The evolutionary lesson of Xigris

July 4, 2016

Here are 10 common pitfalls in medical practice that could be avoided if doctors paid more attention to evolutionary principles.

1) Interfering with adaptations (e.g. not recognizing host defenses in our patient's symptoms). The classic example is trying to reduce fever with medications like tylenol.

Yumiko Kayukawa

- Sepsis is an important cause of mortality, causing an estimated 60K deaths yearly.
- Sepsis is also expensive to treat, associated with expensive procedures, life support, and intensive care.
- Despite advances in supportive care, the mortality rates have remained high.

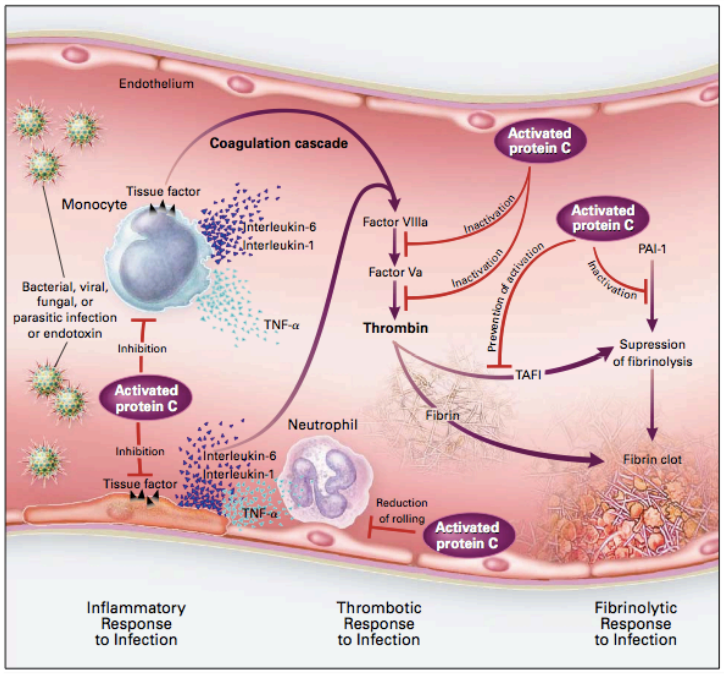

Figure 1. Proposed Actions of Activated Protein C in Modulating the Systemic Inflammatory, Procoagulant, and Fibrinolytic Host Responses to Infection.

The New England
Journal of Medicine

VOLUME 344 MARCH 8, 2001 NUMBER 10

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*

- Recombinant human activated protein C or dotrecogin alfa – aka Xigris, by Eli Lilly was approved for treatment of severe sepsis in 2001
- Xigris' FDA was approved despite a split 10-10 vote, based on the Eli Lilly-funded PROWESS study, a phase 3 randomized trial that was stopped early because Xigris' results seemed remarkable
- an absolute mortality reduction of 6% (number needed to treat to save a life was ~ 17)

Source: http://pulmccm.org/2012/randomized-controlled-trials/xigris-epitaph-prowess-shock-results-nejm/

$7000 per patient, The cost per life-year gained by treating all patients with activated protein C estimated at $27,936.

Special Article

AN ECONOMIC EVALUATION OF ACTIVATED PROTEIN C TREATMENT FOR SEVERE SEPSIS

BRADEN J. MANNS, M.D., HELEN LEE, M.A., CHRISTOPHER JAMES DOIG, M.D., DAVID JOHNSON, M.D., AND CAM DONALDSON, PH.D.

TABLE 1. OUTCOME DATA FROM THE PROWESS TRIAL BEFORE AND AFTER AMENDMENT OF THE PROTOCOL.

GROUP OF PATIENTS	MORTALITY BEFORE AMENDMENT			MORTALITY AFTER AMENDMENT		
	PLACEBO GROUP	ACTIVATED PROTEIN C GROUP	ABSOLUTE DIFFERENCE*	PLACEBO GROUP	ACTIVATED PROTEIN C GROUP	ABSOLUTE DIFFERENCE*
	no./total no. (%)		%	no./total no. (%)		%
All patients	109/360 (30)	102/360 (28)	−2	150/480 (31)	108/490 (22)	−9
APACHE II score						
<25	34/185 (18)	48/195 (25)	7	49/252 (19)	34/241 (14)	−5
≥25	75/175 (43)	54/165 (33)	−10	101/228 (44)	74/249 (30)	−15
Amended eligibility criteria						
Would not be met	17/40 (42)	14/41 (34)	−8	0/0	0/0	
Would be met	92/320 (29)	88/319 (28)	−1	150/480 (31)	108/490 (22)	−9

*The difference is shown as the mortality in the activated protein C group minus the mortality in the placebo group.

