ACTA Traditional Medicine

Review Article: 50 to 53 (2023)
ISSN 2583-7532
www.traditionalmedicine.actabotanica.org

Utility and feasibility of Phosphodiesterase inhibitors in the treatment COVID-19 patients

Ashiq Hussain[1], Mohd Ishaq[2], Aniketa Sharma[3]

[1]Department of Pediatrics, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh 462026, India
[2]Sheri Kashmir Institute of Medical Sciences, SKIMS Main Rd, Soura, Srinagar, Jammu and Kashmir 190011, India
[3]Department of Medicine, DYSP Govt. Medical College Nahan H.P India

Citation: Ashiq Hussain, Mohd Ishaq, Aniketa Sharma (2023). Utility and feasibility of Phosphodiesterase inhibitors in the treatment COVID-19 patients. Acta Traditional Medicine. V2i01, 50-53. **DOI:** https://doi.org/10.51470/ATM.2023.2.1.50

Corresponding Author: **Ashiq Hussain** | E-Mail: **(ashiqmagrey@gmail.com)**

Received 15 February 2023 | Revised 01 June 2023 | Accepted 20 July 2023 | Available Online July 23 2023

ABSTRACT

Phosphodiesterase inhibitors (PDE inhibitors) are a class of drugs that have been used for various medical conditions, primarily in the treatment of cardiovascular and pulmonary diseases, but they have also been explored for their potential utility in the management of COVID-19. Some PDE inhibitors, such as theophylline, have anti-inflammatory properties. In COVID-19, there is an excessive immune response that can lead to cytokine storms and inflammation in the lungs. PDE inhibitors may help modulate the immune response, potentially reducing inflammation. PDE inhibitors can lead to vasodilation and bronchodilation. In COVID-19, the virus can cause respiratory distress, and PDE inhibitors might help improve oxygenation and reduce breathing difficulties. Some studies suggest that PDE inhibitors can interfere with viral replication. By inhibiting certain phosphodiesterase's, these drugs might impact the ability of the virus to reproduce in host cells. PDE inhibitors are often considered in combination with other medications. The combination of antiviral drugs and anti-inflammatory agents may be more effective in treating COVID-19 patients with severe symptoms. While some preclinical studies and small clinical trials have shown promising results, larger, well-designed clinical trials are necessary to confirm the effectiveness of PDE inhibitors in treating COVID-19. PDE inhibitors can have side effects, such as gastrointestinal issues, cardiovascular effects, and interactions with other medications. Their safety and potential for adverse reactions in COVID-19 patients need further evaluation. The feasibility of using PDE inhibitors in COVID-19 treatment may depend on patient profiles, including their underlying medical conditions, severity of illness, and potential contraindications. The use of PDE inhibitors for COVID-19 is subject to regulatory approval in different countries. Health authorities and regulatory agencies evaluate the safety and efficacy of medications for specific indications. while there is ongoing interest in the potential utility of PDE inhibitors in treating COVID-19 patients, their feasibility and safety as a part of COVID-19 treatment protocols are still under investigation. It's important for healthcare providers and researchers to continue conducting rigorous studies to determine their role and to consider the overall clinical context and individual patient characteristics in treatment decisions. Patients should consult with their healthcare professionals for the most up-to-date information and guidance on COVID-19 treatments.

Keywords: COVID-19, SARS-CoV-2, patients, pandemic, health, diseases

Introduction

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the subsequent COVID-19 pandemic have indeed presented a global health crisis of unprecedented magnitude. The rapid spread of the virus, along with the severe health and economic impacts it has had on communities around the world, underscores the urgent need for effective treatments and management of the disease [13-16]. One of the most promising approaches to managing the COVID-19 pandemic has been the development and distribution of vaccines. Multiple vaccines have been developed and authorized for emergency use, offering hope for controlling the spread of the virus and reducing the severity of illness [17-21].

