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Exploring the Novel Therapeutic options in Global Pandemic COVID 19

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Introduction

In the prevailing novel coronavirus disease 2019 (COVID-19) Global Pandemic spreads, major focus is interrupting its transmission with the standard public health measures on early diagnosis, tracing of contacts and isolation of patients. The current scenario warrants an urgent development of potential strategies and therapeutic options which is a major public health concern. More robust data on antiviral drugs which are effective against COVID 19 is yet to come. Both coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS) are characterised by an overexuberant inflammatory response and, for SARS, viral load is not correlated with the worsening of symptoms[1][2].

In this short commentary, We would like to discuss the possible therapeutic options with Montelukast, Leflunamide and Pycnogenol for this novel pandemic, Covid-19.

Montelukast is one of the most commonly used drug among the pulmonologists as an add on therapy in the clinical management of Asthma.Standard dosage in adults is usually 10mg once a day.Various studies quote montelukast as potential anti inflammatory agent when given in higher doses .Doses upto 1000mg is found non toxic in clinical trials.

Cysteinyl leukotrienes (CysLTs) are lipoxygenase products derived from the metabolism of arachidonic acid and they are potent endogenous mediators of inflammation. Montelukast is a leukotriene receptor antagonist (LTRA) that acts as an antagonist of CysLT1R, blocking its signal transduction without affecting cysteinyl-LT signalling through CysLT2R, or the action of leukotriene B4 (LTB4) via the BLT receptors.

Mahir Igde et al studied the antiviral properties of montelukast in human herpes and adeno viruses invitro which showed significant decrease in viral infectivity [3].

Morever, Montelukast (MK) have potent anti-inflammatory properties which are beneficial in reducing cytokine storm by reducing cytokines(IL1,IL6,TNF-alpha) when given in higher doses. MK had a significant inhibitory effect on Fetal bovine serum- induced GM-CSF, IL-6, and IL-8 secretion.[4]

Ali Kagan Coskun et al studied the potential protective effects of montelukast (MLK) on cecal ligation and puncture (CLP)–induced tissue injury in vital organs — liver, heart, kidneys, and especially lungs — through inhibition of the proinflammatory cytokine response and the generation of reactive oxygen species (ROS) in rats[5]

Maeba et al studied the effect of montelukast on NF kappa B and major proinflammatory cytokines demonstrated high doses of montelukast modulate the production of IL-6, TNF-alpha, and MCP-1 through the inhibition of NF-kappaB activation [6]

Al amran et al studied the possible protective effect of montelukast against haemorrhagic shock-induced acute lung injury by interfering with inflammatory and oxidative pathways. Montelukast treatment significantly reduced the total lung injury score, compared with the Hemorrahagic shock group ($P < 0.05$). Montelukast also significantly decreased serum TNF-α and IL-6 [7]. Ilknur Basyit et al studied the protective effects of montelukast on both inflammatory and histopathological aspects of smoke-induced lung injury [8].

Sepsis with its effect on lung tissue is a kind of inflammatory storm and it is therefore not easy to control all steps in this inflammatory pathway. On the other hand, the leukotriene receptor antagonist, montelukast, has been shown to ameliorate sepsis induced hepatic and intestinal injury including oxidative stress in rats [9].

Montelukast has also been used as an effective agent to decrease fibrosis and oxidative stress in lungs in some animal studies[10][11]. Given the multiple lines of evidence that have emerged to support a central role of leukotrienes, we hypothesize that leukotriene receptor antagonist treatment, particularly with montelukast, may reduce the fibrotic phase of acute lung injury due to sepsis.

