Clinical Infectious Diseases

IDSA GUIDELINES

2025 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Treatment and Management of COVID-19: Vilobelimab

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This article provides a focused update to the clinical practice guideline on the treatment and management of patients with COVID-19, developed by the Infectious Diseases Society of America. The guideline panel presents a recommendation on the use of vilobelimab in hospitalized adults with critical COVID-19. The recommendation is based on evidence derived from a systematic literature review and adheres to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.

Keywords. COVID-19; SARS-CoV-2; vilobelimab; monoclonal antibody; guideline

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In adults hospitalized with critical COVID-19, should vilobelimab compared to no vilobelimab be added to standard care?

Recommendation: In hospitalized adults with critical COVID-19* requiring mechanical ventilation or ECMO, the IDSA guideline panel recommends vilobelimab only in the context of a clinical trial *(knowledge gap)*.

*Critical illness is defined as patients on mechanical ventilation and/or ECMO.

BACKGROUND

Vilobelimab is a monoclonal antibody that targets C5a, a component of the complement system, which is known to play a key role in the excessive inflammation seen in critical COVID-19 cases [1]. C5a has been found to be elevated in patients with critical COVID-19, contributing to acute respiratory distress syndrome (ARDS) and end organ failure [2]. A study in mice demonstrated that an anti-C5a monoclonal antibody can reduce immune system activation and inhibit lung injury [3]. Vilobelimab specifically binds to C5a and blocks its interaction with the C5a receptor, thereby inhibiting its pro-inflammatory effects. By targeting this pathway, vilobelimab reduces the inflammatory response without compromising the rest of the immune system.

On April 4, 2023, the FDA issued an Emergency Use Authorization for the use of vilobelimab to treat COVID-19 in hospitalized adults, specifically when administered within 48 hours of mechanical ventilation or extracorporeal membrane oxygenation [4]. This authorization was based on results of the PANAMO trial [5].

In this focused update to the 2023 guideline [6], a recommendation is provided for vilobelimab. The primary audience for this recommendation is clinicians treating hospitalized adults with critical COVID-19.

METHODS

The panel's recommendation is based upon a systematic review of available evidence and adheres to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach (Supplementary Figure 1) [7]. The recommendation has been endorsed by the Society of Infectious Diseases Pharmacists, the Society for Healthcare Epidemiology of America, and the Society of Critical Care Medicine.

Strong recommendations are made when the recommended course of action would apply to most people with few exceptions. Conditional recommendations are made when the suggested course of action would apply to the majority of people with many exceptions and shared decision making is important.

Literature searches (up to November 2024) were conducted as part of a systematic review. Key eligibility criteria at both the topic and clinical question levels guided the selection of studies for inclusion. For this clinical question, only hospitalized adults were included. The primary comparison of interest was vilobelimab versus no vilobelimab.

A critical appraisal of the evidence according to the GRADE approach, along with an assessment of the benefits and harms of care options, informed the recommendation(s) [7,8]. Details of the systematic review and guideline development processes are available in the Supplementary Material.

SUMMARY OF EVIDENCE

The search identified 2 randomized controlled trials that reported on adults ≥18 years with critical COVID-19 who were randomized to treatment with vilobelimab (800 mg IV) or placebo/best supportive care (Supplementary Table 1) [5,9]. One phase 2 open-label, multicenter trial (n=30) treated patients in the vilobelimab arm with a maximum of 7 doses of 800 mg IV. In the subsequent blinded, placebo-controlled, phase 3 trial, PANAMO (n=369), patients were treated with a maximum of 6 doses of vilobelimab 800 mg IV. Of participants in the PANAMO trial, approximately 17% received treatment with tocilizumab, 6% with remdesivir, and 3% with baricitinib. These trials reported on the outcomes of mortality at 28 days and serious adverse events (Table 1).

Table 1. GRADE Evidence Profile: In adults hospitalized with critical COVID-19, should vilobelimab compared to no vilobelimab be added to standard care?

