Received: 7 September 2022 | Accepted: 5 January 2023

DOI: 10.1002/rmv.2423

REVIEW

WILEY

The immune paradox of SARS-CoV-2: Lymphocytopenia and autoimmunity evoking features in COVID-19 and possible treatment modalities

Joachim Gerlach[1] | Abdul Mannan Baig[2] | Mark Fabrowski[3] | Valentina Viduto[4]

[1]Health-Shield, Langenfeld, Germany

[2]Department of Biological and Biomedical Sciences, Aga Khan University, Karachi, Pakistan

[3]Department of Emergency Medicine, Royal Sussex County Hospital, University Hospitals Sussex, Brighton, UK

[4]Long-COVID Foundation, Leeds, West Yorkshire, UK

Correspondence
Abdul Mannan Baig, Aga Khan University, Karachi, Pakistan.
Email: abdul.mannan@aku.edu

Abstract

SARS-CoV-2 causes multiorgan damage to vital organs and tissue that are known to be due to a combination of tissue tropisms and cytokine-mediated damage that it can incite in COVID-19. The effects of SARS-Co-2 on the lymphocytes and therefore on the immune response have attracted attention recently in COVID-19 to understand its effects in causing a chronic state of ongoing infection with Long-COVID. The associated lymphopaenia and autoimmune disease state, which is an apparent paradox, needs to be researched to dissect possible mechanisms underlying this state. This paper attempts to unravel the aforesaid immune paradox effects of SARS-CoV-2 on the lymphocytes and discusses appropriate treatment modalities with antiviral drugs and nutraceuticals which could prove virucidal in SARS-CoV-2 seeding monocytes and lymphocytes in patients with COVID-19 and Long-COVID. Importantly it proposes a new in vitro treatment modality of immune regulating cells that can help patients fight the lymphopaenia associated with COVID-19 and Long-COVID.

1 | INTRODUCTION

The SARS-CoV-2 is now been established to produce organ damage due to its direct invasion of target cells by using diverse types of cell surface receptors[1–3] and non angiotensin-converting enzyme 2 (ACE2) receptor-mediated host cell entry mechanisms like clathrin-assisted cellular uptake.[2] The mechanism of cell invasion by SARS-CoV-2 is one of the top niches in COVID-19 research worldwide. The immune response of the human immune system to SARS-CoV-2 is also a pivotal area of research to understand the differential immune response that is mounted by individuals against SARS-CoV-2 in COVID-19 and long-COVID.[4,5] Interesting questions which need clarity to understand the pathogenesis of immunopathology caused by SARS-CoV-2 and therefore the response mounted against the virus are (a) how does SARS-CoV-2 invade the immune system regulating cells? (b) Does the virus causes cell death after and if so, what are the mechanisms involved when it targets the lymphocytes? (c) Why has a coexisting state of autoimmunity been reported if lymphocytes are undergoing cell death when COVID-19 enters into a chronic phase of Long-COVID? (d) Is there an existing treatment other than corticosteroids that can help patients with autoantibodies in Long-COVID without making them susceptible to infections? Published literature addressing these questions is surfacing but there is a need for clarity to understand the pathogenetic mechanism involved in lymphotropism[6,7] that can answer the above questions without any ambiguity. To address the questions mentioned above, the receptor and non-receptor mediated mechanism involved in lymphocyte entry of the virus needs to be dissected as targeting

Abbreviations: ACE2, Angiotensin 2 receptor; Ag, Antigen; ASGR1, Asialoglycoprotein receptor 1; AXL, AXL receptor tyrosine kinase; IL-6, Interleukin-6; ITGB2, Integrin Subunit Beta 2; KIM-1/TIM-1, phosphatidylserine receptor expressed on epithelial cells; KREMEN1, Kringle Containing Transmembrane Protein 1; LFA-1, leukocyte-associated molecule-1; NRP1, Neuropilin 1; TMPRSS2, Transmembrane serine protease 2.

Joachim Gerlach and Abdul Mannan Baig are the first authors and have equally contributed to the Manuscript.

them may reduce the lymphocytic infection by SARS-CoV-2. The translational effects of knowing the mode of cell death induced by SARS-CoV-2 in lymphocytes can help design drugs and molecules which can interfere with the ability of SARS-CoV-2 to cause cell death and therefore minimise the effects of lymphocytopenia. Also, a challenging question that needs clarity is the ways by which an autoimmune response is being evoked in COVID-19 and long-COVID which are now known to develop an array of antibodies against cell surface receptors including neuronal antigens.[8–11] An in-depth understanding of these mechanisms can help patients with pharmacotherapy or selective aphaeresis to dilute the autoantibody levels in the blood. The ideal approach would be a drug or therapy that can selectively suppress the autoimmune response without predisposing patients with COVID-19 and Long-COVID to opportunistic infections. Below these challenging topics are been discussed with possible ways to resolve or research treatment approaches to find the answers to the immune paradox seen in patients suffering from COVID-19 and Long-COVID.

