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Research Article

Rolitetracycline as a Potential Adjunctive Treatment In Sars-Cov-2 Suspected or Infected Non-Critically Ill Patients

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Abstract: Since the world wide spreading of SARS-COV2 2,406,745 suspected cases with 165,257 death ones have been recorded. COVID-19 is a highly contagious disease that spread via direct exposure to the droplets generated when an infected person cough or sneeze or touching surfaces that are contaminated with those droplets and then toughing the nose, eyes, mouth or any mucous membrane. The deleterious impact of COVID-19 on all life sectors and without the availability of specific treatment or protective vaccine, researchers started the adoption of repurposing principle to help with the management and containment of the virus. As we are running out of time, the discovery and development of new selective anti-COVID19 drugs is not a practical option; leaving us with the enrollment of already available drugs in this crisis. Many drugs are currently under clinical trials suggesting to decrease the mortality of infected patients using the theory of "cytokine storm", hyper inflammatory status as an example have shown that “oxidant storm” instead of cytokine storm is the primary pathogenesis cascade for causing mortality in the late stages of COVID-19. In this review article, we repurpose the well-known antibiotic Rolitetracycline as adjunctive management of COVID-19 suspected or infected patients based on the documented non antibiotic activities of tetracycline and hiring the docking technique.

Keywords: COVID-19, Rolitetracycline, Tetracycline, Cytokine storm, Hyper-Oxidative storm, M-Pro inhibition , Phospholipase A2 and COX2 inhibitor.

INTRODUCTION

COVID-19 infected patients commonly manifest with fever, sore throat, cough, muscle pain, and shortness of breath beside laboratory data indicating multiorgan failure. Elevated serum levels of ALT, AST, LD, ALP, unconjugated and total bilirubin with simultaneous decrease in albumin levels indicate liver injury. Whereas increased levels of D-dimer, FDP, prothrombin time, activated partial thromboplastin time and bleeding tendency indicate platelets dysfunction and DIC as coagulation abnormalities. While bilateral ground glass and consolidation opacities found on chest CT scan indicate lung injury. In consistence with these clinical findings and the massive increase in proinflammatory cytokines and chemokines levels in COVID-19 affected people, " cytokine storm-hyperinflammatory status" theory has been proposed as the best pathogenesis explaining mechanism. The balance between pro and anti- inflammatory mediators is highly important to maintain the immune homeostasis. The observed increase in proinflammatory cytokines (ex: IL-6, IL-12, IL-18,etc) and chemokines (ex: CCL2, CCL3, CXCL9,etc) cause hyperactive immunity that attack the body's own systems leading to systems dysfunction with hepatic and pulmonary ones being the most affected. The current management practice is mainly supportive, focusing on hemodynamic and respiratory support. It is worthy to mention, that another key player also contributes to the disease pathogenesis namely called as " iron oxidant storm- hyperoxidative status" theory. COVID-19 invade the hemoglobin ß chains releasing iron to the blood causing iron overload, that pose serious oxidative damage as iron is a strong oxidant. This theory has been supported by the observed increase in iron-neutralizing mechanisms such as ferritin and monocytosis.

Four classes of coronavirus exist named as alpha, beta, gamma, and delta with SARS-COV2 being a

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member of the ß class. COVID-19 is a single stranded positive sense RNA virus with large envelope and very long RNA genome coding for multiple structural and non-structural proteins. Among the structural proteins there is glycosylated spike protein (S-pro) that aid with the attachment of COVID-19 at ACE2 receptors of the host cells membrane and triggering the host immunity. Following the attachment, the priming of S-pro is mandatory to complete the entrance process; and this is mediated by the activity of host cell produced serine protease TMPRSS211. Once the virus enter the host cells it will utilize their machinery for the translation of its genome to non-structural proteins including main protease (M-pro/ 3CLpro) and papain like protein (PL-pro) and non-functional large polyproteins; the functionalization of these proteins is carried by the viral proteases that cleaves them in a specific sites. Targeting M-pro would provide fruitful outcomes with excellent safety and efficacy due to its crucial role in the virus replication and the absence of homology with human proteins. COVID-19 M-pro mediates proteolytic activity by cleaving the target substrate at specific sites with the assistance of its catalytic dyad. This catalytic pocket with its cysteine containing unit Cys145-His41 work as nucleophiles and aid in the catalytic reaction.