Eickhacker 2003 – we need more trials

Recombinant human activated protein C in sepsis: Inconsistent trial results, an unclear mechanism of action, and safety concerns resulted in labeling restrictions and the need for phase IV trials

[CUTTING EDGE THERAPEUTICS: SCIENTIFIC REVIEWS: CON]

Eichacker, Peter Q. MD; Natanson, Charles MD

SAFETY

Further review of rhAPC raised two important safety concerns. The first of these related to the prevalence of serious bleeding that would occur with wide usage. Evident in the information provided for the FDA evaluation was that significant bleeding associated with APC during the phase III trial was more frequent (APC, 2.4%, vs. placebo, 1.0%) and significantly (p = .02) increased during the period of drug infusion (4).

Address trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death

Edward Abraham, M.D., Pierre-François Laterre, M.D., Rekha Garg, M.D., Howard Levy, M.D., Ph.D., Deepak Talwar, M.D., Benjamin L. Trzaskoma, M.S., Bruno François, M.D., Jeffrey S. Guy, M.D., Martina Brückmann, M.D., Álvaro Rea-Neto, M.D., Rolf Rossaint, M.D., Dominique Perrotin, M.D., Armin Sablotzki, M.D., Ph.D., Nancy Arkins, R.N., Barbara G. Utterback, M.S., M.B.A., and William L. Macias, M.D., for the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group*

2005

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TEACHING BRIEF™

Study Rules Out Xigris in Low Death-Risk Sepsis Patients

By Michael Smith, MedPage Today Staff Writer
Reviewed by Robert Jasmer, MD; Assistant Professor of Medicine, University of California, San Francisco
September 29, 2005
Also covered by: Forbes, MSN

MedPage Today Action Points

- Note that this study showed no benefit but increased risk in using Xigris to treat patients with sepsis who have a low risk of death.
- Note also that the FDA has approved Xigris for patients with sepsis who have a high risk of death, in whom the benefit outweighs the risk.

Review

DENVER, Sept. 28-Xigris (drotrecogin alfa, activated) should not be used in patients with severe sepsis but a low risk of death, researchers have concluded.

A large, prospective, randomized, placebo-controlled Phase 4 trial of Xigris was stopped early because there was no evidence of a beneficial effect and there was an increased incidence of serious bleeding complications among patients receiving the drug, said Edward Abraham, M.D., of the University of Colorado Health Sciences Center here.

"The study is important because it tells us much more than we knew before about how to use this drug appropriately," Dr. Abraham said.

CME SPOTLIGHT

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Xigris may be related to risk of death after surgery, Lilly announces

March 18, 2005

ST. LOUIS (MD Consult) - On March 17, 2005, the U.S. Food and Drug Administration (FDA) notified health care professionals about revisions to the Warnings section of labeling for Xigris (drotrecogin alfa [activated]), a biological therapeutic product indicated for the treatment of adult patients with severe sepsis who are at high risk of death.

The warning is based on exploratory analyses of the ADDRESS clinical trial database and subsequent reanalysis of the PROWESS (Phase 3 registration) clinical trial database. Among patients with single organ dysfunction and recent surgery, all-cause **mortality** was numerically higher in the Xigris group compared with the placebo group. Patients with single organ dysfunction and recent surgery may not be at high risk of death and therefore may not be among the indicated population. Xigris should be used in these patients only after careful consideration of the risks and benefits.

This information was also communicated to health care professionals in a letter from the drug's manufacturer, Eli Lilly and Company.

The revised portion of the Xigris prescription information is as follows:

Medscape Alert

Pediatric Xigris Study Stopped

Yael Waknine

April 29, 2005 — The U. S. Food and Drug Administration (FDA) and Eli Lilly & Co. have notified healthcare professionals via letter of the discontinuation of a pediatric clinical trial of drotrecogin alfa (activated) (Xigris) for severe sepsis. Interim results suggest lack of benefit over placebo, according to an alert sent yesterday from MedWatch, the FDA's safety information and adverse event reporting system.

