Neutralizing Antibodies for Pre-Exposure and Post-Exposure Prophylaxis

Section last reviewed and updated on 1/12/2023

Last literature search conducted 4/30/2022

Recommendation 1: For areas of the world where predominant regional variants are susceptible* to the agent, in moderately or severely immunocompromised individuals, the IDSA guideline panel suggests pre-exposure prophylaxis with tixagevimab/cilgavimab rather than no tixagevimab/cilgavimab for patients for whom vaccination is not likely to be adequate or is not possible. (Conditional recommendation†, Low certainty of evidence)**

Remarks:

- **In the United States, predominant variants are resistant to tixagevimab/cilgavimab, such that efficacy is unlikely.-In the US in late 2022, Omicron sub-variants with >100 to >1000-fold reduced susceptibility to tixagevimab/cilgavimab emerged.**

For in vitro susceptibility information of SARS-CoV-2 variants, please visit **Stanford University's Coronavirus Antiviral & Resistance Database.*

***See **Figure 1** below*

†The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Figure 1. FDA EUA criteria for the use of tixagevimab/cilgavimab for pre-exposure prophylaxis of COVID-19 in moderately or severely immunocompromised patients [1]

According to the FDA Emergency Use Authorization of Evusheld, medical conditions or treatments that may result in moderate to severe immune compromise include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, chancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization of Evusheld™. Available at: https://www.fda.gov/media/154701/download. Accessed 22 December 2021.

Figure 2. FDA EUA criteria for the use of tixagevimab/cilgavimab for pre-exposure prophylaxis of COVID-19 [1]

This EUA for the use of the unapproved products tixagevimab and cilgavimab for pre-exposure prophylaxis in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are:

- Not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **AND**:
    - have moderate to severe immune compromise due to a medical condition **OR** receipt of immunosuppressive medications or treatments **AND** may not mount an adequate immune response to COVID-19 vaccination **OR**
    - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or a COVID-19 vaccine component(s).

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization of Evusheld™. Available at: https://www.fda.gov/media/154701/download. Accessed 22 December 2021.

Neutralizing antibodies for post-exposure prophylaxis

As the pandemic progressed, new SARS CoV-2 variants emerged with reduced susceptibility to various anti-SARS-CoV-2 neutralizing antibodies in assays performed using infectious (also referred to as authentic) and pseudotyped viruses. The first two authorized anti-SARS-CoV-2 neutralizing antibody combinations, bamlanivimab/etesevimab and casirivimab/imdevimab, were found to be largely inactive against the Omicron BA.1 and BA.2 variants, rendering these products no longer useful for either treatment or post-exposure prophylaxis.

As a result, Emergency Use Authorization was withdrawn by the US FDA for both bamlanivimab/etesevimab and casirivimab/imdevimab, leaving no available neutralizing antibody product for use in the United States for post-exposure prophylaxis. Should new variants become susceptible to an existing neutralizing antibody or should newly developed, more susceptible neutralizing antibodies be authorized for post-exposure prophylaxis, the panel will offer recommendations regarding use.

For areas of the world where a significant proportion of circulating variants retain susceptibility to at least one neutralizing antibody authorized for post-exposure prophylaxis, use could be considered. However, data are scarce on how susceptibility reductions affect clinical efficacy, relative to that observed prior to emergence of novel variants.

Why are neutralizing antibodies considered for prophylaxis?

Neutralizing antibodies directed at the receptor-binding domain of SARS-CoV-2 spike protein have been evaluated as prophylactic agents for COVID-19. In animal models there is evidence that antibody therapy may more rapidly reduce viral load in the upper and lower airways of infected animals resulting in reduced viral-induced pathology, demonstrating *in vivo* prophylactic and treatment efficacy [1, 2]. Additionally, antibody mediated enhancement of disease, a theoretical adverse effect of neutralizing antibody prophylaxis, has not been detected in animal models or seen in clinical studies [2]. In a large, randomized study of unvaccinated nursing home patients and staff where there was at least one confirmed case of

COVID-19 at the facility, a single dose of bamlanivimab appeared to significantly reduce the incidence of “mild or worse” COVID-19 among the nursing home residents [3].

