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Anti-cytokine and anti-inflammatory therapies for the treatment of severe sepsis: progress and pitfalls

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The medical care of patients with sepsis or severe inflammatory response syndromes has seen tremendous technological advancements in recent years; yet, several clinical studies with anti-cytokine therapies targeted to this population have met with disappointing results. Four primary factors have been identified that represent potential pitfalls involving the use of biological response modifiers in critically-ill patients. First, the physiological response in the stressed patient is complex. Redundancy within this system may not allow a single intervention to produce a clinical response. Second, the critically-ill patient population is heterogeneous and important factors including the age of the patient, associated co-morbidities, the nature of the original injury and the presence or absence of an ongoing injury can modulate the effectiveness of a specific therapy. Third, the timing of the therapeutic intervention can be difficult to standardize among patients and can often produce differing results. A greater understanding of the physiological response to injury has shown that there are both proinflammatory and anti-inflammatory processes ongoing simultaneously. Determining the optimal time to intervene within this framework can be problematic. Fourth, the presence of genetic polymorphisms within the general population has identified subsets of individuals who may have different physiological responses to similar stresses. The relative proportions of patients with these polymorphisms within clinical trials may affect outcome and data analysis. Thus, a better understanding of these issues will result in improvement of the experimental design of clinical trials involving anti-cytokine therapies and critically-ill patients. Avoidance of these pitfalls will enhance the quality and utility of outcomes research in this subset of patients.

Clinical trials: Critical care: Sepsis: Genetic polymorphism

The systemic inflammatory response syndrome (SIRS) refers to the inflammatory state resulting from a variety of injuries including trauma, burns, ischaemia–reperfusion, infection or pancreatitis. The clinical criteria for the diagnosis of SIRS include changes in core body temperature (>38 °C or <36 °C), tachycardia (heart rate >90 beats/min), tachypnea (respiration rate >20 breaths/min) and alterations in leucocyte number or composition. Specifically, the leucocyte alterations may include leucocytosis (>12 000 cells/mm³), leucopenia (<4000 cells/mm³) or the presence of >10% immature leucocyte forms. SIRS accompanied by a focus of infection defines sepsis. Sepsis may be associated with hypotension (septic shock) or may progress to multiple organ dysfunction syndrome (MODS; Mandell et al. 2000). The term ‘sepsis syndrome’ has been proposed as a replacement for the generalized term ‘sepsis’ in order to include those patients demonstrating the physiological indices of sepsis without a documented infection (Fry, 2000).

In 2004 the treatment of sepsis still consists primarily of supportive measures for the failing organ systems. Patients may require mechanical ventilation for respiratory failure, inotropic and vasopressor support for cardiac failure or dialysis for renal failure (Cecil et al. 2000). The addition of antibiotic therapy during the middle of the twentieth century markedly reduced the mortality from sepsis (Martin

Abbreviations: MODS, multiple organ dysfunction syndrome; SIRS, systemic inflammatory response syndrome; VNTR, variable number of tandem repeats.

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et al. 2003). Since that time, however, there have been relatively few therapeutic advancements that have produced clinical improvement (Wheeler & Bernard, 1999). The annual incidence of sepsis in the USA has been estimated at 750,000 cases. Despite refinements in mechanical ventilation and haemodynamic monitoring, the annual mortality remains >200,000 patients (Angus et al. 2001). The modern intensive care unit has become replete with technological advancements in an effort to provide the highest quality of care to this segment of patients. In the era of evidence-based medicine numerous clinical trials have been conducted to assess the benefit of these therapeutic interventions. Only one therapy specifically aimed at the metabolic basis of care to this segment of patients. In the era of evidence-based medicine numerous clinical trials have been conducted to assess the benefit of these therapeutic interventions. Only one therapy specifically aimed at the metabolic basis of care to this segment of patients.

