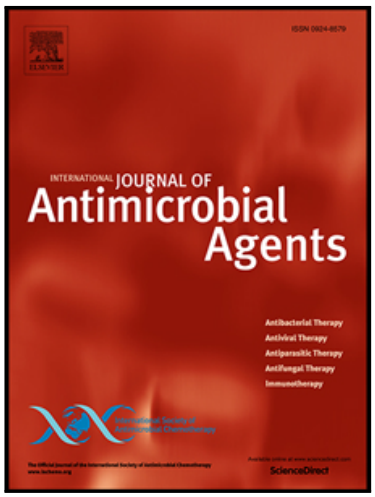

Teicoplanin: an alternative drug for the treatment of coronavirus COVID-19?

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Highlights

- A new coronavirus, SARS-CoV-2, has emerged from China and is spreading worldwide
- Due to the lack of specific treatment, we suggest the use of drug repurposing
- Teicoplanin, an antibiotic, has already shown activity against previous coronavirus.
- Its activity seems conserved in vitro against this new coronavirus.
- Further works are needed to confirm its activity in vivo

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Abstract

In December 2019, a new coronavirus, named SARS-CoV-2, has emerged from China causing pneumonia outbreaks first in the Wuhan region and have now spread worldwide because of its probable high transmission efficiency. Due to the lack of efficient and specific treatments and the need to contain the epidemic, drug repurposing appears to be the best tool to find therapeutic solution. Chloroquine, remdesivir, lopinavir, ribavirin or ritonavir have shown efficacy to inhibit coronavirus in vitro. Teicoplanin, an antibiotic used to treat staphylococci infection, previously showed efficacy to inhibit the first stage of MERS-coronarivus viral cycle in human cells. This activity is conserved on the SARS-Cov-2, thus placing teicoplanin as a potential treatment for patients with this virus.

Keywords

SARS-CoV-2; drug repurposing; teicoplanin; COVID-19

Hot topic

In December 2019, a new coronavirus has emerged from China causing pneumonia outbreaks first in the Wuhan region and have now spread worldwide because of its probable high transmission efficiency [1,2]. This coronavirus, named SARS-CoV-2 (formerly 2019-nCoV), is responsible for respiratory infections including pneumonia with a mortality rate estimated about 2%-2.5%, increasing with age and the existence of underlying diseases. On the first days of March 2020, an estimated 89,068 cases had been confirmed worldwide by WHO (a number likely underestimated due to the existence of asymptomatic carriers) and the epidemic has already left 3,046 dead from COVID-19 disease, the majority of them occurring in China. Because COVID-19 is now becoming pandemic and in the absence of known validated efficient therapy, efforts of laboratories and medical teams have focused on repurposing FDA-approved drugs to treat the most severe cases of infection. Drug repurposing is an effective way to quickly identify therapeutic drug with a known safety profile to treat an emerging disease. Chloroquine/hydroxychloroquine, a front-line drug used in the treatment and prophylaxis of malaria also used in autoimmune disease had been shown to inhibit the replication of several DNA and RNA viruses, including most of human coronaviruses [3]. Recently, chloroquine was found to inhibit SARS-CoV-2 *in vitro* and its hydroxylated form has been proposed as a possible therapy to treat patients infected with SARS-CoV-2 [4,5]. In this contest, other drug showed significant efficacy against SARS-Cov-2 *in vitro* such as remdesivir, lopinavir, ribavirin or ritonavir (https://drugvirus.info/) [6].

Teicoplanin, a glycopeptide antibiotic routinely used to treat bacterial infection was found to be active *in vitro* against SARS-CoV, has joined the list of molecules that could be used as

therapeutic arsenal against COVID-19 [7]. This antibiotic, currently used in the treatment of Gram-positive bacterial infection, especially in Staphylococcal infections, has already showed efficacy against various viruses such as Ebola, influenza virus, flavivirus, hepatitis C virus, HIV virus and on coronavirus such as MERS-CoV and SARS-CoV [8,9]. A patent was filed for the treatment of infection caused by MERS-CoV in 2016 [10]. According to Zhou and colleagues, in coronaviruses, teicoplanin acts on the early step of the viral life cycle by inhibiting the low pH cleavage of the viral spike protein by cathepsin L in the late endosomes thereby preventing the release of genomic viral RNA and the continuation of virus replication cycle. A recent study by the same authors showed that this activity was conserved on SARS-Cov-2 (the target sequence that serve as cleavage site for cathepsin L is conserved among SARS-CoV spike protein) [7]. The concentration of teicoplanin required to inhibit 50% of viruses (IC_{50}) *in vitro* was 1.66 µM, which is much lower than the concentration reached in human blood (8.78 µM for a daily dose of 400 mg) [7]. These preliminary results need to be confirmed now by a randomized clinical trial.

Based on our experience of teicoplanin usage in the treatment of infectious diseases, we encourage further investigation of the antiviral effect of this molecule on SARS-CoV-2 and suggest teicoplanin as another potential alternative for the treatment of COVID-19 disease.

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Competing Interests

The authors declare that they have no competing interests.

Ethical Approval
Not required

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727–33. https://doi.org/10.1056/NEJMoa2001017.

[2] Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020:105924. https://doi.org/10.1016/j.ijantimicag.2020.105924.

[3] Devaux C, Rolain J-M, Colson P, Raoult D. New insights for antiviral effects of chloroquine against coronavirus: what to expect for COVID 19? Int J Antimicrob Agents 2020. https://doi.org/submitted.

[4] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020. https://doi.org/10.1038/s41422-020-0282-0.

[5] Colson P, Rolain J-M, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. Int J Antimicrob Agents 2020:105923. https://doi.org/10.1016/j.ijantimicag.2020.105923.

[6] Ko W-C, Rolain J-M, Lee N-Y, Chen P-L, Huang C-T, Lee P-I, et al. Remdesivir for SARS-CoV-2 pneumonia. Int J Antimicrob Agents 2020. https://doi.org/sudmitted.

[7] Zhang J, Ma X, Yu F, Liu J, Zou F, Pan T, et al. Teicoplanin potently blocks the cell entry of 2019-nCoV. BioRxiv 2020:2020.02.05.935387. https://doi.org/10.1101/2020.02.05.935387.

[8] Zhou N, Pan T, Zhang J, Li Q, Zhang X, Bai C, 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;291:9218–32. https://doi.org/10.1074/jbc.M116.716100.

[9] Colson P, Raoult D. Fighting viruses with antibiotics: an overlooked path. Int J Antimicrob Agents 2016;48:349–52. https://doi.org/10.1016/j.ijantimicag.2016.07.004.

[10] Pan T, Zhou N, Zhang H. USE OF TEICOPLANIN ANTI-MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS. WO/2016/201692, 2015.