The study by AEKhodir et al investigates the possible protective effects of montelukast (MNT) against lipopolysaccharide (LPS)-induced cardiac injury, in comparison to dexamethasone (DEX), a standard anti-inflammatory. They demonstrated that Montelukast might have cardioprotective effects against the inflammatory process during endotoxemia. This effect can be attributed to its antioxidant and/or anti-inflammatory properties[12]

Leflunomide

Leflunomide is an immunosuppressive disease-modifying antirheumatic drug (DMARD), used in active moderate-to-severe rheumatoid arthritis and psoriatic arthritis. It is a pyrimidine synthesis inhibitor that works by inhibiting dihydroorotate dehydrogenase[13]

Teriflunomide,an active metabolite of leflunamide prevents the expansion of activated and autoimmune lymphocytes by interfering with their cell cycle progression while nonlymphoid cells are able to use another pathway to make their ribonucleotides by use of salvage pyrimidine pathway, which makes them less dependent on *de novo* synthesis.

Teriflunomide also has antiviral effects against numerous viruses including CMV, HSV1 and the BK virus, which it achieves by inhibiting viral replication

by interfering with nucleocapsid tegmentation and hence virion assembly [14]

Pycogenol

French maritime pine bark extract (Pycnogenol) displays a variety of anti- inflammatory effects *in vivo*. Bioavailable active principles of Pycnogenol exert anti- inflammatory effects by inhibition of proinflammatory gene expression which is consistent with documented clinical observations [15]

The anti-viral activity of Pycnogenol was higher than its components procyanidin and taxifolin. Further, treatment of infected chimeric mice with Pycnogenol suppressed HCV replication and showed a synergistic effect with interferon-alpha. In addition, Pycnogenol® treatment resulted in dose-dependent reduction of reactive oxygen species in HCV replicon cell lines. Pycnogenol is a natural product that may be used to improve the efficacy of the current standard antiviral agents and even to eliminate resistant HCV mutants [16]. Regular doses of per orally administered French maritime pine bark extract moderately inhibited NF-κB activation and MMP-9 secretion *ex vivo* [17].

PBE (Pine bark extracts) rich in procyanidins inhibited not only the binding of human immunodeficiency virus type-1 (HIV-1) to host cells but also inhibited HIV viral replication and T-cell interaction in cell culture experiments [18]. PBE was found to induce expression of an intracellular antioxidant protein and manganese superoxide dismutase, and inhibition of phosphorylation of the ribosomal S6 protein. It seems that these biochemical alterations induced by Pycogenol play an important role in its antiviral effects. PBE is a promising agent for inhibition of encephalomyocarditis viral replication, prevention of development of viral myocarditis, and improvement of inflammation and myocardial necrosis. It was reported that Pycnogenol (100 mg/kg) had beneficial effects on viral myocarditis by inhibition of viral replication and by suppression of pro-inflammatory cytokines, genes related to cardiac remodelling, and mast cell-related genes in the heart muscle of mice (gene expressions of tumor necrosis factor, type-1 procollagen, stem cell factor, and mast cell tryptase[18][19].

However further studies are needed invitro and in vivo on COVID 19 on these therapeutic agents with these evidence of robust literature.

References

1. Peiris JS1, Chu CM et al Clinical progression and viral load in a community outbreak or coronavirus-associated SARS pneumonia: a prospective study. *Lancet.* 2003; 361: 1767-177
2. Huang C Wang Y ,LI et al Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.*Lancet.* 2020; 395: 497-506
3. Mahir Igde,Zafer,Possible Antiviral activity of montelukast against Herpes Simplex Virus type-1 and Human Adeno Virus in vitro African journal of microbiology research 6(1):203-205 January 2012.
4. Mullol J1, Callejas FB, Méndez-Arancibia E et al Montelukast reduces eosinophilic inflammation by inhibiting both epithelial cell cytokine secretion (GM-CSF, IL-6, IL-8) and eosinophil survival J Biol Regul Homeost Agents. 2010 Oct-Dec;24(4):403-11.
5. Ali Kagan Coskun, Murat Yigiter et alThe Effects of Montelukast on Antioxidant Enzymes and Proinflammatory Cytokines on the Heart, Liver, Lungs, and Kidneys in a Rat Model of Cecal Ligation and Puncture–Induced Sepsis Scientific World Journal. 2011; 11: 1341–1356.

