VOLUME - 11, ISSUE - 11, NOVEMBER - 2022 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Ophthalmology

A REVIEW OF DRUG REPROFILING FOR COVID-19: TEICOPLANIN, A POTENTIAL AGENT AGAINST SARS-COV-2

Saurabh Kushwaha Resident (Ophthalmology), Dept of Ophthalmology, Army College of Medical Sciences, Delhi Cantt, New Delhi – 110010

ABSTRACT COVID-19 caused by Sever Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) first identified at Wuhan, China has rapidly spread across over 6 continents to become a pandemic and a Public Health Emergency of International Concern (PHEIC). Till date there is no specific drug for the disease. So there is an imminent requirement to identify an effective drug to control the outbreak. A number of COVID-19 cases are reported to be associated with co-bacterial infections especially in immunocompromised individuals. Teicoplanin, a glycopeptide antibiotic, in the past has been reported to possess antiviral efficacy against coronaviruses such as MERS-CoV and SARS-CoV. In a recently conducted *in vitro* study, it has also been observed to possess antiviral activity against SARS-CoV-2. Here we summarize, Teicoplanin, an antibiotic as a potential therapeutic repurposing option for the treatment of COVID-19, especially in severely ill patients and those having co-bacterial infections.

KEYWORDS : COVID-19; Cathepsin L; SARS-CoV-2; Spike protein; Teicoplanin

BACKGROUND

The first case of Coronavirus disease 2019 (COVID-19) caused by a highly infectious agent Sever Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was confirmed in December 2019 in Wuhan, China and then spread rapidly across China and more than 220 countries worldwide [1-4] . As of 28 October, 2022, a total of 626,337,158 confirmed cases of COVID-19 were reported and 6,566,610 of them died [4]. Thus there is an urgent demand to identify an effective, safe, available and affordable therapeutic regimen against SARS-CoV-2. But till date no drug has been approved to treat COVID-19. Hence, repurposing an existing chemotherapeutic agent with a known safety profile would be a significant near term strategy to control the pandemic. Teicoplanin, a glycopeptide antibiotic, in the past has been reported to possess efficacy against coronaviruses such as MERS-CoV and SARS-CoV [5, 6]. In recently conducted studies, Teicoplanin was also observed to inhibit *in vitro* replication of SARS-CoV-2 and thus make it a potential repurposing drug against SARS-CoV-2 [7].

SARS-CoV-2

SARS-CoV-2 belongs to the family of viruses known as Coronaviriade [8]. It is an enveloped positive sense single stranded RNA (+ssRNA) virus [9]. It is large pleomorphic spherical particle with bullous surface projections with an approximate diameter of 50-200 nanometers [10, 11]. It consists of four structural proteins namely Spike (S), Membrane (M), Envelope (E) and Nucleocapsid (N) protein. The N protein integrates the viral genome whereas the rest three proteins together constitute the viral envelope. S protein present on the envelope is responsible for binding to the cell surface receptors of the host cell membrane [12].

Pathogenesis of COVID-19

The primary mode of transmission of SARS-CoV-2 is via respiratory droplets from coughs and sneezes among close contacts of infected personnel [13]. The World Health Organisation has reported an incubation period of approximately 2 to 14 days [14].

In S Protein modeling experiments, it has been observed that when SARS-CoV-2 comes in close contact with the host cell, the S protein of the virus binds to the Angiotensin Converting Enzyme-2 (ACE2) cellular receptors of the host cells and produce conformational changes within the S protein and makes S protein suitable for attachment to the host cell proteases like transmembrane protease serine 2 (TMPRSS2) for host cell entry [15-18]. After attachment to the host cell membrane, TMPRSS2 of the host cell membrane cleaves the S protein and activates the receptors attached to the S protein which facilitates its entry inside the host cell. This S protein proteolytic priming process is essential for entry of the virus inside the host cell [16, 17, 19, 20]. Then by the process of endocytosis or macropinocytosis, the virus particle is taken inside the endosomes of the host cell and subsequently acidifies [17, 21, 22]. Cysteine protease Cathepsin L is present inside the endosomes of the host cell and it further cut opens the S protein and thereby facilitates virus endosome membrane fusion process. Studies have proposed that subsequent breakdown of S protein by both protease TMPRSS2 and Cathepsin L are essential for the complete denudeation of S2 subunit of S protein to the endosome/ lysosome membrane [23, 24]. Eventually, the virus inside the host cell produces virulence factors that promotes shedding of new progeny viruses and suppresses the host immune response [12]. The progeny viruses thus produced inside the host cells are liberated by the process of exocytosis via secretory vesicles [25].