2 | MOLECULAR MECHANISM UNDERLYING ENTRY OF SARS-CoV-2 INTO THE IMMUNE REGULATING CELLS

The invasion and effects of SARS-CoV-2 on the immune cells of the human body have attained attention to understanding the diverse response that is mounted against SARS-CoV-2 in COVID-19. Detailed knowledge of the ways by which the virus enters the cells is expected to design drugs that could prevent immune cell invasion. The mechanism by which SARS-CoV-2 infection may result in immune system dysfunction is not fully understood. Much of this response has focussed, appropriately, on the mechanisms of SARS-CoV-2 entry into host cells, and in particular the binding of the spike (S) protein to its receptor, ACE2, and subsequent membrane fusion.[1,3] Binding to the ACE2 receptor and the cleavage of the spike glycoprotein between the S1 and S2 domains, mediated by the type II transmembrane serine proteaseTMPRSS2 and perhaps by furin[2]. Neuropilin receptor 1 (NRP1) was also shown to bind S1 through the multibasic furin-cleavage site and promote S1 shedding and expose the S2' site to TMPRSS2[1,2] The possible multiorgan tissue invasion due to ACE2 receptor expression in diverse tissues was hinted at in the early months of the year 2020.[12] Here the infection of the immune regulating cells leading to a decrease in the count of lymphocytes is detailed that is known to result in immune suppression and serious complications. It has been proposed that viral-induced lymphopenia might be due to direct infection, cytokine-mediated cell death, tissue sequestration of lymphocytes, or suppression of the bone marrow or thymus for T-cell generation.[13] The expression of the known SARS-CoV-2 receptors or co-factors that have been identified in primary T cells from public single-cell Next-generation sequencing data and in Jurkat T cells in RNA-seq analysis with or without activation, including ACE2/TMPRSS2, AXL, NRP1, KIM-1/TIM-1, ASGR1, and KREMEN1 has been reported. Moreover, ITGB2 (leucocyte-associated molecule-1, LFA-1), the leucocyte cell Adhesion molecule, has been suggested to bind to SARS-CoV-1 ORF7a. Reports have shown a minimal expression of ACE2, TMPRSS2, ASGR1, KREMEN1, and NRP1 and in contrast, AXL and LFA-1 that were seen to be expressed in these cells. Taken together, AXL and LFA-1 appeared to be the targets of SARS-CoV-2 as host cell entry molecules (Figure 1).

Another study revealed a novel virus entry route with the reports that membrane fusion and endocytosis are the two main entry modes for virus infection. CD147 was shown to assist SARS-COV-2 host cell entry through clathrin-independent endocytosis.[14] On the other hand, it was also revealed that SARS-CoV-2 uses CD4 to infect T-helper lymphocytes. As such, SARS-CoV-2 infects human CD4+ T helper cells, but not CD8+ T cells, and is present in blood and bronchoalveolar lavage T helper cells of severe COVID-19 patients. SARS-CoV-2 spike glycoprotein (S) directly binds to the CD4 molecule, which in turn mediates the entry of SARS-CoV-2 in T helper cells in a mechanism that also requires ACE2 and TMPRSS2. Once inside T helper cells, SARS-CoV-2 assembles viral factories, impairs cell function, and can lead to cell death. SARS-CoV-2 infected T helper cells express higher amounts of IL-10 and were associated with viral persistence and disease severity[15]

Monocytes, B, and T lymphocytes are susceptible to SARS-CoV-2 active infection and viral replication inside these cells. The studies have revealed that SARS-CoV-2 was frequently detected in monocytes and B lymphocytes from COVID-19 patients, and less frequently in CD4 + T lymphocytes.[16] SARS-CoV-2-positive monocytes and B and CD4+T lymphocytes have also been detected by immunohistochemistry in post-mortem lung tissue.[17]

3 | MECHANISM OF CELL DEATH FOLLOWING INFECTION OF MACROPHAGES, LYMPHOCYTES, AND NK CELLS

Lower lymphocyte counts reflected as lymphopenia have been identified as a marker of COVID-19 disease severity and this was particularly seen in males, intubated, and moribund.[18] This theme of low lymphocyte counts after the first week of illness in COVID-19 was seen to be associated with in-hospital death.[19] In the elderly, where there is a higher mortality rate with COVID, lymphopenia has been noted to occur more frequently in severe cases. Why does lymphopenia occur? T Cell counts have been noted to be decreased - in particular CD4+ and CD8+ T cell levels. Higher levels of these appear to predict less severe disease. In recovery, these T cells usually normalise while B cell counts do not usually decrease.[20] Additionally, an increased neutrophil: lymphocyte ratio, monocyte: lymphocyte ratio, and raised interleukins are linked with the severity of the disease and a poorer prognosis. The study[20] has identified the below.

a) The inflammatory cytokine storm is suggested to be a reason behind COVID lymphopenia. It has been noted that autopsy results on lymphoid organs who died due to COVID showed

