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Opinion

Colchicine Plus Fosfomycin In Coronavirus Infection

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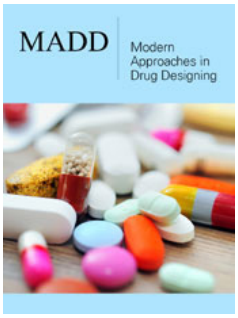

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Opinion

1. Following Covid-19 outbreak, the scientific community focused on several alternatives for either preventing or therapeutically treating the illness.
2. It is clear enough at this time that vaccines will not be available at least for the few months to came. An association between an antibiotic (Azithromycin) and an antimalarial drug (chloroquine) has already been tested.
3. Safety and toxicity issues has raised some concern regarding Chloroquine doses needed to reach a therapeutic activity and some clinical trials must be aborted (Chloroquine Diphosphate for the Treatment of Severe Acute Respiratory Syndrome Secondary to SARS-CoV2 (CloroCOVID19) this study was registered with ClinicalTrials.gov, number NCT04323527).
4. Some antibiotics can act as immunomodulators and particularly, Fosfomycin, has an immunomodulatory effect on human B-cell activation. Fosfomycin is considered an unique antibiotic which is chemically unrelated to any other known antibacterial agent. The effect of Fosfomycin on human T-cells function was yet studied and the inhibition of proliferation of human lymphocytes induced induced by polyclonal T-cell mitogens studied as a function of Fosfomycin dose.
5. It was also described the supression by Fosfomycin of mixed lymphocyte reaction and interleukin-2 (IL-2) production by T cells along with the expression of IL-2 receptor (CD25) on the activated T-cell surfaces. Previous research demonstrated that Fosfomycin blocks T-cell division during the transition from G1 to S phase of the cell cycle.
6. Actually it is also known that SARS Coronavirus replicates in mononuclear cells of peripheral blood (PBMCs) from SARS infected patients (Journal of Clinical Virology, Vol 28,Issue 3, December 2003, Pag 239-244).
7. Fosfomycin exerts a direct effect on proliferation of PBMC when stimulated with Concanavalin A, in fact , at concentrations between 1,6 to 200 micrograms/ml , particularly, 50% inhibition of T-cell proliferation was observed at the dose range between 8 and 40 micrograms/ml. It was also found that this antiproliferative effect had no relationship with antibiotic activity since the inactive enantiomer had the same antiproliferative effect than the active optical enantiomer responsible for the antibacterial effect.
8. Effect of oral colchicine on T cell subsets, monocytes and Concanavalin A-induced suppressor cell function in asthmatic patient was studied by Dr D. N. Ilfeld of the Institute of Pulmonary Diseases and Clinical Pharmacology Unit,(Beilinson Medical Center, Petah Tikva; Department of Cell Biology, Weizmann Institute of Science, Rehovot; and Clinical Immunology Laboratory, Soroka Medical Center, Beer Sheva, Israel) and found that

Asthmatic patients have a deficiency of concanavalin A-(Con A) induced suppressor cell function which can be corrected by using Colchicine regime of oral colchicine 0·5mg twice daily for 7 days .

9. Peripheral blood mononuclear cells were incubated with Con A and then suppression of proliferation was measured by co-culture of these cells with healthy volunteers'mononuclear cells and phytohaemagglutinin. Asthmatic patients had an increased number of monocytes and a normal number of lymphocytes, then oral colchicine have corrected the deficiency of Con A-induced suppressor cell function by decreasing the number and/or modulating the activity of monocytes.

10. Kinetic studies on the effect of Fosfomycin on Concanavallin A induced DNA synthesis in PBMCs , showed a 90% inhibition, experiment carried on incubating PBMCs in the presence of Con-A plus Fosfomycin seeded at times zero, 24 and 48 hs before harvesting at time 72hrs.

11. Concanavalin A (Con A), a phytagglutinin, binds to the envelope of hemagglutinating encephalomyelitis virus, a Coronavirus. Concanavalin A treated virus suspensions lose their hemagglutination properties and there is a transient interference with infectivity. Electron micrographs show the Concanavalin A as a granular deposit adhering to the viral envelope and there is aggregation of the virus. Concanavalin A does not bind to virions stripped of their envelopes.

12. Immune response to respiratory coronavirus is T-cell mediated and begins with direct infection of airway epithelium. Following initial infection, lung-resident respiratory dendritic cells (rDCs) acquire the invading pathogen or antigens from infected epithelial cells, become activated, process antigen and migrate to the draining lymphnodes (DLN).Once in the DLNs, rDCs present the processed antigen in the form of MHC/peptide complex to native circulating T cells.

13. Following engagement of the T cell receptor (TCR) with peptide–MHC complex and additional co-stimulatory signals, T cells become activated, proliferate vigorously and migrate to the site of infection . Once at the site of infection, activated virus-specific effector T cells produce antiviral cytokines (IFN-c, TNF-a, IL-2), chemokines (CXCL-9, 10 and 11) and cytotoxic molecules (perforin and granzyme B) .

14. Patiens suffering from Covid-19 present B lymphocyte reduction early in the disease, which may affect antibody production in the patient. In severe type patients, lymphocytes were significantly reduced . We speculate that lymphocytes in patients with COVID-19 might gradually decrease as the disease progress. But the mechanism of significant lymphocyte reduction in severe type patients remains unclear. Besides, the inflammatory factors associated with diseases mainly containing IL-6 were significantly increased, which also contributed to the aggravation of the disease around 7–14 days after onset. Non-survivors had higher levels of neutrophils, blood urea nitrogen, and creatinine than the survivors.

15. A controlled release inhalatory formulation including Fosfomycin and Colchicine either as a multiple emulsion nanoparticulate system or micronized spheres formulated with lactose for inhalation can fully address therapeutic objectives both in the pre-viremia phase, viremia phase and acute (phneumonia) phase.