Treatment Development: While effective cures for COVID-19 have not yet been found, researchers and pharmaceutical companies have been working to develop treatments that can alleviate symptoms, reduce the severity of complications, and improve patient outcomes. Various antiviral drugs and therapies have been explored for this purpose.

Antiviral Medications: Several antiviral medications, such as remdesivir, have received Emergency Use Authorization for treating COVID-19. These drugs aim to inhibit the replication of the virus within the body and may help to reduce the severity and duration of illness.

Monoclonal Antibodies: Monoclonal antibody treatments have been developed and authorized for emergency use. These treatments involve the infusion of lab-created antibodies that can neutralize the virus and potentially reduce the severity of the disease, especially in high-risk patients.

Research and Clinical Trials: Ongoing research and clinical trials are essential in the search for effective treatments. Scientists and medical professionals continue to explore a

range of therapeutic options, including existing drugs that may have potential benefits against COVID-19.

Public Health Measures: In addition to treatments, public health measures such as mask-wearing, social distancing, testing, contact tracing, and quarantine efforts are vital for controlling the spread of the virus and reducing its impact.

Vaccination Campaigns: Worldwide vaccination campaigns are crucial for achieving herd immunity and ending the pandemic. Ensuring equitable access to vaccines for all countries and populations is a significant challenge.

Healthcare System Strengthening: The pandemic has highlighted the importance of strengthening healthcare systems to handle surges in cases. Adequate resources, infrastructure, and a healthcare workforce are essential components in managing the pandemic.

Variants and Adaptation: The emergence of new variants of the virus underscores the need for ongoing vigilance and adaptability in public health and treatment strategies. Continued surveillance and monitoring are essential.

International Collaboration: Global cooperation is critical in responding to a pandemic. Sharing information, resources, and best practices is essential for an effective response [23-29].

Seven known coronaviruses are reported to infect humans i.e. MERS-CoV, SARS-CoV, HKU1, OC43, 229E, NL63, and the latest SARS-CoV-2 has brought the world on its feet [1]. Till now SARS-COV2 (COVID- 19 an RNA virus) has infected lakhs around the globe has killed thousands and is moving the human race toward possible extinction. Research scientists all over the world are looking for a drug or Vaccine that will save humans from this dangerous Pandemic disease. Human Coronavirus encoded 2-5 OC43 ns2 /HEC4408 ns2 phosphodiesterases help these viruses to escape the host immunity [2,3]. In search of new drugs, our group is trying to address the possibility of using FDA-approved phosphodiesterase inhibitors or their structural analog for the treatment of COVID-19 infection. Currently, various Phosphodiesterase inhibitors have been approved by FDA.PDE4 inhibitors apremilast, roflumilast, and Crisbarole are the FDA-approved [4,5] drugs, used respectively for the treatment of psoriatic arthritis, COPD, and atopic dermatitis [4,5]. Moreover, PDE4 inhibitor Roflumilast has been shown to inhibit respiratory s syncytial viral infection in human differentiated bronchial epithelial cells [6]. Also, Type 4 phosphodiesterase inhibitors have been shown to attenuate viral-induced respiratory inflammation FDA approved PDE5 inhibitors sildenafil, tadalafi, vardenafil, avanafil, udenafil are primarily used for the treatment of erectile dysfunction [4,5]. About 30% of PDE inhibitors in clinical development are PDE4 and PDE5 inhibitors [PDE Inhibitors Market, 2026 (DUBLIN, November 3, 2016 /PRNewswire)]. About 36% of the PDE inhibitors are under development for the treatment of neurological disorders like Alzheimer's, Schizophrenia, and Huntington's disease (DUBLIN, November 3, 2016 /PR News wire. Various PDE5 inhibitors and Pan PDE inhibitors have been shown to induce neuro differentiation in IMR32 neuroblastoma cells [7,8,9, 10, 11]. Structural analogs of sildenafil have been shown to induce death of plasmodium species by inhibition of plasmodial-phosphodiesterases [12]. Humans produce IFN gamma in response to viral infections. In response to coronoviral infection, Interferon gamma-induces 2'-5' oligoadenylate (2-5A) synthetases (OASs) and ribonuclease (RNase) L are the main components host antiviral pathway. Human and murine coronavirus produce ns2 phosphodiesterase that helps the virus to survive by degradation of 2'-5'oligoadenylate (2-5A) [2,3]. ns2 coronoviral phosphodiesterases are the important targets of phosphosphodiesterase inhibitors [2]. Since currently available phosphodiesterase inhibitors are nonspecific and inhibit many phosphodiesterase family members in humans and may target the coronavirus ns2 phosphodiesterases also (Fig1).

