

COVID-19: GEMFIBROZIL AS A POTENTIAL ADJUVANT IMMUNE MODULATING TREATMENT

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November 3, 2020

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Keywords:

COVID-19, GEMFIBROZIL, IMMUNE MODULATING TREATMENT

Abstract:

The current Covid-19 viral infection has been declared a pandemic causing significant global morbidity and mortality predominantly from the manifestation of severe acute respiratory syndrome (SARS). It has been designated as SARS-CoV 2. Epidemiological studies show predilection in patients with associated chronic medical conditions including those with cardiovascular disease. Exaggerated host immune response known as cytokine storm syndrome (CSS) leading to acute lung injury (ALI) and acute respiratory distress

syndrome (ARDS) is the proposed mechanism for the development of SARS in Covid-19 infection. Gemfibrozil has proven benefits in patients with cardiovascular disease. More importantly, it has established anti-inflammatory, anti-oxidative, and anti-migratory properties. Gemfibrozil has shown survival benefits as immune modulation of ALI/ARDS from viral pathogens. This article reviews the potential of gemfibrozil as adjunctive immune modulating therapy for SARS associated with Covid-19 infected patients who have associated cardiovascular disease.

Introduction:

The severe acute respiratory syndrome (SARS) seen in Covid-19 infection share similarities with previous coronavirus epidemics, particularly SARS-CoV 1 and the Middle East Respiratory Syndrome (MERS-CoV). (1) It has been designated SARS-CoV 2. Acute lung injury (ALI) with subsequent development of acute respiratory distress syndrome (ARDS) from robust host hyper-immune response is the proposed pathophysiological mechanism. This so called "cytokine storm" may be independent of viral load and replication. (2) Thus, the rationale for adding immune modulating strategies on top of antiviral/antimicrobial therapies is warranted to prevent this complication and hopefully improve survival. The development of ALI/ARDS amplifies mortality in Covid-19 infection, more so in patients with associated chronic medical conditions including cardiovascular disease. (3)

Gemfibrozil, a drug discovered over 40 years ago, have beneficial effects and safety profile in both primary and secondary prevention of cardiovascular disease. (4) In addition to its lipid lowering ability, it has important immune modulating properties that inhibit pro-inflammatory factors involved in cytokine storms.(5) It is a peroxisome proliferators-activated receptor (PPAR) agonist known to reduce the release of inflammatory cytokines including interleukin-6 (IL-6), tumor necrosing factors (TNF) and interferon-gamma (IFN-g).

IL-6 elevation have been reported as an important marker of severity with Covid-19 infection. (3) Together with other markers for inflammation such as CRP, the degree of IL-6 elevation correlates with increased morbidity and mortality.

Gemfibrozil has shown survival benefits by attenuating ALI/ARDS development from viral etiologies. (6) Since gemfibrozil is currently indicated for patients with cardiovascular disease, its adjunctive use does not have to be repurposed for SARS associated with Covid-19 infection. Therefore, Gemfibrozil's potential as an immune modulating strategy to prevent ALI/ARDS cannot be ignored.

Immune Modulating Targets for Gemfibrozil in Covid-19 SARS pathogenesis:

Gemfibrozil has been shown to attenuate pro-inflammatory effects of disease states through its immune-modulating, anti-inflammatory and anti-migratory properties. (5). It belongs to the fibrate family of drugs used to lower plasma lipids and cholesterol. They are one of several known synthetic ligands acting as agonists to the PPARs. (7) Their action in turn decrease serum levels of TNF, IFN-g and IL-6. (8,9)

As an an anti-inflammatory, gemfibrozil reduces superoxide production and expression of nuclear factor kB (NF-kB). (10) Moreover, it inhibits astrocyte production of TNF, IL-1b, IL-6 and nitric oxide (NO) production. (11) Gemfibrozil also promotes the production of anti-inflammatory cytokine IL-4. (12) It reduces the production of C-reactive protein (CRP), TNF-a and IL-6 in peripheral blood mononuclear cells. It inhibits the production of cyclooxygenase-2 (COX-2) and prostaglandins. (13)

