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BC COVID THERAPEUTICS COMMITTEE (CTC) & COVID TREATMENT REVIEW AND ADVISORY WORKING GROUP (CTRAWG)

Therapeutic Update – Monoclonal Antibodies

November 21, 2022

Summary:

On October 18, 2022, Health Canada approved the monoclonal antibody (mAb) tixagevimab/cilgavimab (Evusheld®) for the treatment of COVID-19 on the basis of the TACKLE trial. However, based on emerging data, many variants of concern (VoC) have demonstrated greatly reduced affinity or complete resistance to both tixagevimab/cilgavimab and/or sotrovimab. ***Fully resistant VoCs currently comprise 29.6% of all sequenced VoCs in BC.*** Therefore, the CTC and CTRAWG have issued the following updated treatment recommendations for tixagevimab/cilgavimab and sotrovimab, and prophylaxis recommendations for tixagevimab/cilgavimab:

Recommendations for **tixagevimab/cilgavimab for treatment**
Tixagevimab/cilgavimab 600mg IM x 1 dose has demonstrated a 50.5% relative risk reduction (RRR) in COVID-19 hospitalization and death in unvaccinated, non-hospitalized adults with mild-moderate COVID-19 (TACKLE), which is lower than the RRR seen with other COVID-19 treatments in similar trials. Tixagevimab/cilgavimab is likely ineffective against many currently circulating VoCs including BA. 4.6, BF. 7, BA. 2.75.2, BQ 1, BQ 1.1 and XBB. If tixagevimab/cilgavimab is used as a last line treatment in cases where nirmatrelvir/ritonavir, IV remdesivir or sotrovimab cannot be used, disclosure to patients of risks, including cardiovascular serious adverse events (SAEs), and benefits and consideration of individual circumstances (clinical and immune status, patient values, logistics) is necessary. The convenience of the IM route of administration of tixagevimab/cilgavimab should not be the primary indication for use.

Recommendations for **sotrovimab for treatment**
Sotrovimab 500mg IV X 1 dose has reduced efficacy against the BA. 5.1, BA. 5.2 and 5.2.1 variants, although it may retain some activity. Real-world evidence shows limited efficacy against the BA 1. and BA. 2 variants of concern (VoCs) in immunocompromised or non-immune individuals, which may predict its performance against most BA. 5 VoCs. Sotrovimab has unknown clinical efficacy against many currently circulating VoCs (e.g., BA. 4.6, BQ. 1, BQ 1.1, XBB and BF. 7) where a reduction in binding is seen. If sotrovimab is used in cases where remdesivir or nirmatrelvir/ritonavir cannot be used, patient disclosure to risks and benefits in consideration of individual circumstances (clinical and immune status, patient values, logistics) is necessary. The

convenience of single-dose sotrovimab should not be the primary indication for use.

Recommendations for **tixagevimab/cilgavimab for prophylaxis**
Currently, there is a lack of high-quality evidence demonstrating a benefit of tixagevimab/ cilgavimab (EVUSHELD®) in preventing hospitalization from COVID-19, particularly in patients infected with omicron variants. Tixagevimab/cilgavimab was evaluated in unvaccinated, non-immunocompromised patients to prevent symptomatic infection with the COVID-19 alpha and delta variants and is likely ineffective against many currently circulating omicron variants of concern (VoCs) including BA. 4.6, BF. 7, BA. 2.75.2, BQ 1, BQ 1.1 and XBB. (See: VoCs), which may not be fully overcome by a dose increase (See: Dosing). Therefore, its role in prevention of COVID-19 in vaccinated or immunocompromised individuals who were not represented in the study, is unclear. Further, any theoretical benefit may not be outweighed by the potential risk of cardiac serious adverse events (SAEs), (See: Cardiovascular SAEs). Further research and real-world evaluation are needed. Tixagevimab/cilgavimab is not a replacement for vaccination or other recommended therapies for of COVID-19. Patients should be encouraged to receive scheduled booster doses and be offered therapy if they have symptomatic COVID-19.

Background:

Prior to October 18, 2022, sotrovimab was the only monoclonal antibody approved by Health Canada for treatment of COVID-19. Due to the decreased affinity against the BA. 2 VoC, sotrovimab was moved to last-line treatment of COVID-19 in April 2022. Since then, tixagavimab/ cilgavimab has also been approved for treatment in addition to prophylaxis. Real-world data regarding the use of sotrovimab has also been published. Finally, the findings in these studies need to be taken into context of the currently circulating variants of concern in BC.

