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.

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 al[1] 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.

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