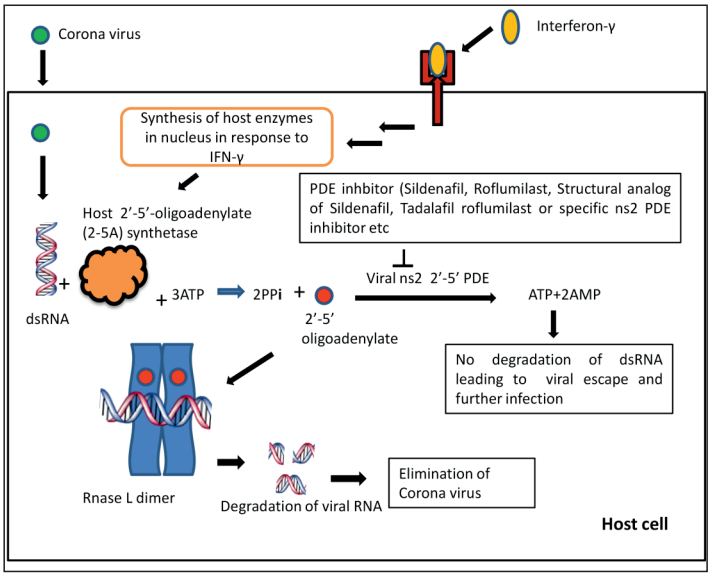

Fig 1. Mechanism of host immune evasion by Coronaviruses with the help of viral nS2 phosphodiesterase's

Currently, available phosphodiesterase's inhibitors are safer for use in humans and can be tried in coronavirus patients. Since phosphodiesterase inhibitors increase the cellular cAMP and cGMP levels which may be lethal to the survival of coronavirus in host cells [2,3] (Fig 2).

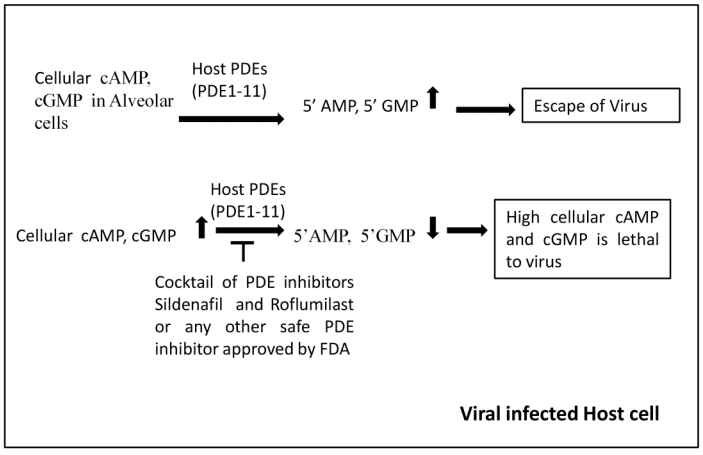

Fig 2. Role of Currently available FDA approved Phosphodiesterase inhibitors in eradication of Virus