Assessment/Recommendation:

The CTC and CTRAWG agreed to maintain a limited role for the use of mAbs. Generally, sotrovimab was regarded more favourably than tixagevimab/cilgavimab, but the rationale and concerns were:

1. **Resistance**: Although the BA. 5.1, BA 5.2 and BA 5.2.1 variants are predominant, over 50% of VoCs in BC are labeled as "other". This represents a heterogeneous mix of variants, including BA. 4.6, BQ. 1, BQ 1.1, XBB, BA. 2.75 and BF. 7, many of which are resistant to or have greatly reduced affinity to the mAbs. Resistance to tixagevimab/cilgavimab is worse than it is to sotrovimab. All of these are present in BC in varying proportions, and evidence from jurisdictions that use these mAbs shows that these are rapidly on the rise.

   The BCCDC VoC report dated November 18th summarized the results of whole genome sequencing up to and including November 5, 2022. In the last 7 days of this report, ***29.6% (65/219) of all VoCs were completely resistant to all mAbs available in BC.***

2. **Lack of robust and timely Whole Genome Sequencing (WSG) of community cases**: While WGS is performed in hospitalized patients, it is not consistently performed in outpatients. Therefore, the breakdown of VoCs in the general population is not well captured. Furthermore, a summary of VoC is typically released about one-month after collection. This gives a lack of visibility as to what VoCs are being targeted by these therapies.
3. **Lack of RCT and real-world evidence in immunized/immune patients for both mAbs:** While real-world evidence for treatment with sotrovimab against BA. 1 and BA 2. (which shows similar binding affinity to most BA. 5 VoCs) exist (OpenSafely study), these data are solely focused on those who are immunocompromised or non-immune patients. There is no real-world data for the use of tixagevimab/cilgavimab for treatment in any population, and data are limited to in-vitro studies for using a double dose in prophylaxis.

For tixagevimab/cilgavimab specifically:

1. **Lower relative-risk reduction:** The TACKLE study demonstrated a 50.5% relative risk reduction of severe disease or death in non-hospitalized, unvaccinated adults with mild-moderate COVID-19. However, this risk reduction is lower than that demonstrated with other drugs in very similar trials of 85-90% for sotrovimab, remdesivir and nirmatrelvir/ritonavir.
2. **Dosing uncertainty:** The prophylactic dose was increased from 300 mg to 600 mg to overcome VoC resistance. However, there are no studies that characterize the effectiveness of the 600 mg treatment dose to any of the current VoC. This dose is currently used for prophylaxis, but as viral loads are orders of magnitude higher in active COVID-19 infection vs. inoculation/exposure situations, it is unclear if this dose would be effective.
3. **Safety remains a concern** as cardiovascular serious adverse events were found to be higher in selected patients.
4. **IM dosing challenges:** Intra-muscular (IM) injection given by 4 x 1.5mL injections is likely to be painful requiring sufficient muscle mass for a high-volume injection and therefore, may not be as operationally advantageous or convenient as expected. Nurses who are not familiar with the drug may take as much time administering it as a 30-minute remdesivir infusion.

   The IM route may, in the rare case, represent **a last-resort option** over no treatment in high-risk patients residing in LTC, lack of access to an infusion site, or inability for a patient to take nirmatrelvir/ritonavir. If giving tixagevimab/cilgavimab in this case, the patient must be aware of the limitations above.

   Tixagevimab/cilgavimab remains available through the same distribution channels as for the prophylaxis indication. Tixagevimab/cilgavimab prescriptions should be faxed to 604-941-0532. Special Authority is not required. Injections are delivered through physician clinics (couriered to the location where it will be administered to the patient) OR hospital

inpatient or a hospital-based clinic (where the order is processed through the hospital pharmacy). Tixagevimab/cilgavimab is provided free of charge to patients.

For sotrovimab specifically:

1. Generally, if a mAb is being entertained, **sotrovimab is preferred** over tixagevimab/cilgavimab but remdesivir remains the first line injectable option.
2. Real-world data suggest effectiveness against at least the BA. 2 variant and similar performance against most BA. 5 variants is expected, although these data are entirely from non-immune or immunocompromised individuals.
3. Sotrovimab has **less loss of activity** against BA 4.6, BA. 2.75, XBB and BQ 1 variants than tixagevimab/cilgavimab, which shows complete resistance to these subvariants.
4. Sotrovimab has demonstrated a higher risk reduction (87% from COMET ICE) than tixagevimab/cilgavimab (50.5% from TACKLE).
5. There are so far no signals of serious adverse events.

The treatment role of sotrovimab is unchanged, with tixagevimab/cilgavimab moving to last line after sotrovimab for the treatment indication. Sotrovimab remains available through Health Authority-based COVID-19 infusion clinics where remdesivir is given and continues to be provided free of charge through the Public Health Agency of Canada.