Homeopathic Cyclosporin: Taming the Immune Response Using Isopathic Methodology

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Abstract:
Coronavirus disease of 2019 (Covid-19) infection has exposed the lack of sufficient understanding of the immune processes of human body responsible for optimum antiviral action. With conventional medicine proving less than adequate in taming the virus, it is quite possible that homeopathy, acting on the subcellular level, may be better suited to facilitate in vivo immunological responses against SARS Cov2. Based on the current understanding of our immune system, encouraged by a previous experiment showing in vitro stimulation of lymphocytes with homeopathic dilutions of *Cyclosporin* and constructing on the basic homeopathic tenet of '*Similia similibus curentur*', but applying it on the immunological level too, we propose that homeopathic form of *Cyclosporin* should be examined as a potential candidate to fight Severe Acute Respiratory Syndrome Coronavirus 2 (SARS Cov2). Lower potencies of *Cyclosporin* should help in reversing the initial immunosuppression and likely prevent the consequent uninhibited immune dysregulation that causes cytokine storm.

Introduction

Covid19 is the name ascribed by the World Health Organization (WHO) to the pandemic illness caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS Cov2).[1] It is an enveloped, single stranded, positive sense RNA virus, around 29.9 kb in length, 65-125nm diameter, belonging to genus betacoronavirus, family Coronaviridae.[2,3]

SARS Cov2 virus has four major structural proteins — spike (S), envelope (E), membrane (M) and nucleocapsid (N), 16 non-structural proteins (1-16 nsp) and 5-8 accessory proteins. S protein is needed for attachment, fusion, entry and transmission into the host cell.[4] It uses the ACE2 receptor to enter the host cell. S1 subunit of S protein has two domains — N terminal domain (NTD) and C terminal domain (CTD), the latter also called receptor binding domain (RBD). RBD is responsible for the first interaction with the host cell receptor causing conformational change in S2 leading on to membrane fusion. Protein cleavage between S1 and S2 is mediated by the transmembrane serine protease 2 (TMPRSS2). Once inside the cell, the infecting RNA acts as a messenger RNA (mRNA), this is then translated by host ribosomes to produce the viral replicative enzymes. After replication and sub genome RNA synthesis, the S, E and M viral structural proteins are translated and inserted into the endoplasmic reticulum (ER), and subsequently moved into endoplasmic reticulum-Golgi intermediate compartment (ERGIC). There, N protein encapsulates viral genome and buds into a membrane containing ERGIC to form mature viruses, which are transported to the cell surface in vesicles and released by exocytosis.[5,6]

ACE2 receptors in humans are found in the heart (endothelium of coronary arteries, myocytes, fibroblasts, epicardial adipocytes), vessels (vascular endothelial cells and smooth cells), gut (intestinal epithelial cells), lungs (tracheal and bronchial epithelial cells and type 2 pneumocytes, macrophages), kidneys (luminal surface of tubular epithelial cells), testes and brain.[7] ACE2 is highly expressed in oral mucosa.[8] The ACE2 gene is expressed on X chromosome and increased expression has been found in Asians.[7] The SARS Cov2 virus attaches to the ACE2 receptors on the host. Severe Acute Respiratory Syndrome Coronavirus (SARS Cov) also attaches on the same receptor and both viruses share approximately 80% genome sequence homology. However, compared to the latter, the former has more atomic interactions to the receptor increasing the affinity by 10-20 folds.[9]

Pathophysiology of SARS Cov2 [10,11]

SARS Cov2 infection usually stays asymptomatic over the first few days when a decrease in innate immune responses and reduced expression of ACE2 in upper airways can be seen. Over the next few days upper airways and conducting airways are affected and reduction in T cells is evident. Eventually in some clients, the infection reaches the lower airways causing hypoxia with lungs showing ground glass infiltrates and ARDS-like picture. Alveolar type 2 cells are destroyed either directly by virus or undergo apoptosis. With reduction in type 2 cells, there is a reduction in production of type 1

pneumocytes too. Type 1 pneumocytes are responsible for gas exchange while type 2 are responsible for production of type 1 cells and surfactant. Eventually severe fibrosis ensues. The elderly seem to have increased viral load due to reduced immune function and reduced ciliary response of the airways.