Till the time of this review, no antiviral therapy or vaccine has been conformed for SARS-CoV-2 virus (Yi, Y. *et al*., 2020). At the same time, the costs and slow pace of new drug discovery and development make the goal is to do repurposing for drugs that are available with known profile (Pushpakom, S.*et al*.2018). We see a repurposing opportunity for Rolitetracycline in COVID-19 crisis. Rolitetracycline was the first semi-synthetic tetracycline launched in late 1950s. Rolitetracycline is a pro-drug of tetracycline. Formed by a Mannich condensation of formaldehyde and pyrrolidine with tetracycline, in which the pyrrolidine moiety improves bioavailability compared with tetracycline (Liu, F.*et al*, .2016). its bacteriostatic activity by interfering with protein synthesis following its passive penetration across the bacterial membrane and reversible inhibition of its 30S ribosomal subunit. Rolitetracycline share the same basic SAR (structure activity relationship) with other tetracycline members, but carry the advantage of being the only drug of this family to be administered via the parenteral route. This unique character makes Rolitetracycline one of the best resorts when oral administration of tetracyclines is not applicable due to persistent vomiting, nausea, dysphagia particularly in elderly and sedated mechanically ventilated patients.

DISCUSSION

Taking into consideration the " cytokine storm-hyperinflammatory status" and " iron oxidant storm-hyperoxidative status" as constituents of the underlying pathology along with the vital role of main protease M-pro in the virus survival, the implantation of a drug with impact on those three contributors such as Rolitetracycline would provide very promising positive results in the treatment and progression of COVID-19 patients. As Rolitetracycline is a mannich base prodrug; giving it will result in its protonation and destabilization thus liberation of the biologically active tetracycline. Tetracyclines have other effects beside the antibiotic activity including anti-inflammatory and anti-oxidative ones as they inhibit the free radicals formation and proinflammatory cytokines production. Focusing on their anti-inflammatory properties, several molecular mechanisms have been proposed. At normal conditions, matrix metalloproteases (MMPs) mediate tissue remodeling. But during pathological states hyperactivity of them cause matrix degradation and tissue destruction. Tetracyclines attenuate this MMPs-mediated damage by chelation with Ca and Zn at the enzyme catalytic site; leaving it no more active, decrease the expression of inducible nitric oxide synthase (iNOS) that is needed for the induction of MMPs synthesis and inhibition of COX-2 mediated prostaglandin E2 production that is needed for their activation. Tetracyclines decrease the production of NO a potent proinflammatory mediator by two major ways;(1) decrease the stability thus increase the degradation of iNOS-mRNA (2) inhibit the expression of iNOS-mRNA. In addition to that, they decrease the production and secretion of proinflammatory cytokines and prostaglandin E2, by decreasing the stability of cytokines coding mRNA and sequential inhibition at phospholipase A2 and COX2, respectively. The immunomodulatory and anti-inflammatory effects of tetracycline have been elucidated by their productive outcomes obtained from their application in the management of Dengue and Dengue hemorrhagic fever patients. Dengue fever is mosquito transmitted disease from which 2.5% progress to the more sever Dengue hemorrhagic fever. The hallmark pathogenesis is the elevation of serum proinflammatory cytokines (TNF-α, IL-1ß) and decrease in their anti-inflammatory counterparts. The administration of tetracycline to the affected patients has been shown to decrease the levels of TNF-α and IL-1ß with increase in the levels of IL-1 RA. By doing so, better progression with lower disease severity was observed.

Now, we slightly touch the basis of Rolitetracycline mediated M-pro inhibition. Ligand N3 is synthetic inhibitor with selective and optimal fitting in COVID-19 M-pro catalytic site which has a Cys–His catalytic dyad, and the substrate-binding site is located in a cleft between Domain and N3. Mpro showing asymmetric unit containing only one polypeptide and by hiring the X-ray crystallographic technique, docking method with other needed tests the energy of binding (EOB) of different ligands with COVID-19 M-pro was obtained. By the end of the test, EOB = -7.7716 Kcal/mole was recorded for N3 with -7.1222 Kcal/mole for Rolitetracycline. And keeping in mind that similar

