Neutralizing Antibodies for Pre- and Post-Exposure Prophylaxis

Section last reviewed and 5/23/2022

Last literature search conducted 4/30/2022

Resources:

- **CDC**: SARS-CoV-2 variants
- **FDA**: Qualifications for SARS-CoV-2 exposure
- **FDA**: EUA for Evusheld™ (tixagevimab co-packaged with cilgavimab)
- **NIH**: National Center for Advancing Translational Science

Recommendation 1 (UPDATED 5/23/2022): In moderately or severely immunocompromised individuals* at increased risk for inadequate immune response to COVID-19 vaccine or for persons whom COVID-19 vaccine is not recommended due to a documented serious adverse reaction to the vaccine, the IDSA guideline panel suggests pre-exposure prophylaxis with tixagevimab/cilgavimab rather than no tixagevimab/cilgavimab, when predominant regional variants are susceptible to the agent (Conditional recommendation, Low certainty of evidence)

Remarks:

- Dosing for tixagevimab/cilgavimab is 300 mg of tixagevimab and 300 mg of cilgavimab administered as two separate consecutive intramuscular injections once.

See **Figure 1 below*

Real-time weekly updates to regional circulating variant proportions can be found here: CDC COVID Data Tracker: Variant Proportions

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.

Recommendation 2 (UPDATED 5/23/2022): In persons exposed to COVID-19 who are at high risk of progression to severe COVID-19, the IDSA guideline panel suggests against post-exposure casirivimab/imdevimab, unless predominant regional variants are susceptible to the agent. (Conditional recommendation, Low certainty of evidence)

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).

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

In a meta-analysis published as a preprint, the combination of tixagevimab/cilgavimab displayed a median 86-fold (IQR: 27-151) reduction in activity against Omicron BA.1 in 15 studies, and a median 5.4-fold (IQR: 3.7-6.9) reduction in activity against Omicron BA.2 in six studies.

As a result of the reduced susceptibility of tixagevimab/cilgavimab to the BA.1 variant, the FDA recommended on February 24, 2022, that the dosage for each mAb in this combination be increased from 150 mg to 300 mg intramuscularly.

Summary of the evidence

Tixagevimab/cilgavimab

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).

Casirivimab/imdevimab

Our search identified one RCT reporting on post-exposure prophylaxis (PEP) with neutralizing antibodies (combination of casirivimab/imdevimab) for patients exposed to COVID-19 who are at high risk of progression to severe disease [6] (**Table 2**).

One RCT reported on 1,505 persons testing negative for SARS-CoV-2 infection (by reverse-transcriptase-quantitative polymerase-chain-reaction assay [RT-qPCR]) within 96 hours following household contact with a diagnosis of SARS-CoV-2 infection [6]. Of those included in the trial, 30.5% participants were categorized as having a high risk of COVID-19 (e.g., ≥65 years of age, body mass index [BMI] ≥35, chronic kidney disease, etc.). Participants in the treatment group received a total dose of 1200 mg of casirivimab/imdevimab subcutaneously.

Benefits

Tixagevimab/cilgavimab

PrEP with tixagevimab/cilgavimab appears to have little or no effect on mortality through a median of 6 months (risk ratio [RR]: 0.50; 95% confidence interval [CI]: 0.13, 2.0; absolute risk reduction: 1 fewer per 1,000 [from 2 fewer to 2 more]; moderate certainty of evidence [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).

Casirivimab/imdevimab

Persons receiving post-exposure prophylaxis with casirivimab/imdevimab reduced symptomatic SARS-CoV-2 infection from 7.8% to 1.5% (RR: 0.19; 95% CI: 0.10, 0.35; moderate

CoE). Of the 70 persons who developed symptomatic infection, those who received casirivimab/imdevimab rather than placebo experienced a shorter duration of symptoms (mean difference [MD]: -2.0 weeks; 95% CI: -2.91, -1.09; low CoE).

Harms

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).

Casirivimab/imdevimab

Serious treatment-emergent adverse events may be less frequent among persons receiving casirivimab/imdevimab compared to those receiving placebo; however, this may not be meaningfully different from those receiving placebo (RR: 0.66; 95% CI: 0.30, 1.47; low 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.

Casirivimab/imdevimab

The panel agreed that the overall certainty of evidence for post-exposure prophylaxis with casirivimab/imdevimab was low due to low number of events (fragility of results). The panel notes some indirectness between the trial participants (30.5% with any high-risk factor for COVID) and the current approved indications for post-exposure prophylaxis within the EUA.

Conclusions and research needs for this recommendation

Tixagevimab/cilgavimab

The guideline panel suggests PrEP with tixagevimab/cilgavimab in moderately or severely immunocompromised individuals at increased risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended due to documented severe reactions to the COVID-19 vaccine. Data on the efficacy of pre-exposure prophylaxis specifically in immunocompromised individuals who have received COVID-19 vaccines are needed.

Casirivimab/imdevimab

The guideline panel suggests against post-exposure casirivimab/imdevimab, unless predominant regional variants are susceptible to the agent

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

New evidence profile developed 12/23/2021

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].