Initial infection shows increased total white cell count. Coronaviruses seem to be able to evade the innate immune response, suggested by their longer incubation period of 2-14 days when compared to 1-4 days of influenza virus.[12] Decreased secretion of interferons and TNF alpha leads to dampening of immune cells recruitment and therefore leads to unabated viral replication.[13] This later on leads to increased release of pro-inflammatory cytokines like TNF alpha, IL-1 beta, IL-2, IL-6, IL-8, Interferon gamma induced protein 10 (IP10), IFN gamma induced protein 1 and macrophage inflammatory protein 1alpha leading to lung damage. This cytokine storm can lead to significant inflammatory pulmonary damage, with some clients meeting a fatal end. Pneumocytes, macrophages and dendritic cells all contribute to cytokine production. Studies of SARS Cov showed inflammation being mediated by pathogen recognition receptors (PRR) like TLR3, 7 and 8, and also by retinoic acid inducible gene I and NOD like receptor.

With conventional medicine not providing a concrete answer to how SARS Cov2 moulds the immune system to its advantage, it may be prudent to explore the complementary medical system.

Clients with severe Covid-19 exhibit marked lymphopenia. Chen Y et al. used immunohistochemistry and immunofluorescence to characterize hilar and subscapular lymph nodes and spleens post-mortem from six clients who died from Covid-19.[14] In addition to splenic and lymph node atrophy and necrosis, the authors reported significant lymphocytic apoptosis. Of note, ACE2-expressing CD68+CD169+ macrophages were detected in the splenic marginal zone and in marginal sinuses of lymph nodes, and these macrophages contained SARS-CoV-2 nucleoprotein antigen and showed upregulation of IL-6. Virally infected tissues also showed higher expression of FAS. This suggests that CD169+ macrophages could contribute to viral spread, excessive inflammation and activation-induced lymphocytic cell death during SARS-CoV-2 infection. Secretion of cytokines including TNF-α, IL-6, and IL-10 was increased in Covid-19 clients. Interestingly, the numbers of total T cells, CD4+ T and CD8+ T cells are negatively correlated to levels of TNF-α, IL-6, and IL-10, respectively, suggesting these cytokines may be involved in the decrease of T cells detected in Covid-19. T cells are possibly decreased and exhausted.[15]

CD4 and CD8 cells tend to show a decline even before chest X-ray changes are seen. Viral particles are seen inside peripheral blood T cells, liver, spleen and lymph nodes. T cell decrease may be secondary to direct viral effect causing cell lysis, Fas-Fas ligand interaction or TNF related apoptosis-inducing ligand signaling axis. Studies with MERS showed that disease progression seemed to be associated with a skewing towards Th2 immune response and recovery was associated with enhanced Th1 response, which may be true for SARS Cov2 too.[16] Viremia after pulmonary involvement can result in viral sepsis. Metabolic acidosis may be associated with microcirculation dysfunction. A large number of deaths in Covid-19 clients had evidence of disseminated intravascular coagulation. Increase in D-dimers or other fibrin degradation products are associated with poor prognosis.

The condition is also characterized by high ferritin, akin to macrophage activation syndrome (MAS), catastrophic antiphospholipid syndrome, septic shock or reaction to anti CD28. These hyperferritinemic conditions are also characterized by a cytokine storm with increase of IL1, IL6, IL17 etc and mortality approaching 50%. The H chain of the ferritin may be involved in activating macrophages. Soluble CD163 (sCD163) is a marker of macrophage activation and may be used as a marker of cytokine storm.[17] High NLR (Neutrophil:lymphocyte) ratio is prognostic marker for severe infection.[18,19]

Recovery of the immune system is quicker in mild cases with T cells showing improvement in 15 days and almost normalizing in 25 days. However in clients who died, the T cells kept on decreasing till the end. We still don't know if neutralizing antibodies function well and how long they last. There seems to be a difference between total measurable antibodies and protective neutralizing antibodies. 10-20 percent of symptomatic clients have little or no measurable antibodies; whether this signifies mild infection or inhibition of immune response by a strain is unknown. Most hospitalized clients show IgM response by day 9 and then IgG response by two weeks, the latter coinciding with the disappearance of the virus.[20] It's still unclear how long the protective immunity would last after the infection.

