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Review

Curcumin Suppression of Cytokine Release and Cytokine Storm. A Potential Therapy for Patients with Ebola and Other Severe Viral Infections

PETER P. SORDILLO and LAWRENCE HELSON

SignPath Pharma, Inc., Quakertown, PA, U.S.A.

Abstract. *Background: The terminal stage of Ebola and other viral diseases is often the onset of a cytokine storm, the massive overproduction of cytokines by the body's immune system. Materials and Methods: The actions of curcumin in suppressing cytokine release and cytokine storm are discussed. Results: Curcumin blocks cytokine release, most importantly the key pro-inflammatory cytokines, interleukin-1, interleukin-6 and tumor necrosis factor-α. The suppression of cytokine release by curcumin correlates with clinical improvement in experimental models of disease conditions where a cytokine storm plays a significant role in mortality. Conclusion: The use of curcumin should be investigated in patients with Ebola and cytokine storm. Intravenous formulations may allow achievement of therapeutic blood levels of curcumin*

The high fatality rate in patients infected with the Ebola virus is thought to be due partly to the onset of a cytokine storm in the advanced stages of the infection (1, 2). Cytokine storm can occur after a wide variety of infectious and non-infectious stimuli. In cytokine storm, numerous cytokines, both pro-inflammatory such as interleukin-1 (IL1), IL6, tumor necrosis factor-α (TNFα), and anti-inflammatory (IL10), are released, resulting in hypotension, hemorrhage, and, ultimately, multi-organ failure. The term 'cytokine storm' is most associated with the 1918 H1N1 influenza pandemic and the more recent cases of bird flu H5N1 infection (3-5). In these cases, young people, with presumably healthy immune systems, died disproportionally from this disease, and aberrant activity of their immune systems is thought to be the cause. This syndrome has been also known to occur in advanced or terminal cases of severe acute respiratory syndrome (SARS) (6), Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (7), gram-negative sepsis (8), malaria (9) and numerous other infectious diseases. Cytokine storm can occur from non-infectious causes, such as acute pancreatitis (10), severe burns or trauma (11), or acute respiratory distress syndrome secondary to drug use or inhalation of toxins (12). In a recent phase I trial, injection of the monoclonal antibody TGN1412, which binds to the CD28 receptor on T-cells, resulted in severe cases of cytokine storm and multi-organ failure in the six human volunteers who received this agent. This happened despite the fact that the dose of this agent given was 500-times lower than which had been found to be safe in animals (13).

Curcumin Suppression of Cytokines

Curcumin has been shown to inhibit the release of numerous cytokines. Abe *et al*. showed that curcumin suppresses IL1β, IL8, TNFα, monocyte chemoattractant protein-1 (MCP1) and macrophage inflammatory protein-1α (MIP1α) release from monocytes and macrophages (14). Jain *et al*. showed that curcumin markedly reduced the release of IL6, IL8, TNFα and MCP1 from monocytes that had been cultured in a high glucose environment (15). These same investigators studied rats with streptozotocin-induced elevated plasma blood sugar levels and significantly elevated levels of IL6, TNFα and MCP1; these levels were markedly reduced by curcumin (15). Curcumin has been reported to block the release of IL6 in rheumatoid synovial fibroblasts (16), of IL8 in human esophageal epithelial cells (17) and alveolar epithelial cells (18), and of IL1 in bone marrow stromal cells (19), colonic epithelial cells (20) and human articular chondrocytes (21).

Correspondence to: Lawrence Helson, MD, SignPath Pharma, Inc. 1375 California Road, Quakertown PA 18951, U.S.A. Tel:+1 2155389996, Fax: +1 2155381245, e-mail: lhelson@comcast.net

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Table I. *Effect of curcumin on interleukins (IL).*

Effect, biomolecule	Key functions	Reference
↓ IL1	Major pro-inflammatory cytokine, hematopoesis, CNS development	14, 19-21
↓ IL2	T-Cell lymphocyte differentiation	22
↓ ↑ IL4	B-Cell proliferation	36, 39
↓ IL5	Immunoglobulin secretion, eosinophil function, allergy	37
↓ IL6	Major pro-inflammatory cytokine, B-cell differentiation, nerve cell differentiation	15, 16, 39
↓ IL8	Neutrophil chemotaxis, angiogenesis	14, 15, 17, 18
↑ IL10	Anti-inflammatory cytokine, also has T-cell stimulatory effects	23
↓ IL11	Induces acute phase proteins, antigen–antibody reactions, bone remodeling	40
↓ IL12	Defense against intracellular pathogens	22, 23
↓ IL13	Induces matrix metalloproteinases, induces IgE	39
↓ IL17	Pro-inflammatory cytokine	38

