Treating severe sepsis with drotrecogin alfa (activated)

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Severe sepsis is a complex condition with mortality rates ranging from 30 to 50% in spite of advances in critical care. Xigris (drotrecogin alfa (activated)) is associated with an absolute reduction in the risk of death of 6.1% and was granted European Union marketing authorization in August 2002.

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Granted European Union marketing authorization in August 2002, Xigris (drotrecogin alfa (activated), Lilly, Indianapolis) is a recombinant version of the human activated protein C molecule. This novel biotechnology therapy is, when added to current best standard care, approved for the treatment of adults with severe sepsis with multiple organ failure.

DEFINING SEPSIS

Sepsis is complex to diagnose and treat, and until comparatively recently there was no agreement on its precise definition. In 1992, however, a consensus panel of the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) defined sepsis as the systemic inflammatory response to infection based on the clinical criteria shown in *Table 1* (Bone et al, 1992). Severe sepsis is defined as sepsis associated with organ dysfunction. Examples of organ dysfunction include hypoxaemia, oliguria, persistent hypotension despite adequate fluid resuscitation and lactic acidosis as shown in *Table 2*. The commonest types of severe infection are pneumonia, peritonitis resulting from a perforated viscus, urinary and soft tissue infections, and meningitis.

UNDERSTANDING SEPSIS

The normal response to infection and subsequent production of endotoxins or exotoxins is to release inflammatory mediators such as cytokines. These attract activated neutrophils to the site of infection. However, in some individuals, this response results in excessive inflammation, coagulation and impaired fibrinolysis that causes widespread damage to the microcirculation. This occurs through a number of mechanisms, including activation of the extrinsic coagulation pathway and the generation of thrombin, and also upregulates plasminogen activator inhibitor which prevents breakdown of thrombin. There are also decreased levels of natural circulating anticoagulants such as antithrombin III and protein C (Matthay, 2001).

TABLE 1.
American College of Chest Physicians and Society of Critical Care Medicine definition of sepsis

The systemic inflammatory response to infection, including but not limited to, more than one of:
Temperature > 38°C or < 36°C
Elevated heart rate > 90 beats per minute
Tachypnoea (respiratory rate > 20 breaths per minute) or hyperventilation ($PaCO_2$ < 32 mmHg)
Alteration in white blood cell count (>12000/mm^3, <4000/mm^3, or > 10% immature neutrophils)
These physiological changes should represent an acute change from baseline in the absence of other causes for such abnormalities such as chemotherapy and leucopenia

From Bone et al (1992). $PaCO_2$ = partial pressure of arterial carbon dioxide

TABLE 2.
Definitions of sepsis-induced organ dysfunction

Hypotension despite adequate fluid replacement and/or requirement for vasopressors to achieve satisfactory blood pressure
Persistent oliguria despite adequate fluid replacement
Acute hypoxaemia: PaO_2:FiO_2 ratio <33kPa (<26.6 kPa in the setting of pneumonia)
Platelet count < 80x 10^9/litre or a 50% decrease over last 3 days
Sepsis-induced metabolic acidosis and elevated lactate levels

From London New Drugs Group (2002). PaO_2:FiO_2 = partial pressure of arterial oxygen:fractional inspired oxygen

Protein C may be particularly important since severe sepsis reduces its conversion to activated protein C, an important modulator of coagulation, fibrinolysis and inflammatory processes associated with sepsis (Bernard et al, 2001). Activated protein C decreases the formation of thrombin by inhibiting activated factors V and VIII and stimulates fibrinolysis by inhibiting plasminogen-activator inhibitors. It also reduces serum levels of pro-inflammatory cytokines such as interleukin-6 and tumour necrosis factor alpha (TNF-α) (Matthay, 2001) (*Figure 1*).