It's clearly evident that Covid19 is characterized by initial immunosuppression which subsequently, in some clients, paves the way to a cytokine storm likely due to uninhibited dysregulation of the immune system which is not able to control itself. With conventional medicine not providing a concrete answer to how SARS Cov2 moulds the immune system to its advantage, it may be prudent to explore the complementary medical system. Homeopathic philosophy, S*imilia similibus curentur*, suggests that when a toxic substance is given in dilu-

tions (potentised form), it brings cure for the toxic effects it produces, or some other toxin with similar effects produces, when given in crude form. *Cyclosporin-A* or *Cyclosporin* is one such molecule which produces immunosuppression and has similarities to SARS Cov2 infection.

Cyclosporin

Cyclosporin (a toxic substance in larger doses) is a homodetic cyclic-11 hydrophobic peptide isolated from the fungal species Tolypocladium Inflatum gams.[21] It binds to the eight stranded antiparallel beta barrels structured cyclophilin and the prolyl isomerase substrate binding site is coincident with the *Cyclosporin* binding site. Cyclosporin-cyclophilin complex then binds to calcineurin contributing to immunosuppression produced by *Cyclosporin*.[22]

Cyclophilins play a key role in the lifecycle of many coronaviruses, including human coronaviruses 229E (HCoV-229E) and NL-63 (HCoV-NL63), feline infectious peritonitis coronavirus (FPIV), SARS-CoV and Middle-East Respiratory Syndrome coronavirus (MERS-CoV). *Cyclosporin A* (*Cyclosporin*), a potent cyclophilin pathway inhibitor, blocks the replication of various coronaviruses in vitro, including HCoV-229E, HCoV-NL63, FPIV, mouse hepatitis virus (MHV), avian infectious bronchitis virus, and SARS-CoV. However, *Cyclosporin* cannot be used in clients with Covid-19 because of its strong immunosuppressive properties.[23] However, by virtue of the aforementioned Homeopathic principle, dilutions of *Cyclosporin* should help reverse initial imunosuppression and thereby may mitigate the toxic effects of Covid19 immune dysregulation.

Cyclosporin and SARS cov2 — analogy (Conforming to principle of similia similibus curentur)

Both *Cyclosporin* and SARS Cov2 lead to lymphopenia and suppression of innate immune responses. *Cyclosporin* can promote superantigen mediated cell death in CD4+ lymphocytes.[24] Generation of suppressor cells and reversal of TH:TS ratio is seen after *Cyclosporin* therapy.[25] *Cyclosporin* directly interferes with antigen presenting function of macrophages.[26] SARS Cov2 clients present with lymphopenia causing reduction in CD4, Treg, Th1 and CD8 cells.[27] Also, the cytokine storm of proinflammatory cytokines — IL-6, TNF alpha, IL-1B, C-reactive protein suggest a super antigen component of the virus.[28]

Cyclosporin can directly inhibit the activation of B-lymphocytes to a variety of stimuli by interfering with Ca++ dependent signals.[29] Lun et al (1991) have shown that along with inhibiting B cell activation, *Cyclosporin* may also decrease or increase the differentiation and immunoglobulin production by B cells, depending on the antigen used.[30] By suppressing CD4 numbers, *Cyclosporin* has indirect inhibitory effects on the growth and differentiation of B lymphocytes (IL-4 and IL-6). B cells probably contribute to the cytokine storm in Covid19 by producing IL-6, as one case series showed that clients with agammaglobulinemia developed only mild symptoms while those with Common Variable Immunodeficiency showed significant severity.[31]

Natural Killer (NK) cell activity is only mildly impaired under normal *Cyclosporin* therapeutic dose.[32] However, a dose dependent inhibition of NK cell activity is noted when NK cells are exposed in vitro to *Cyclosporin*.[33] Zheng et al (2020) showed that the total number of NK and CD8+ T cells was decreased markedly in clients with SARS-CoV-2 infection.[34] The function of NK and CD8+ T cells was exhausted with the increased expression of NK group 2 member A receptor (NKG2A) in Covid-19 clients. As an inhibitory receptor, NKG2A has been demonstrated to induce NK cell exhaustion in chronic viral infections. Importantly, in clients convalescing after therapy, the number of NK and CD8+ T cells was restored with reduced expression of NKG2A. These results suggest that the functional exhaustion of cytotoxic lymphocytes is associated with SARS-CoV-2 infection. Hence, SARS-CoV-2 infection may break down antiviral immunity at an early stage.

