseline and 90 days

For both the in-hospital survivors and the all-survivors groups, mean changes and standard deviations between baseline and 90 days are shown. Differences in QoL between AT III and placebo were estimated for each attribute. Two-sample Wilcoxon statistical tests were used to determine whether the changes were different between treatment groups.

Differences among patient subgroups

Similarly, Wilcoxon tests were used to identify whether changes in the QoL scores differed for subgroups between

Table 3**Characteristics of patients in the KyberSept trial**

Parameter	Overall population*		All 90-day survivors		90-day in-hospital	
	Placebo (n = 1157)	AT III (n = 1157)	Placebo (n = 437)	AT III (n = 460)	Placebo (n = 55)	AT III (n = 63)
Age (years; mean \pm SD [range])	58 \pm 17 (18–96)	57 \pm 17 (18–93)	53 \pm 17 (18–96)	53 \pm 17 (18–88)	57 \pm 15 (22–81)	56 \pm 14 (21–79)
Sex (%)						
Male	61	62	62	64	67	65
Female	39	38	38	36	33	35
Country (%)						
USA	15	15	14	15	6	6
Czech Republic	11	11	12	11	18	10
South Africa	11	11	9	8	2	5
UK	8	8	9	9	13	13
Denmark	7	7	6	7	6	11
Germany	6	6	6	5	4	8
Other (13 countries)	40	40	43	46	53	48
SAPS II risk group (%)						
Moderate risk (<30%)	27	29	43	40	24	24
High risk (30–60%)	45	42	40	43	36	41
Very high risk (>60%)	28	29	17	18	40	35
Admitting diagnosis (%) [†]						
Respiratory system	34	35	33	34	33	24
Digestive system	28	27	29	27	38	40
Genitourinary system	8	6	11	8	4	2
Injury	6	7	5	7	0	10
Other	24	24	22	25	26	25
Concomitant heparin (%)						
No	30	30	29	32	13	30
Yes	70	70	71	68	87	70

*All 2314 patients evaluable for efficacy in KyberSept study. [†]According to the International Classification of Diseases (9th edition). Percentages may not add to 100 because of rounding. AT, antithrombin; SAPS, Simplified Acute Physiology Score.

baseline and 90 days. This analysis was done on the all-survivors population.

Changes in quality of life between baseline and 28, 56, and 90 days

For the all-survivors and in-hospital survivors subgroups, comparative differences in changes between baseline and 28, 56, and 90 days were estimated. For each attribute, the difference in mean change between treatment groups is presented, together with two-sided 95% confidence intervals, so that the differences between placebo and AT III over time are clearly shown.

Statistical considerations

Nominal *P* values should be regarded as descriptive because no formal null hypothesis was prespecified and no type I error probability can be indicated. No adjustment of *P* values for multiple testing or multiple confidence intervals was made. *P* values less than or equal to 0.05 were considered statistically significant. *P* values above 0.05 but less than or equal to 0.10 were considered indicative of a trend. Confidence intervals for the difference between mean

changes were constructed assuming a normal distribution of changes from baseline.

Results

Patient characteristics

Table 3 shows baseline patient demographic data and heparin administration for the 2314 patients who entered the KyberSept trial. The all-survivors group using the last observation carried forward analysis totaled 897 patients, whereas the in-hospital group totaled 118. The patients included in this study population were from a broad mixture of countries.

The mean \pm SD age of the overall population was 58 \pm 17 years in the placebo group and 57 \pm 17 years in the AT III group. Mean age was lower (53 \pm 17 years) in the all-survivors population. A clear majority of patients were men (61.5% men versus 38.5% women). In the three populations (overall, all 90 day survivors, and 90 day in-hospital survivors), the sex distribution for the AT III groups was similar. There was a shift toward the lower risk strata of SAPS II score from the overall population to the all-survivors population, whereas the risks in the in-hospital population were slightly higher than

Table 4**Mean changes between baseline and 90 days for the attributes of survivors in the KyberSept trial: patients in hospital at 90 days and all-survivors**