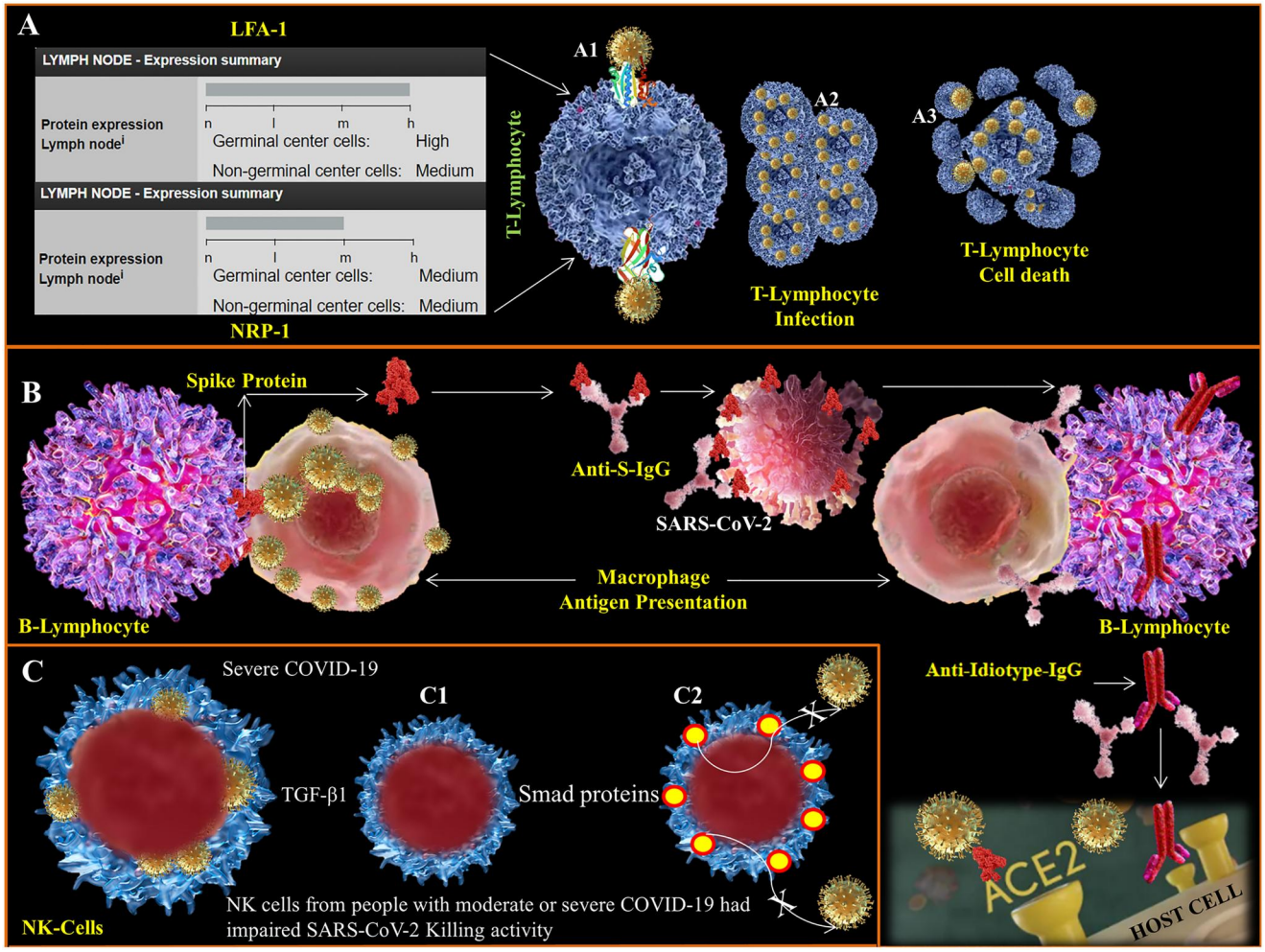

FIGURE 1 Lymphotropic cell entry and damage mechanisms enforced by SARS-CoV-2. Of many receptors expressed by the T lymphocytes, two are shown (a), LFA-1 and NRP-1 that can facilitate entry (A1) to that cause cell infection and death by mechanisms like apoptosis (A2-A3). Antigen (S-protein) presentation by macrophages to the B-lymphocytes elicits IgG production against them (B-pink Y structures). The immune system can develop an Idotype antibody (Y-shaped red structures) against the S-protein binding epitope that can cross-react with the angiotensin-converting enzyme 2 (ACE2) receptor on host cells (B, autoantibody, right panel). The NK cells are also targeted by SARS-CoV-2 (c) which by TGF-beta-1 and Smad proteins (C1) decrease the granule release capability by them affecting the virucidal capability of these cells (C2).

lymphocyte death likely due to high IL-6 and interactions with Fas-FasL. Treating with tocilizumab (IL-6 antagonist) showed an increase in circulating lymphocytes This would suggest that IL-6 is involved in lymphocyte death.

b) Exhaustion of T cells where an increased expression of programed cell death protein (PD-1) along with T cell immunoglobulin and Tim-3 correlated with the severity of the disease. NKG2A on T cells has also been noted to mark CD8+ T cell exhaustion together with decreased T cell activation markers CD107a and IFN-γ. T cell exhaustion is postulated to occur independently of T cell regulation (Tregs).

c) COVID may infect T cells with ACE2 mRNA infection which still requires research.

d) T cell expansion interference from SARS-CoV2.T cell activation and function, such as the MAP2K7 and SOS1 genes are down-regulated in the T cells of severe COVID-19. The authors of this letter postulate immunosuppressive drugs suppressing T cell response, specifically on Th1 cells could cause immunosuppression when battling COVID. They suggest their avoidance in those with pre-existing autoimmune dysfunction.