Apart from an effect on the immune system, the effects on the various body organs show similarity too. The primary organs of involvement in SARS Cov2 infection are the lungs causing damage to the alveoli leading on to the cytokine storm. *Cyclosporin* therapy may lead to ARDS and it's believed that high concentration of *Cyclosporin* in the pulmonary vasculature causes a localized 'capillary leak' or it may be an idiosyncratic reaction to *Cyclosporin*.[35,36]

Both *Cyclosporin* therapy and Covid19 infection are associated with nervous system afflictions. *Cyclosporin* can lower seizure threshold, can enhance viral induced T cell mediated demyelination and has been associated with demyelinating polyneuropathy, Guillain-Barre syndrome and Parkinsonism.[37,38,39,40,41,42,43]. *Cyclosporin* therapy is also associated with a dose dependent toxic myopathy characterized by myalgias, muscle weakness or rhabdomyolysis.[44] A variety of neurological manifestations have been described in SARS Cov2 infection over the period of previous few months including encephalopathy, encephalitis, Guillain-Barre syndrome, myelitis, rhabdomyolysis and acute cerebrovascular events.[45]

Cyclosporin, similarly produces renal side effects, but in a dose dependent manner, including tubular changes (isometric vacuoles, inclusion bodies, microcalcifications), striped interstitial fibrosis and more seriously, focal and segmental glomerulosclerosis.[46,47,48] Covid19 has been associated with acute kidney injury, proteinuria, hematuria and collapsing glomerulopathy.[49]

Cyclosporin therapy is related to the development of a syndrome resembling thrombotic thrombocytopenic purpura

(TTP) or hemolytic uremic syndrome (HUS). Probable mechanisms include defective synthesis and release of prostacyclin from endothelial cells and excessive platelet aggregation due to increased utilization of high molecular weight multimers of factor VIII, whose levels are raised after vascular injury induced by *Cyclosporin*.[50,51,52,53,54,55] Covid19 may be associated with coagulopathy and may resemble HUS/TTP or DIC.[56]

Cyclosporin induces a dose dependent decrease in serum and intratesticular testosterone levels and produces impairment of testicular spermatogenesis, steroidogenesis, epididymal sperm maturation and fertility in rats.[57] There has been increasing evidence that SARS Cov2 infection is likely associated with male genital damage. As we know that testes have high expression of ACE2 receptors, they are a likely target for the virus. One study found significantly increased LH with significantly decreased testosterone: LH and FSH:LH ratios in a study of 81 male clients affected with Covid19.[58]

Considering the similarities and construction on the tenet of *similia similibus curentur,* Cyclosporin in low homeopathic dilutions should help in reversing the initial immunological immunosuppression and likely prevent the subsequent immune dysregulation that leads to the cytokine storm.

Cholestasis, manifested by increased levels in serum bilirubin, alkaline phosphatase and gamma-glutamyl transferase, is the most frequent manifestation of *Cyclosporin* hepatotoxicity.[59,60] It is dose dependent and is often associated with a variable component of cholangitis and pericholangitis. Covid19 has been associated with hepatic dysfunction, particularly in those with severe disease. Liver dysfunction includes increase in transaminases and even acute hepatic injury. It may be multifactorial including roles of direct viral cytopathic effect, immune mediated or secondary to sepsis or drugs.[61]

Evidence indicates that *Cyclosporin* has a direct toxic effect on pancreatic islet cell functions, leading to impaired insulin synthesis and secretion.[62] Hyperglycemia has been noted in a significant number of Covid19 clients and it has been speculated that SARS Cov2 may enter islets causing acute beta cell dysfunction.[63,64]

Cyclosporin produces glutathione deficiency and the resultant oxidative stress contributes to its hepatotoxicity and nephrotoxicity.[65] Glutathione, glutathione precursors (N-acetylcysteine) and alpha lipoic acid may represent a novel treatment approach for blocking NF-κB and addressing "cytokine storm syndrome" and respiratory distress in clients with Covid-19 pneumonia.[66]