Attribute	In-hospital at day 90			All survivors*		
	Placebo (mean ± sd)	AT III (mean ± sd)	<i>P</i> [†]	Placebo (mean ± sd)	AT III (mean ± sd)	<i>P</i> [†]
Mobility (%)	33 ± 26	38 ± 28	>0.1	49 ± 24	51 ± 24	>0.1
Physical activity (%)	33 ± 27	39 ± 26	>0.1	48 ± 23	50 ± 23	>0.1
Communication/speech (%)	42 ± 42	61 ± 35	0.01	52 ± 34	57 ± 32	0.03
Level of alertness (%)	41 ± 39	59 ± 33	0.02	51 ± 32	56 ± 31	0.02
Energy level (%)	34 ± 27	43 ± 26	0.09	47 ± 23	51 ± 22	0.02
Overall QoL (%)	35 ± 28	44 ± 27	>0.1	51 ± 23	53 ± 23	>0.1
Karnofsky scale (%)	22 ± 19	31 ± 19	0.03	45 ± 19	47 ± 19	>0.1

Scores range from 0 to 100, and changes may range from -100 to +100. Higher scores represent better quality of life (QoL) and increases (i.e. positive changes) represent improvement. *90-day values calculated by last observation carried forward analysis (see text). [†]Nominal *P* value for two-sided, two-sample Wilcoxon test for differences between changes from baseline to 90-day QoL. AT, antithrombin.

Table 5**Mean increase in scores from baseline to 90 day in the KyberSept Trial by subgroups: all-survivors**

Parameter	Mobility		Physical activity		Communications/speech		Level of alertness		Energy level		Overall QoL		Karnofsky	
	Placebo	AT III	Placebo	AT III	Placebo	AT III	Placebo	AT III	Placebo	AT III	Placebo	AT III	Placebo	AT III
SAPS II risk														
Moderate	49±23	51±24	48±22	50±23	43±35	48±33	43±34	47±33	47±22	49±22	50±23	50±21	49±18	49±18
High	51±24	52±23	50±22	51±22	58±31	61±30	56±28	60±29	48±23	51±22 [†]	53±22	54±23	44±19	46±19
Very high	47±26	52±26	44±25	50±25	59±35	66±29	59±33	67±28 [†]	46±23	51±24	50±25	55±25	41±21	43±19
Admitting diagnosis														
Respiratory	50±25	54±23 [†]	48±23	52±23	51±35	59±33	52±32	58±32 [†]	46±23	51±22 [†]	52±24	55±22	46±19	49±18
Digestive	50±23	52±24	49±23	50±23	55±35	60±31	54±33	59±31	46±24	49±22 [†]	52±23	51±24	45±19	46±19
Genitourinary	46±21	43±26	46±20	43±25	40±36	40±34	40±34	37±34	49±19	44±22	48±21	44±25	47±20	45±18
Injury	51±24	47±27	52±22	48±26	58±26	55±29	55±27	59±29	49±21	52±26 [†]	53±18	53±24	67±21	70±19
Other	48±25	51±24	48±23	51±23	53±33	56±31	52±30	56±31	48±23	53±22	51±24	54±21	69±21	68±18
Concomitant heparin														
No	44±22	48±24 [†]	43±21	48±22 [*]	42±36	51±31 [†]	42±33	49±31	43±22	49±22 [†]	47±22	51±23	43±19	43±19
Yes	51±24	53±24	50±23	52±24	55±33	60±32 [†]	54±31	59±31 [*]	48±23	52±22 [†]	52±23	54±23	46±19	46±19

Values are expressed as mean ± sd. **P* < 0.05 versus placebo; [†]*P* < 0.1 versus placebo. Mean scores represent changes between the 90-day and the baseline values for all-survivors (those in hospital 90 days from study enrollment, or closest time point to 90 days [last observation carried forward analysis; see text]). All mean scores increased (higher scores indicate better quality of life [QoL]). AT, antithrombin.

those in the overall population. In the all-survivors group respiratory disorders were the most common diagnostic admitting category, whereas digestive causes of sepsis were the most common among the in-hospital group.