Effect of Teicoplanin on SARS-COV-2

Teicoplanin, is a glycopeptide antibiotic, clinically effective against different Gram positive bacterial infections such as septicemia, endocarditis, pneumonia and meningitis. It has a long half life and hence recommended in once daily intramuscular or intravenous administration. It has a good safety profile. A few adverse effects have been reported, generally limited to local skin reactions or hypersensitivity reactions [26].

In vitro, Teicoplanin has been reported to possess significant antiviral efficacy for various viruses such as Influenza virus, Ebola virus, Flavivirus, HIV, Hepatitis C virus and Coronaviruses such as MERS-CoV and SARS-CoV [5,6]. Regarding coronaviruses, the potential therapeutic efficacy of Teicoplanin was notably reported for MERS-CoV and patent for the same was filed in the year 2016 [27]. In experimental study conducted by Zhou and his confreres in 2016, it was observed that Cathepsin L activated cleavage of S protein can be significantly blocked by Teicoplanin during the late endosome/ lysosome phases of SARS-CoV invasion and thereby preventing the release of viral genome and subsequently terminating the viral replication cycle [5]. Similar, *in vitro* study done by the same set of researches in the year 2020 revealed that the corresponding cleavage site of Cathepsin L was preserved in the pandemic strain of SARS-CoV-2 [7] (Figure. 1). They concluded that Teicoplanin in a dose dependent manner inhibited SARS-CoV-2 entry with half maximal inhibitory concentration (IC_{50}) of 1.66 μM [7].

DISCUSSION

The most commonly used clinical dose of Teicoplanin against

Gram positive bacterial infections is 400 mg/day or 8.78 μM. IC_{50} of Teicoplanin against SARS-CoV-2 was found to be 1.66 μM [7]. This indicates that Teicoplanin could be administered at a higher dosage as required for optimal antiviral efficacy and may therefore achieve a more powerful antiviral effect.

Recent study done by Lingxi and his colleagues, reported that 26.7% of hospitalized COVID-19 cases had bacterial co-infection which included A. baumannii, K. pneumoniae, E. coli, S. maltophilia, S. aureus, H. influenza, P. aeruginosa and S. haemolyticus. Bacterial co-infection would worsen the clinical outcomes, prolong the hospital stay and is a leading cause of mortality in these cases [28]. Hence, Teicoplanin could have a significant role in the treatment of COVID-19 cases with Gram positive bacterial co-infection.

In 2020, a descriptive study suggested that COVID-19 cases with low immune system when treated along with antibiotics to prevent infections would show better clinical outcomes [29]. Thus, co-administration of Teicoplanin might also be useful in reducing morbidity and mortality in persons with low immune function such as old aged persons, pregnant women, HIV positive cases, diabetics and persons on immunosuppressive agents.

Finally, we conclude that Teicoplanin may have good therapeutic potential to combat COVID-19, especially in severely ill patients and those having co-bacterial infections. We recommend that the clinical efficacy and safety profile of Teicoplanin in the treatment of COVID-19 may be explored by further *in vivo* studies and randomized controlled clinical trials.

Conflict of interest : Nil

Funding : Nil

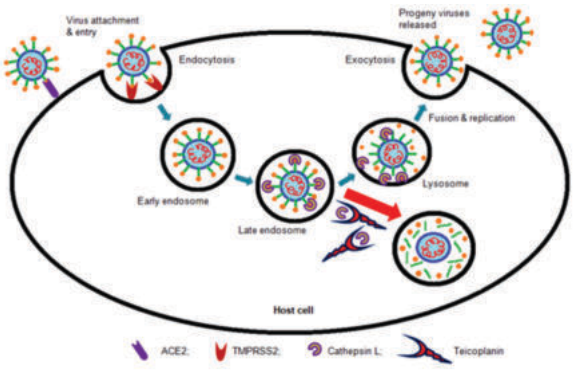

Figure. 1Schematic representation of effects of Teicoplanin on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication cycle.

