



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Using cyclosporine in the COVID era: An emergent need for caution



To the Editor: We read the paper “Cyclosporine therapy during the COVID-19 pandemic is not a reason for concern” by Rudnicka et al¹ and wish to highlight some interpretations that can encourage complacency in the use of a drug where caution is needed.

As rightly pointed out, there are in vitro data showing inhibitory effects of cyclosporine A (CsA) on coronaviruses (CoVs); along with many other classes of virus, prominently hepatitis C virus and HIV.² CsA binds to cyclophilins, a family of ubiquitous proteins present in all prokaryotes and eukaryotes. Functional interactions between viral proteins (chiefly the nonstructural protein 1) and members of cyclophilin family form an important part of the virus-host interaction.² Genome-wide analysis of protein-protein interactions between severe acute respiratory syndrome (SARS)-CoV and human host proteins identified both cyclophilins and FK506-binding protein (FKBP) as interaction partners for SARS-CoV proteins.³ The exact function of cyclophilins' viral pathogenicity is not known, but they are probably essential for viral growth and replication.

The immunosuppressive action of calcineurin inhibitors (CNIs), on the other hand, relies on calcineurin inhibition by the CsA-cyclophilin A complex, which blocks the translocation of nuclear factor of activated T cells to the nucleus and prevents the transcription of cytokine genes, prominently interleukin 2. Thus, the antiviral effect of CsA, via binding cyclophilin, largely occurs a step upstream of that essential for their immunosuppressive effect. Trials of some novel cyclophilin inhibitors and nonimmunosuppressive analogs of CsA have been undertaken for potential use in hepatitis C virus and other viral infections.⁴

There are well-researched aspects regarding the intricacies of the interaction of viruses with host cells. Interestingly, mycophenolic acid and 6-thioguanine also have in vitro activity against CoVs, but again, the clinical implications are unclear.^{5,6}

Another important point to consider for clinical use of immunosuppressives during the ongoing pandemic is the effect on host antiviral immune responses.⁷ The cytotoxic T lymphocytes and natural killer cells are the most important immune cells in this regard, along with antibody-dependent cellular cytotoxicity and certain cytokines, prominently interferons.⁷ CsA not only suppresses the helper T cells and precursors of cytotoxic T lymphocytes but also causes depression of innate immune response via an inhibitory effect on natural killer cells. Increased risk

of viral infections, such as multiple viral warts and Epstein-Barr virus reactivations in transplant patients, and of cytomegalovirus infections in transplant recipients and ulcerative colitis patients taking CsA is probably related to this.⁷ Further, animal models have demonstrated an inability to mount an effective immune response to viral infections with administration of CsA.⁸ Thus, the prominent interference with host antiviral responses by CsA should not be ignored. Further, none of the immunosuppressives have so far been conclusively shown to be beneficial for the “cytokine storm” associated with severe coronavirus disease 2019 (COVID-19) infection, and use on that premise is speculative.

Hence, we believe that the use of immunosuppressive drugs requires a guarded approach during the ongoing pandemic, with initiation only in most essential cases and with continued close monitoring for infectious adverse effects.

Ananta Khurana, MD, DNB, and Khusboo Sethia, MBBS

From the Department of Dermatology, Dr. Ram Manohar Lobia Hospital & Atal Bihari Vajpayee Institute of Medical Sciences, New Delhi, India.

Funding sources: None.

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

Reprints not available from the authors.

Correspondence to: Ananta Khurana, MD, DNB, Department of Dermatology, Dr. Ram Manohar Lobia Hospital & ABVIMS, New Delhi 110001, India

E-mail: drananta2014@gmail.com

REFERENCES

1. Rudnicka L, Goldust M, Glowacka P, et al. Cyclosporine therapy during the COVID-19 pandemic is not a reason for concern [e-pub ahead of print]. *J Am Acad Dermatol*. 2020; 83(2):e151-e512.
2. de Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y, et al. Cyclosporin A inhibits the replication of diverse coronaviruses. *J Gen Virol*. 2011;92:2542-2548.
3. Pfefferle S, Schöpf J, Kögl M, et al. The SARS-coronavirus-host interactome: identification of cyclophilins as target for pan-coronavirus inhibitors. *PLoS Pathog*. 2011;7:e1002331.
4. Gally PA. Cyclophilin inhibitors: a novel class of promising host-targeting anti-HCV agents. *Immunol Res*. 2011;52:200-210.
5. Hart BJ, Dyal J, Postnikova E, et al. Interferon- β and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. *J Gen Virol*. 2014;95:571-577.

6. Chen X, Chou CY, Chang GG. Thiopurine analogue inhibitors of severe acute respiratory syndrome-coronavirus papain-like protease, a deubiquitinating and deISGylating enzyme. *Antivir Chem Chemother.* 2009;19:151-156.
7. Khurana A, Saxena S. Immunosuppressive agents for dermatological indications in the ongoing COVID 19 pandemic: rationalizing use and clinical applicability [e-pub ahead of print]. *Dermatol Ther.* 2020. <https://doi.org/10.1111/dth.13639>. Accessed June 11, 2020.
8. Kim JH, Perfect JR. Infection and cyclosporine. *Rev Infect Dis.* 1989;11:677-690.
<https://doi.org/10.1016/j.jaad.2020.06.990>