SARS-CoV2 mRNA and Ag have been identified in T cells via ACE2 receptors and CD4+ with spike-ACE2/TMPRSS2-independent infection, together with viral Ag + T cell apoptosis via mitochondrial ROS-HIF-1a-dependent pathways mechanisms. It was also shown that LFA-1 which is expressed in leucocytes is likely to be the entry molecule for COVID via ACE2.[13]

Very alarming are the finding of syncytium formation that were observed when human peripheral blood mononuclear cells were co-cultured with SARS-CoV-2 spike protein-induced syncytia, they could be engulfed by and die inside the syncytia, thus providing a possible explanation for lymphopenia in SARS-CoV-2 infections.

SARS-CoV-2 spike glycoprotein was capable of inducing a rapid membrane fusion to produce syncytium, which was seen to readily internalise multiple lines of lymphocytes to form typical cell-in-cell structures, remarkably leading to the death of internalized cells.[21] Interestingly, prolonged hospitalizations with COVID resulted in no overt recovery of B or CD4+ T cell lymphocytes.[22] Whereas in SARS-CoV1, CD8+ T lymphocytes normalised after 3 months of symptom onset, and CD4+ lymphocytes were still decreased in almost half of people after a year; total lymphocytes were still decreased after 16 weeks. A CD4+ reduction suggests high susceptibility to opportunistic infections. Wang Z, Yang L, Chen Y, et al. A longitudinal follow-up of COVID-19 patients in the convalescent phase showed recovery in radiological results, the dynamics of lymphocytes, and a decrease in the level of IgG antibody: a single-centre, observational study.[23]

4 | THE IMMUNE PARADOX OF COVID-19 IN CHRONIC COVID SYNDROME IN LONG-COVID

A puzzling aspect of the effect of the SARS-CoV-2 in the patients who show a protracted course of Long-COVID is a combination of lymphopenia and formation of IgG against self-antigens in form of autoantibodies. It is difficult to comprehend how a failing immune cell count and autoimmunity coexist in the same patient. One of the possible explanations that can explain this paradox is the effect of SARS-CoV-2 on T-Killer lymphocytes sparing the B-lymphocytes and CD4+ve T-helper lymphocytes in patients with Long-COVID, which remains to be established as conflicting reports have emerged as detailed above. Comparatively more specific targeting of suppressor T lymphocyte can also drive the autoimmune response seen in a substantial number of patients with Long-COVID. Also, it would be interesting to see if the T-killer lymphocytes play any role in the autoimmune response seen in the above-mentioned patients with autoimmune diseases that have emerged after COVID-19 and continue into the protracted phase of long-COVID. Though the mechanism behind the provocation of autoantibodies against receptor-like ACE2 has been postulated[24] but the phenomenon of autoantibodies against adrenergic, cholinergic, and neuronal antigens[11] needs to be researched in detail.

5 | TREATMENT OPTIONS IN PATIENTS WITH LYMPHOPENIA AND AUTOIMMUNITY CAUSED BY SARS-COV-2

Most possibly the lymphopenia observed in COVID-19 and Long-COVID is due to the presence of and persistence of SARS-CoV-2 respectively. The bigger question is what could be a more translational approach to prevent the loss of lymphocytes in COVID-19 and Long-COVID? With the known evasion of the immune response by SARS-CoV-2, antiviral therapy is a viable option to replenish the lymphocytes that are being targeted. In vitro treatment of the lymphocytes of COVID-19 and Long-COVID patients and infusion of them back to the patient can also be thought of, as it could prevent the adverse effects associated with any such therapy sought for management of lymphopenia. Recently Paxlovid has gained attention for its use in targeting SARS-CoV-2 in COVID-19 and cases of reinfection with SARS-CoV-2.[25,26] This drug has been debated for its use in COVID-19 after rebound has surfaced after its use[27–30] the mechanism behind which is poorly understood. This situation has further increased the demand for the search for an effective SARS-CoV-2 targeting compound that can prove effective and can eradicate the virus in COVID-19 and Long-COVID. Use of other drugs like Remdesivir and Maraviroc in COVID-19[31] have been reported in COVID-19 individuals (including PASC, Mild, Severe) reporting to reflect high levels of CCL5.[32] Several components of a formulation Vedicinals-9 which contains Baicalin, Quercetin, Diosmin –Hesperidin, Curcumin, and Piperine have undergone clinical trials[33] and have been used to treat COVID-19 and long-COVID to eradicate the SARS-CoV-2 from the body. Hesperidin has been tested for its effectiveness alone in an NIH-sponsored randomized double-blind controlled parallel study clinical trial as well[34] The cell membrane solubility of the agents included in the preparation is expected to exert their antiviral effect on intracellular SARS-CoV-2 which can recover the infected lymphocytes, monocytes, and NK cells. In vitro drug assays (Figure 2) testing these drugs on infected lymphocytes can establish the effectiveness of individual agents and the combination of them. Lipid solubility and therefore transport across the cell membrane would be an integral factor to determine the effectiveness of any antiviral agent designed to restore infected lymphocytes. Combination of antiviral compounds in lower doses can also be beneficial in COVID-19 and Long-COVID, as implementing the rationale of drug synergism can improve the clinical efficacy of these compounds; many of which like hesperidin are known antivirals against SARS-CoV-2.[35,36] One challenge in targeting intracellular SARS-CoV-2 would be the plasma membrane solubility of the immune-regulating cells like lymphocytes, kN cells, and monocytes. Selective compounds which have known pharmacokinetic and pharmacodynamics attributes and cross the cell membrane phospholipids due to their lipid solubility, after observing their effectiveness in vitro. can be tested in clinical trials to assess for their effectiveness in targeting intracellular SARS-CoV-2 in lymphocytes, NK cells, and macrophages within the body. Some of the drugs with the potential to cross the cell membrane and therefore enter the lymphocytes and other immune regulating cells are shown (Figure 2).