The combinatorial approach of FDA-approved phosphodiesterase inhibitors can be used in optimal doses to prevent the viral escape and its pathogenesis. Moreover, structural analogs of of FDA approved phosphodiesterase inhibitors can be synthesized which will specifically target the viral ns2 phosphodiesterases leading to the elimination of the

virus. Since PDE4 inhibitor roflumilast is an FDA-approved PDE4 inhibitor used for chronic obstructive pulmonary disorder it can also be used in a patient infected with coronavirus because they also have respiratory complications moreover it may also increase the cellular cAMP levels in bronchial cells and may lead to degradation of corona viral RNA. Furthermore, phosphodiesterase inhibitors can be also used in combination with the already approved antivirals, In conclusion, a cocktail of PDE, Viral Protease, and reverse transcriptase inhibitors could be a possible treatment for corona viral infection (Fig 3).

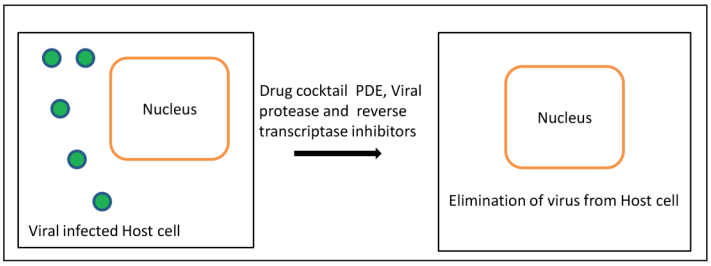

Fig 3. Combinatorial Approach Viral protease inhibitors, reverse transcriptase inhibitors, and Phosphodiesterase inhibitors for the treatment and elimination of viruses.

Conclusion

The COVID-19 pandemic has posed a significant challenge to the global community. While the search for effective treatments continues, vaccination campaigns, public health measures, and international collaboration remain key elements in controlling the spread of the virus and mitigating its impact on public health and the economy. The urgency to address this ongoing crisis remains high, and ongoing research and development are essential in the quest for more effective treatments and long-term solutions. the utility and feasibility of Phosphodiesterase inhibitors (PDE inhibitors) in the treatment of COVID-19 patients are subjects of ongoing research and clinical evaluation. While there is a theoretical basis for considering PDE inhibitors in COVID-19 treatment due to their anti-inflammatory, vasodilatory, and potential antiviral properties, Current research on PDE inhibitors for COVID-19 is in the early stages, with limited clinical data. Robust, well-designed clinical trials are needed to establish the safety and efficacy of these drugs in the context of COVID-19. COVID-19 is a complex disease with diverse clinical presentations, and patient outcomes can vary significantly. The feasibility and effectiveness of PDE inhibitors may depend on factors such as the stage of the disease and the patient's overall health. In the absence of conclusive clinical evidence, decisions about the utility and feasibility of PDE inhibitors in the treatment of COVID-19 patients should be made on a case-by-case basis, with careful consideration of the latest research findings and in consultation with healthcare professionals. The ongoing research and clinical trials will provide further insights into the role of PDE inhibitors in the management of COVID-19. It's important to stay updated on the latest developments and recommendations from public health authorities and regulatory agencies.