The action was based on a recommendation from an external, independent data monitoring committee that the trial be stopped for futility after interim results showed the drug was "highly unlikely" to show improvement over placebo in the study's primary end point of "composite time to complete organ failure resolution" over 14 days.

In the EVBP study, 399 pediatric patients with severe sepsis were randomized to receive drotrecogin alfa (activated) or placebo over 28 days. Preliminary data at 14 days showed that time to complete organ failure resolution was similar between groups (9.7 ± 5.0 days vs 9.8 ± 5.1 days).

Rates of mortality, other serious adverse events, overall serious bleeding events, and major amputation were similar between groups.

Results also showed that an increased number of children experienced intracranial hemorrhage (ICH) during the six-day infusion period in the drotrecogin alfa (activated) group compared with placebo (4 vs 1). Three of the four ICH events in the drotrecogin alfa group occurred in patients aged two months or younger.

Wolters Kluwer Health | Lippincott Williams & Wilkins

Critical Care Medicine
OFFICIAL JOURNAL OF THE SOCIETY OF CRITICAL CARE MEDICINE

Volume 35(12), December 2007, pp 2877-2878

Separating practice guidelines from pharmaceutical marketing

[Special Letter to the Editor]

Eichacker, Peter Q. MD; Natanson, Charles MD; Danner, Robert L. MD

Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, MD

To the Editor:

Our *New England Journal of Medicine* perspective and other publications (1–4) have raised concerns about the Surviving Sepsis Campaign (SSC) (5, 6) and marketing efforts by industry. Practice guidelines and performance bundles emanating from the SSC contain questionable recommendations (2, 4)

Links
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Outline
- To the Editor:
- REFERENCES

Recent History

Saving Sepsis

is often incomplete or absent (14). Even when properly provided, disclosure is not synonymous with transparency (15).

Belsito and Co, a public relations firm that simultaneously worked for Eli Lilly, the SSC, and the Values, Ethics, and Rationing in Critical Care Task Force, viewed marketing recombinant human activated protein C (rhAPC) as their primary mission (16). A public relations case study posted on the Internet (but removed shortly after publication of our perspective) stated that the company "initiated a wide-ranging media outreach program to raise awareness of rationing, severe sepsis and as a result, generate demand for Xigris [rhAPC]."

Eli Lilly funded researcher

320 *Clinical Microbiology and Infection*, Volume 15 Number 4, April 2009

REVIEW 10.1111/j.1469-0691.2009.02751.x

Activated protein C for the treatment of severe sepsis

G. Houston[1] and B. H. Cuthbertson[1,2]

1) *Intensive Care Unit, Aberdeen Royal Infirmary, Foresterhill Road, Aberdeen and* 2) *Health Services Research Unit, Health Sciences Building, University of Aberdeen, Foresterhill, Aberdeen, UK*

Abstract

In 2001, the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial demonstrated a 6.1% absolute decrease in mortality in patients with severe sepsis. Recombinant human activated protein C was subsequently licensed for use

Nufs nuf!

European Medicines Agency

London, 24 September 2009
EMA/CHMP/729233/2009

No further study has confirmed the efficacy results of the single pivotal trial

RESEARCH | OPEN ACCESS

Drotrecogin alfa (activated): real-life use and outcomes for the UK

Kathryn M Rowan ✉, Catherine A Welch, Emma North and David A Harrison

Critical Care 2008 12:R58 | DOI: 10.1186/cc6879 | © Rowan et al.; licensee BioMed Central Ltd. 2008
Received: 13 August 2007 | Accepted: 22 April 2008 | Published: 22 April 2008

Abstract

Format: Abstract Send to

Crit Care. 2009;13(3):R78. doi: 10.1186/cc7893. Epub 2009 May 20.

Early drotrecogin alpha (activated) administration in severe sepsis is associated with lower mortality: a retrospective analysis of the Canadian ENHANCE cohort.

Hodder RV[1], Hall R, Russell JA, Fisher HN, Lee B.