Table II. *Curcumin suppression of other key cytokines.*

Effect, biomolecule	Key functions	References
↓ TNFα	Major pro-inflammatory cytokine, insulin resistance, induces secretion of corticotropin-releasing hormone	14, 15
↓ Interferon-γ	Macrophage activation, T- and B-cell activation and differentiation	22, 23
↓ MCP1 (CCL2)	Neuroinflammation, monocyte and basophil chemotaxis	14, 15
↓ MIP1α (CCL3)	Activates granulocytes, induces synthesis of pro-inflammatory cytokines	15
↓ GROα (CXCL1)	Neutrophil chemoattractant, angiogenesis, wound healing	24
↓ GROβ (CXCL2)	Neutrophil and monocyte chemoattractant	24
↓ IP10 (CXCL10)	Monocyte and macrophage chemoattractant, NK cell chemoattractant, angiogenesis	26
↓ SDF1 (CXCL12)	Lymphocyte chemoattractant, angiogenesis, suppresses osteoclastogenesis	25

Curcumin also prevents release of IL2 (22), IL12 (22, 23), interferon-γ (22, 23) and many other key cytokines (24-26) (Tables I and II).

Cytokine Suppression by Curcumin Correlates with Clinical Improvement in Conditions Associated with Cytokine Storm

Curcumin has positive effects on numerous disease conditions in patients and in animal systems. Avasarala *et al*. reported on the effects of curcumin on cytokine expression and disease progression in a mouse model of virus induced acute respiratory distress syndrome. Curcumin reduced the expression of key cytokines IL6, IL10, interferon γ and MCP1, and this correlated with a marked decrease in inflammation and reduction in fibrosis (27). Yu *et al*. showed suppression of TNFα levels by curcumin was associated with decreased pancreatic injury in a mouse model of acute pancreatitis (28). Cheppudira *et al*. reported that suppression of IL8 and growth-regulated protein-α (GROα), and ultimately of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), by curcumin correlated with reduction in thermal injury in a rat model (29). Curcumin suppression of cytokines also correlates with clinical improvement in models of severe viral infection. Song *et al*. showed that curcumin administration reduced expression of IL1β, IL6 and TNFα and ultimately NFκB, and protected against coxsackie virus-induced severe myocardial damage in infected mice (30). Curcumin has been shown to have activity against numerous viruses, including human immunodeficiency virus-1(HIV1), HIV2, herpes simplex virus (HSV), human papillomavirus (HPV), human T-lymphotropic virus-1 (HTLV1), hepatitis B virus (HBV), HCV, and Japanese encephalitis virus (31). In addition, curcumin has been shown to have specific activity against the H1N1 virus in culture (32, 33), although cytokine levels were not measured in these two studies. Most importantly, curcumin has been shown to stimulate the suppressor of cytokine signaling (SOCS) proteins (34). These proteins have been shown to be crucial in protecting against severe cytokine storm in mice infected with influenza virus (35).

Conclusion

The activity of curcumin in suppressing multiple cytokines, and its activity in experimental models of diseases and conditions associated with cytokine storm, suggest it may be useful in the treatment of patients with Ebola and cytokine storm. Curcumin is poorly absorbed from the intestinal tract; however, intravenous formulations may allow therapeutic blood levels of curcumin to be achieved in patients diagnosed with cytokine storm. Clinical status and levels of important cytokines, such as IL1β, IL6 and TNFα, should be monitored carefully when patients are treated with curcumin.

Conflicts of Interest

The Authors acknowledge a potential conflict of interest. Dr. Sordillo is a member of the Scientific Advisory Board of SignPath Pharma, which makes several formulations of intravenous curcumin. Dr. Helson is CEO of SignPath Pharma. The Authors believe that this article is of substantial scientific interest and should be published with acknowledgement of this potential conflict.

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