Proof of concept review

Eritoran: the evidence of its therapeutic potential in sepsis

Shahzad G. Raja, Gilles D. Dreyfus

Department of Cardiothoracic Surgery, Harefield Hospital, Harefield, Middlesex, UK

Abstract

Introduction: Sepsis and its sequelae are the leading causes of morbidity and mortality in critically ill patients. The burden to healthcare economies is also considerable. As the pathophysiology of sepsis is better defined, interventions aiming to treat sepsis are emerging. Eritoran (E5564), a toll-like receptor 4 (TLR4)-directed endotoxin antagonist, is one such emerging therapeutic option for treatment of sepsis.

Aims: This review assesses evidence for the potential therapeutic value of eritoran in the management of sepsis.

Evidence review: Evidence from a single phase II trial of eritoran usage in sepsis suggests that it is a safe and effective therapeutic option for patients with sepsis, and is especially beneficial for patients at high risk of mortality. However, the cost effectiveness of eritoran and its place in therapy compared with other available treatment options and those currently in development remains to be determined.

Clinical potential: Eritoran is a potential therapeutic option for management of sepsis and other TLR4- and lipopolysaccharide-mediated disorders with a reasonable safety and tolerability profile that must be validated by several rigorous, blinded, placebo-controlled, adequately powered, multicenter, randomized clinical trials.

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Key words: eritoran, evidence, outcome, sepsis, systemic inflammatory response syndrome, toll-like receptor

Core evidence proof of concept summary for eritoran in sepsis

Outcome measure	Emerging evidence
Efficacy	Potential to use as monotherapy in patients with newly diagnosed sepsis and endotoxemia; effective dose is 105 mg per 6 days
Response rates	Some evidence that mortality is reduced by 13.0–17.6% in septic patients at highest risk of mortality
Marker of efficacy	Most clinical studies do not report any constant marker of efficacy, although reduction in 28-day all-cause mortality appears to be a reliable objective marker
Tolerability	Good tolerability with daily dosing alone as well as with 72-hour continuous infusion
	No consensus on maximum tolerated dose or dosage regimen
Safety	Dose-dependent phlebitis most commonly experienced side effect

Scope, aims, and objectives

Sepsis is a generalized activation of the immune system in the presence of clinically suspected or culture-proven infection. Severe sepsis is sepsis with organ system dysfunction. Sepsis and its sequelae are the leading causes of death in critically ill patients. Advances in our understanding of the sepsis syndrome have enabled researchers to identify new therapeutic targets and design therapies for existing mediators of sepsis; one such therapeutic target is toll-like receptor 4 (TLR4), which is involved in the pathogenesis of sepsis and septic shock. Eritoran (E5564) is a TLR4-directed endotoxin antagonist currently being investigated for the treatment of severe sepsis, septic shock, and other endotoxin-mediated indications. The objective of this article is to present an overview of sepsis and current options in its treatment, and to review the current evidence for the therapeutic potential of eritoran in the management of sepsis and septic shock.

Methods

A literature search was conducted on July 6, 2007 in the following databases using the search terms "Eritoran OR E5564." The cut-off date was from the beginning of the database to the date of search unless otherwise stated:

- PubMed, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi, 1966 to date. Search strategy "Eritoran OR E5564" limited to English language results only

- EMBASE, http://www.datastarweb.com, 1974 to date. Search strategy: "Eritoran OR E5564" limited to English language results only

- Database of Abstracts of Reviews of Effects (DARE), National Health Service (NHS) Economic Evaluation Database (NHSEED), Health Technology Assessment (HTA), http://www.york.ac.uk/inst/crd/darehp/htm. All three databases searched together. All fields searched

- National Guideline Clearinghouse, http://www.guideline.gov

- National Institute for Health and Clinical Excellence (NICE), http://www.nice.org.uk

- Cochrane Database of Systematic Reviews (CDSR), http://www.cochrane.org/index.htm

- Eisai Inc., http://www.eisai.com/view_press_release.asp?ID=210&press=124

After removal of duplicates, a total of 32 records were retrieved from PubMed. Records were manually reviewed and any animal studies, *in-vitro* studies, general narrative reviews, and articles which mentioned eritoran but did not discuss trial data were excluded. The remaining six records were included. In addition, a further phase II trial conducted by Eisai Inc. was included (Anon. 2005).