MORBIDITY AND MORTALITY

Patients with 'sepsis' are not equally ill, since sepsis, severe sepsis and septic shock represent different stages in a disease spectrum and are correlated with increasing organ dysfunction and mortality (International Sepsis Forum, 2001). Severe sepsis remains an important cause of morbidity and mortality throughout the world with mortality rates ranging from 30 to 50% in spite of advances in critical care (Bernard et al, 2001). Analyses from the Case Mix Programme Database provided by the Intensive Care National Audit and Research Centre report that the ultimate hospital mortality for admissions meeting the criteria for severe sepsis within the first 24 hours of admission to adult, general intensive care units (ICUs) in England, Wales and Northern Ireland is 44.7% (Young et al, 2001).

Risk factors for the development of sepsis are shown in *Table 3*. Many of these risk factors have become more common and, not surprisingly, the incidence of severe sepsis is increasing (Balk, 2000). It is difficult to be precise about the number of deaths since sepsis is a progressive syndrome, and death may be attributed to co-morbidities rather than sepsis itself. However, a US study estimated that the incidence of severe sepsis is increasing by 1.5% each year (Angus et al, 2001), while analyses from the Case Mix Programme Database provided by Intensive Care National Audit and Research Centre report an increasing prevalence of severe sepsis in the first 24 hours in adult, general ICUs in England, Wales and Northern Ireland: 26.3%, 27.4% and 29.6% in 1997, 1998 and 1999 respectively (Padkin et al, 2001).

There are currently about 21 000 admissions with severe sepsis to ICUs in England and Wales each year (Padkin et al, 2001) and the economic implications for the NHS are obvious. Such direct costs include those for staff, ICU beds and equipment, diagnostic equipment, treatment and increased length of hospital stay, but sepsis also causes indirect costs from lost income and reduced productivity. For patients who survive severe sepsis, the implications are serious, and include pain, disability, and psychological morbidity for both the individual and family,

Figure 1. Proposed actions of activated protein C (aPC) in modulating the systemic inflammatory, procoagulant and fibrinolytic host responses to infection. From Bernard et al (2001). IL = interleukin; PAI-1 = plasminogen activator inhibitor type 1; TAFI = thrombin activatable fibrinolysis inhibitor; TNF = tumour necrosis factor.