References

1. KG Andersen *The proximal origin of SARS-CoV-2*. Nature medicine Mar 17, 2020
2. Zhang R, Babal K. J, Kristen M. Ogden, Beihua Dong, Ling Z,, Ruth E John T. P, Robert H. Silverman and Susan R W. *Homologous 2′-5′ phosphodiesterases from disparate RNA viruses antagonize antiviral innate immunity*PNAS,vol. 110 no. 32 - p-13114–13119 (2013)
3. Robert H. S and Susan R. W *Viral Phosphodiesterases that antagonize double-Stranded RNA Signaling to RNase L by degrading 2-5A.*Journal of Interferon & cytokine Research .Vol 34, 6, (2014)
4. Maurice, D.H., et al., *Advances in targeting cyclic nucleotide phosphodiesterases.* Naturereviews Drug discovery.13(4): p. 290-314.
5. Huang, S.A. and J.D. Lie, *Phosphodiesterase-5 (PDE5) inhibitors in the management of erectile dysfunction.* Pharmacy and Therapeutics.38(7): p. 407.
6. Manuel M, Isidoro M, Jose A. M, Herman T and Julio C. *Roflumilast Inhibits Respiratory Syncytial Virus Infection in Human Differentiated Bronchial Epithelial Cells.*PLoS ONE 8(7):e69670 (2013)
7. Dar M I, Priya M, Suraya J, Shreyans K. J, Harshita T, Jagjeet S, Sandip B, Amit N, Sajad H *Rottlerin is a pan phosphodiesterase inhibitor and can induce neurodifferentiation in IMR-32 human neuroblastoma cells.*European Journal of Pharmacology 857 (2019) 172448
8. Sanghapal D. Sawant, G. Lakshma Reddy, MohdIshaq Dar, M. Srinivas, Gourav Gupta ,Promod Kumar Sahu , Priya Mahajan , Amit Nargotra , Surjeet Singh, Subhash C. Sharma,Manoj Tikoo , Gurdarshan Singh , Ram A. Vishwakarma, Sajad Hussain Syed. *Discovery of novel pyrazolopyrimidinoneanalogs as potentinhibitors of phosphodiesterase type-5* Bioorganic& Medicinal Chemistry 23 (2015) 2121–2128
9. Dar MI, Jan S, Reddy GL, Wani R, Syed M, Dar MJ, Sawant SD, Vishwakarma RA, Syed SH*Differentiation of human neuroblastoma cell line IMR-32 by sildenafil and its newly discovered analogue IS00384.*Cellular Signalling .2020 Jan;65:109425
10. Sawant, S.D, Reddy, G.L, Srinivas, M, Hussain, S.S, Dar, M.I, Nargotra, A, Mahajan, P,Vishwakarma, R.A. Novel *Pyrazolopyrimidinones for the treatment of impotence and process for the preparation thereof.* (Us Patent 2015)
11. Reddy G L, Dar M I, Hudwekar A D, Mahajan P, Nargotra A, Baba A M, Nandi U, Wazir P, Singh G, Vishwakarma R A, Syed S H, Sawant S D. *Design, synthesis and biological evaluation of pyrazolopyrimidinone based potent and selective PDE5 inhibitors for treatment of erectile dysfunction. Bioorg Chem.* 2019 Aug; 89:103022.
12. Wang, G, Liu, Z, Chen T, Wang Z, Yang H, Zheng, M and Jiang, H. *"Design, synthesis, and pharmacological evaluation of monocyclic pyrimidinones as novel inhibitors of PDE5".* J Med Chem. (2012)55 (23): 10540–10550.

13. Maldonado, V., Hernandez-Ramirez, C., Oliva-Perez, E. A., Sanchez-Martinez, C. O., Pimentel-Gonzalez, J. F., Molina-Sanchez, J. R., & Loza-Mejia, M. A. (2021). Pentoxifylline decreases serum LDH levels and increases lymphocyte count in COVID-19 patients: Results from an external pilot study. *International immunopharmacology*, *90*, 107209.

14. Sanders, J. M., Monogue, M. L., Jodlowski, T. Z., & Cutrell, J. B. (2020). Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *Jama*, *323*(18), 1824-1836.

15. Cameli, P., Bargagli, E., Bergantini, L., d'Alessandro, M., Giugno, B., Gentili, F., & Sestini, P. (2021). Alveolar nitric oxide as a biomarker of COVID-19 lung sequelae: a pivotal study. *Antioxidants*, *10*(9), 1350.

16. Passos, G. R., Leonardi, G. R., de Oliveira, M. G., Gomes, E. D. T., Ghezzi, A. C., Antunes, E., & Mónica, F. Z. (2023). Serum from Men with the Severe Form of COVID-19 Impairs the Nitric Oxide Signaling Pathway in Isolated Corpus Cavernosum from Mice: An In Vitro Study. *Andrologia*, *2023*.