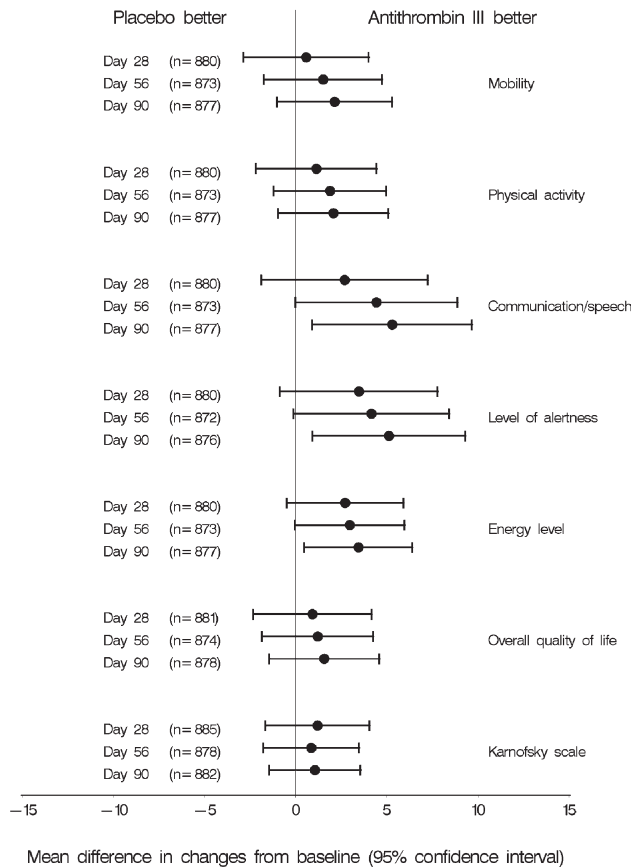
Among all patients enrolled in the trial, 70% received heparin concomitantly. Among the all-survivors, placebo and AT III differed by 3% with respect to concomitant heparin administration. In this population 71% of placebo patients were administered heparin concomitantly; 68% of those administered AT III received heparin. Among the in-hospital survivors

at 90 days, 87% in the placebo group received heparin as compared with 70% of those receiving AT III. Comparing AT III groups across populations, the use of concomitant heparin was nearly the same.

Changes in 90-day quality of life

Table 4 shows data for the six attributes of the visual analog scale and the Karnofsky scale (objective physical performance and dependency) measured from baseline to 90 days. Assessment of the changes among the all-survivors, based on two-sided, two-sample Wilcoxon tests, suggests advan-

Figure 1



Difference in changes between treatment groups in quality of life attributes over time: all-survivors.

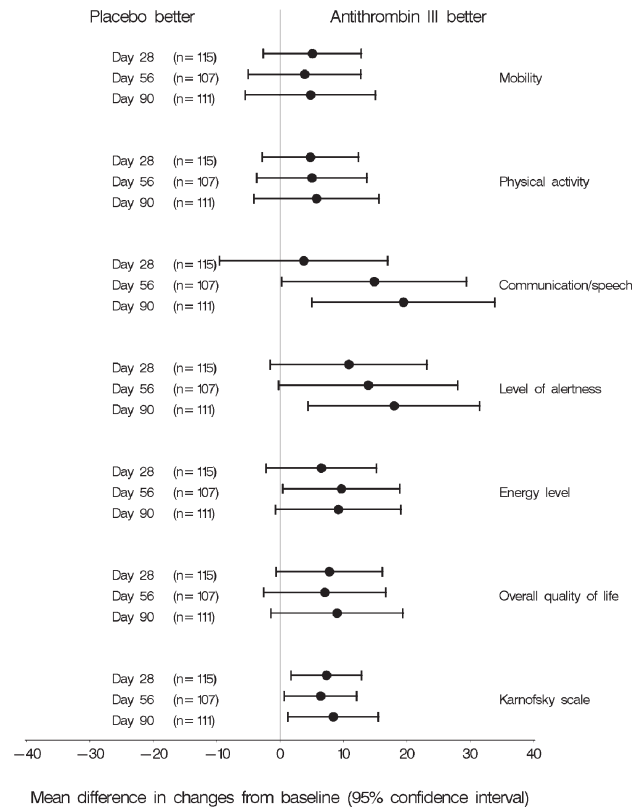
tages for the AT III group as compared with the placebo group in three of the attributes; namely, patient communication and speech, level of alertness, and energy level. In the in-hospital population, the differences indicated that communication and speech, level of alertness, and the Karnofsky scale were all more improved for the AT III group than for placebo.

In neither population was the change in patient overall QoL judged to be statistically different. In the in-hospital group, a trend toward greater patient energy levels in the AT III group was found ($P < 0.10$).

Differences across patient subgroups

As shown in Table 5, although there were generally greater increases in attribute scores in the SAPS II risk for AT III in the all-survivors, none of the differences were statistically significant. There were also no significant differences between placebo and AT III according to the diagnostic subgroups on hospital admission, although a few 'trends' favoring AT III (notably the 'energy level' attribute of QoL) were found. In the heparin subgroups, there was an advantage in some attrib-

Figure 2



Difference in changes between treatment groups in quality of life attributes over time: in-hospital survivors.

utes for AT III. Compared with placebo, physical activity was improved significantly more in the AT III subgroup than in the placebo subgroup not receiving heparin. There was also a trend toward greater improvement in three other attributes in the no concomitant heparin subgroup, namely patient mobility, communication and speech, and patient energy level. Excluding the Karnofsky scores that were unchanged, mean nominal changes in the AT III QoL attributes of the no concomitant heparin group ranged from +4 to +9, whereas those receiving concomitant heparin experienced nominal increases in scores ranging from +2 to +5.