Selenium is an important component of glutathione peroxidase, which is depleted in *Cyclosporin* treated individuals and its supplementation seems to prevent the vascular toxicity.[67] Sodium selenite, but not selenate, can oxidize thiol groups in the virus protein disulfide isomerase rendering it unable to penetrate the healthy cell membrane. In this way selenite inhibits the entrance of viruses into the healthy cells and abolishes their infectivity.[68]

Homeopathic Cyclosporin

Use of homeopathic potentized form of *Cyclosporin* has previously been studied in vitro where lymphocytes from mice sensitized with Salmonella antigens (live or inactivated) when incubated with the homeopathic form of *Cyclosporin* showed increase in inositol phosphate 3, intracellular calcium, increased phosphokinase C, increased production of IL-2 & gamma IFN (Th1) and increased production of IL4 (Th2) and increased TNF- alpha.[69] Safety of the drug was tested by using three potencies i.e., 30, 200 and 1000 in albino mice by oral route once a day for three months whereby no change was observed in the behavior, weight, and food intake. Autopsy did not reveal any gross abnormality in liver, kidney, thymus, spleen, and lymph nodes (routine histology). When lymphocytes from two HIV-1 infected clients (CD4 count 400 to 500) were incubated with this drug, an increase in lymphocyte counts was observed, with no obvious adverse effects. Dr Sudhir Gupta, USA and Dr N K Ganguly, Professor and Head, Department of Experimental Medicine, PGI, Chandigarh, India provided the laboratory support during these previous experiments. These in vitro experiments show that homeopathic form of *Cyclosporin* has the potential to stimulate lymphocytes. It is possible that reversal of initial immunosuppression may suffice to inhibit the subsequent cytokine storm, as it is quite likely that removal of some deterrent by the immunosuppressed state is probably the cause of uninhibited cytokine storm which then damages the self to a much greater extent than what the virus ever does. Lower potency of drug is likely to reverse immunosuppression without subsequent hyperstimulation or aggravation.

We know that classical homeopathy is based on looking at similarity between symptom complex of the client and that produced by the remedy on healthy volunteers, we have tried taking the concept to the pathological and molecular level, using isopathic methodology and with a hypothesis that simi-

larity in the latter micro-environment may follow homeopathic principles too.

The notion to use *Cyclosporin* in Covid19 developed after studying similarities between toxic effects of *Cyclosporin* and HIV in late 1990s. (Mathur NK, Bhargava P. Immunosuppression — Bliss or curse: Tale of two poisons. Indian J Sex Transm Dis 1998; 19: 1-21) (accessible at nkmathur.com/immunosuppression-bliss-and-curse-a-tale-of-two-poisons/)

Considering the similarities and construction on the tenet of *Similia similibus curentur*, *Cyclosporin* in low homeopathic dilutions should help in reversing the initial immunological immunosuppression and likely prevent the subsequent immune dysregulation that leads to the cytokine storm. Pilot *in vitro* studies on mice using a few potencies of the drug showed encouraging results.

Conclusion

Covid-19 infection has exposed the lack of complete understanding of the immune processes of the human body responsible for optimum antiviral action. With conventional medicine proving less than adequate in taming the virus, it is quite possible that homeopathy, acting on the subcellular level, may be better suited to facilitate in vivo immunological responses against SARS Cov2. Based on the current understanding of immune system and previous in vitro experiment showing potential of *Cyclosporin* in homeopathic dilutions to stimulate lymphocytes, we propose that homeopathic form of *Cyclosporin* should be examined as a potential candidate to fight the current pandemic, which is raging relentlessly, despite the best of scientific efforts.

We should consider further proving homeopathic *Cyclosporin* to be able to add more symptoms to what we currently have in our materia medica.

Reference Works application, using Marsh's Clinical Drug Pictures, currently lists some symptoms of the remedy as confusion, headaches, convulsions, hypertension, pancreatitis, vomiting, diarrhea, thrombocytopenia, hemolytic anemia, immunosuppression and increased susceptibility to infections, muscle weakness and burning sensations of hands and feet, to name a few.

In this article, though we rely on the isopathic method for treatment, we also advocate that with further provings, we may be able to prove a classical use of the remedy in Covid cases, and other future forms of SARS related illnesses, as well.