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vilobelimab	no vilobelimab	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mortality (follow-up: 28 days)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	vilobelimab	no vilobelimab	Relative (95% CI)	Absolute (95% CI)		
2[5,9]	randomized trials	not serious	not serious	not serious[a]	very serious[b,c]	none	56/192 (29.2%)	81/206 (39.3%)	**HR 0.73** (0.50 to 1.05)	**88 fewer per 1,000** (from 172 fewer to 15 more)	⨁◯◯ Low	CRITICAL

Serious adverse events (follow-up: 21 days)

2[5,9]	randomized trials	not serious	not serious	not serious[a]	very serious[d]	none	112/190 (58.9%)	127/204 (62.3%)	**RR 0.95** (0.81 to 1.11)	**31 fewer per 1,000** (from 118 fewer to 68 more)	⨁◯◯ Low	CRITICAL

CI: confidence interval; **HR**: hazard ratio; **RR:** risk ratio

Explanations

a. Not rated down for indirectness; however, clinical trials excluded immunocompromised persons and limited administration of study drug to participants receiving invasive mechanical ventilation within 48 hours before vilobelimab infusion.

b. Few events do not meet optimal information size and suggest fragility of the estimate.

c. 95% CI includes potential for reduction in mortality, as well as no meaningful difference with 1% mortality threshold.

d. 95% CI crosses multiple thresholds and cannot exclude the possibility of harm.

BENEFITS

Among hospitalized patients, vilobelimab showed a trend toward reduced mortality at 28 days compared to no vilobelimab treatment (HR: 0.73; 95% CI: 0.50, 1.05; Supplementary Figure 2).

HARMS

Serious adverse events among patients receiving vilobelimab did not differ from those receiving usual care (RR: 0.95; 95% CI: 0.81, 1.11; Supplementary Figure 3).

OTHER CONSIDERATIONS

The panel agreed that the overall certainty of evidence was low (Table 1, Supplementary Table 2), given the sparseness in mortality data and because the upper boundary of the 95% CI failed to exclude the risk of possible harms. The panel also expressed concerns regarding the generalizability and indirectness of the results, as both studies excluded immunocompromised populations, had fewer than 33 participants concomitantly receiving tocilizumab or baricitinib, and were conducted during time periods with different circulating variants of COVID-19 than now. Further concerns included the potential toxicity and uncertain efficacy of adding vilobelimab to other immunomodulators (e.g., baricitinib or tocilizumab) for which there is greater evidence for benefit. The panel also examined the post-hoc, subgroup analysis of vilobelimab given with tocilizumab or baricitinib but recognized the need for more information, given the small number of patients in the subgroup (34 vilobelimab versus 37 placebo) [10]. Additionally, the panel noted the post hoc analysis of vilobelimab's effect by sepsis phenotypes and concluded that future prospective studies are necessary to validate these findings and establish their clinical utility [11].

Because the studies excluded patients <18 years, no statement of benefits vs. harms can be made for this age group.

CONCLUSIONS AND RESEARCH NEEDS

The guideline panel recommends vilobelimab only in the context of a clinical trial. Additional data are needed to assess the efficacy and toxicity of vilobelimab when given to patients receiving

tocilizumab or baricitinib, immunomodulators for which there is greater evidence of benefit. More information is needed to assess the efficacy and adverse events of vilobelimab in people who are immunocompromised. In addition, more research is needed on the effects of vilobelimab when given after 48 hours of intubation, which may better represent current clinical practice. Further studies should focus on exploring whether certain subgroups could consistently and reliably benefit more from targeted treatment.

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Drs. Adarsh Bhimraj and Rajesh T. Gandhi are chair and vice chair of the panel, respectively. The Hospitalized Patients subgroup, under the leadership of Dr. Nandita Nadig, led the development of the recommendation. Remaining panelists assisted with interpretation of data, as well as drafting, revising, and approving the recommendation and manuscript. Drs. Rebecca Morgan, lead methodologist, and Yngve Falck-Ytter, methodologist, were responsible for designing and performing the data analyses and leading the panel according to the GRADE process. Jennifer Loveless, methodologist, was responsible for project planning and management, including revisions to and final approval of the recommendation and manuscript.

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Possible conflicts of interest. Evaluation of relationships as potential conflicts of interest is determined by a review process. The assessment of disclosed relationships for possible COIs is based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The following panelists have scientific advisory/consultant roles with indicated companies that are not related to the topic of COVID-19: R.B. with Merck and Gilead, E.D. with Gilead, D.G. with Merck and Gilead, S. S. with Pfizer (concluded), P.T. with Merck, and R.G. with Merck. The following panelists have scientific advisory/consultant roles with indicated companies that are related to COVID-19 but not critical COVID-19: R.B. with Shionogi, K.C. with Pardes Biosciences (concluded), A.K. with Shionogi, S.S. with Adamis and Immunome (concluded), and P.T. with Shionogi. J.P. had a scientific advisory/consultant role (concluded) with InflaRx related to vilobelimab. His participation was carefully managed during discussions, and he recused from all voting. No disclosures were reported for all other authors (the majority of panelists), including chair and vice chair.

Additional Information: More detailed information on the analysis and development of the recommendation is available in the Supplementary Material.

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