17. DiNicolantonio, J. J., & Barroso-Aranda, J. (2020). Harnessing adenosine A2A receptors as a strategy for suppressing the lung inflammation and thrombotic complications of COVID-19: Potential of pentoxifylline and dipyridamole. *Medical Hypotheses*, *143*, 110051.

18. Kifle, Z. D., Ayele, A. G., & Enyew, E. F. (2021). Drug repurposing approach, potential drugs, and novel drug targets for COVID-19 treatment. *Journal of Environmental and Public Health*, *2021*.

19. Bikdeli, B., Madhavan, M. V., Gupta, A., Jimenez, D., Burton, J. R., Der Nigoghossian, C., & Global COVID-19 Thrombosis Collaborative Group. (2020). Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. *Thrombosis and haemostasis*, *120*(07), 1004-1024.

20. Bikdeli, B., Madhavan, M. V., Jimenez, D., Chuich, T., Dreyfus, I., Driggin, E., & Lip, G. Y. (2020). COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *Journal of the American college of cardiology*, *75*(23), 2950-2973.

21. Jackson, E. K., Kitsios, G. D., Lu, M. Y., Schaefer, C. M., Kessinger, C. J., McVerry, B. J. & Macatangay, B. J. (2022). Suppressed renoprotective purines in COVID-19 patients with acute kidney injury. *Scientific Reports*, *12*(1), 17353.

22. Luu, J. C., Saadane, A., Leinonen, H., Choi, E. H., Gao, F., Lewandowski, D., & Palczewski, K. (2023). Stress resilience-enhancing drugs preserve tissue structure and function in degenerating retina via phosphodiesterase inhibition. *Proceedings of the National Academy of Sciences*, *120*(19), e2221045120.

23. Chu, R., van Eeden, C., Suresh, S., Sligl, W. I., Osman, M., & Cohen Tervaert, J. W. (2021). Do COVID-19 infections result in a different form of secondary hemophagocytic lymphohistiocytosis. *International Journal of Molecular Sciences*, *22*(6), 2967.

24. Ohadian Moghadam, S. (2020). A review on currently available potential therapeutic options for COVID-19. *International Journal of General Medicine*, 443-467.

25. Desborough, M. J., Salman, R. A. S., Stanworth, S. J., Havard, D., Woodhouse, L. J., Craig, J., ... & Werring, D. (2023). Desmopressin for patients with spontaneous intracerebral haemorrhage taking antiplatelet drugs (DASH): a UK-based, phase 2, randomised, placebo-controlled, multicentre feasibility trial. *The Lancet Neurology*, *22*(7), 557-567.

26. Mehta, H., Soufila, K. T., Kumar, S., Sarkar, R., & Kumaran, M. S. (2021). Use of immunosuppressants in vitiligo during COVID-19 pandemic: a quick review. *Pigment International*, *8*(1).

27. Shih, L., Ferry, A. M., Gravina, P. R., Wang, E. D., Reece, E. M., Maricevich, M., & Winocour, S. J. (2023). Acute digital necrosis in a patient with Raynaud's phenomenon and COVID-19 infection. *The American Surgeon™*, *89*(4), 1129-1132.

28. Ranjbar, T., Oza, P. P., & Kashfi, K. (2022). The renin–angiotensin-aldosterone system, nitric oxide, and hydrogen sulfide at the crossroads of hypertension and COVID-19: Racial disparities and outcomes. *International Journal of Molecular Sciences*, *23*(22), 13895.

29. Sahu, K. K., & Cerny, J. (2021). A review on how to do hematology consults during COVID-19 pandemic. *Blood reviews*, *47*, 100777.

30. Mehta, P., Machado, P. M., & Gupta, L. (2021). Understanding and managing anti-MDA 5 dermatomyositis, including potential COVID-19 mimicry. *Rheumatology International*, *41*(6), 1021-1036.