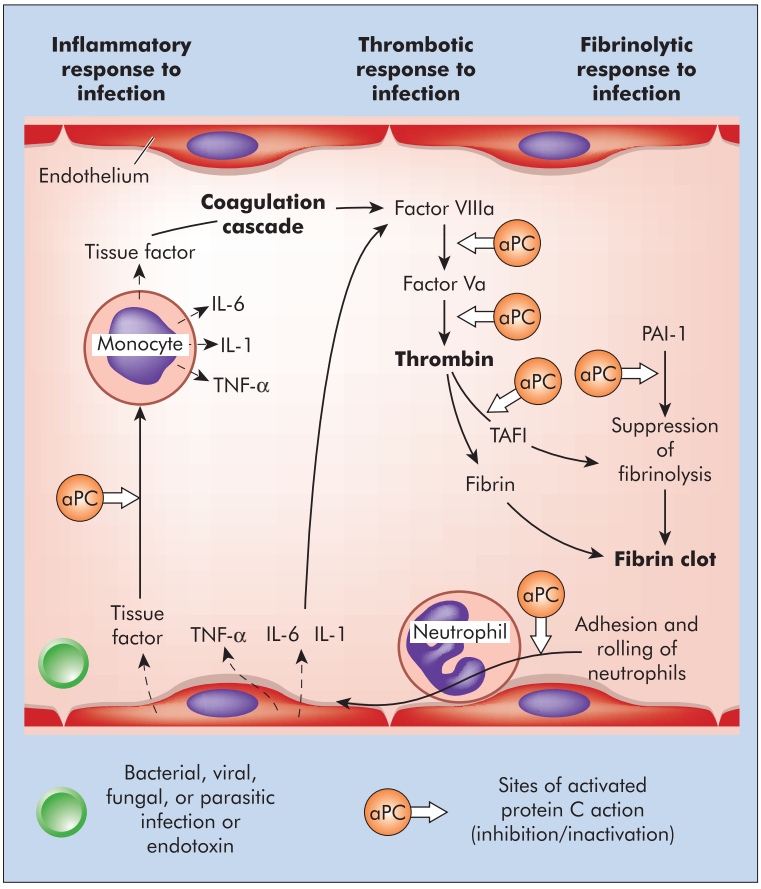

TABLE 3.
Risk factors for the development of sepsis

Acquired immunodeficiency syndrome
Treatment with cytotoxic or immunosuppressant agents
Malnutrition
Alcoholism
Malignancy
Diabetes mellitus
Organ transplantation
Use of aggressive invasive procedure in diagnosis and treatment
Resistant micro-organisms
Old age

From Balk (2000)

together with long-term reductions in health-related quality of life following discharge (Heyland et al, 2000).

CURRENT MANAGEMENT

Sepsis is one of the most challenging conditions to manage as its course and clinical manifestations vary widely between patients. However, timely diagnosis and treatment are essential to avoid rapid deterioration and death. A patient with sepsis is already critically ill – and the outlook is even worse with severe sepsis – so treatment has to be initiated before confirmation of the diagnosis.

Blood cultures should be taken as soon as possible after the onset of symptoms such as fever or chills. The early administration of effective antibiotic therapy reduces the risk of septic shock and mortality (Balk, 2000). Consequently, current practice is to initiate treatment with broad-spectrum antibiotics, which can be narrowed once the type of infection has been identified. The choice of antibiotic is based on the probable source of infection, local patterns of resistance and the individual patient's condition. Antifungal therapy can be initiated in patients at risk of candidaemia.

Other therapies are mainly supportive. In hypotension, intravenous fluids restore circulating volume and improve tissue perfusion. However, therapy with vasopressor agents such as norepinephrine is required in many patients. Support for failing organs is clearly essential, and patients often require mechanical ventilation and, less frequently, renal replacement therapy. Nutritional support should be established and prophylaxis for deep vein thrombosis initiated. Once stabilized, patients may require surgical drainage or debridement of infected material if relevant (e.g. empyema).

XIGRIS

Because of the role of inflammation in the aetiology of sepsis (see above), there has been considerable interest in the use of anti-inflammatory and immunological therapeutic agents. However, the current consensus is that there is little evidence to support the use of compounds such as ibuprofen, prostaglandins, selenium, antithrombin III, tissue factors, antibodies directed at TNF-α, or immunoglobulins (International Sepsis Forum, 2001). Similarly, high-dose, short-course corticosteroids should not be used in severe sepsis. However, corticosteroids are recommended if used in low doses for about 7 days in patients with 'refractory' septic shock, associated with relative adrenocortical insufficiency (International Sepsis Forum, 2001).

Until recently, therefore, there was no specific medical treatment for severe sepsis. This has changed with the availability of Xigris, recombinant human activated protein C that has been modified so that its antithrombotic and inflammatory activity is enhanced compared with that of native activated protein C. Administration of Xigris therefore replaces native activated protein C that, as discussed above, is depleted during severe sepsis. Promising results were achieved in animal and human phase II studies, but approval of Xigris is based on the results of the phase III PROWESS trial (Bernard et al, 2001).

PROWESS

PROWESS (Recombinant Human Activated PROtein C Worldwide Evaluation in Severe Sepsis) was a prospective, double-blind, placebo-controlled study conducted in 164 centres in 11 countries. A total of 1690 patients were randomized – recruitment criteria are shown in *Table 4* – with 850 randomized to active treatment and 840 to placebo. Active treatment consisted of Xigris at a dose of 24 μg/kg body weight for a total of 96 hours.