Author information

Critical Care

ABOUT ARTICLES SUBMISSION GUIDELINES

RESEARCH OPEN ACCESS

Activated protein C in septic shock: a propensity-matched analysis

Farid Sadaka, Jacklyn O'Brien, Matthew Migneron, Julie Stortz, Alexander Vanston and Robert W Taylor

Critical Care 2011 15:R89 | DOI: 10.1186/cc10089 | © Sadaka et al.; licensee BioMed Central Ltd. 2011

Received: 15 December 2010 | Accepted: 8 March 2011 | Published: 8 March 2011

Xigris arm as compared to before the change. Another large trial was "requested" by the European Medicines Agency (like the FDA), and Eli Lilly's **PROWESS-SHOCK** was born. On May 31, 2012, results were published in the *New England Journal of Medicine*.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 31, 2012 VOL. 366 NO. 22

Drotrecogin Alfa (Activated) in Adults with Septic Shock

V. Marco Ranieri, M.D., B. Taylor Thompson, M.D., Philip S. Barie, M.D., M.B.A., Jean-François Dhainaut, M.D., Ivor S. Douglas, M.D., Simon Finfer, F.R.C.P., Bengt Gårdlund, M.D., John C. Marshall, M.D., Andrew Rhodes, M.D., Antonio Artigas, M.D., Ph.D., Didier Payen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Hussein R. Al-Khalidi, Ph.D., Vivian Thompson, M.P.H., Jonathan Janes, M.B., B.Ch., William L. Macias, M.D., Ph.D., Burkhard Vangerow, M.D., and Mark D. Williams, M.D., for the PROWESS-SHOCK Study Group*

Xigris didn't work:

- Mortality at 28 days: **26%** in Xigris group vs. **24%** in placebo.
- Mortality at 90 days: **34%** in Xigris group vs. **33%** in placebo.

Source: http://pulmccm.org/2012/randomized-controlled-trials/xigris-epitaph-prowess-shock-results-nejm/

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Xarelto (rivaroxaban) gets FDA indication for DVT and PE; no heparin bridging needed

Azithromycin associated with cardiovascular death

Dec 29 2012

Xigris' epitaph: "I Never Worked a Day in My Life" (PROWESS-SHOCK)

Critical Care, Infectious Disease and Sepsis, New England, Policy, Ethics, Education, Randomized Controlled Trials

Add comments

Source: http://pulmccm.org/2012/randomized-controlled-trials/xigris-epitaph-prowess-shock-results-nejm/

Secondary outcomes (Xigris study)

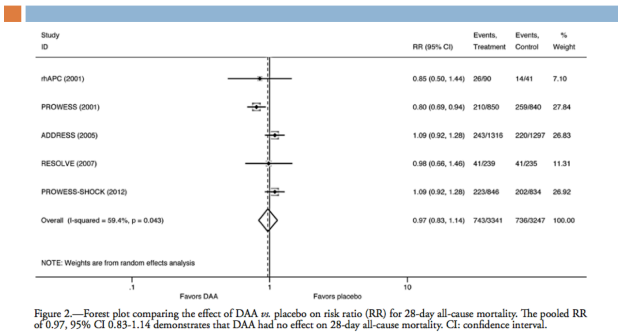


Figure 2.—Forest plot comparing the effect of DAA *vs.* placebo on risk ratio (RR) for 28-day all-cause mortality. The pooled RR of 0.97, 95% CI 0.83-1.14 demonstrates that DAA had no effect on 28-day all-cause mortality. CI: confidence interval.

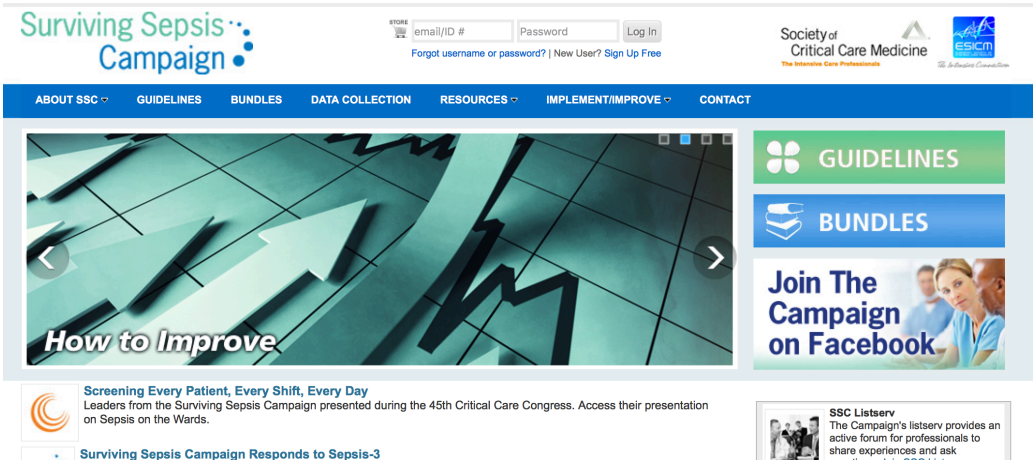
Lai et al. Minerva Anesth. 2013

Open Access Research

BMJ Open

The efficacy of activated protein C for the treatment of sepsis: incorporating observational evidence with a Bayesian approach

