COVID-19 (nCorona) Virus Outbreak Control and Prevention State Cell

Health & Family Welfare Department

Government of Kerala

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TECHNICAL NOTE TO OPTIMIZE THE USE OF MONOCLONAL ANTIBODY COCKTAIL [CASIRIVIMAB PLUS IMDEVIMAB] IN THE CURRENT CONTEXT OF SARS-CoV-2 PANDEMIC IN KERALA

In the wake of OMICRON COVID infection, superseding all the previous guidelines regarding use of mAB in the state, the following guidelines are issued for follow up by all Hospitals in the state.

The decision for the use of mAB shall be taken by the concerned Institutional Medical Boards appropriately as per the guidelines. The Institutional Medical Board shall appropriately decide tests to detect OMICRON as per the ICMR approved testing technology and kits.

Introduction:

Efficacy of mAB during OMICRON Covid infection wave –

The B.1.1.529 (Omicron) variant of concern (VOC) has become the dominant variant in many parts of India. Due to numerous mutations in the spike protein (S), which is the antigenic target of vaccine-elicited antibodies, Omicron raises serious concerns of a significant reduction in vaccine efficacy and an increased risk of reinfection. Compared to the parental variant (B.1), Omicron S has 30 non-synonymous substitutions, three small deletions and an insertion. Fifteen of these mutations are in the receptor-binding domain (RBD), a major target of neutralizing antibodies (NAbs). This variant due to numerous mutations in the spike protein has markedly reduced susceptibility to monoclonal antibody cocktail; casirivimab plus imdevimab.

The Omicron genome (lineage BA.1) contains the spike deletion at position 69-70 which is associated with SGTF [S gene target failure] in some PCR tests with S gene detection probes. Such PCR tests evaluate the presence of 3 SARS-CoV-2 genes: Spike (S), N and ORF1ab. SGTF is defined as a PCR test where the N and ORF1ab genes are detected but the S gene is not. SGTF patterns can

be used to assess the spread of Omicron. S-gene target failure (SGTF) can be used as a screening method for Omicron.

In a setting with the Delta variant dominating or probable co-circulation of delta and Omicron is occurring, SGTF can be used as a sensitive proxy for Omicron. In the Kerala scenario, for next few weeks, a co-circulation of delta with Omicron is expected after which Omicron is expected to fully replace delta. In this regard surrogate marker like SGTF which is easy to perform will help in identifying relative proportion of SGTF positive [omicron BA1] and SGTF neg [delta or Omicron BA2] cases. Alternatively Omisure RTPCR kit which targets SGTF, S-gene mutation Amplification [SGMA] and confirmatory RDRP target and internal control, can be used to identify Omicron.

CLINICAL IMPACT OF SGTF DETECTION

Till Omicron fully replaces delta, co-circulation of both is expected in Kerala. In this regard SGTF detection is very important as in infection with delta variant, monoclonal antibodies are an effective treatment option for those with highest risk factors for disease progression. If SGTF is detected, then the isolate is likely to be Omicron and casirivimab and imdevimab will fail to neutralize the variant and hence are not indicated. As the therapeutic window for administration of monoclonal antibodies is very short, waiting for genotyping is not a pragmatic approach especially in a pandemic scenario and hence surrogate markers like SGTF should be used to make the decision.

DISADVANTAGE OF USING SGTF IN DECIDING PATIENT SELECTION FOR ADMINISTRATION OF CASIRIVIMAB AND IMDEVIMAB

SARS-CoV-2 Omicron (B.1.159) lineage is split into two sub-lineages: BA.1 and BA.2. While both lineages share a number of common defining mutations and appear to be co-circulating, the new recognised BA.2 sub-lineage does not carry the Spike del 69-70 mutation which may hinder the use of commercially available PCR tests to diagnose Omicron based on "S-gene target failure".

KERALA CONTEXT

As of Jan 18, 2022, 98% of eligible population in Kerala has received one dose of COVID vaccine and 78% has received two doses of vaccine. Majority have acquired hybrid immunity too. Acquired immunity through vaccination as well as hybrid immunity has been proved to prevent progression of SARS-COV-2 infection. So even in the case of delta virus, maximum benefit for administration of monoclonal antibody cocktail will be for the unvaccinated and for those who are unable to mount a robust neutralizing antibody response to vaccination as in Immunocompromised. In this context, casirivimab and imdevimab should be prioritized for the following subgroups

1. Unvaccinated with highest risk factors
2. Immunocompromised.
3. CKD on dialysis
4. Congestive cardiac failure
5. Decompensated cirrhosis
6. COPD/ILD
7. Pregnancy with GDM/BMI>30/Eclampsia/AFLP [compassionate ground]

CONTRAINDICATIONS

Aim of administration of anti-SARS-COV-2 monoclonal antibodies is to prevent disease progression. So it has to be administered early in the disease course before hypoxia develops. It should NOT BE administered in

1. Those who require oxygen therapy due to COVID-19; or

2. Those who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and, because of COVID-19, require an increase in oxygen flow rate from baseline.

3. More than 10 days from symptom onset.

PATIENT SELECTION MATRIX FOR ADMINISTRATION OF IMDEVIMAB AND CASIRIVIMAB

Highest-risk individuals who will benefit from Monoclonal antibody cocktail

- Body mass index (BMI) ≥35
- Chronic kidney disease stage with eGFR<60ml/min especially in those on MHD.
- Diabetes mellitus [HBA1C >10] or diabetes with end organ damage.
- Chronic liver disease
- Immunocompromising conditions.
- Currently receiving immunosuppressive treatment
- Age ≥65 years
- Cardiovascular disease
- Chronic respiratory diseases.
- Malignancies with chance of survival.
- Other indications as deemed fit by institutional medical board.

- In those between 12 to 17 years with BMI ≥85th percentile for their age and gender Mab cocktail may be considered in
  - Sickle cell disease
  - Congenital or acquired heart disease
  - Neurodevelopmental disorders (e.g., cerebral palsy)
  - A medical-related technological dependence that is not related to COVID-19 (e.g., tracheostomy, gastrostomy, positive pressure ventilation)
  - Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.

PERFORM RTPCR WITH S GENE PROBE OR RTPCR WITH OMISURE KIT

SGTF DETECTED / OMICRON DETECTED BY OMISURE

CASIRIVIMAB-IMDEVIMAB **SHOULD NOT** BE ADMINISTERED

CASIRIVIMAB AND IMDEVIMAB IS <u>INEFFECTIVE IN NEUTRALIZING OMICRON</u> BA1, BA2 and BA3 SUBLINEAGES .

SGTF NOT DETECTED

MAY BE DELTA OR OMICRON BA2 sublineage.
In this situation monoclonal antibody should be prioritized for

1. Unvaccinated with highest risk factors
2. Immunocompromised.
3. CKD on dialysis
4. Congestive cardiac failure
5. Decompensated cirrhosis
6. COPD/ILD with respiratory failure
7. Pregnancy with GDM/BMI>30/Eclampsia/AFLP [compassionate ground]

IF ACCESS TO SGTF DETECTING PCR KITS / OMISURE KIT/SPIKE PROTEIN SEQUENCING IS NOT THERE, THEN USE OF CASIRIVIMAB PLUS IMDEVIMAB SHOULD BE PRIORITIZED FOR THE FOLLOWING CATEGORIES

1. Unvaccinated with highest risk factors
2. Immunocompromised.
3. CKD on dialysis
4. Congestive cardiac failure
5. Decompensated cirrhosis
6. COPD/ILD with respiratory failure
7. Pregnancy with GDM/BMI>30/Eclampsia/AFLP [compassionate ground]

Principal Secretary