The identified studies were then classified into five classes of evidence based on the design of the study, with level 1 evidence presenting the strongest evidence and level 5 representing the weakest evidence, as indicated in Table 1. No systematic reviews or meta analyses were identified. Two phase II trials providing level 2 evidence were retrieved, one a full manuscript and another an abstract. Publications relating to pharmacoeconomic evidence with eritoran were not identified.

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	32	0
records excluded	26	0
records included	6	0
Additional studies identified[a]	1	0
records excluded	0	0
records included	0	1
Level 1 clinical evidence (systematic review, meta analysis)	0	0
Level 2 clinical evidence (RCT)	1	1
Level ≥3 clinical evidence	6	0
trials other than RCT	3	0
case reports	0	0
pharmacokinetic studies	2	0
pharmacodynamic studies	1	0
Economic evidence	0	0

For definition of levels of evidence, see Editorial Information on inside back cover or on *Core Evidence* website (http://www.coremedicalpublishing.com).
[a]Any relevant study that was identified from a source other than the main searches, e.g. a reference list.
RCT, randomized controlled trial.

Disease overview

Incidence of sepsis

Sepsis remains a critical problem with significant morbidity and mortality even in the modern era of critical care management. Multiple derangements exist in sepsis involving several different organs and systems, although controversies exist over their individual contribution to the disease process (Remick 2007). The reported rates of severe sepsis average around 10 cases per 100 intensive care unit (ICU) admissions (Linde-Zwirble & Angus 2004). Epidemiologic studies of the incidence of sepsis indicate that between 11% and 27% of ICU admissions have severe sepsis (Kleinpell et al. 2006). Estimates of the incidence of sepsis in adult patients vary from 51 per 100 000 in England and Wales (Padkin et al. 2003) to 77 per 100 000 in Australia and New Zealand (Finfer et al. 2004) and 240 per 100 000 in the USA (Martin et al. 2003). Mortality remains high (20–50%) and sepsis is consistently reported as a leading cause of death in noncardiac ICUs (Angus et al. 2001; Dremsizov et al. 2004). Severe sepsis has a significant impact on quality of life, with survivors of severe sepsis having substantial impairment (Heyland et al. 2000;

Korosec Jagodec et al. 2006). Care of septic patients in the ICU also imposes considerable burden on healthcare economies. It has been estimated that in the USA the average expenditure per patient is around $US22 000, with a total annual cost approaching $US17 billion (Angus & Wax 2001). The median daily costs of care for septic patients at the time of admission to the ICU are $US930.74 (interquartile range, $US851.59 to $US1263.96) in the UK (Edbrooke et al. 1999).

Pathophysiology of sepsis

Emerging evidence regarding the pathophysiology of sepsis, or systemic inflammatory response syndrome (SIRS) caused by infection, suggests that all pathogenic organisms have pathogen- or microorganism-associated molecular patterns (PAMPs) that can initiate a septic response (Cohen 2002). PAMPs bind to pattern recognition receptors, of which three families are central to the pathogenesis of septic response, namely TLRs, nucleotide-oligomerization domain (NOD) leucine-rich repeat proteins, and retinoic-acid-inducible gene 1-like (RIG-1) helicases (Uematsu & Akira 2006). TLRs are predominantly present on the surface of immune cells and play a major role in human innate immunity (Verstak et al. 2007).

Binding of TLRs activates intracellular signal-transduction pathways that lead to the activation of cytosolic nuclear factor-κB. Activated nuclear factor-κB moves from the cytoplasm to the nucleus, binds to transcription sites, and induces activation of a set of genes, as well as enzymatic activation of a cellular protease. TLRs induce pro-interleukin-1-beta (IL-1-beta) production and prime NOD-like receptor-containing multiprotein complexes, termed "inflammasomes," to respond to bacterial products and products of damaged cells. This results in caspase-1 activation and the subsequent processing of pro-interleukin-1-beta to its active form (Trinchieri & Sher 2007). Thus, TLR-mediated dysregulation of the immune response to pathogens results in organ dysfunctions in severe sepsis.

Concomitant phenotypic modification of the endothelium including changes in procoagulant and proadhesive properties, increased endothelial permeability, endothelial cell apoptosis, and changes in vasomotor properties leading to vasoplegia, further contribute to the morbidity and mortality associated with septic shock (Aird 2007).