Experimental models of systemic inflammation have been conducted in rodents and primates in an effort to recreate the physiological response in man (Tracey et al. 1986, 1987a,b; Fischer et al. 1991, 1992; Hinshaw et al. 1990, 1992). Exaggerated TNF-α and IL-1 production has been shown to be central to the initiation of the proinflammatory response. Preclinical studies in primates have shown good effectiveness when the drugs are administered before the inflammatory challenge (Fischer et al. 1992; Van Zee et al. 1996; Rosenberg et al. 2001). As a result of these preclinical studies, several clinical trials have examined therapies directed against TNF-α and IL-1. These therapies have included monoclonal antibodies against TNF-α (Fischer et al. 1993; Cohen & Carlet, 1996; Abraham et al. 1995, 1998), soluble TNF receptors (Fischer et al. 1996; Abraham et al. 1997), IL-1 receptor antagonists and soluble IL-1 receptors (Fisher et al. 1994a,b,c; Opal et al. 1997). Despite the encouraging results of similar interventions in experimental models, these agents have failed to demonstrate a decrease in the primary end point of all-cause 28 d mortality in phase II and III clinical studies (Zeni et al. 1997; Baue, 2000).

As previously noted, only one biological response modifier has been approved for the treatment of severe sepsis, Bernard et al. (2001) have published the results of a randomized double-blind placebo-controlled multicentre trial evaluating the effect of drotrecogin alpha activated, Xigris™, on mortality in patients with severe sepsis. Xigris™ is recombinant human-activated protein C, which has demonstrated anti-thrombotic, anti-inflammatory and procoagulant properties. In this study a total of 1690 patients were randomized to Xigris™ or placebo with the primary end point of all-cause 28 d mortality. The treatment group showed a significant 6.1% absolute risk reduction in mortality (19.4% relative risk reduction). The administration of drotrecogin alpha activated has been the first clinical modulation of the systemic inflammatory response that has achieved widespread use.

**Problems with clinical trials involving the systemic inflammatory response**

Before data on drotrecogin alpha activated became available, there had been several attempts to modulate the systemic inflammatory response that did not produce a significant reduction in mortality. These results were especially discouraging, because the preclinical data in experimental models had shown therapeutic benefit and were highly reproducible. Reviews of the major clinical trials involving the inflammatory response have suggested several reasons why these approaches may have failed to show a therapeutic benefit (Abraham, 1999). These factors include the complexity of the physiological response to injury, the heterogeneity of the patient population being studied, the timing of therapeutic intervention and the presence of genetic polymorphisms in the general population (Huber et al. 2000).

**Complexity of the physiological response to injury**

As stated previously, experimental models have identified TNF-α and IL-1 as central mediators of the proinflammatory response. These same models have demonstrated a decreased inflammatory response when TNF-α and IL-1 inhibitors are administered following an endotoxin or Gram-negative bacteraemic challenge. In the clinical setting, however, there may be multiple injurious stimuli of different durations. The physiological response to ongoing infection in the setting of pre-existing co-morbidities is not likely to be equivalent to that encountered with a single infusion of endotoxin. In addition, the systemic inflammatory response involves a complex series of physiological changes regulated by numerous cytokines that may exhibit redundancy of certain pathways (Oberholzer et al. 2001). The inhibition of one of these mediators may not be sufficient to alter the end result of the inflammatory response. In recognition of this difficulty Glauser (2000) has proposed that inhibition of the bacterial components or the resulting intracellular pathways may be a more effective strategy.

**Heterogeneity of the patient population**

SIRS and sepsis are not specific disease entities by themselves; rather, they represent a physiological response to
a variety of clinical situations. Potential stimuli include trauma, thermal injury, ischaemia–reperfusion, infection or pancreatitis. Each of these injuries produces a systemic inflammatory response that may progress to MODS. Sepsis and MODS represent the culmination of numerous clinical scenarios involving patients of all ages with varying comorbidities. Entry criteria for clinical trials must account for these variations in order to ensure comparable patients for outcome analysis (Huber et al. 2000).

