Mathematical Model Predicting Outcomes of Sepsis Patients Treated with Xigris®: ENHANCE Trial

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ABSTRACT

Introduction: The PROWESS trial demonstrated that administration of Drotrecogin alpha [activated] (DAA) to patients with severe sepsis resulted in a 6.1% absolute reduction in 28-day all-cause mortality. Whether the approved treatment regimen is optimal for all patients is unknown, suggesting a role for simulation in exploring this question.

Methods: We developed a differential equation-based model describing the time course of immune response and coagulation activation during the course of sepsis. This model incorporates known interactions between components of these responses. The outcome for a given virtual patient is predicted by persistence or resolution of a "*damage function*" linked to those components, which serves as a measure of tissue damage caused by sepsis. Known biological effects of DAA were incorporated into the model along with its pharmacokinetic/pharmacodynamic properties to simulate treatment. The model was calibrated to data from the PROWESS patient population, with the entire cohort divided into several subgroups based on factors such as age, surgery, acquired protein C (PC) deficiency, organ dysfunction, and treatment assignment. Each of these subgroups is associated with a subset of model parameters along with their values and biological effects. Simultaneous fit of the model to data from all subgroups allowed us to compute free parameters of the model. The model also provided for patient heterogeneity in septic insult and ability to mount a response.

Results: We used this model to predict results of the ENHANCE study (a phase 3B, open-label study of DAA in Severe Sepsis), which used enrollment criteria similar to those of PROWESS, although the average time from first organ dysfunction (FOD-time) to the start of treatment was longer in ENHANCE. Using distributions of FOD-time and age reflecting the ENHANCE patient population, the model predicted a treatment mortality well within the limit of statistical error when compared with the real outcome. In addition, the model provided correct mortality predictions within patient subgroups, except for the non-PC deficiency surgical patients.

Conclusion: Considering that we used only two inputs taken from actual ENHANCE data, we find the results of the model encouraging and believe that the model may ultimately provide valuable help in optimizing treatment protocols for different subgroups of patients with severe sepsis.

BACKGROUND

- Sepsis remains a major clinical problem affecting thousands of patients in the United States each year[1]
- With a 28-day mortality rate that ranges from 28% to 50%, severe sepsis accounts for an estimated 215,000 deaths annually[2,3,4,5]
- The incidence of severe sepsis has been projected to increase at a rate of 1.5% per year well into the middle of this century[1].
- It is well accepted in the Critical Care Community that early recognition and treatment can decrease mortality associated with severe sepsis6.
- DAA, the first drug approved specifically for severe sepsis, regulates the coagulation cascade and demonstrates anti-inflammatory properties.
- A mathematical simulation model of severe sepsis could lead to better understanding of the complex pathophysiology and assist with future clinical trial design[7].

OBJECTIVES

- To construct a mathematical model of severe sepsis which incorporates the known biological effects and pharmacokinetic/ pharmacodynamic properties of DAA
- Refine and calibrate the model with the baseline characteristics and outcome data from the pivotal phase 3 study of DAA, PROWESS.
- Simulate 28-day mortality including subgroups from the large open-label study of DAA, ENHANCE.

METHODS

Model: The mathematical model consists of a set of non-linear first order differential and algebraic equations. These equations describe the behavior of the components of immune and coagulation systems during the course of sepsis, and were developed on the basis of known interactions between these components. Effects of possible trauma and surgery were included in the model. The outcome for a given virtual patient is determined by so called "damage function" which serves as a measure of damage/dysfunction caused by the disease. This function by design has two different fixed points; if by the end of a time period this function approaches the lower fixed point, the patient is considered alive but if the bifurcation occurs in the system and the function approaches its higher fixed point, the patient is dead. All known interactions of DAA were incorporated into the model along with its pharmacokinetic and pharmacodynamic properties to simulate the therapeutic effect.

Trial Simulation: Large cohorts of virtual patients (typical size is 40,000) were simulated. These virtual patients differ from each other by values of certain parameters; these differences reflect heterogeneity of real patients in genetic and environmental factors, their age, severity of the disease, and timing of the treatment. The distributions of the age, severity, and treatment timing were taken from the PROWESS data. The distributions of genetic and environmental factors were taken from other published studies. Then the model was applied to each generated patient to compute the course of the disease and its outcome. Comparison of the simulation results with those of PROWESS allowed fine tuning of the model.