During sepsis, in addition to extensive stimulation of the innate immune system and phenotypic modification of the endothelium, white blood cell activation and complement system activation leads to the release of a number of mediators or cytokines (Jean-Baptiste 2007). These include the release of IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-alfa (TNF-alfa), platelet-activating factor, endorphins, nitric oxide, reactive oxygen species, tissue factor, macrophage migration inhibitory factor, and chemokines, which lead to a variety of immune system responses including vasodilatation, enhanced expression of adhesion molecules, increased capillary permeability, increased clot formation, and decreased fibrinolysis. Free radicals are generated by leucocytes, including neutrophils and monocytes, during

inflammation and lead to proinflammatory and ischemia-induced injury (Kleinpell et al. 2006; Jean-Baptiste 2007).

Side by side with the proinflammatory response, activation of counterinflammatory mechanisms and the release of antiinflammatory cytokines also takes place. Antagonists, such as soluble TNF receptors, IL-1 receptor type II, complement inactivators, and antiinflammatory cytokines such as IL-10 and IL-4, are released. Furthermore, extensive lymphocyte-programmed cell death (apoptosis), conversion of proinflammatory cytokine-producing type 1 helper T cells to antiinflammatory cytokine-producing type 2 helper T cells, and permanent T cell unresponsiveness also occurs (Kleinpell et al. 2006). It is theorized that this antiinflammatory response aimed primarily at counteracting overamplified proinflammatory response of sepsis in reality hampers the ability of the body to combat the triggering infectious event when overamplified itself (Cavaillon & Annane 2006).

A large number of coagulation, cardiovascular, metabolic, and endocrine abnormalities further contribute to multiple organ dysfunction syndrome, the eventual cause of death in sepsis. These include a procoagulant state with formation of microthrombi, disseminated intravascular coagulation, impaired cardiac contractility, adrenal insufficiency, vasopressin deficiency leading to vasoplegia, and—last but not least—insulin deficiency and its sequelae such as impaired wound healing, reduced granulocyte function, and increased risk of infections (Tsiotou et al. 2005).

Current therapy options

Surviving Sepsis Campaign guidelines

The treatment of severe sepsis includes three essential principles: eradication of the inciting infection using source control measures and empiric antibiotics, hemodynamic resuscitation of hypoperfusion to avoid acute life-threatening organ dysfunction, and sustained support of organ system dysfunction using interventions that minimize organ injury (Cinel & Dellinger 2006). Therapy can be divided into immediate steps taken to stabilize the patient, followed by more definitive therapeutic intervention. The evidence for best clinical practice for resuscitation, management of infection, and ICU supportive care has recently been synthesized by the Surviving Sepsis Campaign and published as evidence-based guidelines for management of severe sepsis and septic shock (Cinel & Dellinger 2006).

The Surviving Sepsis Campaign was launched in 2002 by the Society of Critical Medicine, the European Intensive Care Society, and the International Sepsis Forum. The aim of this collaboration was to improve the standard of care offered to patients with sepsis, with the hope of reducing mortality due to sepsis by 25% by the year 2007 (Poulton 2006). Under the auspices of the campaign, international experts reviewed the relevant literature available, with the goal of producing guidelines that would be of practical use in the management of the septic patient. These guidelines covering more than 50 areas of sepsis management

published in 2004 and backed by eight other infectious disease, critical care, and nursing organizations suggest a "resuscitation bundle" and a "management bundle" aimed at achieving the goal of a 25% reduction in mortality from severe sepsis (Dellinger et al. 2004).

The Severe Sepsis Resuscitation Bundle describes seven tasks (Table 2) that should begin immediately, but must be accomplished within the first 6 hours of presentation for patients with severe sepsis or septic shock. Some items may not be completed if the clinical conditions described in the bundle do not prevail in a particular case, but clinicians must assess for them. The goal is to perform all indicated tasks 100% of the time within the first 6 hours of identification of severe sepsis (IHI 2007).

Table 2	The tasks of the Severe Sepsis Resuscitation Bundle (IHI 2007)
1.	Serum lactate measured
2.	Blood cultures obtained prior to antibiotic administration
3.	Improve time to antibiotic administration
4.	Treat hypotension and/or elevated lactate with fluids
5.	Administer vasopressors for ongoing hypotension
6.	Maintain adequate central venous pressure
7.	Maintain adequate central venous oxygen saturation

The Sepsis Management Bundle lists four management tasks (Table 3). Efforts to accomplish these tasks should also begin immediately, but these items may be completed within 24 hours of presentation for patients with severe sepsis or septic shock (IHI 2007).