Changes in quality of life between baseline and 28, 56, and 90 days

Figs 1 and 2 show the differences in mean changes in scores between baseline and later periods for the seven attributes measured in the AT III group as compared with placebo. Fig. 1 shows results for the all-survivors population, whereas Fig. 2 shows findings in the in-hospital population. Considering point estimates of differences between mean changes at each time point, for all attributes and in both populations AT III patients were more improved than placebo patients. Confi-

dence intervals fully occupying the 'AT III better' side indicate statistically significant improvements in the AT III group. In the all-survivors population, comparative improvements tended to increase over time in the AT III group as compared with the placebo group. An exception was the Karnofsky index, for which the difference between treatment groups remained approximately constant over time. For the in-hospital population, the advantage in the AT III group increased over time for the communication/speech and the level of alertness attributes, whereas the difference between treatment groups remained approximately constant for the other attributes. In the all-survivors, the greatest comparative advantages for the AT III group were found in communication/speech, alertness, and energy level.

Discussion

The present study represents the first attempt to evaluate patient QoL over a relatively long period in a large, randomized, placebo-controlled sepsis trial. The results of the study indicate that, over a 90-day period, survivors of severe sepsis receiving AT III experienced substantial and statistically significant improvements as compared with placebo in several attributes of QoL. These results held for both all-survivors and in-hospital survivors populations. The comparative advantage in QoL for AT III was also maintained from 28 to 56, and 90 days. After 90 days, the study also found an advantage with AT III for some attributes in patients who did not receive heparin concomitantly.

The improvements identified in the study should be interpreted in terms of statistical and clinical significance. Clinical significance deals with the applied value of the change in everyday life. Unfortunately, as with most other QoL instruments, there is not yet a clear standard for 'minimal clinically important differences'. However, improvements by approximately 20% in the in-hospital group of AT III sepsis patients after 90 days in communication/speech and level of alertness probably represent meaningful improvements in many patients.

Another limitation of the present study is the fact that investigators were proxy respondents, rather than patients responding themselves. Like many studies of QoL in critical care settings, physicians were assumed to be sufficiently close to patients to provide valid and reliable data. Although this was not substantiated empirically, there is usually moderate agreement between patients and proxies, although lower levels of agreement have been found in psychosocial functioning [17,18].

Conclusion

Combined with previous findings in 90-day mortality for those without concomitant administration of heparin, this multinational study demonstrates that AT III is associated with meaningful improvements in health for many sepsis patients over an extended 3-month follow-up period. In this subgroup,

Key messages

- In the present study, clinical improvements over an extended time period with AT III were complemented by improvements in QoL, particularly in social and psychologic functioning, in a predefined subgroup of patients who did not receive heparin
- Combined with previous research on 90-day mortality, the study suggests that AT III may confer long-term benefit in sepsis patients
- Among the 'all survivors' group of patients, communication and speech, level of alertness, and energy level exhibited the greatest gains at 90 days
- In most cases, significant differences in patient QoL scores at 90 days after hospital admission were also found at the 28-day and 56-day assessments
- Future studies in patients with severe sepsis should include long-term follow up throughout hospitalization and after hospital discharge

the clinical improvements over a long time period in patients in the AT III group were complemented by improvements in QoL in many patients, particularly in terms of social and psychologic functioning. Although no significant reduction in 90-day mortality was found for the overall population, a nominal advantage in mortality for the AT III group combined with a generally improved QoL profile in the survivors of this group suggests a possible long-term benefit from AT III. Future studies of critically ill patients with severe sepsis or other conditions should include long-term follow up of patients throughout hospitalization and after hospital discharge. In sepsis, long-term follow up appears to provide more meaningful outcome data for patients, families, and society than do standard 28-day, all-cause mortality statistics.

Competing interests

DR, HOK, and SK are employees of Aventis Behring, the latter also owning Aventis stock options. SO is supported by a grant from the Genetics Institute, Cambridge, MA. He also is principal investigator in the PAF Acetylhydrolase study carried out by ICOS, Bothell, WA.

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