Patients began treatment within 24 hours of meeting the study inclusion criteria. The infusion was interrupted 1 hour before any percutaneous procedure or major surgery, resuming respectively 1 and 12 hours later in the absence of bleeding complications. Otherwise there was no standardized approach to treatment, and clinical management was based on individual need as assessed by the local centre. The primary efficacy end point was death from any cause, assessed 28 days after the initiation of the infusion.

PROWESS originally intended to enrol 2280 patients, but the study was stopped at the second interim analysis because of a statistically significant reduction in mortality in favour of Xigris. Twenty-eight days after the start of the infusion, 259 (30.8%) patients in the placebo group had died compared with 210 (24.7%) in the Xigris group – an absolute reduction in the risk of death of 6.1% and a relative reduction of 19.4% (Bernard et al, 2001). As a consequence, the Data Safety Monitoring Board deemed it unethical to continue to randomize patients to receive placebo. In a subsequent trial, which followed 1221 PROWESS survivors for up to 2.5 years, the reduction in mortality was sustained (P=0.097) and over the first 90 days survival benefit was significantly

improved (P=0.048) in patients treated with Xigris (Angus et al, 2002).

In PROWESS, there were no differences between the two groups when patients were stratified according to prospectively defined criteria such as baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) score, age and protein C activity. However, the absolute difference in survival between active and placebo was seen within days of the start of the infusion and continued to increase throughout the study period (Bernard et al, 2001).

A similar percentage of patients in the two groups had at least one serious adverse event. The incidence of serious bleeding was similar, except during infusion when it was higher in the Xigris treated group. In both groups serious bleeding occurred primarily in patients with an identifiable risk factor, such as gastrointestinal ulceration, haematological abnormalities, or traumatic injury to a blood vessel or highly vascular organ. There were no other safety concerns associated with active treatment based on assessment of organ dysfunction, vital signs, or inflammatory markers. There was a similar number of new infections in both groups (25.5% in the active group *vs* 25.1% in the placebo group), and no patient developed neutralizing antibodies against activated protein C (Bernard et al, 2001).

The PROWESS study has been subject to further scrutiny from some members of the Food and Drug Administration (FDA) Anti-Infective Drugs Advisory Committee who voted to reject approval of Xigris based on their interpretation of the clinical findings. The FDA states, however, that 'the data currently available for APC strongly support the conclusion that use of APC as labelled will save many lives as we gather the information necessary to further refine its use' (Food and Drug Administration, 2000). With regards to exclusion criteria, the amendment executed in the PROWESS trial was done in a blinded fashion before the first interim analysis of the trial. The amendment was deemed, following an extensive independent review by the FDA, not to have had an effect on the outcome of the trial.

HEALTH OUTCOMES

In PROWESS there was no difference in length of stay between patients receiving Xigris and placebo, both when comparing 28-day survivors and 28-day non-survivors. Although survivors had a longer ICU stay than non-survivors (≈13 days *vs* ≈8 days), the overall difference in length of stay and therapeutic burden was not significant for patients treated with Xigris.

The cost-effectiveness of Xigris under UK treatment patterns has recently been examined in patients meeting the European licence criteria – that is, the treatment of adult patients with severe sepsis with multiple (two or more) organ failure when added to best standard care. In this subgroup analysis, the absolute risk reduction in hospital mortality at 28 days was 7.3%. The mean ICU length of stay was the same for hospital survivors and non-survivors (means of 8.6 *vs* 8 days respectively), although there was a difference in total ward stay between hospital survivors and non-survivors (24.7 *vs* 12 days respectively) (Davies et al, 2002).