Zhongheng Zhang



Trends in Molecular Medicine April 2014, Vol. 20, No. 4

Table 1. Clinical trials of biologic response modifiers in sepsis

Target	Strategies
Endotoxin (LPS)	Monoclonal antibodies
	LPS: HA-1A, E5
	Enterobacterial common antigen
	Toll-like receptor 4 (TLR4) antagonists
	Eritoran
	TAK-242
	Anti-CD14
	Bactericidal permeability increasing protein
	Taurolidine
	Alkaline phosphatase
	Polymyxin B
	Conjugate
	Extracorporeal column
	Lipid emulsion
Tumor necrosis factor (TNF)	Monoclonal or polyclonal antibodies
	Soluble receptor constructs
Interleukin-1 (IL-1)	Recombinant IL-1 receptor antagonist
Platelet activating factor (PAF)	Small molecule inhibitors
	PAF acetylhydrolase
Eicosanoids	Ibuprofen
	Soluble phospholipase A2 (sPLA2) inhibitor
Nitric oxide	L-NMMA
	Methylene blue
Hypercoagulability/disseminated intravascular coagulation (DIC)	APC, Protein C concentrate
	TFPI
	Antithrombin
	Anti-tissue factor antibody
	Heparin
	Thrombomodulin
Immune suppression	Intravenous immunoglobulin
	G-CSF, GM-CSF
	Interferon γ
Endocrinopathy	Corticosteroids
	Vasopressin
Others	Selenium
	Lactoferrin
	Bradykinin antagonists
	Statins
	Extracorporeal hemoperfusion

PLOS | ONE

RESEARCH ARTICLE

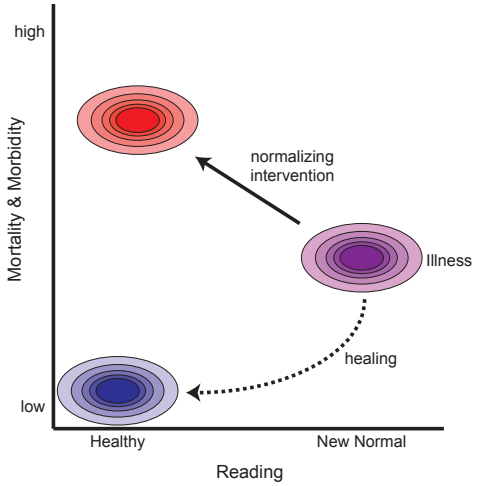
Blockade of Thrombopoietin Reduces Organ Damage in Experimental Endotoxemia and Polymicrobial Sepsis

Alessandra Cuccurullo[1☯], Elisabetta Greco[1☯], Enrico Lupia[1☯], Paolo De Giuli[2], Ornella Bosco[1], Erica Martin-Conte[3], Tiziana Spatola[1], Emilia Turco[4], Giuseppe Montrucchio[1]*

1 Department of Medical Sciences, University of Turin, Turin, Italy, **2** Anatomia Patologica, San Lazzaro Hospital, Alba, Italy, **3** Department of Anaesthesiology and Critical Care, University of Turin, Turin, Italy, **4** Department of Genetics, Biology and Biochemistry, University of Turin, Turin, Italy

☯ These authors contributed equally to this work.
* giuseppe.montrucchio@unito.it

- Continuing to search for elusive so-called "magic bullets" in sepsis is a losing strategy. As cited in a recent article about the failure of anti-TNF-α in sepsis:
- "Success is the ability to go from one failure to another with no loss of enthusiasm," a quotation attributed to Sir Winston Churchill.
- On the other hand, repeating same thing while expecting different results is also…well you know the cliché.



Published in final edited form as:
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Survival advantage of heterozygous fV *Leiden* carriers in murine sepsis

Edward Kerschen[1], **Irene Hernandez**[1], **Mark Zogg**[1], **Matthias Maas**[1], and **Hartmut Weiler**[1]
[1]Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI, 53226, USA