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Journal
Critical Care, 12(2)

ISSN
1364-8535

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Publication Date
2008

DOI
10.1186/cc6859

Peer reviewed

Commentary

Protein C as a surrogate end-point for clinical trials of sepsis

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Published: 24 April 2008
This article is online at http://ccforum.com/content/12/2/139

Critical Care 2008, **12:**139 (doi:10.1186/cc6859)

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Abstract

Identification of good surrogate end-points can greatly facilitate the design of clinical trials. Using data from PROWESS and ENHANCE, Shorr and colleagues explore the potential value of several plasma biomarkers for treatment trials of activated protein C for severe sepsis. Based on the framework proposed by Vasan, they tested the utility of several factors (protein C, interleukin-6, antithrombin III, prothrombin time, protein S, and d-dimers) as type 0, 1 and 2 biomarkers. Only protein C had acceptable performance characteristics as a type 2 biomarker, or surrogate end-point. The utility of protein C as a surrogate end-point for studies of severe sepsis must be validated in future prospective studies.

In this issue of *Critical Care*, Shorr and colleagues [1] tested the potential value of surrogate markers for the treatment of patients with severe sepsis with activated protein C, also known as Drotrecogin alfa (activated; DrotAA), using data from the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) and ENHANCE (Extended Evaluation of Recombinant Activated Protein C) clinical trials. PROWESS [2] was a double-blind, randomized clinical trial of DrotAA for the treatment of severe sepsis, which identified a mortality benefit of treatment with DrotAA in patients at a high risk for death. ENHANCE [3] was a subsequent open-label trial of DrotAA in severe sepsis that was designed to confirm the findings of PROWESS and to provide additional data on drug safety.

Using a biomarker as a surrogate end-point in a clinical trial is challenging but potentially innovative and valuable. Whereas definitive phase III clinical trials that are based on mortality are large and expensive, phase II clinical trials that are powered to test differences in surrogate end-points can provide safety and efficacy data that determine whether a large phase III trial is indicated. In general, a biomarker can be considered to be a reasonable surrogate end-point if changes in the biomarker predict changes in a clinical end-point, such as death. Thus, the degree to which a surrogate end-point is influenced by a given therapy should correlate with the influence of that treatment on the disease of interest.

However, caution must be used when considering surrogate end-points [4]. In a classic example, although antiarrhythmic drugs reduce cardiac arrhythmias, these agents were subsequently associated with an increased rather than decreased risk for death in CAST (Cardiac Arrhythmia Suppression Trial) [5]. If the clinical outcome of interest is influenced by several different factors in addition to the surrogate end-point, then the surrogate marker may not be a valid surrogate end-point. Consequently, Freedman and colleagues [6] recommended that a valid surrogate end-point should explain at least 50% of the impact that a therapy has on the outcome of interest.

Because plasma protein C levels are low early in the course of severe sepsis and then rise in those who recover and survive, Shorr and colleagues [1] hypothesized that protein C might be a good surrogate end-point (type 2 biomarker) for treatment of sepsis with DrotAA. Because several other biomarkers had been measured in these cohorts, those investigators also explored the potential value of interleukin-6, antithrombin III, prothrombin time, protein S, and d-dimers. For this analysis, they used the conceptual framework for biomarkers proposed by Vasan [7]. In this model, a type 0 biomarker is defined as 'a marker of the natural history of the disease and correlates longitudinally with known clinical indices.' The authors tested the association of these six

DrotAA = Drotrecogin alfa (activated); ENHANCE = Extended Evaluation of Recombinant Activated Protein C; PROWESS = Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis.

biomarkers with 28-day mortality and selected cut-offs for biomarker levels based on sensitivity and specificity analyses. However, even at the optimum cut-off, baseline levels of all six biomarkers, including protein C, exhibited poor discriminant function for death, with areas under the receiver operator characteristic curve ranging from 55% to 60%.

The authors next examined whether any of these biomarkers could identify a subgroup of patients in whom a greater treatment benefit was observed. The cohort was divided into groups with a higher and lower risk for death, based on the baseline biomarker cut-off levels. The relative risk for death was compared in those treated with DrotAA in each of these two risk groups. Of the biomarkers studied, the only significant difference was in the protein C group. In patients with lower baseline plasma protein C levels (who were at greater risk for death), treatment with DrotAA resulted in a statistically significant reduction in risk for death.

Finally, to test whether these biomarkers could serve as a potential surrogate end-point by predicting clinical benefit, the authors found that 57% of the DrotAA effect was explained by the change in protein C levels. The authors also demonstrated that in DrotAA-treated patients, a higher proportion of individuals had normal protein C levels (>80% of normal) at the end of the drug infusion compared with control individuals, and that survival in those with normal protein C levels was higher in those patients treated with activated protein C, as compared with control individuals. To be a valid surrogate end-point, there should be some plausible mechanism by which treatment influences the surrogate end-point. The mechanism by which DrotAA influences protein C levels is not entirely clear but may be due to decreased consumption or increased hepatic production of endogenous protein C; the proposed mechanisms should be explored in future studies.

Based on the data and analysis presented in the report by Shorr and colleagues [1], what is the potential value of protein C as a surrogate end-point for treatment trials using DrotAA? The authors propose several potential but untested benefits, including identification of patients with severe sepsis who are most likely to benefit from treatment with DrotAA as well as to monitor patient response to therapy. The use of protein C as a surrogate end-point may allow tailoring of infusion length or drug dose to an individual patient; rather than treating patients with a fixed dose of DrotAA for a fixed period of time, it might be possible to tailor the infusion to normalize protein C levels by 96 hours. Indeed, the RESPOND (Research Evaluating Serial PC Levels in Severe Sepsis Patients on DrotAA) study [8] is examining the safety of higher doses of DrotAA (up to 48 μg/kg per hour) and longer infusion times (up to 7 days), and the efficacy of these infusions for normalization of protein C levels. We agree that these are clinical scenarios in which protein C may have value as a surrogate end-point. However, the true test of protein C as a surrogate end-point will depend on demonstrating that normalization of plasma protein C levels by DrotAA correlates with patient benefit in future studies, including the PROWESS-SHOCK trial [9].

Competing interests

The authors declare that they have no competing interests.

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