Table 3	The tasks of the Sepsis Management Bundle (IHI 2007)
1.	Administer low-dose steroids by a standard policy
2.	Administer activated protein C (drotrecogin alfa) by a standard policy
3.	Maintain adequate glycemic control
4.	Prevent excessive inspiratory plateau pressures

Therapeutic options with strong evidence base (evidence level 2)

Early goal-directed therapy

Early goal-directed therapy is an algorithmic approach to restoration of systemic oxygen delivery through a manipulation of preload (volume), afterload (blood pressure), and contractility (stroke volume) guided by central venous pressure, mean arterial pressure, and central venous oxygen saturation monitoring to preserve effective tissue perfusion within the first 6 hours of disease presentation (Nguyen & Smith 2007).

Early timing of hemodynamic intervention is critical, and it is extremely important that only normal, rather than supranormal, goals should be sought (Rivers et al. 2001). This concept has been validated by two large, randomized controlled trials which showed that supranormal hemodynamic goals, started at various points in the course of the sepsis process, had no impact on survival (Hayes et al. 1994; Gattinoni et al. 1995). The efficacy of early goal-directed therapy or early hemodynamic optimization was proven in a randomized controlled trial involving 263 patients with infection associated with hypotension after a fluid bolus and/or serum lactate ≥4 mmol/L who were randomly assigned to receive standard resuscitation or early goal-directed therapy in the emergency department before ICU transfer. During the first 6 hours in the emergency department, the early goal-directed therapy group had significantly greater amount of fluid therapy than the control group (5.0 vs 3.5 L, respectively), red blood cell transfusion (64.1% vs 18.5%, respectively), and inotrope (dobutamine) administration (13.7% vs 0.8%, respectively). The primary outcome variable, in-hospital mortality, was 46.5% in the control group versus 30.5% in the early goal-directed therapy group (P=0.009). Of the patients who survived to hospital discharge, early goal-directed therapy resulted in a significant 3.8-day shorter length of hospital stay (P=0.04). The early goal-directed therapy was associated with a significant two-fold decrease in the incidence of sudden cardiopulmonary complications, such as cardiac arrest, hypotension, or acute respiratory failure (P=0.02) (Rivers et al. 2001).

Activated drotrecogin alfa rhAPC (recombinant human activated protein C)

Activated protein C (APC) has antiinflammatory, antithrombotic, and fibrinolytic actions (Esmon 2001). Production of endogenous APC is reduced in patients with sepsis due to downregulation of thrombomodulin (Nguyen & Smith 2007) and there is an inverse relationship between the level of protein C and the risk of mortality in these patients (Fourrier et al. 1992). This fact was verified by the investigators of the PROWESS study (Bernard et al. 2001).

The PROWESS study, a randomized, double-blind, placebo-controlled trial, was conducted at 164 centers in 11 countries. Patients with three SIRS criteria and at least one organ failure of less than 24 hours' duration were eligible for the trial. A total of 1690 patients were randomized to receive activated drotrecogin alfa (24 mcg/kg per hour) or placebo for 96 hours. The primary endpoint for the trial was mortality at 28 days. The trial was terminated at second interim analysis because of the survival advantage found for activated drotrecogin alfa. The 28-day mortality was 30.8% in the placebo group and 24.7% in the drotrecogin alfa group, indicating a relative risk reduction of 19.4% [95% confidence interval (CI) 6.6%, 30.5%]. The absolute risk reduction was greater (12.8%) in those patients at greatest risk [Acute Physiology and Chronic Health Evaluation (APACHE) II scores >25]. Reductions in the relative risk of death were seen regardless of the baseline level of APC (Bernard et al. 2001).

As expected from the antithrombotic activity of activated drotrecogin alfa, bleeding was the most common adverse incident associated with the drug. The authors estimated that one additional serious bleeding event would occur for every 66 patients treated. Patients with a predisposing history were most at risk (Bernard et al. 2001).

Activated drotrecogin alfa has Food and Drug Administration approval and is currently recommended in patients at high risk of death [APACHE II scores ≥25, sepsis-induced multiple organ failure, septic shock, or sepsis-induced acute respiratory distress syndrome (ARDS)] and with no absolute contraindication related to bleeding risk or relative contraindication that outweighs the potential benefit.

