Cytokine milieu in COVID-19 and therapeutical intervention of oral low dose cytokine therapy

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Background:

In COVID-19 or any viral infection, cytokines of both innate and adaptive immune system are required to create an effective antiviral state. We postulate that converting injectable cytokines into an oral low dose product will be safe and efficacious for oral administration and at low cost. Cytokines are transformed into oral low dose form using sequential serial dilution and kinetic activation (SKA) method. SKA method employed by GUNA Lab (GUNA S.p.a., Milan, Italy) was used to amplify the therapeutic potential without adverse effects [1]. Precedent for such a method is already established with published papers showing efficacy of low dose oral cytokines. The oral low dose form of Interferon beta, Interferon gamma, Interferon lambda, Lactoferrin, IL 12 and IL 15 are combined together as a potential anti viral product [2].

Basic Cytokine Milieu :

For a virus to survive in the body it needs to switch off the cytokine signaling pathways of innate immune system. The virus then triggers deleterious immune responses which drives inflammation and produces tissue damage.

In the initial stage of COVID-19 infection interferon lambda protects the epithelial cells from viral invasion. Being an anti-inflammatory cytokine, it prevents the trigger for a cytokine storm. If the body fails in stopping viral entry with lambda, then interferon beta blocks viral entry into adjacent healthy cells. If that fails, then NK cells are used to kill off the infected cells using IL-15. If NK cells also fail, then the job goes to the adaptive immune system consisting of TH1 cells which enable macrophages to secrete interferon gamma and IL-12. The virus blocks TH1 activity and induces TH2 activity by increasing IL-4, this not only inhibits viral die off but also induces fibrotic healing. The failed TH1 cell activity blocks IGG2a antibody formation and enables the virus to spread. The viral infection then spreads into the alveoli which causes cell death, this then drives the innate immune response with a release of TNFα, IL-1 and IL-6 from the neutrophils and macrophages. As the neutrophils increase, they cause a depletion of lymphocytes; this is the cytokine storm which causes further damage leading to respiratory, CVS and kidney failure.

Managing cytokine storm :

Vasoactive intestinal peptide is already approved for use in inflammation. It could be a good alternative to corticosteroids since it doesn't cause/trigger secondary infection or alters glucose and sodium levels. It works by stopping the cytokine release of TNF, IL-l 1 from the immune cells. Trichostatin A is a novel HDAC inhibitor which allows the T cells especially the CD4 and the CD8 cells to stop switching off their genes allowing them to stay active. Quite rightly within 4 days of a viral infection the T cells start switching off in order to protect against the Interferon gamma release and the ensuing oxidative damage, but if the cells switch off completely the virus cannot be removed. The addition of Trichostatin A stops the drop in the lymphocyte count. Hence while VIP reduces neutrophil counts, Trichostatin A helps increase the lymphocyte counts.

Managing ROS via NOX2 Blockade :

NOX2 is NADPH oxidase, it's released from the neutrophils and causes oxidative stress. Apocyanin blocks NOX2 and hence reduces oxidative stress and helps upregulate glutathione formation. It also hence reduces ferritin, CRP and LDH levels.

Conclusion :

Low dose cytokines can be administered orally, have no side effects and remove the virus without any adverse side effects such as secondary infections. The goal of treatment is to enhance innate immune activity, enhance TH1 while blocking TH2 CD4 T cells, block neutrophils and NADPH oxidase, reduce neutrophil counts while increasing lymphocytes and reduce ferritin, LDH and CRP levels.

References:

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2. Ratheesh M, Sheethal S, Svenia P. Jose, Sony Rajan, Sulumol Thomas, Tariq Jagmag & Jayesh Tilwani(2020) Biochemical and immunological aspects of COVID-19 infection and therapeutical intervention of oral low dose cytokine therapy: a systematic review, Immunopharmacology and Immunotoxicology, DOI: 1080/08923973.2020.1842444.

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