TABLE 4.
Criteria for recruitment to PROWESS

Inclusion criteria	Known or suspected infection based on clinical data at screening
	With a 24-hour period ≥ three signs of systemic inflammation and sepsis-induced dysfunction of at least one organ or system lasting no longer than 24 hours
Exclusion criteria	Pregnancy or breast feeding
	Age < 18 years or weight > 135 kg
	Platelet count < 30 000/mm^2
	Conditions that increase the risk of bleeding or known hypercoagulable conditions
	Patient not expected to survive 28 days because of uncorrectable medical condition or death perceived to be imminent
	HIV infection associated with last known CD4 count of ≤ 50/mm^2
	History of bone marrow, liver, pancreas or small bowel transplantation
	Chronic (not acute) renal failure treated with haemodialysis or peritoneal dialysis
	Known or suspected portosystemic hypertension, chronic jaundice, cirrhosis or chronic ascites
	Acute pancreatitis with no established source of infection
Medical treatment resulting in exclusion from PROWESS	Unfractionated heparin to treat an active thrombotic event within 8 hours before the infusion
	Low-molecular-weight heparin at a higher dose than recommended for prophylactic use (as specified in the package insert) within 12 hours before the infusion
	Warfarin (if used within 7 days before study entry and if the prothrombin time exceeded the upper limit of the normal range for the institution)
	Aspirin at a dose >650 mg/day within 3 days before the study
	Thrombolytic therapy within 3 days before the study
	Glycoprotein IIb/IIIa antagonists within 7 days before the study
	Antithrombin III at a dose >10 000 U within 12 hours before the study

From Bernard et al (2001) HIV = human immunodeficiency virus; PROWESS = Recombinant Human Activated PROtein C Worldwide Evaluation in Severe Sepsis

Davies also calculated the cost per quality-adjusted life year to be £6835 (Davies et al, 2002). The benchmark for cost-effectiveness currently used by the National Institute for Clinical Excellence (NICE) is £30 000 per quality-adjusted life year (Timmins, 2001).

IMPLICATIONS FOR CLINICAL PRACTICE

Further, larger studies are underway to assess the role of Xigris in patients who were excluded from PROWESS. For example, the treatment is being investigated in 500 patients aged under 18 years, while another study will enrol 11 444 adult patients with early stage severe sepsis with lower APACHE II scores and/or single organ failure.

It is not clear how many of the approximately 23 000 adults admitted annually to ICUs in the UK with severe sepsis would be suitable for treatment with Xigris. However, data from the adult ICU at St Thomas' Hospital, which has collected a sepsis log for the last 18 months, suggests that it may amount to 20–25% of all sepsis patients (London New Drugs Group, 2002).

Clearly, any new treatment should be introduced properly into the NHS, but awaiting the verdict from NICE should not be used as a reason to deprive appropriate patients of the potential benefits of Xigris. According to the PROWESS investigators, Xigris plus best standard care reduced the risk of death in one in every 16 patients in the study population (Bernard et al, 2001). Twenty-five per cent of patients in the PROWESS trial had single organ dysfunction. This means that in practice the number needed to treat to save one life should be 14, rather than 16. This is a very low number needed to treat compared with many other standard medical therapies, but is especially attractive when treating patients with this potentially devastating illness. It clearly demonstrates that Xigris is an important advance in the management of severe sepsis. **HM**

Conflict of interest: Dr Wyncoll was a key triallist in the ENHANCE trial and is involved in ongoing studies with APC. He is reimbursed for travel expenses by Eli Lilly and Company Ltd to attend meetings.

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KEY POINTS

- Severe sepsis is a complex condition to diagnose and treat. It is associated with a ultimate hospital mortality of 44.7%.
- There are currently about 21 000 admissions with severe sepsis to intensive care units in England and Wales each year.
- Xigris (drotrecogin alfa (activated)), a recombinant version of the human activated protein C molecule, was granted European Union marketing authorisation in August 2002.
- Xigris is associated with an absolute reduction in the risk of death of 6.1%.
- The cost per quality-adjusted life year of Xigris is £6835. The benchmark for cost-effectiveness currently used by the National Institute for Clinical Excellence is £30 000 per quality-adjusted life year.