Commentary

Immune modulation in the treatment of respiratory infection

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Abstract

The limitations of currently available treatment for severe respiratory infection are demonstrated by the relatively fixed mortality associated with these infections despite advances in nutrition, vaccines, antibiotics, and critical care. This might be due in part to the changing spectrum of pathogens and development of drug resistance. Cytokines are potent molecules that function as growth factors and orchestrate both innate and adaptive immune responses. Several of these factors have entered the clinical arena to support or augment the immune response. Moreover, the use of cytokines has recently been expanded to patients without an overtly defective immune system but who have either significant infection or infection with drug resistant organisms. The use of cytokines as adjuvants in the treatment of respiratory infections is reviewed.

Keywords: cytokine, gene therapy, immunotherapy, pneumonia

Critical factors that determine the severity of a respiratory infection include the strain of the pathogen, specific virulence factors of the pathogen, and often the integrity of the pulmonary host defense response. Acquired defects include abnormal mucociliary clearance associated with cigarette smoking [1] to co-morbid conditions such as diabetes mellitus [2], ethanol abuse [3], and an abnormal hematopoietic or immune response to the invading pathogen [4]. Among these host factors, neutropenia at the time of presentation has been shown to be an independent variable correlated with mortality. Over the past decade and a half there have been several trials of anti-inflammatory agents in patients with severe pneumonia who developed sepsis or the systemic inflammatory response syndrome. The trials have included inhibitors of tumor necrosis factor-α (TNF) [5] and endotoxin [6,7]. The rationale for these trials was based on preclinical models of endotoxin-induced sepsis demonstrating a survival benefit if pro-inflammatory cytokines were neutralized [8]. Why have these clinical trials failed to show a survival benefit, or in some cases an adverse effect on survival? Some investigators have suggested that the timing of anti-inflammatory therapy might be too late, that patient selection was not ideal, or that the preclinical models of sepsis

CAP = community-acquired pneumonia; G-CSF = granulocyte-colony stimulating factor; HLA-DR = human leukocyte antigen-DR; TNF = tumour necrosis factor.

were not an accurate reflection of human disease. Furthermore, it is now known that many of these cytokines, specifically TNF, are critical to host defense against both intracellular and extracellular pathogens [9–12].

Moreover, these pro-inflammatory molecules are relatively compartmentalized to the site of infection in pneumonia patients [13–15]. However, there are data to suggest that in severe infection and lung injury the inflammatory response is not compartmentalized, and thus the infection can lead to a systemic inflammatory response, which might be associated with other organ injury [16–19]. In fact it has recently been shown that patients with sepsis/systemic inflammatory response syndrome have an 'immunoparalysis' and are in fact, immunosuppressed [20,21]. This has led to the use of growth factors or cytokines to augment the host response to infection. Not all growth factors or cytokines show this compartmentalized response; for example, data from our laboratory and others demonstrate that granulocyte-colony stimulating factor (G-CSF), a critical growth factor for neutrophil production and maturation, is released in the lung in response to a bacterial challenge and is readily detectable in the serum within 2 h [22]. This makes teleological sense in the fact that an infected organ would need to send signals to the bone marrow for a continued supply of neutrophils, which are required for a sufficient host defense response.

On the basis of favorable preclinical studies with G-CSF, clinical trials have been initiated in community-acquired pneumonia (CAP), multilobar pneumonia, and pneumonia with sepsis. Hustinx *et al* [23] compared neutrophil function and phenotype in the blood and bronchoalveolar lavage fluid of 10 patients with severe ventilator-dependent pneumonia, at baseline and after the initiation of G-CSF treatment as an adjunct to standard therapy. These investigators showed that treatment with G-CSF was associated with a threefold increase in blood neutrophil count at day 3 of treatment compared with baseline counts [23]. Mean serum G-CSF concentration increased from 313 to 2007 pg/ml. The mortality in this group of 10 patients was 30% and compared favorably with the predicted mortality of 60%, derived from APACHE II. These data suggested that G-CSF might be an effective immunomodulator in a variety of non-neutropenic settings such as hospital-acquired pneumonia or in persons immunosuppressed by alcohol.

Recently, a phase III, randomized, double blind, placebo-controlled trial of G-CSF for CAP in hospital has been completed [24]. Over 756 patients were enrolled in this multicenter trial in the USA, Canada, and Australia. Patients were randomized to receive 300 μg/day of G-CSF subcutaneously or placebo in addition to conventional antibiotic therapy. The duration of treatment was up to 10 days. Primary objectives were to determine the safety and efficacy of G-CSF in this patient population and the effect on the time to resolution of morbidity [25] (TRM), which was a clinical index of factors associated with the need for continued treatment in hospital. The TRM was 4 days in both groups and G-CSF was well tolerated. Mortality was only 6% in this study and no significant difference was seen between groups in this variable. G-CSF treatment resulted in a threefold increase in peripheral blood neutrophil count. *Post hoc* analysis showed faster radiological resolution in patients treated with G-CSF, which was associated with fewer complications including adult respiratory distress syndrome and disseminated intravascular coagulation.