References

1. Qing E, Gallagher T. SARS Coronavirus Redux. Trends in Immunology 2020: 41(4); 271-3
2. Wu F., Zhao S., Yu B., Chen Y.-M., Wang W., Song Z.-G. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579:265–9
3. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response [published online ahead of print, 2020 Apr 18]. Diabetes Metab Syndr. 2020;14(4):407-12.
4. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A et al. Cell entry mechanisms of SARS-CoV-2. Proceedings of the National Academy of Sciences of the United States of America 2020; 117 (21): A71
5. Fehr A.R., Perlman S. Springer; New York: 2015. Coronaviruses: an overview of their replication and pathogenesis. Coronaviruses; pp. 1–23.
6. Masters PS. The molecular biology of coronaviruses. Adv Virus Res. 2006;66: 193–292.
7. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med. 2020; 76:14-20.
8. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020 12, 8. doi.org/10.1038/s41368-020-0074-x
9. Xia S, Liu M, Wang C, Xu W, Lan Q, Feng S et al. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell Res 2020; 30: 343–55.
10. Yuki K, Fujiogi M, Koutsogiannaki S. Covid-19 pathophysiology: A review. Clin Immunol. 2020;215: 108427.
11. Mason RJ. Pathogenesis of Covid-19 from a cell biology perspective. European Respiratory Journal Apr 2020; 55 (4): 2000607
12. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis. 2009; 9: 291-300
13. Lau SKP, Lau CCY, Chan KH, Li CPY, Chen H, Jin DY et al. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. J General Virol 2013; 94: 2679–90.
14. Chen Y, Feng Z, Diao B, Wang R, Wang G, Wang C et al. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. Preprint at medRxiv doi.org/10.1101/2020.03.27.20045427 (2020)
15. Liu J, Li S, Liang B, Wang X, Wang H et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected clients. EBioMedicine 2020; 55: 102763.
16. Shin HS, Kim Y, Kim G, Lee JY, Jeong I, Joh JS et al. Immune responses to Middle East respiratory syndrome coronavirus during the acute and convalescent phases of human infection. Clin Infect Dis. 2019; 68: 984-92.
17. Shoenfeld Y. Corona (Covid-19) time musings: Our involvement in Covid-19 pathogenesis, diagnosis, treatment and vaccine planning. Autoimmune Rev 2020; 19(6): 102538.

18. Kerboua KE. NLR: A Cost-effective Nomogram to Guide Therapeutic Interventions in Covid-19, Immunological Investigations 2020 Jun: 1-9.

19. Zhang B, Zhou X, Zhu C, Song Y, Fang F, Qiu Y et al. Immune phenotyping based on neutrophil-tolymphocyte ratio and IgG predicts disease severity and outcome for clients with Covid-19. MedRxiv. 2020 (Preprint); DOI: 2020.03.12.20035048.

20. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020; 579: 270-73

21. Borel JF, Kis ZL The discovery and development of *Cyclosporin* (Sandimmune) Transplant. Proc. 1991; 23:1867-74

22. Kallen J, Spitzfaden C, Zurini MG, Wider G, Widmer H, Wuthrich K et al. Structure of human cyclophilin and its binding site for *Cyclosporin* A determined by X-ray crystallography and NMR spectroscopy. Nature. 1991; 353(6341): 276-79.

23. Softic L, Brillet R, Berry F, Ahnou N, Nevers Q, Morin-Dewaele M et al. Inhibition of SARS-CoV-2 infection by the cyclophilin inhibitor alisporivir (Debio 025). Antimicrob Agents Chemother 2020; 64: e00876-20.

24. Vanier LE, Prud'homme GJ. *Cyclosporin* A markedly enhances superantigen-induced peripheral T cell deletion and inhibits anergy induction. J Exp Med 1992; 176: 37–46

25. Kerman RH, Flechner SM, Buren CTV, Lorber MI, Kahan BD. Immunoregulatory mechanisms in *Cyclosporin* treated renal allograft recipients. Transplantation 1987; 43:205-10

26. Yonish-Rouach E, Fischer DG, Rubinstein M. *Cyclosporin* A regulates the expression of HLA DR on human monocytes by two different mechanisms. Cell Immunol 1991; 134(2): 402-13

27. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storms in severe Covid-19 clients. Natl Sci Rev 2020; 7(6): 998-1002.