Protective ventilation of patients with sepsis-induced acute lung injury/ARDS

The traditional approach to ventilation in patients with acute lung injury (ALI)/ARDS has been to aim for a normal partial pressure of CO_2 ($PaCO_2$) and pH. However, because there are fewer functioning alveoli, there is much greater stretching than usual in these functional alveoli if normal tidal volumes are maintained. It has been demonstrated that volutrauma to alveoli induces release of proinflammatory cytokines, which in turn leads to a perpetuation of the process (Poulton 2006). The Surviving Sepsis Campaign guidelines recommend that high tidal volumes that are coupled with high plateau pressures should be avoided in ALI/ARDS. Clinicians should use as a starting point a reduction in tidal volumes over 1–2 hours to a low tidal volume (6 mL/kg predicted body weight) as a goal, in conjunction with the goal of maintaining end-inspiratory pressures <30 cm H_2O.

A small randomized controlled trial conducted in Brazil, recruiting 53 patients with early ARDS, was the first to suggest a dramatic improvement in mortality when lower tidal volumes were used at the expense of a higher $PaCO_2$ (Amato et al. 1998). The patients, all of whom were receiving identical hemodynamic and general support, were subjected to conventional or protective mechanical ventilation. Conventional ventilation was based on the strategy of maintaining the lowest positive end-expiratory pressure (PEEP) for acceptable oxygenation, with a tidal volume of 12 mL/kg of bodyweight and normal arterial carbon dioxide levels (35 to 38 mmHg). Protective ventilation involved end-expiratory pressures above the lower inflection point on the static pressure–volume curve, a tidal volume of less than 6 mL/kg, driving pressures of less than 20 cm of water above the PEEP value, permissive hypercapnia, and preferential use of pressure-limited ventilatory modes. After 28 days, 11 of 29 patients (38%) in the protective-ventilation group had died, compared with 17 of 24 (71%) in the conventional-ventilation group (P<0.001). The rates of weaning from mechanical ventilation were 66% in the protective-ventilation group and 29% in the conventional-ventilation group (P=0.005); the rates of clinical barotrauma were 7% and 42%, respectively (P=0.02), despite the use of higher PEEP and mean airway pressures in the protective-ventilation group. The difference in survival to hospital discharge was not significant; 13 of 29 patients in the protective-ventilation group died in the hospital, compared with 17 of 24 in the conventional-ventilation group (45% vs 71%, P=0.37).

The results of the Brazilian trial prompted the US ARDS Network to evaluate the strategy in a large, multicenter, randomized controlled trial in which patients with ALI or ARDS were randomized to receive ventilation with tidal volumes of 12 mL/kg

(control) or 6 mL/kg (treatment). The primary endpoint for the trial was death before discharge home. The trial was stopped early after enrollment of 861 patients. The low tidal volume group had a mortality of 31% compared with 39.8% in the control group (P=0.007). Those patients with low tidal volumes also spent fewer days on ventilatory support and had lower levels of circulating IL-6 (Anon. 2000).

Low-dose steroids

The role of systemic administration of corticosteroids in modifying the course and outcome of septic shock has been the subject of considerable debate since the 1950s (Sessler 2003). Despite the many proven antiinflammatory properties of corticosteroids, the wealth of favorable studies utilizing various animal models of septic shock, and many anecdotal positive reports in clinical sepsis, until recently multicenter clinical trials had generally failed to support this form of treatment (Anon. 1987; Bone et al. 1987). In fact, there is now widespread agreement that high-dose, short-course therapy with methylprednisolone or dexamethasone in septic shock is ineffective. In contrast, the new paradigm of prolonged treatment with low- to modest-dose hydrocortisone for relative adrenal insufficiency in septic shock is attracting attention.

Support for this new paradigm is provided by three randomized controlled trials (Bollaert et al. 1998; Briegel et al. 1999; Annane et al. 2002). The largest of these trials was conducted in France involving 19 ICUs (Annane et al. 2002). In this study 300 patients with septic shock were randomized to receive either placebo or hydrocortisone 50 mg four times a day and fludrocortisone 50 mcg once a day. Treatment was continued for 7 days if survival time was sufficient. A short synacthen test was performed on all patients at randomization. The primary outcome measure was 28-day mortality.

A total of 229 patients had an inadequate response to synacthen. In these nonresponders, 28-day mortality was significantly lower in those patients treated with steroids (53%) compared with those assigned to placebo (63%) (hazard ratio 0.67; 95% CI 0.47, 0.95; P=0.02). Patients assigned to receive steroids were also weaned from inotropic support more rapidly and received lower doses of inotropes. There was no apparent survival advantage for steroid treatment in those patients who had demonstrated an adequate response to synacthen.