Table 2. GRADE evidence profile, Recommendation 2

Question: Prophylactic casirivimab/imdevimab compared to no prophylactic casirivimab/imdevimab for persons exposed to COVID-19 at high risk for progression to severe disease

Developed 8/17/2021; last reviewed 9/19/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prophylactic casirivimab /imdevimab	no prophylactic casirivimab/ imdevimab	Relative (95% CI)	Absolute (95% CI)		
Symptomatic SARS-CoV-2 infection (1,200 mg SC) (follow-up: 28 days; assessed with: RT-qPCR plus broad-term definition)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	11/753 (1.5%)	59/752 (7.8%)	**RR 0.19** (0.10 to 0.35)	**64 fewer per 1,000** (from 71 fewer to 51 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of symptomatic infection (1,200 mg SC)												
1 [1]	randomized trials	not serious	not serious	not serious	very serious [a]	none	11	59	-	**MD 2 weeks fewer** (2.91 fewer to 1.09 fewer)	⨁⨁◯◯ LOW	CRITICAL
COVID-19 related hospitalizations or ER visits (1,200 mg SC) (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious [b]	very serious [a,c]	none	0/753 (0.0%)	4/752 (0.5%)	**RR 0.11** (0.01 to 2.06)	**5 fewer per 1,000** (from 5 fewer to 6 more)	⨁⨁◯◯ LOW	CRITICAL
Serious treatment-emergent adverse events (1,200 mg SC) (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	serious [d]	serious [a,c]	none	10/1311 (0.8%)	15/1306 (1.1%)	**RR 0.66** (0.30 to 1.47)	**4 fewer per 1,000** (from 8 fewer to 5 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; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Small number of events; fragility present
b. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down.
c. 95% CI cannot exclude meaningful harm
d. Serious treatment emergent adverse events reported for entire study population (including symptomatic and asymptomatic) and may not be generalizable to seronegative population.

Reference

1. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med **2021**; 385: 1184-95.

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].
6. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med **2021**; 385: 1184-95.

Supplementary Materials

Study characteristics

- **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?
- **Table s2.** Should persons exposed to COVID-19 who are at high risk of progression to severe disease receive post-exposure casirivimab/imdevimab vs. no casirivimab/imdevimab?

Risk of bias

- **Table s3a.** Randomized controlled studies (pre-exposure tixagevimab/cilgavimab vs. no pre-exposure tixagevimab/cilgavimab)
- **Table s3b.** Randomized controlled studies (post-exposure casirivimab/imdevimab vs. no post-exposure casirivimab/imdevimab)

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. Should persons exposed to COVID-19 who are at high risk of progression to severe disease receive post-exposure casirivimab/imdevimab vs. no casirivimab/imdevimab?

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
O'Brien/ 2021 [2] Part A	United States (110 sites) Romania (1 site) Moldova (1 site)	RCT	1505 (753/752)	54.1	Mean: 42.9 (range of 12-92)	Previously and currently uninfected (RT-PCR negative) household contacts of persons with SARS CoV-2 infection	REGEN-COV 1200 mg (casirivimab 600 mg /imdevimab 600 mg) x 1 subcutaneous injection	Placebo	None	Symptomatic RT-PCR confirmed SARS-CoV-2 infection within 28 days Symptomatic and asymptomatic RT-PCR confirmed infection within 28 days Number of weeks of symptoms present Number of weeks of high viral load COVID-19 related hospitalization or ER visit Safety	Regeneron Pharmaceuticals F. Hoffman-La Roche COVID-19 Prevention Network grant, which is funded by cooperative awards from National Institute of Allergy and Infectious Diseases and National Institutes of Health
O'Brien/ 2021 [3] Part B	United States (110 sites) Romania (1 site) Moldova (1 site)	RCT	314 (155/156)	55	Mean: 40.9 (18)	RT-PCR positive for SARS CoV-2 and asymptomatic	REGEN-COV 1200 mg (casirivimab 600 mg /imdevimab 600 mg) x 1 subcutaneous injection	Placebo	None	Proportion of patients who developed signs and symptoms of COVID-19 within 14 days of positive RT-PCR Number of weeks of symptomatic	Regeneron Pharmaceuticals F. Hoffman-La Roche COVID-19 Prevention Network grant, which is funded

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
										SARS CoV-2 infection Number of weeks of high viral load over 28 days COVID-19 related hospitalization or ER visit Safety	by cooperative awards from National Institute of Allergy and Infectious Diseases and National Institutes of Health

Table s3a. 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

Table s3b. Risk of bias for randomized controlled studies (post-exposure casirivimab/imdevimab vs. no casirivimab/imdevimab for persons exposed to COVID-19 at risk of progression to severe disease)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
O'Brien 2021 (Part A) [2]							
O'Brien 2021 (Part B) [3]							

Low	High	Unclear

References for Supplementary Materials

1. Levin M, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab/cilgavimab) for prevention of COVID-19. **2021**: [Under review].
2. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med **2021**; 385: 1184-95.
3. O'Brien MP, Forleo-Neto E, Sarkar N, et al. Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial. JAMA **2021**; 327(5): 432-41.