28. Zhang, JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ et al. Clinical characteristics of 140 clients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020; 75(7): 1730-41.

29. Thomson A.W. The effects of *Cyclosporin* A on non-T cell components of the immune system. Autoimmunity 1992; 5:167-76

30. Lun MT, Cochi S, Fioravanti D, Nazzari C, Raponi G, Mannella E, et al. Effect of *Cyclosporin* A on B cell maturation and differentiation. Drugs Exp Clin Res. 1991; 17:493–500

31. Quinti I, Lougaris V, Milito C, Cinetto F, Pecoraro A, Mezzaroma I et al. A possible role for B cells in Covid-19? Lesson from clients with agammaglobulinemia. J Allery Clin Immunol 2020; 146(1): 211-13e4.

32. Gui XE, Rinaldo CR Jr, Ho M. Natural killer cell activity in renal transplant recipients receiving *Cyclosporin*. Infect Immun. 1983; 41(3): 965-970.

33. Introna M, Allavena P, Spreafico F, Mantovani A. Inhibition of human natural killer activity by *Cyclosporin* A. Transplantation 1981;31:113-16

34. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D et al. Functional exhaustion of antiviral lymphocytes in Covid19 clients. Cell Mol Immunol 2020; 17(5): 533-35.

35. Powell-Jackson PR, Carmichael FJL, Calne RY, Williams B. Adult respiratory distress syndrome and convulsions associated with administration of *Cyclosporin* in liver transplant recipients. Transplantation 1984; 38:341-43

36. Carbone L, Appel GB, Benevisty AI, Cohen DJ, Kunis CL, Hardy MA. Adult respiratory syndrome associated with oral *Cyclosporin*. Transplantation 1987; 43(5):767

37. Ghany AM, Tutschka PJ, McGhee RB Jr. *Cyclosporin* associated seizures in bone marrow transplant recipients given busulfan and cyclophosphamide preparative therapy. Transplantation 1991; 52(2):310-14

38. Baliga R, Etheredge EE. *Cyclosporin*-associated convulsions in a child after renal transplantation. Transplantation. 1991; 51(5): 1126-28.

39. Racusen LC, McCrindle BW, Christenson M, Fivush B, Fisher RS. *Cyclosporin* lowers seizure threshold in an experimental model of electroshock-induced seizures in Munich-Wistar rats. Life Sciences. 1990 ;46(14): 1021-26

40. Appleton RE, Farrell K, Teal P, Hashimoto SA, Wong PK. Complex partial status epilepticus associated with *Cyclosporin* A therapy. J Neurol Neurosurg Psychiatry 1989; 52(9): 1068-71

41. Fazakerley JK, Webb HE. *Cyclosporin* enhances virally induced T-cell-mediated demyelination. The effect of *Cyclosporin* on a demyelinating virus infection. J Neurol Sci 1987; 78: 35–50.

42. Qureshi AI, Cook AA, Mishu HP, Krendel DA. Guillain-Barré syndrome in immunocompromised clients: a report of three clients and review of the literature. Muscle Nerve 1997;20(8):1002-7

43. Wasserstein PH, Honig LS. Parkinsonism during *Cyclosporin* treatment. Bone marrow transplant 1996; 18(3): 649-50.

44. Arellano F, Krupp P. Muscular disorders associated with *Cyclosporin*. Lancet 1991; 337: 915

45. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A et al. Neurological associations of Covid19. The Lancet Neurology 2020; 19(9): 767-83.

46. Mason J. Renal side-effects of *Cyclosporin*. Transplant Proc. 1990;22(3):1280-83

47. Woolfson RG, Neild GH. *Cyclosporin* nephrotoxicity following cardiac transplantation. Nephrol Dial Transplant. 1997;12(10):2054-56

48. Perico N, Detcheva A, Khalil EI, Remuzzi G. *Cyclosporin* induces glomerulosclerosis: three-dimensional definition of the lesions in a rat model of renal transplant. Kidney Int 1996;49(5):1283-88

49. Nasr SH, Kopp JB. Covid-19-Associated Collapsing Glomerulopathy: An Emerging Entity [published online ahead of print, 2020 May 4]. Kidney Int Rep. 2020;5(6):759-61.