Timing of the therapeutic intervention

The appropriate time of therapeutic intervention relative to the patient’s clinical course can be crucial to the outcome. Administration of a therapeutic agent following the establishment of sepsis may be ineffective, while dosing too early may produce immune suppression and an increased rate of infectious complications (Grau & Maennel, 1997). In addition, a greater understanding of the inflammatory response has led to the notion of the development of a compensatory anti-inflammatory response syndrome that follows SIRS, with intervening periods of mixed anti-inflammatory response syndrome (Bone, 1996a; Oberholzer et al. 2001). Compensatory anti-inflammatory response syndrome is characterized by defects in antigen presentation, T-cell anergy, suppressed T-cell proliferation and an increase in T-cell and B-cell apoptosis (Bone, 1996b). This relative period of immunosuppression may predispose the patient to iatrogenic infection that could ultimately potentiate the inflammatory response and lead to progression to MODS. SIRS, compensatory anti-inflammatory response syndrome and mixed anti-inflammatory response syndrome vary in the presence and time-course of each component within individual patients; thus, determining the optimal time to administer a specific anti-cytokine therapy can be problematic (Oberholzer et al. 2001).

Genetic polymorphisms in the general population

Knowledge of stable genomic variation as provided by the Human Genome Project has identified components of the inflammatory cytokine cascade that affect an individual’s response to a stimulus (Tabrizi et al. 2001). A recent review has examined the prevalence of several genetic polymorphisms as they relate to outcomes of patients with sepsis (Feezor & Moldawer, 2003). Examples of polymorphisms include single nucleotide polymorphisms and variable numbers of tandem repeats (VNTR). Single nucleotide polymorphisms are single nucleotide substitutions within the sequence of an allele. A VNTR is a duplication of a short segment of non-coding DNA that is arranged in tandem (Feezor & Moldawer, 2003).

Polymorphisms of clinical relevance have been described for TNF-α, IL-1α, IL-1β, IL-1 receptor antagonist, IL-10, IL-6, NF-κB and CD14. Genetic polymorphisms that have been examined in patients demonstrating clinical criteria of the sepsis syndrome include the following examples. A single nucleotide polymorphism for TNF-α present in 20% of the general population has been found in 39% of patients with septic shock and is associated with a 3.7-fold increased risk of death (Mira et al. 1999). Patients homozygous for an IL-1 receptor antagonist VNTR have a >2-fold increase in the relative risk of developing severe sepsis (Fang et al. 1999). Septic patients homozygous for an IL-1α VNTR demonstrate higher mortality rates than non-carriers of the VNTR or patients that are heterozygous for the IL-1α VNTR (Ma et al. 2002). Preliminary data have suggested a survival benefit for patients homozygous for an IL-6 single nucleotide polymorphism (Schluter et al. 2002).

Genetic polymorphisms may be one explanation for the variable outcomes that occur in patients with seemingly the same injury. For example, two physiologically-equivalent patients may undergo the same operative procedure without incident. While one patient develops no post-operative complications, the other patient may demonstrate an increased inflammatory response to the surgical injury with subsequent MODS. Genetic polymorphisms that confer a predisposition to develop an exaggerated inflammatory response introduce an additional variable in the assignment of critically-ill patients to treatment protocols as part of clinical trials. This technology may also allow the preoperative identification of patients at increased risk of a poor outcome from a given stimulus.

Conclusions

At the beginning of the twenty-first century the SIRS and sepsis syndrome with MODS remain a major public health problem consuming substantial resources (Angus et al. 2001). A greater understanding of the cytokine cascade has prompted many clinical trials attempting to modulate the inflammatory response. With the exception of drotrecogin alpha activated in severe sepsis, the results of these trials have not demonstrated a significant reduction in mortality. Some of the reasons why these interventions, which were successful in preclinical experimental models, may have failed to show an improvement in mortality have been outlined. These reasons include the complexity of the physiological response, the heterogeneity of the patient population, the timing of the intervention and the presence of genetic polymorphisms affecting the patient’s response to a stimulus. Future experimental designs that account for these shortcomings may provide more accurate outcome data.

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