6 | IN VITRO TREATMENT OF LYMPHOCYTES AND NK CELLS WITH INFUSION TO THE PATIENT IN COVID-19 AND LONG-COVID

This paper proposes a treatment modality to address the actual and functional lymphocytopenia in COVID-19 and Long-COVID patients. The infected or affected lymphocytes and NK cells (Figure 2a) can be extracted from patients and treated in vitro with drugs (Figure 2b). Candidate drugs that restore the function of the lymphocytes can be spotted and the recovered lymphocyte (Figure 2c panel) can be

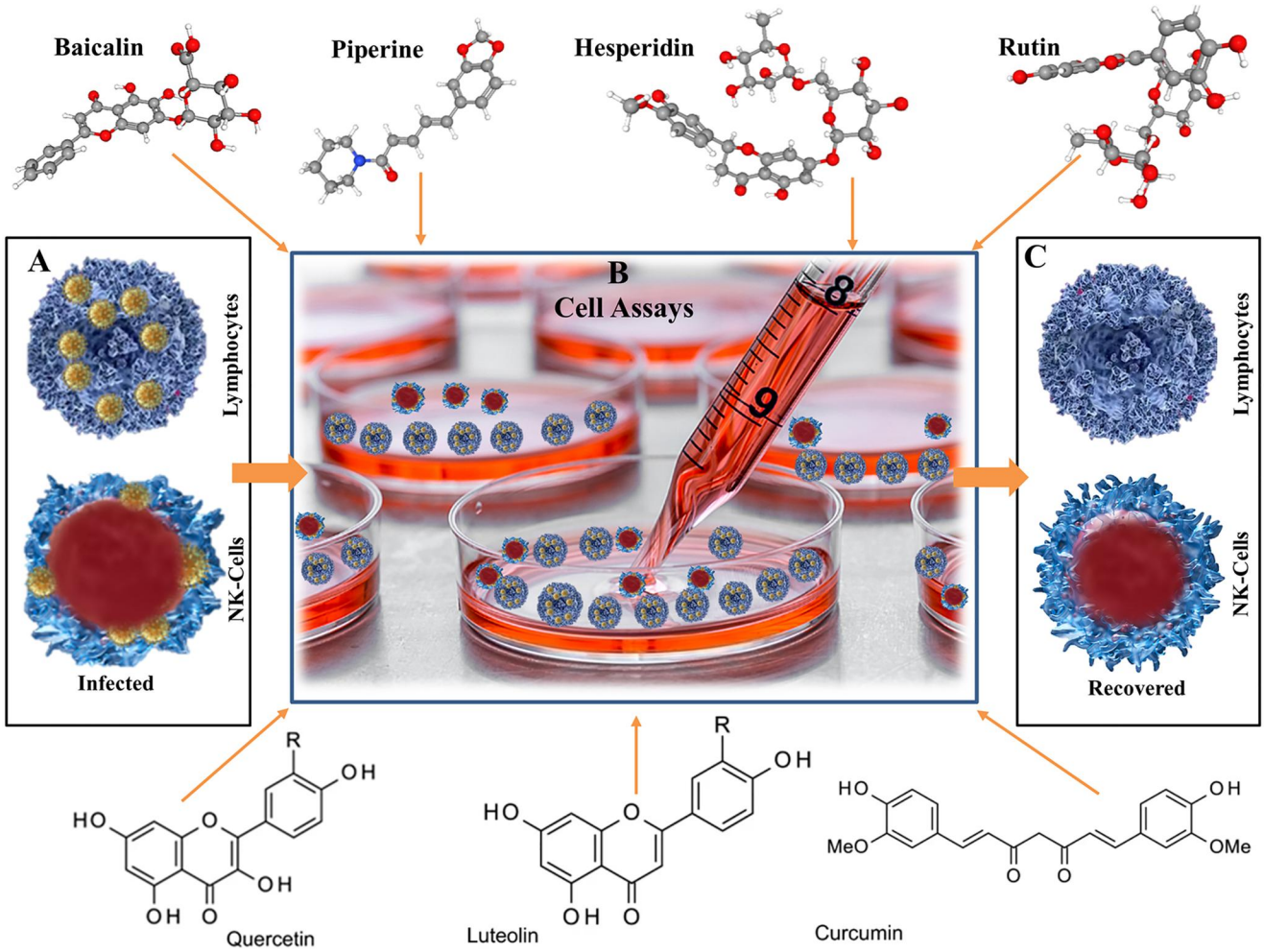

FIGURE 2 Proposed in vitro treatment of Lymphocytes and NK cells. Shown is a list of drugs, chemicals, and compounds (see main text) that have diverse mechanisms to act as antiviral agents in COVID-19 and long-COVID. The potential antiviral effects of these drugs (indicated by names and formula) alone or in combination can be tested in vitro on infected T-lymphocytes and NK cells (a) Drug assays in vitro (b) can show recovery of the infected cells (c). The compounds that can kill SARSCoV-2 in vitro can be taken into clinical trials in the next step to assess their efficacy in COVID-19 and long-COVID patients suffering from lymphopenia resulting from the death of the immune regulating cells by SARS-CoV-2.

infused as an autologous transfusion to address the actual and functional lymphocytopenia.

For the autoimmunity observed in COVID-19 and Long-COVID patients, drugs like immunosuppressive agents can slow down the production of the IgG directed against the self-antigen but the use of these agents would be associated with increased predisposition to opportunistic infection in patients who might be lymphopenic as well. Immunoadsorption of the IgG using aphaeresis could be of help, but understanding the pathogenesis of the autoimmunity seen in COVID-19 and Long-COVID patients can help design more specific therapies.

7 | DISCUSSION AND CONCLUSION

Many successes and developments in the understanding of COVID-19-related research niches have occurred in the past 2 years after the pandemic was declared. The effect of the virus on the immune regulating cells has gained attention to understand the complex effects that the SARS-CoV-2 causes on them.[14,16,17] The fact that SARS-CoV-2 uses not only ACE2 or NRP-1 receptors to gain entry inside the cells, but has diverse mechanisms to gain entry inside host cells particularly the lymphocytes, monocytes, and NK cells (6, 7, 13, 17) has dazzled scientists worldwide. The fact that the virus can use AXL, NRP1, KIM-1/TIM-1, ASGR1, LFA-1and KREMEN1 to gain entry inside the lymphocyte and cause its death by apoptosis or other mechanisms is alarming as it can induce a state of immunodeficiency. It is not known if it is capable of causing a qualitative immunodeficiency by making the lymphocytes, monocytes, and NK cells incapable of responding to antigenic stimuli. The fact that patients who exhibit long-COVID have been reported to have low levels of lymphocyte counts with an array of symptoms is worrying.[18,19] In many patients who remain symptomatic for months to a year following the acute phase of COVID-19 the reports of reactivation of herpes virus, fungal infection, and in particular Epstein–Barr virus[37]