G-CSF has also been studied in 18 patients with pneumonia and severe sepsis [22]. The patients were randomized 2:1 to G-CSF (300 μg/day given intravenously) or placebo for a maximum of 5 days. Inclusion criteria were a chest X-ray compatible with pneumonia, an identifiable pathogen, fever, tachycardia, tachypnea, or need for ventilator support, and either hypotension despite volume resuscitation requiring vasopressors or, in the absence of shock, two end-organ dysfunctions. Four of six placebo-treated patients died and three of twelve G-CSF patients died. Septic shock was resolved in nine of ten G-CSF patients and in none of the control patients. G-CSF was well tolerated; on the basis of these favorable trends further studies in multilobar pneumonia and severe pneumonia with sepsis were initiated. They have recently been completed and are under analysis.

IFN-γ has been investigated in patients with immunoparalysis associated with sepsis. Docke and colleagues have shown that downregulation of monocyte human leukocyte antigen (HLA)-DR expression identifies a subgroup of septic patients with a higher risk of hospital-acquired infection [20]. Moreover, the investigators showed that the administration of IFN upregulated HLA-DR expression, increased lipopolysaccharide-induced TNF responses *ex vivo*, and improved clinical parameters of sepsis in eight of nine patients treated with IFN [20]. IFN has also been investigated as an aerosol in patients with persistent *Mycobacteria avium* complex (MAC) infection in hosts not infected with HIV and in multidrug resistance tuberculosis. Williams and colleagues from our group recently reported on a phase I trial of aerosol-administered IFN to patients with persistent MAC infection [26]. All patients tolerated the aerosol well and three of eight had sputum smears for acid-fast bacilli (AFB) that converted to negative. Condos *et al* [27] have recently reported five patients with multidrug resistant tuberculosis who received 500 μg of IFN aerosol-administered three times a week for 1 month [27]. Again, the drug was well tolerated and all patients had sputum smears for AFB that converted to negative and a time to positive culture that increased (from 17 to 24 days; not significant), suggesting a reduction in organism burden. In addition,

patient weight increased or stabilized, and there were objective decreases in the size of cavitary lesions in all patients for up to 2 months after treatment had ended.

There has clearly been a paradigm shift in recent years from inhibiting pro-inflammatory cytokines to selectively augmenting the cytokine response within a specific compartment in infected patients that have some objective parameter of immunoparalysis. Which specific cytokines or growth factors have the greatest therapeutic index and what patient population(s) will derive the greatest benefit remain to be defined. In addition, what are the best clinical parameters to follow? For G-CSF, the absolute neutrophil count might be adequate. However, for drugs such as IFN, the expression of HLA-DR or *ex vivo*-stimulated TNF responses might be required. If so, these assays will be more difficult to standardize between laboratories. Despite these unknowns, the incidences of both hospital-acquired infections and antibiotic resistance are increasing and immunoadjuvants will probably be a key component of the weaponry for treating respiratory infections.