or approximate binding energy values indicate similar binding affinities and behavior, the assumption of Rolitetracycline as promising selective COVID-19 M-pro inhibitor will be valid. Rolitetracycline showed the best binding with the catalytic center of the protease enzyme through binding with CYS 145 and HIS 41. Earlier outbreak episodes of viral infections like SARS-CoV and MERS-CoV as well as hemorrhagic fever viruses like Ebola were treated with this category of drugs. The limited clinical data available suggest that its therapeutic effectiveness is identical to that of the other tetracyclines. Rolitetracycline produces the same toxic effects as the other tetracyclines when used in animals. And to eliminate any source of bias, Rolitetracycline may cause side effects including irritative effects, thrombophlebitis of the injected vein, phototoxicity, antianabolic effect, hypersensitivity reactions, superinfection and Some cases of discoloration of the teeth of children have been caused by tetracyclines administered orally to pregnant women or to children, the possibility exists that a similar effect could be produced by Rolitetracycline, although none has been reported. Despite these side effects documented for our drug, they are much more harmless and manageable compared to that of Chloroquine and Hydroxychloroquine commonly used in COVID-19 management practice.

CONCLUSION

Rolitetracycline is an amazing in its binding mode in the active site of the protease pocket and has high affinity binders for virus. Also, we are predicting Rolitetracycline to suppress cytokine which is what we need since patients are suffering from cytokine storm. Our suggestion to incorporate rolitetracycline in COVID-19 management protocol based on its demonstrated anti-inflammatory, antioxidative and COVID-19 M-pro inhibitory properties provide highly shinning positive outcomes. But we need clinical trials to be conducted on Rolitetracycline to test its clinical usefulness in COVID-19 patients.

REFERENCES

1. Anand, K. (2002). Structure of coronavirus main proteinase reveals combination of a chymotrypsin fold with an extra alpha-helical domain. The EMBO Journal, *21*(13), 3213–3224. https://doi.org/10.1093/emboj/cdf327
2. Báez-Santos, Y. M., St. John, S. E., & Mesecar, A. D. (2015). The SARS-coronavirus papain-like protease: Structure, function and inhibition by designed antiviral compounds. *Antiviral Research*, 115, 21–38. https://doi.org/10.1016/j.antiviral.2014.12.015
3. Liu, C., Zhou, Q., Li, Y., Garner, L. V., Watkins, S. P., Carter, L. J., … Albaiu, D. (2020). Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. *ACS Central Science*, *6*(3), 315–331. https://doi.org/10.1021/acscentsci.0c00272
4. Liu, F., & Myers, A. G. (2016). Development of a platform for the discovery and practical synthesis of new tetracycline antibiotics. *Current opinion in chemical biology*, *32*, 48-57. https://doi.org/10.1016/j.cbpa.2016.03.011
5. Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., ... & Duan, Y. (2020). Structure of Mpro from COVID-19 virus and discovery of its inhibitors. *bioRxiv*.
6. ul Qamar, M. T., Alqahtani, S. M., Alamri, M. A., & Chen, L.-L. (2020). Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. *Journal of Pharmaceutical Analysis*. https://doi.org/10.1016/j.jpha.2020.03.009
7. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., … Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 181(2), 271-280.e8. https://doi.org/10.1016/j.cell.2020.02.052
8. Kouznetsova, V. (2020, April 9). Potential COVID-19 Protease Inhibitors: Repurposing FDAapproved Drugs. Retrieved from https://chemrxiv.org/articles/Potential_COVID-19_Protease_Inhibitors_Repurposing_FDAapproved_Drugs/12093900/1
9. Wang, F., Chen, C., Tan, W., Yang, K., & Yang, H. (2016). Structure of Main Protease from Human Coronavirus NL63: Insights for Wide Spectrum Anti-Coronavirus Drug Design. *Scientific Reports*, 6(1) 22677. https://doi.org/10.1038/srep22677
10. Tilakaratne, A., & Soory, M. (2014). Anti-inflammatory Actions of Adjunctive Tetracyclines and Other Agents in Periodontitis and Associated Comorbidities. *The Open Dentistry Journal*, *8*(1), 109–124. https://doi.org/10.2174/1874210601408010109
11. Abelson, M. B., MD. (2008, June 13). The Other Side of Antibiotics. Retrieved from https://www.reviewofophthalmology.com/article/the-other-side-of-antibiotics?fbclid=IwAR2uQxuklerPfpKfrjWt4gj7FTmiZ50KqDpQFZ1zO_g4DhEIs3xIQKsi7LU
12. Eklund, K., & Sandler, C. (2007). Antibiotic or Anti-inflammatory Agent? The Double-Edged Sword of Tetracyclines. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, *6*(4), 253–263. https://doi.org/10.2174/187152307783220013
13. Ce, M. S.-. (2020, April 8). Hydroxychloroquine, Oral Tablet. Retrieved from https://www.healthline.com/health/hydroxychloroquine-oral-tablet?fbclid=IwAR3P9R--HuIi5Vu8-hZxz9UqOWWNygACPotYrHgyvQdD2smrtlqPEJL7KhQ