50. Bonser RS, Adu D. Franklin I, McMaster P. *Cyclosporin* induced haemolytic uraemic syndrome in liver allograft recipient. Lancet 1984; 2: 1337

51. Brown Z, Neild GH, Willoughby JJ, Somia NV, Cameron SJ. Increased factor VIII as an index of vascular injury in *Cyclosporin* nephrotoxicity. Transplantation. 1986;42(2):150-53

52. Buren D van, Buren CT van, Flechner SM, Maddox AM, Verani R, Kahan BD. De novo haemolytic uraemic syndrome in renal transplant recipients immunosuppressed with *Cyclosporin*. Surgery 1985, 98:54–62

53. Neild GH, Rocchi G, Imberti L, Fumagalli F, Brown G, Remuzzi DG et al. Effect of *Cyclosporin* A on prostacyclin synthesis by vascular tissue. Throb Res 1983; 32: 373-79.

54. Sommer BG, Innes JT, Whitehurst RM et al. *Cyclosporin*-associated renal arteriopathy resulting in loss of allograft function. Am J Surg 1985; 149:756–64

55. Wolfe JA, McCann RL, Sanfilippo F. *Cyclosporin*-associated microangiopathy in renal transplantation. A severe but potentially reversible form of early graft injury. Transplantation 1986, 41: 541–43.

56. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of Covid-19 coagulopathy. Crit Care. 2020; 24(1): 360.

57. Seethalakshmi L, Menon M, Malhotra RK, Diamond DA. Effect of *Cyclosporin* A on male reproduction in rats. J Urol 1987; 138(4 Pt 2): 991-95.

58. Ma L, Xie W, Li D, Shi L, Mao Y, Xiong Y et al. Effect of SARS-CoV-2 infection upon male gonadal function: A single center-based study. medRxiv; 2020. DOI: 10.1101/2020.03.21.20037267.

59. Klintmalm GB, Iwatsuki S, Starzl TE. *Cyclosporin* A hepatotoxicity in 66 renal allograft recipients. Transplantation. 1981; 32(6):488-89.

60. Lorber MI, Van Buren CT, Flechner SM, Williams C, Kahan BD. Hepatobiliary and pancreatic complications of *Cyclosporin* therapy in 466 renal transplant recipients. Transplantation. 1987;43(1):35-40

61. Jyothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. Covid-19 and liver. J Hepatol 2020 Jun 15 doi: 10.1016/j.jhep.2020.06.006 [Epub ahead of print]

62. Nielsen JH, Mandrup-Poulsen T, Nerup J. Direct effects of *Cyclosporin* A on human pancreatic beta-cells. Diabetes. 1986;35(9):1049-52

63. Chen N., Zhou M., Dong X. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395:507–13

64. Mukherjee S, Banerjee O, Singh S, Maji BK.. Covid-19 could trigger global diabetes burden — A hypothesis [published online ahead of print, 2020 Jun 26]. Diabetes Metab Syndr. 2020;14(5):963-64.

65. Inselmann G. Lawerenz H.U. Nellessen U. Heidemann H.T. Enhancement of *Cyclosporin* A induced hepato and nephrotoxicity by glutathione depletion. Eur. J. Clin. Invest. 1994; 24: 355–59.

66. Horowitz RI, Freeman PR, Bruzzese J. Efficacy of glutathione therapy in relieving dyspnea associated with Covid-19 pneumonia: A report of 2 cases [published online ahead of print, 2020 Apr 21]. Respir Med Case Rep. 2020; 30: 101063.

67. Berkenboom G, Brekine D, Fang ZY, Neve J, Fontaine J. Prevention by selenium supplementation of *Cyclosporin* A induced vascular toxicity. Cardiovasc Res 1997; 33: 650-54

68. Kieliszek M, Lipinski B. Selenium supplementation in the prevention of coronavirus infections (Covid-19) [published online ahead of print, 2020 May 24]. Med Hypotheses. 2020; 143: 109878.

69. Mathur NK, Bhargava P. Immunosuppression — Bliss or curse: Tale of two poisons. Indian J Sex Transm Dis 1998; 19: 1-21

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