World Health Organization

WHO R&D Blueprint

WHO Joint Advisory Group on COVID 19 Therapeutics Prioritization

DRAFT Statement on the possible effects of the new SARS CoV-2 Omicron variant on treatment of hospitalized COVID-19 patients

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Background

The Joint Advisory Group (AG) on COVID 19 Therapeutics Prioritization is set up with the aim of establishing an independent process to advise WHO on the selection of therapeutics for COVID-19. The AG provides expert, impartial and timely advice on candidate drugs for treatment and prevention of COVID-19 to be evaluated in WHO-sponsored platform studies, including trials in hospitalized patients as well as outpatients, pre-exposure prophylaxis (PrEP), and post-exposure prophylaxis (PEP). The Joint AG comprises up to 30 experts, who serve in their personal capacity and represent a broad range of affiliations and disciplines encompassing many aspects of therapeutics and health products.

Members are acknowledged experts from around the world in the fields of coronavirus case management and COVID-19 treatment, epidemiology/public health, paediatrics, internal medicine, intensive care, infectious diseases, immunology, animal models and assays for therapeutic evaluation, drug regulation, drug manufacturing, clinical evaluation of therapeutics, health-care administration, virology, and translational sciences.

On 1 December 2021, WHO convened its Joint AG to perform a preliminary review and analysis of the potential impact of the SARS CoV-2 Omicron variant on drugs against COVID-19, either in use or under investigation.

Key points

The group agreed to this task on the understanding that such a review and the resulting conclusions could, in the absence of experimental and clinical evidence, only represent an early and speculative exercise which would have to be repeated as new evidence emerges. Furthermore the group cautioned that it had not been established to undertake this type of analysis and therefore lacked a depth of expertise in some relevant disciplines such as virology and structural biology. With these caveats in mind, the group considered the treatments by target effects and concluded the following:

Monoclonal antibodies targeting the SARS-CoV-2 S-protein: As the S-protein gene is the RNA sequence where extensive and defining mutations of the Omicron variant are located, monoclonal antibodies which were developed to target the original Wuhan variant S protein are highly likely to lose some or all of their binding and/or neutralizing ability. However, different monoclonal antibodies target different epitopes and may therefore be affected to differing degrees or, possibly, not all. A case-by-case analysis, in silico, in vitro and in vivo will be necessary.

Antiviral agents targeting polymerase and protease: Drugs targeting these viral non-structural proteins are less likely to have significantly reduced efficacy against the Omicron variant. The genes encoding these proteins are more conserved than the S-gene and the Omicron variant has only single amino acid substitutions in both the protease and RNA-dependent RNA polymerase. Neither mutation is anticipated to be critical to the mechanism of action of drugs targeting these proteins that are currently

in late stage development. However, this assumption is yet to be proven experimentally and the situation needs to be monitored carefully.

Immunomodulators and anti-thrombotics: In general, drugs which target host responses to SARS-CoV-2 infection are expected to retain clinical efficacy for all variants. It is possible that the Omicron variant modifies the COVID-19 clinical disease phenotype and so the use of these drugs in clinical practice may be altered, but there are currently insufficient data to know.

Conclusion and next steps

With the above in mind, the group recommends to focus initial research efforts in this area on

a) antigen binding and virus neutralization by antiviral monoclonal antibodies and

b) characterization of the COVID-19 phenotype caused by infection with the Omicron variant, in a diverse (age, comorbidities, etc) patient population.

Also, it was noted that the Omicron variant of the SARS-CoV-2 virus should be shared with the international SARS CoV-2/COVID-19 research community as rapidly as possible.