Potential advantages of neutralizing antibodies include the ability to standardize the amount of neutralizing activity and the possibility of conferring protection more rapidly than with vaccine-induced immune responses (which generally take several weeks).

Emergence of SARS-CoV-2 variants resistant to neutralizing antibodies

As the pandemic progressed, new SARS CoV-2 variants emerged with reduced susceptibility to various anti-SARS-CoV-2 neutralizing antibodies in assays performed using infectious (also referred to as authentic) and pseudotyped viruses. For example, the first two authorized neutralizing antibody combinations, bamlanivimab/etesevimab and casirivimab/imdevimab, were found to be largely inactive against the Omicron BA.1 and BA.2 variants.

During the course of 2022, multiple Omicron sub-variants emerged with progressively increased resistance to multiple neutralizing antibodies including to the combination of tixagevimab/cilgavimab. Throughout most of 2022, tixagevimab/cilgavimab was recommended for the prevention of SARS-CoV-2 in persons at high risk of not responding to SARS-CoV-2 vaccination and of developing severe COVID-19 infection because most Omicron sub-variants retained some degree of in vitro tixagevimab/cilgavimab susceptibility and because there are no alternative pharmacological options for preventing SARS-CoV-2 infection. However, with the emergence in the US in late 2022 of Omicron sub-variants with >100 to >1000-fold reduced susceptibility to tixagevimab/cilgavimab, the markedly reduced benefits of prophylaxis ceased to outweigh the small but known risk of adverse effects. Furthermore, use when predominant regional variants are resistant would offer a false sense of security and require clinical resources that could better be spent elsewhere.

Summary of the evidence

<u>Tixagevimab/cilgavimab</u>

Our search identified one randomized controlled trial (RCT) reporting on pre-exposure prophylaxis (PrEP) with a single dose of intramuscular tixagevimab/cilgavimab administration in adults ≥18 years of age who are at increased risk of inadequate response to COVID-19 vaccination or SARS-CoV-2 infection [4, 5]. Patients included were those that were either age ≥60 years, immunocompromised, had severe renal or liver impairment, COPD, or those who had an increased risk of exposure including those working in healthcare or living in congregate living settings. All participants had a negative SARS-CoV-2 serology test result at screening, had no history of SARS-CoV-2 infection, and had not received vaccine or biologic indicated for prevention of SARS-CoV-2 or COVID-19. Study participants received a single combined 300 mg intramuscular dose of the combination of tixagevimab (150 mg)/cilgavimab (150 mg).

Benefits

Tixagevimab/cilgavimab

PrEP with tixagevimab/cilgavimab appears to have little or no effect on mortality through a median of 6 months (RR: 0.50; 95% CI: 0.13, 2.0; absolute risk reduction: 1 fewer per 1,000 [from 2 fewer to 2 more]; moderate CoE). Symptomatic COVID-19 infection within six months after administration was reduced in those who received tixagevimab/cilgavimab compared to placebo (RR: 0.18; 95% CI: 0.09, 0.35; moderate CoE).

Tixagevimab/cilgavimab

Serious adverse events were not meaningfully different in those that received PrEP with tixagevimab/cilgavimab compared to placebo (RR: 1.09; 95% CI: 0.67, 1.78; moderate CoE).

Other considerations

Tixagevimab/cilgavimab

The panel agreed that the overall certainty of evidence for PrEP with tixagevimab/cilgavimab was low due to concerns with the generalizability of the trial population to the FDA-authorized indications (e.g., immunocompromised persons) and low number of events (fragility of results). The panel noted concerns with feasibility at different centers given the large number of potentially eligible individuals and supply constraints.

