Commentary

Coagulation cascade in sepsis: getting from bench to bedside?

Glen Brown

Clinical Coordinator, Pharmacy Department, St. Paul's Hospital, Vancouver, British Columbia, Canada

Correspondence: Glen Brown, gbrown@providencehealth.bc.ca

Published online: 6 November 2002 *Critical Care* 2003, **7**:117-118 (DOI 10.1186/cc1842)
This article is online at http://ccforum.com/content/7/2/117

Abstract

The relationship between blood coagulation factors and the promotion or inhibition of the anti-inflammatory response continues to be defined through basic research. The potential key role of blood coagulation factors in the response during sepsis provides an exciting potential mechanism(s) for modification through the application of new therapies. The complexity of the potential multiple actions of the proteins, such as protein C, should allow for development of new therapies to minimize the detrimental inflammatory response. However, several gaps in our current understanding must be bridged before the clinician can take the basic knowledge 'to the bedside', where individual patients will benefit.

Keywords blood coagulation factors, protein C, sepsis

The relationship between the clotting cascade and the promotion or inhibition of the anti-inflammatory response continues to be defined through basic research. The potential key role of proteins that were originally believed to be exclusively involved in coagulation in the inflammatory response provides an exciting potential mechanism(s) for modification through the application of new therapies. The accompanying review by Riewald and Ruf [1] outlines the available information on the possible steps involving some of the various proteins that are common to both coagulation and inflammation. The complexity of the multiple actions of the proteins in both inflammation and coagulation should excite the clinician with regard to potential new therapies that may be beneficial via activation of one or both of the concurrent pathways [2]. However, before clinicians can administer new therapies that utilize new knowledge on the actions of coagulation cascade components, and hence improve the outcomes of their patients, several gaps in our current understanding must be addressed. This information is imperative if the clinician is to take basic knowledge 'to the bedside', where individual patients can benefit.

Optimum balance between pro-/anti-coagulation and pro-/anti-inflammation

Administration of intrinsic or synthetic analogues of coagulation cascade components (e.g. protein C, thrombin, and factor VIIa or Xa), coagulation inhibitors (e.g. heparin or analogues), or agonists or antagonists of the protease-activated receptors, in an attempt to alter the individual patient's coagulation/inflammation balance, could theoretically produce responses ranging from beneficial to detrimental. Knowledge of the 'most beneficial' balance between augmenting or inhibiting the contribution of the clotting cascade components to inflammation would be required for determining the selection and dosing of potential new therapies.

Altering the intrinsic balance of coagulation and inflammation: detrimental consequences

A safe assumption is that any new therapies that alter the intrinsic response to coagulation and inflammatory stimulants would also potentially produce detrimental effects on these, and potentially other, physiological responses. A simple example of such a potential for detrimental effects is the administration of protein C resulting in undesirable haemorrhage [3]. This example illustrates that a broader knowledge of the impact of altering the coagulation/inflammatory response will be required before clinicians can comfortably utilize new therapies in patient care.

Patient variables that must be considered if the balance is to be altered

All critically ill septic patients are not the same. It is unlikely that any new therapies resulting from the new knowledge of

the contribution of the clotting cascade to inflammation can be applied to all patients. It can be anticipated that certain patients would have contraindications to the new therapies or that dosages would need to be adjusted on the basis of pharmacokinetic or pharmacodynamic variables. The clinician will need to know what these contraindications and variables are before the new therapies can be used confidently. Some, such as coagulation disorders, may be known and obvious, but any new strategies that could potentially alter the balance of a complex physiological response may be anticipated to be influenced by many, as yet unknown, factors in the individual patient. An example is the concurrent administration of heparin, which appears to antagonize the anti-inflammatory effect of antithrombin III in septic patients [4]. A more complete understanding of the impact of concurrent conditions, therapies and the patient's genetic make-up on outcome will be required if we are to obtain the maximum benefit from new therapies.

Assessing individual intrinsic response at the bedside

For any new therapy resulting from our expanded knowledge of the clotting cascade in the inflammatory response to be tailored to the needs of the individual patient, a method(s) for rapidly and easily assessing the patient's dynamic inflammatory response will be required. Unless any new therapies have very benign toxicities, the need to assess the need, dosage and response to treatment will mandate sensitive and specific monitoring techniques. Bedside or clinical laboratory techniques that could be applicable to most clinical environments would allow the benefit of any new therapies to be applied to the greatest number of patients. Conversely, any new treatments that require complex, laborious monitoring techniques will have limited applicability.

What agents have the 'best' activity in altering the intrinsic coagulation/inflammation balance?

As our knowledge of the contribution of the intrinsic coagulation components increases, the development of many potential new therapies will hopefully emerge for clinical use. These may be totally new therapeutic entities or new strategies for using existing drugs or clotting factors. Such developments will create the new dilemma for the clinician, namely that of trying to select between different treatment options for the individual patient. Clinical trials outlining the potential anticipated benefit(s) and the appropriate target patient population for each new therapeutic strategy will need to be completed. This will allow the clinician to ensure that the most appropriate strategy can be selected for the individual patient.

Conclusion

The above-mentioned concerns aside, the clinician should be excited about the expanding knowledge of the role of coagulation cascade components in modifying the inflammatory response [5]. Such knowledge will hopefully result in new strategies and therapies to manage the septic patient. Previous knowledge and therapeutic attempts have been disappointing [6].

Conflicting interests

None declared.

References

1. Riewald M, Ruf W: **Role of coagulation protease cascades in sepsis.** *Crit Care* 2003, **7**:123-129.
2. Marshall JC: **Modulation of the systemic inflammatory response in sepsis: current status, future prospects.** *Crit Care Rounds* 2001, **2**:1-6.
3. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group: **Efficacy and safety of recombinant human activated protein C for severe sepsis.** *N Eng J Med* 2001, **344**:699-709.
4. DePalo V, Kessler C, Opal SM: **Success or failure in phase III sepsis trials: Comparison between drotrecogin alfa (activated) and antithromin III clinical trials.** *Adv Sepsis* 2001, **1**: 144-124.
5. Healy DP: **New and emerging therapies for sepsis.** *Ann Pharmacother* 2002, **36**:648-654.
6. Vincent JL, Wun Q, Dubois MJ: **Clinical trials of immunodulatory therapies in severe sepsis and septic shock.** *Clin Infect Dis* 2002, **34**:1084-1093.