hint towards the ominous effects of SARS-CoV-2 on the immune defence capability of our body. Confusing is the paradoxical appearance of autoimmune states in Long-COVID in which autoantibodies are directed against ACE2, ACE1, Alpha-adrenergic receptors, beta-adrenergic receptors, muscarinic cholinergic receptors, and diverse self-antigens.[8] CD4+ T-cell lymphopenia in COVID-19 patients was seen to be a reliable indicator of severity and hospitalisation in infected patients and a CD4+ T cell count below 200 cells/μL was seen to be associated with critical illness in COVID-19 patients.[38] Nicotinamide adenine dinucleotide+ depletion, critically reduced adenosine triphosphate depletion, and protein 7a, as one of the virus-encoded proteins, role in cell death by induction of apoptosis have been proposed[39]

It can be computed that the effects of SARS-CoV-2 may be selectively targeting the CD8 expressing T-lymphocytes while the B-Lymphocytic system possibly remains spared. Research is needed to understand and resolve this enigma, but both lymphopenia and autoimmune antibodies are dangerous for patients who suffer from these conditions. Many questions remain unanswered and need to be explored to understand the complex effects of COVID-19 and Long-COVID on the immune system. Top of the list of the questions that can help understand the pathogenesis of SARS-CoV-2-related immune system effects is (a) What are the ways by which SARS-CoV-2 can invade the immune regulating cells? (b) What cascade does SARS-CoV-2 use to cause death in lymphocytes and NK cells exhaustion? (c) Does the virus persist in Long-COVID to maintain its deleterious effects on lymphocytes? (d) What are the mechanisms involved in autoantibody production and can immunodeficiency and autoimmune state coexists in the same individual? Last but not least is the implementation of efficacious clinical trials for treatment that can eradicate the SARS-CoV-2 and large cohort clinical trials of drugs and compounds that can potentially treat lymphopenia (Figure 2) and slow down the production of autoimmune IgGs in COVID and Long-COVID patients.

AUTHOR CONTRIBUTIONS

Joachim Gerlach and Abdul Mannan Baig conceived the concept; Abdul Mannan Baig draughted the first MS with etiological factors in effect in Lymphopenia and autoimmunity. Joachim Gerlach contributed to the knowledge, resources, and chemistry of the natural product and nutraceutical agents mentioned in the MS. Valentina Viduto and Mark Fabrowski wrote the section on lymphocyte entry and lymphocyte cell death sections in the MS. Joachim Gerlach collected the references of the MS. Mark Fabrowski reviewed the manuscript version that was submitted to the journal. Abdul Mannan Baig proposed the in vitro treatment of the immune regulating cells and wrote the section. All the authors read the final draft before submission to the journal.