6. Maeba S1, Ichiyama T, Ueno Y, Makata H, Matsubara T, Furukawa S. Effect of montelukast on nuclear factor kappaB activation and proinflammatory molecules Ann Allergy Asthma Immunol. 2005 Jun;94(6):670-4
7. Fadhil G. Al-Amran, Najah R. Hadi, Ali M. Hashim Cysteinyl leukotriene receptor antagonist montelukast ameliorates acute lung injury following haemorrhagic shock in rats European Journal of Cardio-Thoracic Surgery, Volume 43, Issue 2, February 2013.
8. Ilknur Basyigit,corresponding author1 Murat Sahin,2 Deniz Sahin,3 Fusun Yildiz,1 Hasim Boyaci,1 Serap Sirvanci,4 and Feriha Ercan Anti-inflammatory effects of montelukast on smoke-induced lung injury in rats. Multidiscip Respir Med. 2010;5(2): 92–98.
9. Sener G SO, Cetinel S, Ercan F, Yuksel M, Gedik N, Yegen BC. Amelioration of sepsis induced hepatic and ileal injury in rats by the leukotriene receptor blocker montelukast. Prostaglandins Leukot Essent Fatty Acids 2005;73(6):453-62
10. Izumo T, Kondo M, Nagai A. Cysteinyl leukotriene 1 receptor antagonist attenuates bleomycin-induced pulmonary fibrosis in mice. Life Sci 2007;80(20):1882-6.
11. Fireman E, Schwartz Y, Mann A, Greif J. Effect of montelukast, a cysteinyl receptor antagonist, on myofibroblasts in interstitial lung disease. J Clin Immunol 2004;24(4):418-25.
12. Khodir AE1, Ghoneim HA2, Rahim MA3, Suddek GM4. Montelukast attenuates lipopolysaccharide-induced cardiac injury in rats. Hum Exp Toxicol. 2016 Apr;35(4):388-97. doi: 10.1177/0960327115591372. Epub 2015 Jun 18.
13. Pinto P, Dougados M (2006). "Leflunomide in clinical practice" (PDF). Acta Reumatológica Portuguesa. 31 (3): 215–24. PMID 17094333. Archived from the original (PDF) on 2009-02-26. Retrieved 2008-11-01.
14. Teschner, S; Burst, V (September 2010). "Leflunomide: a drug with a potential beyond rheumatology". Immunotherapy. 2 (5): 637–50. doi:10.2217/imt.10.52. PMID 20874647
15. Grimm T1, Chovanová Z, Muchová J, Sumegová K, Liptáková A, Duracková Z, Högger P. Inhibition of NF-kappaB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol). J Inflamm (Lond). 2006 Jan 27;3:1.
16. Ezzikouri S1, Nishimura T2, Kohara M3, Benjelloun S4, Kino Y2, Inoue K5, Matsumori A6, Tsukiyama-Kohara K7. Inhibitory effects of Pycnogenol® on hepatitis C virus replication Antiviral Res. 2015 Jan;113:93-102. doi: 10.1016/j.antiviral.2014.10.017. Epub 2014 Nov 20.
17. Tanja Grimm,1 Zuzana Chovanová,2 Jana Muchová,2 Katarína Sumegová,2 Anna Liptáková,Zdeňka Ďuračková, and Petra Högger Inhibition of NF-κB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol) J Inflamm (Lond). 2006; 3: 1.
18. Feng WY, Tanaka R, Inagaki Y, Saitoh Y, Chang MO, Amet T, et al. Pycnogenol® , a procyanidin-rich extract from French maritime pine, inhibits intracellular replication of HIV-1 as well as its binding to host cells. Jpn J Infect Dis. 2008;61:279–285.

19. Matsumori A, Higuchi H, Shimada M. French maritime pine bark extract inhibits viral replication and prevents development of viral myocarditis. J Card Fail. 2007;13:785–791