Can be Clofazime usefull in the treatment of COVID 19?

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Abstract

The combination of antiviral and anti-inflammatory properties of Clofaximine as experienced in clinical practice, could lead to take into consideration its effects in COVID 19

Clofazimine is a rimophenazine dye originally used as an antitubercolar agent after its first synthesis at Trinity College of Dublin, during 1954, by a group of scientist led by V. Barry. Only few years later it was awarded for leprosy treatment by Y. T. Chang. With the following years, also an anti-inflammatory effectiveness on erythema nodosum leprosum was recognized (1). In the '70s therapeutical activity on discoid lupus erythematosus and pyoderma gangrenosum were documented (2).

Recent papers suggest interesting properties of modulation of the immune responses: first by blockade of Kv 1.3 potassium channel, a voltage dependent transmembrane domain first identified outside electrically excitable tissue, for instance on macrophages and T lymphocytes; in the latters it carries on a critical role for the subset of "effector memory" (CD4+ CD62L lo CD44hi) when blocked, downgrading such function in severe, inflammatory diseases, and expanding, instead, "central memory" population, (CD4+ CD 62Lhi CD44hi), (3, 4).

The induction of long living, antigen specific "central memory" T cells is supported of an efficient and long lasting action against bacterial and viruses, whereas a quick overload of T cells "effector memory" may be detrimental for the organism because instauration of a more severe inflammatory condition during an infectious disease, like tuberculosis and SARS syndromes (5).

Clofazimine is electively accumulated in macrophages , forming crystal- like inclusions, with effects on the microenvironment of phagosomes, resulting in a contrast of bacterial replication, also grounded on an inhibitory action of acid sphingomyelinase, that hinder the ceramide accumulation induced by intracellular pathogens, and restore the autophagic clearance of intracellular pathogens (6). On the other hand, in models of bacterial pathogen killing also an apoptosis inducing activity in macrophages may be promoted (7). Inside these cells, the drug in the inclusions alters immune signaling response pathways, like Toll like receptor (TLR) ligation and then expression, decreasing of NF-kB activation and Tumor necrosis factor (TNF) production, enhancing the interleukin-1 receptor antagonist (IL-1RA) production .

Clofazimine might be able to promote antigen specific Th17 cascade in lymphocytes "central memory", acting as a "self propelled vaccine" in infection and cancer; however an effectiveness to inhibit TCR-mediated IL-2 production was also confirmed in cell lines, resulting in an immunomodulatory effect .

In human immunodeficiency virus/AIDS clofazimine may provide some benefits by enhancing T cell mediated immunity against HIV, on the converse contrasting the well documented neurotoxicity of virus proteins, like the envelope glycoprotein 120 against microglia, additionally it influences the immune reconstitution

following antiretroviral therapy, preventing the immune reconstitution inflammatory syndrome (IRIS) while preserving the integrity of HIV specific effector T-cell responses (7).

The vast majority of infectious disease and cancer also involve pathology induced by the inflammation, because inflammatory responses play a central role in inducing protective immune responses, but a profound inflammation can exacerbate the pathology, like in viral SARS. Patients with severe COVID-19 show higher leukocyte number, but often present lymphopenia, reduced platelet count, abnormal respiratory findings and also a cardiovascular and haemocoagulative affection, increased serum levels of blood C-reactive protein, erythrocyte sedimentation rate, D-dimer, pro-inflammatory cytokines, as TNF-alpha, IL-1 and IL-6, and chemokines, as IL-8, compared to individuals with mild disease or healthy controls (8). A cytokine storm, with vascular inflammation/endothelial damage, could also play a role in the hypercoagulation leading to thrombotic events in lungs, in myocardium and kidneys. An exorbitant host inflammatory response seems to correlate not less than the amount of viral load with the worsening of symptoms; The combination of antiviral and anti-inflammatory drugs as experienced in clinical practice, could lead to take into consideration clofazimine, a drug unexpensive, well tolerated, lipid soluble, bioavailable, orally administrated, then accumulated in monocytes and macrophages in multiple concentrations in comparison with the plasma levels, targeting the endocytic pathway and the autophagy process, with anti-infective and anti-inflamamtory effects (9, 10). We would suggest a trial of an additional regimen of clofazimine, roughly at 200 mg/day, lying on a contrast to viral pathogenic factors and a regulation of immune system to reduce excessive and detrimental inflammatory fire.

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