ACKNOWLEDGEMENTS

The authors would like to thank the encouragements and healthy discussions on this topic by his Twitter followers at @AMannanBaig.

CONFLICT OF INTEREST

Authors have no competing interests to declare. JG is the head of the research and development of nutraceuticals mentioned in this MS as Vedicinals-9. This submission, particularly the in vitro lymphocyte treatment with drugs and molecules is original work and is not under review at any other journal or publication resource.

ORCID

Abdul Mannan Baig https://orcid.org/0000-0003-0626-216X

REFERENCES

1. Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol*. 2022;23(1):3-20. https://doi.org/10.1038/s41580-021-00418-x
2. Bayati A, Kumar R, Francis V, McPherson PS. SARS-CoV-2 infects cells after viral entry via clathrin-mediated endocytosis. *J Biol Chem*. 2021;296:100306. https://doi.org/10.1016/j.jbc.2021.100306
3. Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci USA*. 2020;117(21):11727-11734. https://doi.org/10.1073/pnas.2003138117
4. Baig AM. Deleterious outcomes in long-hauler COVID-19: the effects of SARS-CoV-2 on the CNS in chronic COVID syndrome. *ACS Chem Neurosci*. 2020;11(24):4017-4020. https://doi.org/10.1021/acschemneuro.0c00725
5. Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ*. 2020;27(5):1451-1454. https://doi.org/10.1038/s41418-020-0530-3
6. Ni Y, Alu A, Lei H, Wang Y, Wu M, Wei X. Immunological perspectives on the pathogenesis, diagnosis, prevention and treatment of COVID-19. *Mol Biomed*. 2021;2(1):1. https://doi.org/10.1186/s43556-020-00015-y
7. Jafarzadeh A, Jafarzadeh S, Nozari P, Mokhtari P, Nemati M. Lymphopenia an important immunological abnormality in patients with COVID-19: possible mechanisms. *Scand J Immunol*. 2021;93(2):e12967. https://doi.org/10.1111/sji.12967
8. Rojas M, Rodríguez Y, Acosta-Ampudia Y, et al. Autoimmunity is a hallmark of post-COVID syndrome. *J Transl Med*. 2022;20(1):129. https://doi.org/10.1186/s12967-022-03328-4
9. Taeschler P, Cervia C, Zurbuchen Y, et al. Autoantibodies in COVID-19 correlate with antiviral humoral responses and distinct immune signatures. *Allergy*. 2022;77(8):2415-2430. https://doi.org/10.1111/all.15302
10. Wallukat G, Hohberger B, Wenzel K, et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. *J Transl Autoimmun*. 2021;4:100100. https://doi.org/10.1016/j.jtauto.2021.100100
11. Lucchese G, Vogelgesang A, Boesl F, et al. Anti-neuronal antibodies against brainstem antigens are associated with COVID-19. *EBioMedicine*. 2022;83:104211. https://doi.org/10.1016/j.ebiom.2022.104211
12. Baig AM, Khaleeq A, Ali U, Syeda H Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*. 2020;11(7):995-998. https://doi.org/10.1021/acschemneuro.0c00122
13. Shen XR, Geng R, Li Q, et al. ACE2-independent infection of T lymphocytes by SARS-CoV-2. *Sig Transduct Target Ther*. 2022;7(1):83. https://doi.org/10.1038/s41392-022-00919-x
14. Wang K, Chen W, Zhang Z, et al. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Sig Transduct Target Ther*. 2020;5(1):283. https://doi.org/10.1038/s41392-020-00426-x
15. Davanzo G & Codo A & Brunetti N, et al. (2020). SARS-CoV-2 uses CD4 to infect T helper lymphocytes. https://doi.org/10.1101/2020.09.25.20200329