Based on the findings of this trial the Surviving Sepsis Campaign guidelines recommend that intravenous corticosteroids (hydrocortisone 200–300 mg/day for 7 days in three or four divided doses or by continuous infusion) are administered to patients with septic shock who, despite adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure.

Intensive insulin therapy

The Surviving Sepsis Campaign guidelines recommend that following initial stabilization of patients with severe sepsis, blood glucose is maintained at <8.3 mmol/L. Critically ill patients have hyperglycemia and raised levels of insulin-like growth factor

binding protein-1. The latter reflects an impaired hepatic response to insulin and has an inverse relationship with the likelihood of survival (Poulton 2006), hence intensive insulin therapy appears an attractive therapeutic option in septic patients.

The randomized controlled trial that forms the basis of the Surviving Sepsis Campaign recommendation regarding tight glycemic control was conducted in Belgium and randomized 1548 surgical intensive care patients to receive tight blood glucose control (4.4–6.1 mmol/L) or a more traditional target (10–11 mmol/L). Almost all patients (98.7%) allocated to tight control needed insulin, whereas only 39% of the control group did (van den Berghe et al. 2001).

There was a statistically significant difference in intensive care mortality, and this was principally attributable to long-stay patients. In long-stay patients with tight control, there was a four-fold reduction in deaths due to sepsis-induced multiple organ failure, whereas other causes of death were similar between the two groups. Intensive insulin therapy also appeared to reduce overall in-hospital mortality by 34%. Other advantages to tight blood glucose control included shorter intensive care times, a reduced risk of renal failure and, most significantly, a much lower incidence of critical illness polyneuropathy.

Therapeutic options with proven clinical benefit but weak evidence base (evidence level 4/5)

Antimicrobial therapy

Delay in instituting antimicrobial therapy after the onset of hypotension in patients with septic shock is associated with a significant increase in mortality (Nguyen & Smith 2007). This fact has been highlighted by a large retrospective cohort study of 2154 septic shock patients in 14 ICUs in Canada and the United States (Kumar et al. 2006). The study showed that each hour of delay in antibiotic administration during the first 6 hours of persistent hypotension was associated with a 7.6% increase in mortality (range, 3.6–9.9%). The odds ratio for mortality was 1.67 (95% CI 1.12, 2.48) if the delay was 1 hour and continued to increase with progressive delays to a maximum value of 92.54 (95% CI 44.92, 190.53) for delays more than 36 hours after the onset of hypotension.

Interestingly, the guidelines pertaining to antimicrobial therapy are not supported by a strong evidence base, yet they are not controversial and are certainly in line with current mainstream practice. These guidelines are summarized in Table 4.

Unmet needs

Therapy for sepsis remains unsatisfactory despite a concerted effort to develop new treatments for this common, life-threatening syndrome. Current research continues on several fronts to improve the treatment options available to clinicians in the management of these critically ill patients. Recently, a greater understanding of the complex molecular basis of

Table 4	Guidelines pertaining to antimicrobial therapy in sepsis	
Guideline	**Evidence level**
1. Intravenous antibiotic therapy should be started within the first hour of the recognition of severe sepsis, after appropriate cultures have been obtained. It is also recommended that premixed antibiotics should be available to increase the likelihood of early administration	5
2. Choice of initial antibiotics should be empirical, but should clearly be guided by the clinical picture and the sensitivity patterns of local pathogens	4
3. Broad-spectrum antibiotics should be used until the causative organism is identified. At 48–72 hours, antibiotic treatment should be reviewed. At this point, the spectrum should be narrowed if appropriate. The rationale for this recommendation is that it will help to contain costs and reduce the risk of emergence of resistant organisms. The duration of treatment should typically be 7–10 days and guided by clinical response	5
4. Some experts prefer combination therapy for patients with *Pseudomonas* infections, regardless of sensitivities	5
5. Most experts would continue to use combination therapy for neutropenic patients with severe sepsis or septic shock	5
6. If the presenting SIRS is determined to be due to a noninfective cause, antibiotic therapy should be stopped promptly to minimize the risk of development of resistant pathogens	5
SIRS, systemic inflammatory response syndrome.	

endotoxin-mediated pathophysiologic effects in humans has generated a number of novel therapeutic agents for sepsis. Several of these treatment strategies have already entered clinical trials and it is hoped that some of these therapies will become widely available in the near future.

Outcomes achieved with eritoran in clinical development

Eritoran is a second-generation TLR4-directed lipopolysaccharide (LPS) antagonist derived from the structure of *Rhodobacter sphaeroides* (Mullarkey et al. 2003). Clinically, eritoran is being investigated for the treatment of severe sepsis, septic shock, and other endotoxin-mediated indications.

