Precision medicine approach to discover the effective therapy for Hydroxychloroquine No respondents in COVID-19

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INTRODUCTION

The world is gearing up to battle against the Coronavirus disease 19 (COVID-19) outbreak which has already led to more than 323,256 deaths and 4,893,186 confirmed cases globally as on May 22, 2020 [1]. There are currently no drugs licensed for the treatment or prevention of COVID-19. While several drug trials are ongoing, advisories were published on the use of hydroxychloroquine as prophylaxis for SARS-CoV-2 infection [2-4].The existence of hydroxychloroquine failure was even recorded in many cases [5] and that is to be suggested for the resistance developed.

There must be an alternative treatment strategy, and proof that testing for the genotype and subsequently tailoring the treatment strategy based on genetic information are more clinically effective than merely treating everyone in the same manner. In a recent research, the complete genome Sequence of a 2019 Novel Coronavirus (SARS-CoV-2) strain was isolated in Nepal to address questions on its genotypic and serological characterization [6]. Identifing the gene variants will be more efficient than current practice in improving the clinical outcome and preventing the adverse effects. Taking into account the known non-genetic factors that cause variation in response, the remaining variability in patient response can often be managed with appropriate monitoring, or can be reversed by application of precision medicine.Precision medicine now influences the clinical approach to diagnosing and treating several diseases, including common and rare disorders [7].

Proteomic, genetic, and RNA sequencing gene expression analysis could be performed on the lung, proteomic profiling of serum and bronchoalveolar lavage fluid to identity potential molecular pathways contributing to disease and possible therapeutic targets. Concentrations of those analytescytokines, chemokines, growthfactors, and proteases investigated in the patient's serumand bronchoalveolar lavage fluid could be compared to the hydroxychloroquine respondents and normal volunteers. Overall, these data would suggestthe possible pathway associated with the non respondence to hydroxychlorquine. The presence of any variants of unknown significance that could explain the phenotype and the response to treatment could be observed. Family history of any autoimmune disorders to be ruled out and, large scale germline genotyping using a single nucleotide polymorphism array [8], whole exome sequencing, and whole genome sequencing should be performed. Potential candidate disease-associated genes and the up and down regulation of the same can be identified this way.

To identify the therapeutic response for those patient's who did not respond to hydroxychloroquine, those patient's cells to be incubated with hydroxychloroquine with various concentrations. Cell proliferation and cytotoxicity assays revealed that the inhibitory effects of hydroxychloroquine were dose-dependent and may vary from one to other based on the gene expression. With the result to which inhibitory efffect of hydroxychloroqune is observed, the same dose to be adminstered to that particular patient whose proteomics and genomics are studied. Response to therapy should be assessed longitudinally, and clinical outcome measures should include the viral load, upper respiratory tract infections and lower respiratory tract infections. In addition, serum reactive protein concentrations corresponding to the response levels should be be monitored. The potential risk of severe QT

prolongation induced by hydroxychlorquine [9] could even be inhibited through precision medicine. Treatment with hydroxychloroquine at a precised dose will result in clinical improvement in the patient's previously who was not responding to hydroxychloroquine and may not associated to QT prolongation.

Overall, this correspondence expands the role of precision medicine by illustrating how personalized approaches can identify effective dosing strategy for challenging cases where patients do not respond to the therapy. Similar strategies could be considered for other drug candidate that do possess antiviral activity to treat COVID-19 patients to develop individualized therapeutic plans.

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REFERENCE

[1] Coronavirus (COVID-19), https://covid19.who.int.

[2] https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf

[3] https://www.mdmag.com/medical-news/acr-recommendations-hydroxychloroquine-covid-19

[4] https://www.fda.gov/media/136537/download

[5] Philippe G, JeanCL, Philippe P, Van TH, Line M, Morgane M. et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an openlabel non-randomized clinical trial. Int. J. Antimicrob. Agents 2020, doi:https://doi.org/10.1016/j.ijantimicag.2020.105949.

[6] Ranjit S, Alfonso JR, Runa J, Daniel KWC, Haogao G, Malik P. et al. Complete Genome Sequence of a 2019 Novel Coronavirus (SARS-CoV-2) Strain Isolated in Nepal. MicrobiolResourAnnounc2020 ;9:e00169-20.

[7] Bernadette RG, Shira GZ, Nicholas ST, Nicholas JB, Christopher EM, Paul Z. et al. A comprehensive, multidisciplinary, precision medicine approach to discover effective therapy for an undiagnosed, progressive, fibroinflammatory disease. Transl Res. 2020; 215:31-40.

[8] Bryan MM, Tolman NJ, Simon KL,Marjan H, Robert BH, Brian PB. et al. Clinical and molecular phenotyping of a child with Hermansky-Pudlak Syndrome-7, an uncommon genetic type of HPS. Mol Genet Metab 2017;120:378–83.

[9] https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or