As an immune-modulating agent, gemfibrozil attenuates pro-inflammatory transcription factor activation. This includes IFN-g regulatory factor 1 (IRF-1)binding to gamma activation site (GAS), nuclear factor-kB (NF-kB), activator protein 1 (AP-1), and CCAT/enhancer binding protein beta (C/EBPb). (5) It also promotes switching of T helper (Th) cells from the pro-inflammatory Th1 to anti-inflammatory Th2. Production of Th2-specific cytokines is amplified including IL-4, IL-5 and IL-10. (14)

As an anti-oxidant, gemfibrozil not only prevents low density lipoprotein (LDL) peroxidation but also acts on other signals of inflammation. Reactive oxygen species (ROS) have emerged as important signaling molecules during inflammatory conditions. Excessive ROS generation results in damage to most cellular components

of the living organism. Gemfibrozil is known to inhibit ROS-mediated inflammation. (15) It has free radical scavenging ability as well. Its para-hydroxyl metabolite has been shown to reduce the burden of ROS. (16)

As an anti-migratory agent, gemfibrozil affects the expression of cell-surface adhesion molecules including intracellular adhesion molecule 1 (ICAM-1), VCAM-1 and selectins inhibiting trans endothelial migration of mononuclear cells and macrophages. (17) It also down-regulates the expression of chemokines including monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 (MIP-1), monokines induced by IFN- γ (MIG) and IL-8. The expression of IL-8 induces inflammation, monocyte/macrophage recruitment, angiogenesis and vascular smooth muscle migration. Thus, gemfibrozil can function as an anti-migratory factor by down-regulating the expression of different soluble chemokines and inhibit the expression of different cell surface proteins and selectins.

Discussion:

Over the years, viral pathogens including Influenzas and Coronaviruses cause ALI/ARDS from excessive release of pro-inflammatory cytokines and chemokines described in cytokine storm syndromes. They induce much higher transcription and up regulation of TNF genes including TNF related apoptosis-inducing ligand and TNF-mRNA in human monocyte-derived macrophages. (18) This macrophage activation syndrome (MAS) seen with the current SARS-CoV 2 may be a dysregulated host response to Covid-19 viral induced immunosuppression and lymphopenia leading to unintended ALI/ARDS consequences at the site of infection. (19) The development of ALI/ARDS and the need for ventilator support portends to increased mortality rates. Markers of inflammation including CRP and IL-6 have been used as surrogates for MAS, and their degree of elevation have correlated well with disease severity. (3)

Experiments with SARS-CoV indicate that MAS induced cytokine storms result more from amplification of gene related inflammatory signals regardless of viral load. In one model, immune modulation of receptor sites or alteration of recruitment signals resulted in dramatic improvement in host survival with viral load remaining constant. (20) This suggests that immune modulating therapy may have as important a role in addition to antiviral therapy in altering the course of Covid-19 infection. Reports of clinical improvement have been reported with the adjuvant use of IL-6 antagonists including tocilizumab. However, cost and repurposing use of these medications may be limiting factors.

Gemfibrozil has been in clinical use for patients with cardiovascular disease and has achieved generic status. In addition, it has vital immune modulating properties against cytokine storms that mitigate the development of ALI/ARDS from both viral and nonviral pathogens. (21). It not only reduces the levels of IL-6, TNF and IFN- γ . But it has also been shown to attenuate gene recruiting signals of inflammation utilizing human equivalent dosing. In one animal study, the adjuvant use of gemfibrozil resulted in enhanced host survival that developed ALI/ARDS from viral pathogens. (6) Enhanced survival is seen even after exposure to the virus. This implies that gemfibrozil has the potential to be a treatment rather than a preventive therapy in human disease.

Therefore, the potential of gemfibrozil as adjunct immune modulating therapy in conjunction with antiviral treatment for SARS associated with Covid-19 infection in patients with associated cardiovascular disease is emphasized.

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