14. Taccone, F. S., Gorham, J., & Vincent, J.-L. (2020). Hydroxychloroquine in the management of critically ill patients with COVID-19: the need for an evidence base. *The Lancet Respiratory Medicine*. https://doi.org/10.1016/s2213-2600(20)30172-7
15. Zhao, M. (2020). Cytokine storm and immunomodulatory therapy in COVID-19: role of chloroquine and anti-IL-6 monoclonal antibodies. *International Journal of Antimicrobial Agents*, 105982. https://doi.org/10.1016/j.ijantimicag.2020.105982
16. Soto, P. (2020, April 20). Chloroquine and Hydroxychloroquine Can Have Serious Side Effects. Retrieved from https://www.poison.org/articles/chloroquine-hydroxychloroquine?fbclid=IwAR2peVY1KXmiV1C73793RVrSGZVX5bYHRnajiPTBF2QZp1BzhJPV16j7W8o
17. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment for COVID-19. (2020, March 27). Retrieved from https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19?fbclid=IwAR16yOE4S3rAW9j3bfRrLIjD2brTnaNUGvIiRMeg4XTb5GQyMQLqF7iHhhw
18. Myth busters. (2020, April 20). Retrieved from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters?fbclid=IwAR2uQxuklerPfpKfrjWt4gj7FTmiZ50KqDpQFZ1zO_g4DhEIs3xIQKsi7LU
19. Aly, O. (2020, April 3). Molecular Docking Reveals the Potential of Aliskiren, Dipyridamole, Mopidamol, Rosuvastatin, Rolitetracycline and Metamizole to Inhibit COVID-19 Virus Main Protease. Retrieved from https://chemrxiv.org/articles/Molecular_Docking_Reveals_the_Potential_of_Aliskiren_Dipyridamole_Mopidamol_Rosuvastatin_Rolitetracycline_and_Metamizole_to_Inhibit_COVID-19_Virus_Main_Protease/12061302/1?fbclid=IwAR16yOE4S3rAW9j3bfRrLIjD2brTnaNUGvIiRMeg4XTb5GQyMQLqF7iHhhw
20. Coronavirus Disease 2019 (COVID-19) – Symptoms. (2020, April 17). Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html?fbclid=IwAR16yOE4S3rAW9j3bfRrLIjD2brTnaNUGvIiRMeg4XTb5GQyMQLqF7iHhhw
21. Choudhary, D. (2017, June 27). Rolitetracycline : Therapeutic uses, Dosage & Side Effects. Retrieved from https://www.doctoralerts.com/rolitetracycline/?fbclid=IwAR0kx3xOAllH2gxFOdB0iXgaUsu0-LrA86SOIhVVPKUxkSnxZuWBoCkbEHw
22. Tetracyclines proposed as treatment for COVID-19. (2020, April 15). Retrieved from https://www.eurotimes.org/tetracyclines-proposed-as-treatment-for-covid-19/?fbclid=IwAR0HfrBV_0fMykaua7tUk0yDzM5Dwb75M6UYmzqLQL746sS05R6VcyqhGmY
23. Castro, J. E. Z., Vado-Solis, I., Perez-Osorio, C., & Fredeking, T. M. (2011). Modulation of Cytokine and Cytokine Receptor/Antagonist by Treatment with Doxycycline and Tetracycline in Patients with Dengue Fever. Clinical and Developmental Immunology, 2011, 1–5. https://doi.org/10.1155/2011/370872