Efficacy

The therapeutic potential of eritoran as an effective treatment for sepsis and endotoxemia in humans was first highlighted by a randomized, double-blind, placebo-controlled study published in 2003 (Lynn et al. 2003). The study recruited 24 healthy male volunteers, aged 18–45 years (mean 30.1 years) and weighing 55.5–104.5 kg (mean 76.7 kg). Subjects were randomly assigned to receive eritoran or placebo (ratio of 6:2 per dose level). The first cohort of eight subjects assigned to active drug received 250 mcg as a single 30 min intravenous infusion. Subjects in the other two groups assigned to active drug received 100 or 50 mcg. Subjects assigned to the placebo group in each cohort received similar intravenous infusions. All subjects received an intravenous dose of

LPS 4 ng/kg, 15 min after the start of the study drug infusion to produce experimental endotoxemia.

The results of the study revealed that single eritoran doses of 50–250 mcg ameliorated or blocked all of the effects of LPS in a dose-dependent manner. All eritoran dose groups had statistically significant reductions in elevated temperature, heart rate, C-reactive protein levels, white blood cell count, and cytokine levels (TNF-alfa and IL-6), compared with placebo ($P<0.01$). In doses of $\geq$100 mcg, eritoran acted as an LPS antagonist and completely eliminated these signs. Eritoran also blocked or ameliorated LPS-induced fever, chills, headache, myalgia, and tachycardia ($P<0.01$).

To date, one large phase II trial has been conducted to assess the efficacy of eritoran for the management of sepsis. The study, conducted in North America, involved 293 patients randomized to three groups: eritoran high dose (105 mg per 6 days), eritoran low dose (45 mg per 6 days), and placebo (Anon. 2005). Eritoran was administered twice daily by intravenous infusion. The goal of this study, with 80% patient compliance, was to test whether eritoran could reduce the 28-day all-cause mortality by at least 5% compared with placebo. The study was not sized to detect a statistically significant difference in mortality and P values were only of exploratory nature. Patients who received high-dose, but not low-dose, eritoran experienced a reduction in 28-day all-cause mortality of 6.4%, compared with placebo recipients (P=0.34). Moreover, patients who were considered to have the highest risk of death experienced reductions in mortality of 13% (P=0.17) and 17.6% (P=0.07) after treatment with low- and high-dose eritoran, respectively, compared with placebo recipients.

A recently published *ex-vivo* laboratory study has also shown that eritoran in doses of 0.03 ng/mL up to 10 ng/mL causes a dose-dependent inhibitory effect on IL-6 and TNF-alfa production in LPS-stimulated human monocytes (Czeslick et al. 2006).

Safety and tolerability

Safe treatment with eritoran requires that it generates no LPS-like response on its own.

In the North American phase II trial the drug appeared to be well tolerated. Phlebitis, or inflammation of the vein, was observed in 6.7% of patients receiving eritoran through a peripheral vein, and showed a tendency to recover with time (Eisai Inc. 2005).

An earlier study to determine safety, pharmacokinetics, pharmacodynamics, and plasma lipoprotein distribution of eritoran during continuous intravenous infusion in healthy volunteers also demonstrated that the drug was safe and well tolerated (Rossignol et al. 2004). This study was a single-center, randomized, double-blind, placebo-controlled, 72-hour infusion, sequential-group study of eritoran in healthy male volunteers (five eritoran-treated and two placebo-treated subjects per dose group). Three doses of eritoran (500, 2000, and 3500 mcg/hour) were studied. Eritoran or matching placebo was administered as a 72-hour intravenous infusion.

Subjects were observed during the 72-hour infusion and for up to 144 hours following infusion. The only adverse events that occurred more than once in these subjects were: headache in three eritoran-treated subjects (19%) versus four subjects (19%) in the placebo group; rhinitis in two subjects (13%) in the eritoran-treated group; and a self-limiting phlebitis in 57% of the subjects in the placebo group versus 83% of the subjects in the eritoran 500 mcg/hour group and all subjects in the 2000 and 3500 mcg/hour groups. Differences in occurrence of phlebitis between subject groups were not statistically significant, and although there was a trend of worsening severity of phlebitis in the higher dose groups, differences again did not reach statistical significance. This was perhaps due to the fact that the study was not powered to draw such a conclusion.