References

1. Almirall J, Gonzalez CA, Balanzo X, Bolibar I: **Proportion of community-acquired pneumonia cases attributable to tobacco smoking.** *Chest* 1999, **116**:375–379.
2. Valdez R, Narayan KM, Geiss LS, Engelgau MM: **Impact of diabetes mellitus on mortality associated with pneumonia and influenza among non-Hispanic black and white US adults.** *Am J Pub Health* 1999, **89**:1715–1721.
3. Ruiz M, Ewig S, Torres A, Arancibia F, Marco F, Mensa J, Sanchez M, Martinez JA: **Severe community-acquired pneumonia. Risk factors and follow-up epidemiology.** *Am J Respir Crit Care Med* 1999, **160**: 923–929.
4. Chanock S: **Evolving risk factors for infectious complications of cancer therapy.** *Hematol Oncol Clin N Am* 1993, **7**:771–793.
5. Abraham E, Anzueto A, Gutierrez G, Tessler S, San Pedro G, Wunderink R, Dal Nogare A, Nasraway S, Berman S, Cooney R, Levy H, Baughman R, Rumbak M, Light RB, Poole L, Allred R, Constant J, Pennington J, Porter S: **Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. NORASEPT II Study Group.** *Lancet* 1998, **351**:929–933.
6. McCloskey RV, Straube RC, Sanders C, Smith SM, Smith CR: **Treatment of septic shock with human monoclonal antibody HA-1A. A randomized, double-blind, placebo-controlled trial. CHESS Trial Study Group.** *Ann Intern Med* 1994, **121**:1–5.
7. Ziegler EJ, Fisher CJ Jr, Sprung CL, Straube RC, Sadoff JC, Foulke GE, Wortel CH, Fink MP, Dellinger RP, Teng NN: **Treatment of Gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebo-controlled trial. The HA-1A Sepsis Study Group.** *N Engl J Med* 1991, **324**:429–436.
8. Beutler B, Milsark I, Cerami A: **Passive immunization against cachectin/tumor necrosis factor (TNF) protects mice from the lethal effect of endotoxin.** *Science* 1985, **229**:869–871.
9. Kindler V, Sappino A-P, Grau GE, Piguet P-F, Vassalli P: **The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection.** *Cell* 1989, **56**:731–740.
10. Pfeffer K, Matsuyama T, Kundig TM, Wakeham A, Kishihara K, Shahinian A, Wiegmann K, Ohashi PS, Kronke M, Mak TW: **Mice deficient for the 55 kd tumor necrosis factor receptor are resistant to endotoxic shock, yet succumb to *L. monocytogenes* infection.** *Cell* 1993, **73**:457–467.
11. Adams LB, Mason CM, Kolls JK, Scollard D, Krahenbuhl JL, Nelson S: **Exacerbation of acute and chronic murine tuberculosis by administration of a TNF receptor expressing adenovirus.** *J Infect Dis* 1995, **171**:400–405.
12. Kolls JK, Lei D, Greenberg S, Nelson S, Beutler B: **Adenovirus-mediated blockade of tumor necrosis factor in mice protects against endotoxic shock yet impairs pulmonary host defense.** *J Infect Dis* 1995, **171**:570–575.
13. Nelson S, Bagby GJ, Bainton B, Wilson LA, Thompson JJ, Summer WR: **Compartmentalization of intraalveolar and systemic lipopolysaccharide-induced tumor necrosis factor and the pulmonary inflammatory response.** *J Infect Dis* 1989, **159**:189–194.
14. Boujoukos AJ, Martich GD, Supinski E, Suffredini AF: **Compartmentalization of the acute cytokine response in humans after intravenous endotoxin administration.** *J Appl Physiol* 1993, **74**:3027–3033.
15. Dehoux MS, Boutten A, Ostinelli J, Seta N, Dombret MC, Crestani B, Deschenes M, Trouillet JL, Aubier M: **Compartmentalized cytokine production within the human lung in unilateral pneumonia.** *Am J Respir Crit Care Med* 1994, **150**:710–716.
16. Kurahashi K, Kajikawa O, Sawa T, Ohara M, Gropper MA, Frank DW, Martin TR, Wiener-Kronish JP: **Pathogenesis of septic shock in *Pseudomonas aeruginosa* pneumonia.** *J Clin Invest* 1999, **104**: 743–750.
17. Chiumello D, Pristine G, Slutsky AS: **Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome.** *Am J Respir Crit Care Med* 1999, **160**:109–116.
18. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS: **Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial.** *J Am Med Assoc* 1999, **282**:54–61.
19. Tremblay LN and Slutsky AS: **Ventilator-induced injury: from barotrauma to biotrauma.** *Proc Assoc Am Physicians* 1998, **110**:482–488.
20. Docke WD, Randow F, Syrbe U, Krausch D, Asadullah K, Reinke P, Volk HD, Kox W: **Monocyte deactivation in septic patients: restoration by IFN-gamma treatment.** *Nat Med* 1997, **3**:678–681.
21. Volk HD, Reinke P, Docke WD: **Clinical aspects: from systemic inflammation to 'immunoparalysis'.** *Chem Immunol* 2000, **74**:162–177.
22. Nelson S, Summer WR: **Innate immunity, cytokines, pulmonary host defense.** *Infect Dis Clin N Am* 1998, **12**:555–567.
23. Hustinx WN, Van Kessel CP, Heezius E, Burgers S, Lammers JW, Hoepelman IM: **Effects of granulocyte colony-stimulating factor (G-CSF) treatment on granulocyte function and receptor expression in patients with ventilator-dependent pneumonia.** *Clin Exp Immunol* 1998, **112**:334–340.
24. Nelson S, Belknap SM, Carlson RW, Dale D, DeBoisblanc B, Farkas S, Fotheringham N, Ho H, Marrie T, Movahhed H, Root R, Wilson J: **A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hospitalized patients with community-acquired pneumonia. CAP Study Group.** *J Infect Dis* 1998, **178**: 1075–1080.
25. Daifuku R, Movahhed H, Fotheringham N, Bear MB, Nelson S: **Time to resolution of morbidity: an endpoint for assessing the clinical cure of community-acquired pneumonia.** *Respir Med* 1996, **90**:587–592.
26. Williams LM, Snyder DC, Deblieux P, Ali J, Kuebel D, deBoisblanc BP, Summer WR: **Safety and feasibility of combined aersolized and subcutaneous interferon-gamma as adjuvant treatement of *Mycobacterium avium* complex pulmonary infection in non-HIV infected hosts [abstract].** *Am J Respir Crit Care Med* 1994, **149**:A110.
27. Condos R, Rom WN, Schluger NW: **Treatment of multidrug-resistant pulmonary tuberculosis with interferon-gamma via aerosol.** *Lancet* 1997, **349**:1513–1515.

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