REFERENCES

1. World Health Organization (WHO). https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (28 March 2020)
2. Hui DS, I Azhar E, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020. 91: 264–66.
3. World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19. (Press release).
4. World Health Organization (WHO) https://covid19.who.int/ . (28 October 2022)
5. Zhou N, Pan T, et al. Glycopeptide Antibiotics Potently Inhibit Cathepsin L in the Late Endosome/Lysosome and Block the Entry of Ebola Virus, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). J Biol Chem. 2016.
6. Colson P, Raoult D. Fighting viruses with antibiotics: an overlooked path. Int J Antimicrob Agents. 2016. 48:349–52.
7. Zhang J, Ma X, et al. Teicoplanin potently blocks the cell entry of 2019-nCoV. BioRxiv. February 2020.
8. de Groot RJ, Baker SC, et al. "Family Coronaviridae". In King AM, Lefkowitz E, Adams MJ, Carstens EB, International Committee on Taxonomy of Viruses, International Union of Microbiological Societies. Virology Division (eds.). Ninth Report of the International Committee on Taxonomy of Viruses. Oxford: Elsevier. 2011. pp. 806–28. ISBN 978-0-12-384684-6.
9. *Sexton NR, Smith EC, et al.* Homology-Based Identification of a Mutation in the Coronavirus RNA-Dependent RNA Polymerase That Confers Resistance to Multiple Mutagens. *Journal of Virology. 2016. 90(16): 7415–28.* doi:10.1128/JVI.00080-16.
10. Goldsmith CS, Tatti KM, et al. Ultrastructural characterization of SARS coronavirus Emerging Infectious Diseases. 2004. 10 (2): 320–6. doi:10.3201/eid1002.030913
11. Chen N, Zhou M, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020. 395 (10223):507–513.
12. Wu C, Liu Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharmaceutica Sinica B. Feb2020.
13. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200317-sitrep-57-covid-19.pdf?sfvrsn=a26922f2_4 (09 April 2020)
14. https://www.who.int/news-room/q-a-detail/q-a-coronaviruses. (09 April 2020)
15. Xu X, Chen P, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Science China Life Sciences. March 2020. 63 (3):457–460.
16. Glowacka, I.et al. Evidence that TMPRSS2 Activates the Severe Acute Respiratory Syndrome Coronavirus Spike Protein for Membrane Fusion and Reduces Viral Control by the Humoral Immune Response. Journal of Virology. 2011. 85:4122-4134. doi:10.1128/Jvi.02232-10.
17. Simmons G, Zmora P, et al. Proteolytic activation of the SARS-coronavirus spike protein: Cutting enzymes at the cutting edge of antiviral research. Antiviral Research. 2013. 100:605-614.
18. Hoffmann, M. et al. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. Biorxiv.org. 2020.
19. Hoffman M, Kliene-Weber H, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a clinically proven protease Inhibitor. Cell. 4 March 2020. 181:1–10.
20. Bosch B. J, Bartelink W, et al. Cathepsin L functionally cleaves the severe acute respiratory syndrome coronavirus class I fusion protein upstream of rather than adjacent to the fusion peptide. J Virol. 2008. 82: 8887-8890.
21. Zhou, P. et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020. 10.1038/s41586-41020-42012-41587.
22. Wang, M. et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research. 2020 30(3):269-271.
23. Anatomy of a Killer: Understanding SARS-CoV-2 and the drugs that might lessen its power. The Economist. 12 March 2020. Archived from the original on 14 March 2020. Retrieved 14 March2020.
24. Belouzard S, Chu V. C. & Whittaker G. R. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proceedings of the National Academy of Sciences of the United States of America. 2009. 106(14):5871-5876.
25. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015. 1282:1-23
26. Deborah M. Campoli-Richards et al. Teicoplanin: A Review of its Antibacterial Activity, Pharmacokinetic Properties and Therapeutic Potential. Drugs. 1990. 40 (3):449-86.
27. Pan T, Zhou N, Zhang H. Use of Teicoplanin anti-middle east respiratory syndrome coronavirus. 2015. WO/2016/201692.
28. Lingxi Guo et.al. Clinical Features Predicting Mortality Risk in Patients with Viral Pneumonia: The MuLBSTA Score. Front. Microbiol. 2019. 10:2752. doi:10.3389/fmicb.2019.02752
29. Nanshan Chen et.al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020. 395: 507–13 https://doi.org/10.1016/S0140-6736(20)30211-7