Furthermore, no dose adjustment is needed in patients with hepatic impairment. In a study to assess the pharmacokinetics of eritoran in patients with impaired hepatic function, the drug was administered via intermittent intravenous infusion every 12 hours for six times, to 24 hepatic-impaired patients (12 each to Child-Pugh Classifications A and B) and 24 matching healthy volunteers. The results of the study showed that none of the pharmacokinetic parameters exhibited any difference between these two groups (Liang et al. 2003).

Patient group/population

Available evidence from the North American phase II trial suggests that the greatest benefit of eritoran therapy is likely to be seen in the population at the highest risk of mortality due to sepsis. In patients who were considered at higher risk of death in this trial, mortality was 50.9% among placebo recipients, 37.9% in low-dose patients, and 33.3% in high-dose patients. The reduction of mortality in low- and high-dose patients compared with placebo was 13.0% (P=0.17) and 17.6% (P=0.07), respectively, confirming the survival benefit of eritoran. However, it is important to note that in this study P values were only of exploratory nature.

Eritoran may also be useful in other LPS-related diseases. One such patient group which may benefit from eritoran therapy is the population undergoing cardiac surgery. LPS enters the systemic circulation by leakage from the intestinal lumen during surgery, most likely as a result of mesenteric hypoperfusion (Nilsson et al. 1990). Endotoxin levels are in the range of several 100 pg/mL during cardiopulmonary bypass (Rocke et al. 1987). Further evidence implicates endotoxin as one factor that may contribute to poor surgical outcome after cardiac surgery (Bennett-Guerrero et al. 2007).

A double-blind, randomized, ascending-dose, placebo-controlled study was recently conducted at nine hospitals in North America to evaluate safety of eritoran administration in patients undergoing cardiac surgery and obtained preliminary efficacy data for the prophylaxis of endotoxin-mediated surgical complications (Bennett-Guerrero et al. 2007). Patients undergoing coronary artery bypass graft and/or cardiac valvular surgery with cardiopulmonary bypass were enrolled. Patients

received a 4-hour infusion of placebo (n=78) versus 2 mg (n=24), 12 mg (n=26), or 28 mg (n=24) of eritoran initiated approximately 1 hour before cardiopulmonary bypass. No significant safety concerns were identified with continuous safety monitoring, and enrollment continued to the highest prespecified dose (28 mg). No statistically significant differences were observed in most variables related to systemic inflammation or organ dysfunction/injury.

The fact that the drug may not have been administered long enough or the total dose may have been insufficient, the possibility that endotoxin may be a cause of systemic inflammation but not the primary cause in cardiac surgery patients, and that the trial was not sufficiently powered to determine differences in clinical outcomes, may be some of the reasons that explain the lack of a demonstrable effect of eritoran on variables related to systemic inflammation in cardiac surgical patients.

Clinical potential

Current best available evidence from a single phase II trial of eritoran usage in sepsis suggests that it is a safe and effective therapeutic option for patients with sepsis and is especially beneficial for patients at high risk of mortality. However, it is extremely important to realize that presently there are few data on effects of long-term eritoran therapy for sepsis and other potential indications. The available evidence contributes to a building sense of excitement that eritoran may be an effective treatment in sepsis and other LPS-related disorders, especially as eritoran targets TLRs such as TLR4 and has the ability to block the proinflammatory response to LPS or heat shock proteins. However, the duration of therapy and dosage of eritoran for these conditions has still not been established. Moreover, eritoran therapy in most of the novel LPS-related indications as well as sepsis will require continuous exposure to possibly larger doses, suggesting that adverse effects may be more widespread, contrary to what has been suggested so far by the solitary phase II trial and small single-dose studies. Finally, important data on the economic impact of eritoran therapy and its comparative efficacy with other therapeutic options for management of sepsis as well as its use in the pediatric population are currently missing.

Because so many novel therapies in the past have not lived up to their initial promise, we should protect our patients (and ourselves) and refrain from empirically administering eritoran for treatment of sepsis and other emerging indications at present. Several rigorous, blinded, placebo-controlled, adequately powered multicenter, randomized clinical trials evaluating the impact of eritoran therapy on resource utilization as well as long-term safety and efficacy are required to validate the routine use of this novel TLR4-directed endotoxin antagonist in sepsis.

Acknowledgments

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Correspondence: Shahzad G. Raja, Department of Cardiothoracic Surgery, Harefield Hospital, Hill End Road, Harefield, Middlesex UB9 6JH, UK or at drrajashahzad@hotmail.com