SEPSIS TRIALS

	PROWESS[8]	ENHANCE[9]
Type	• Phase 3 study • Efficacy and safety for DAA in Severe Sepsis patients	• Phase 3B study • Open-label study of DAA in Severe Sepsis patients
Period	• 06/1998 – 07/2000	• 03/2001 – 01/2003
Methodology	• Double-blind, placebo-controlled, multicenter (11 countries), randomized study • DAA infusion of 24 µg/kg/hr for 96 hours (± 1 hour)	• Open-label, multicenter study • DAA infusion of 24 µg/kg/hr for 96 hours (± 1 hour)
Patients	• 1690 patients • DAA: 477/373/850 (male/female/total) • Placebo: 487/353/840 (male/female/total)	• 2375 patients (more than 1 organ dysfunction of ≤ 48 hours duration)
Primary outcome	• 28-day, all-cause mortality	• 28-day, all-cause mortality

RESULTS

Overall Mortality

In the following tables, the 28-day mortality rate results are based on 10,000 virtual patients in each case. The baseline characteristics of ENHANCE patients have been loaded in our model to simulate the 28-day mortality for both treated and placebo groups. Importantly, all the patients in ENHANCE were treated with DAA.
Since the sepsis model has been calibrated with the baseline characteristics of PROWESS patients, we included the PROWESS outcomes (grey dark) in the table for comparison.

Sub-groups	ENHANCE Simulation	ENHANCE Outcome[9]	PROWESS Outcomes[8]
Overall - Placebo	33.1%	--	30.8% ±4%
Overall - Treated	25.6%	25.3%	24.7% ±3%

Mortality distributed by Age, Treatment and Surgery

The Age/Treatment groups have been analyzed to access the impact of surgery on mortality. The actual PROWESS data (grey dark) have been included in this table for comparison.

Sub-groups	ENHANCE Simulation	ENHANCE Outcomes[9]	PROWESS Outcomes[8]
Overall (Non-Surgery & Surgery)			
Age < 65 years - Placebo	21.9%	--	22.8% ± 3%
Age > 65 years - Placebo	40.5%	--	40.8% ± 5%
Age < 65 years - Treated	18.9%	18.5% ± 1%	13.7% ± 3%
Age > 65 years - Treated	33.8%	33.7% ± 2%	34.6% ± 4%

Sub-groups	No-Surgery: ENHANCE Simulation	No-Surgery: ENHANCE Outcomes[9]	No-Surgery: PROWESS Outcomes[8]	Surgery: ENHANCE Simulation	Surgery: ENHANCE Outcomes[9]	Surgery: PROWESS Outcomes[8]
Age ≤ 65 years - Placebo	20.6%	--	22.8% ± 3%	24.9%	--	16.3% ±4%
Age > 65 years - Placebo	39.9%	--	40.8% ± 5%	41.1%	--	45.0% ±8%
Age ≤ 65 years - Treated	16.9%	18.4% ± 2%	13.7% ± 3%	23.1%	18.2% ± 2%	20.7% ±5%
Age > 65 years - Treated	33.7%	34.3% ± 3%	34.6% ± 4%	34.0%	32.6% ± 3%	33.8% ±6%

RESULTS (continued)

Impact of the time first organ dysfunction to start of treatment with DAA on the overall mortality

- The first table gives the impact of the average time for treatment on the overall mortality in severe sepsis patients treated with DAA based on the baseline characteristics of patients in ENHANCE and PROWESS studies.
- The second table gives a comparison between the simulated and the real mortality outcome for groups of patients treated before or after 24 hrs in ENHANCE study.

Treatment time from the 1st Organ Dysfunction		Simulated Overall Mortality
ENHANCE average:	26.1 ± 13.1 hours	25.8% (24.5 - 28.6)
PROWESS average:	17.4 ± 11.1 hours	24.8% (23.5 - 27.8)
Impact on Overall Mortality:		+ 1.0%

Sub-groups	ENHANCE Simulation	ENHANCE Outcomes[9]
Overall Population		
DAA Infusion ≤ 24 hrs	24.2%	22.9% [20.5-25.5]
DAA Infusion > 24 hrs	26.6%	27.4% [24.9-29.9]

DISCUSSION

- The model predicted an overall mortality well within the limit of statistical error when compared with the actual outcomes from PROWESS and ENHANCE.
- In the surgical sub-group, the mortality in DAA-treated patients ≤ 65years old was over estimated, demonstrating the need for more detailed modeling of the surgical cohorts.
- The enrollment criteria for the ENHANCE study were similar to those of PROWESS. The model was able analyze the impact of difference in the average time from first organ dysfunction to treatment.

CONCLUSION

Despite limited input from the baseline characteristics of severe sepsis patients, we believe the results of the model are encouraging and believe that the model may ultimately provide valuable in optimizing treatment protocols for different subgroups of patients with severe sepsis.

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