Table 1. GRADE evidence profile, Recommendation 1

Question: Tixagevimab/cilgavimab compared to no tixagevimab/cilgavimab for pre-exposure prophylaxis in adults at increased risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tixagevimab/ cilgavimab	no tixagevimab/ cilgavimab	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: median 6 months)												
1[1,2]	randomized trials	not serious [a]	not serious	serious [b,c]	serious [d]	none	4/3461 (0.1%)	4/1736 (0.2%)	**RR 0.50** (0.13 to 2.00)	**1 fewer per 1,000** (from 2 fewer to 2 more)	⨁⨁◯◯ LOW	CRITICAL
Symptomatic COVID-19 (follow-up: median 6 months; assessed with: RT-PCR-positive symptomatic illness)												
1[1,2]	randomized trials	not serious	not serious	serious [c]	serious [d]	none	11/3441 (0.3%)	31/1731 (1.8%)	**HR 0.17** (0.08 to 0.33)	**15 fewer per 1,000** (from 16 fewer to 12 fewer)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow-up: median 83 days)												
1[1,2]	randomized trials	not serious	not serious	serious [c]	serious [d]	none	50/3461 (1.4%)	23/1736 (1.3%)	**RR 1.09** (0.67 to 1.78)	**1 more per 1,000** (from 4 fewer to 10 more)	⨁⨁◯◯ LOW	CRITICAL

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations

Inconsistency: Unexplained heterogeneity across study findings

Indirectness: Applicability or generalizability to the research question

Imprecision: The confidence in the estimate of an effect to support a particular decision

Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio

Explanations

a. Possible misclassification bias due to unequal rate of drop-outs after unblinding.
b. 2 deaths in the control arm were attributed to COVID-19.
c. Trial population indirect to the population indicated within the FDA EUA (e.g., immunocompromised).
d. Small number of events; fragility present.

References

1. U.S. Food and Drug Administration. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab). Available at: https://www.fda.gov/media/154701/download. Accessed 22 December 2021.
2. Levin M, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab/cilgavimab) for prevention of COVID-19. **2021**: [Under review].

Supplementary Materials

Neutralizing Antibodies for Prophylaxis

Table s1. Should tixagevimab/cilgavimab vs. no tixagevimab/cilgavimab be used for pre-exposure prophylaxis in adults at risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended?

Study/ year	Country/ hospital	Study design	N subjects (intervention /comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Levin/2021[1]	87 sites in Belgium, France, Spain, UK and US	RCT	5197 (3461/1736)	46.1	53.5 (15.0)	Adult patients at increased risk for inadequate COVID-19 vaccine response or increased risk of SARS-CoV-2 infection with negative SARS-CoV-2 serology	Tixagevimab/ cilgavimab 300 mg x 1 dose	Placebo	None	Mortality PCR positive symptomatic illness occurring post dose through day 183 Serious adverse events	AstraZeneca US Department of Health and Human Services US Biomedical Advanced Research and Development Authority

Table s2. Risk of bias for randomized controlled studies (pre-exposure tixagevimab/cilgavimab vs. no tixagevimab/cilgavimab in adults at risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Levin 2021 [1]							

Low	High	Unclear

Reference

1. Levin M, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab/cilgavimab) for prevention of COVID-19. **2021**: [Under review].

References

1. Jones BE, Brown-Augsburger PL, Corbett KS, et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. bioRxiv **2020**: Available at: https://doi.org/10.1101/2020.09.30.318972 [Preprint 9 October 2020].
2. Baum A, Ajithdoss D, Copin R, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science **2020**; 370(6520): 1110-5.
3. Cohen MS, Nirula A, Mulligan MJ, et al. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. JAMA **2021**; 326(1): 46-55.
4. U.S. Food and Drug Administration. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab). Available at: https://www.fda.gov/media/154701/download. Accessed 22 December 2021.
5. Levin M, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab/cilgavimab) for prevention of COVID-19. **2021**: [Under review].