16. Behl T, Kaur I, Aleya L, et al. CD147-spike protein interaction in COVID-19: get the ball rolling with a novel receptor and therapeutic target. *Sci Total Environ*. 2022;808:152072. https://doi.org/10.1016/j.scitotenv.2021.152072
17. Pontelli MC, Castro IA, Martins RB, et al. Infection of human lymphomononuclear cells by SARS-CoV-2. bioRxiv [Preprint]. 2020. 28.225912. https://doi.org/10.1101/2020.07.28.225912
18. Illg Z, Muller G, Mueller M, Nippert J, Allen B. Analysis of absolute lymphocyte count in patients with COVID-19. *Am J Emerg Med*. 2021;46:16-19. https://doi.org/10.1016/j.ajem.2021.02.054
19. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *J intensive care*. 2020;8(1):36. https://doi.org/10.1186/s40560-020-00453-4
20. Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: what it shows and what can be learned. *Immunol Lett*. 2020;225:31-32. https://doi.org/10.1016/j.imlet.2020.06.013
21. Rezaei M, Marjani M, Mahmoudi S, Mortaz E, Mansouri D. Dynamic changes of lymphocyte subsets in the course of COVID-19. *Int Arch Allergy Immunol*. 2021;182(3):254-262. https://doi.org/10.1159/000514202
22. Gozzi-Silva SC, Oliveira LM, Alberca RW, et al. Generation of Cytotoxic T Cells and Dysfunctional CD8 T Cells in Severe COVID-19 Patients. *Cells*. 2022;11(21):3359. https://doi.org/10.3390/cells11213359
23. Wang Z, Yang L, Chen Y, Xu Z, Wang H, Zhang X. A longitudinal follow-up of COVID-19 patients in the convalescent phase showed recovery in radiological results, the dynamics of lyphocytes and a decrease in the level of IgG antibody: a single-centre, observational study. *J Thorac Dis*. 2021;13(5):2986-3000. https://doi.org/10.21037/jtd-20-3011
24. Murphy WJ, Longo DL. A possible role for anti-idiotype antibodies in SARS-CoV-2 infection and vaccination. *N Engl J Med*. 2022;386(4):394-396. https://doi.org/10.1056/NEJMcibr2113694
25. Buxeraud J, Faure S, Fougere É. Le nirmatrelvir-ritonavir (Paxlovid®), un traitement contre la Covid-19 [Nirmatrelvir/ritonavir (Paxlovid®), a treatment for Covid-19]. *Actual Pharmacol* 2022;61(617):10-12. French. https://doi.org/10.1016/j.actpha.2022.05.002
26. Burki T. The future of Paxlovid for COVID-19. *Lancet Respir Med*. 2022;10(7):e68. https://doi.org/10.1016/S2213-2600(22)00192-8
27. Coulson JM, Adams A, Gray LA, Evans A. COVID-19 "Rebound" associated with nirmatrelvir/ritonavir pre-hospital therapy. *J Infect*. 2022;85(4):436-480. https://doi.org/10.1016/j.jinf.2022.06.011
28. Charness M, Gupta K, Stack G, et al. Rapid relapse of symptomatic omicron SARS CoV-2 infection following early suppression with nirmatrelvir/ritonavir. 13 May 2022, PREPRINT (Version 2) https://doi.org/10.21203/rs.3.rs-1588371/v2. [CrossRef].
29. Carlin AF, Clark AE, Chaillon A, et al. Virologic and immunologic characterization of COVID-19 recrudescence after nirmatrelvir/ritonavir treatment. 2022. https://doi.org/10.21203/rs.3.rs-1662783/v1. [PMC free article] [PubMed] [CrossRef].
30. COVID-19 Rebound after Paxlovid Treatment. CDCHAN-00467. 24th May 2022. Accessed on 26th May 2022 at.https://emergency.cdc.gov/han/2022/han00467.asp
31. Minami R, Takahama S, Kaku Y, Yamamoto M. Addition of Maraviroc to antiretroviral therapy decreased interferon-γ mRNA in the CD4+ T cells of patients with suboptimal CD4+ T-cell recovery. *J Infect Chemother*. 2017;23(1):29-34. https://doi.org/10.1016/j.jiac.2016.09.003
32. Patterson BK, Guevara-Coto J, Yogendra R, et al. Immune-based prediction of COVID-19 severity and chronicity decoded using machine learning. *Front Immunol*. 2021;12:700782. https://doi.org/10.3389/fimmu.2021.700782
33. A Clinical Trial to Evaluate the Effectiveness and Safety of Vedicinals-9-A Herbal Formulation in Mild to Moderate COVID-19 Patients. CTRI; 12-10-2020; TrialI D: CTRI/2020/10/028364. https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/en/ictrp-CTRI202010028364 (Accessed on 14th August 2022).
34. Interventional (Clinical Trial); ClinicalTrials.Gov Identifier: NCT04452799. Hesperidin and Diosmin for Treatment of COVID-19. https://clinicaltrials.gov/ct2/show/NCT04452799. (Accessed on 14th August 2022).
35. Cheng FJ, Huynh TK, Yang CS, et al. Hesperidin is a potential inhibitor against SARS-CoV-2 infection. *Nutrients*. 2021;13(8):2800. https://doi.org/10.3390/nu13082800
36. Haggag YA, El-Ashmawy NE, Okasha KM. Is hesperidin essential for prophylaxis and treatment of COVID-19 Infection? *Med Hypotheses*. 2020;144:109957. https://doi.org/10.1016/j.mehy.2020.109957
37. Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of long COVID prevalence and its Relationship to epstein-Barr virus reactivation. *Pathogens*. 2021;10(6):763. https://doi.org/10.3390/pathogens10060763
38. Zhou X, Ye G, Lv Y, et al. IL-6 drives T cell death to participate in lymphopenia in COVID-19. *Int Immunopharm*. 2022;111:109132. https://doi.org/10.1016/j.intimp.2022.109132
39. Rahimmanesh I, Kouhpayeh S, Azizi Y, Khanahmad H. Conceptual framework for SARS-CoV-2-related lymphopenia. *Adv Biomed Res*. 2022;11:16. https://doi.org/10.4103/abr.abr_303_20

How to cite this article: Gerlach J, Baig AM, Fabrowski M, Viduto V. The immune paradox of SARS-CoV-2: lymphocytopenia and autoimmunity evoking features in COVID-19 and possible treatment modalities. *Rev Med Virol*. 2023;e2423. https://doi.org/10.1002/rmv.2423