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Microbiologic correlations with serum TNF-α

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Keywords

Sepsis, serum tumour necrosis factor alpha

Comments

This interesting paper illustrates the difficulties with developing a clinical trial to investigate novel agents for treating sepsis. The paper is of clinical value in that it provides information on the causative organism in 270 patients with microbiologically documented sepsis and, importantly, the diagnosis of sepsis was made in accordance with strict criteria. The finding that obligate anaerobes were cultured from 10% of patients suggests that antibiotics directed at this group of organisms should be added to "blind" antibiotic strategies for septic patients.

Introduction

It is a matter of considerable practical importance to understand the possible microbiological causes of sepsis in order to use sensible antibiotics, often in the absence of positive cultures. Only about 60% of clinical sepsis is associated with positive microbiological findings. Understanding of the mediators in sepsis has led to the recognition that TNF-α has a pivotal role and thus therapeutic strategies to reduce or neutralize TNF-α have been developed. Soluble TNF-α receptors have a role in binding and neutralizing the mediator and a trial of TNF-receptor fusion protein is currently underway. Data gathered during this trial to analyze the causative organisms in over 400 patients with septic shock.

Aims

To determine if there are any differences in the severity of sepsis depending on the organism identified, and also to examine whether different types of organism provoke a different response in terms of TNF-α levels in circulation.

Methods

Patients were recruited to this study as part of an international multicenter dose-finding, double-blind, placebo controlled clinical trial. In all, 498 patients were enrolled in the study to evaluate lenercept, a fusion protein consisting of IgG and the p55 component of the TNF receptor. Patients were then stratified into one of two groups, severe sepsis with early septic shock, and late sepsis. A total of 444 patients were included in this analysis. Criteria for inclusion included objective signs of acute infection, at least three signs of systemic inflammatory response syndrome and at least two organ dysfunctions. Patients were enrolled if they fulfilled the criteria for organ dysfunction in the 12 h prior to study-drug medication. APACHE III scores were collected and TNF-α levels assayed using standard techniques. Blood cultures were taken at baseline and on day 3 (two or more sets from two or more sites). Coagulase-negative *Staphylococci*, *Bacillus*, *Corynebacterium* or *Propionibacterium* species were considered to be contaminants unless isolated from two cultures. Infection was considered "microbiologically documented" when more than one organism that was considered to be clinically significant, was obtained from a clinically relevant sample (blood and other cultures) from day -3 to day 1 (day 1 being the day of study-drug administration).

Results

Of the 444 patients, 311 were from the US and 133 from Europe. A total of 247 (56%) were stratified into the severe sepsis/early septic shock group and 197 (44%) into the late septic shock group. All patients were followed for 28 days or until death. The mean age of the patients was 58 years (range 18-92) and 60% were male. Sixty one percent had microbiologically documented infection and 31% had bacteremia. The proportion of Gram-negative, Gram-positive and mixed infections was the same in each group. Thirteen patients had a viral/parasitic mixed infection. *E. coli* was the single most common isolate. Obligate anaerobes such as *Bacteroides fragilis* and other *Bacteroides* and *Fusobacterium* species were isolated in 29 cases. *Staphylococcus aureus* was the most common Gram-positive organism with other *Staphylococci* occurring less frequently. *Streptococcus pneumoniae* was the most frequently isolated *Streptococcus* species, there were a few cases of *S. milleri* and of *Streptococcus* from Lancefield groups B and G. There was a number of cases of infection with *S. pyogenes* (seven patients). There were 15 cases of fungal infections with Candida species being most common.

The respiratory tract and abdomen were the most common sites for sepsis (46% and 27% respectively). Baseline TNF-α levels were available for 409 patients. Mean serum TNF-α levels were 41 pg/ml (range 5-3310 pg/ml) with severe sepsis and 58 pg/ml (range 5-1870 pg/ml) in patients with late sepsis. Patients with positive cultures had significantly higher TNF-α levels and Gram-negative infections resulted in the highest TNF-α concentrations. In the late septic shock group, there was a significantly higher level of TNF-α in patients with a gram-negative infection, compared to infections with gram-positive.

Discussion

Pure Gram-positive infections were only slightly less common than pure Gram-negative. These findings are consistent with other studies. The finding of obligate anaerobes in blood and other cultures is interesting. The cell wall of these organisms differs from that of *enterobacteriae* and the endotoxin they produce is considerably less toxic. If these organisms were responsible for the sepsis in these patients then there are implications for antibiotic therapy. The fact that other organisms such as *Candida*, *M. tuberculosis* and *L. monocytogenes* appeared in cultures is surprising.

The patients in this study were selected according to rigorous criteria which suggests that, when specific therapies aimed at TNF are available, they are likely to be used in a wide range of patients. This also leads to the conclusion that septic patients are a heterogeneous group and that it may well be difficult to identify novel agents of particular benefit.

No significant correlation could be made between disease severity or presentation and serum TNF-α concentrations, however, TNF-α levels were higher in patients with microbiologically documented infection. Furthermore there were significant TNF-α differences between patients with Gram-positive and Gram negative infections. This suggests firstly that the distinction between "clinically documented" and "microbiologically documented" is a real one that may indicate a difference in biological response, and secondly, Gram-positive and Gram-negative infections produce different host responses and may require different therapeutic interventions.

Additional information

Full details of the p55 TNF receptor protein factor trial can be obtained as follows:Abraham E, Glauser MP, Butler T, *etal*. p55 tumour necrosis factor fusion protein in the treatment of patients with severe sepsis and septic shock. A randomised multicenter trial. *JAMA* 1997; **227**: 1531-1538.

References

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