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

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ABSTRACT. 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 abatacept in hospitalized adults with severe or 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; abatacept; guideline

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In patients hospitalized with severe or critical COVID-19 receiving systemic glucocorticoids, should abatacept compared to no abatacept be added to standard care?

Recommendation: In hospitalized adults receiving systemic glucocorticoids who are experiencing severe, rapidly progressing COVID-19* or critical COVID-19**, when baricitinib and tocilizumab are not available, the IDSA guideline panel suggests abatacept rather than no abatacept *(conditional recommendation, low certainty of evidence)*.

*Severe, rapidly progressing illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen who are worsening despite treatment with systemic glucocorticoids.

**Critical illness is defined as patients requiring high-flow nasal cannula oxygen/non-invasive ventilation or invasive mechanical ventilation or ECMO.

BACKGROUND

Abatacept is a recombinant fusion protein (cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] linked to human immunoglobulin) that is used to block T cell activation [1]. CTLA-4 is a protein

receptor that is expressed by activated T cells. By mediating inhibitory signals, this receptor can decrease T cell proliferation and cytokine production [2]. This mechanism helps suppress immune responses, making it valuable for treating autoimmune conditions. Abatacept is FDA-approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis, and the prevention of acute graft versus host disease [3,4]. Excessive T cell stimulation and proliferation was thought to contribute to the pathogenesis of COVID-19, and hence, abatacept was considered as a potential option for treating COVID-19 by modulating the T cell response [5]. Although abatacept is not approved for the treatment of COVID-19, it has been evaluated in clinical trials for the treatment of hospitalized patients with moderate to severe COVID-19 [6].

In this focused update to the 2023 guideline [7], a recommendation is provided for abatacept. The primary audience for this recommendation is clinicians treating hospitalized adults with severe or 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) [8]. The recommendation has been endorsed by the Pediatric Infectious Diseases Society, Society for Healthcare Epidemiology, 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.

A literature search was conducted in August 2024 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 abatacept versus no abatacept.

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) [8,9]. Details of the systematic review and guideline development processes are available in the Supplementary Material.

SUMMARY OF EVIDENCE

The search identified one randomized controlled trial (N=1049), ACTIV-1 IM, that reported on adults 18 years or older with severe COVID-19 who were randomized into treatment with abatacept (10 mg/kg, maximum dose 1000 mg) plus standard of care or standard of care alone (Supplementary Table 1) [6]. Standard of care across the treatment and control arms included remdesivir (93-94%), corticosteroids (89-93%), tocilizumab (3%), and baricitinib (1-3%). Though the primary endpoint of the study was time to recovery, this trial also reported on the outcomes of mortality at 28 days, recovery at 28 days (assessed by the first day a hospitalized participant did not require oxygen or ongoing care, or patient was not hospitalized with or without limitations on activities, i.e., categories 6, 7, or 8 on an 8-point ordinal scale), and serious adverse events (Table 1).

Table 1. GRADE Evidence Profile: In patients hospitalized with severe or critical COVID-19 receiving systemic glucocorticoids, should abatacept compared to no abatacept be added to standard care?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	abatacept	no abatacept	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 28 days)												
1 [6]	randomized trials	not serious	not serious	not serious[i]	very serious[a,b]	none	56/509 (11%)	77/510 (15.1%)	**RR 0.73** (0.53 to 1.01)[c]	**41 fewer per 1,000** (from 71 fewer to 2 more)	⨁⨁◯◯ Low[a,b]	CRITICAL
Recovery (follow-up: 28 days; assessed with: first day a hospitalized participant did not require oxygen or on-going care or patient was not hospitalized with or without limitations on activities)[d]												
1 [6]	randomized trials	not serious	not serious	not serious[i]	serious[e]	none	414/524 (79.0%)	397/525 (75.6%)	**HR 1.12** (0.98 to 1.28)[f]	**38 more per 1,000** (from 7 fewer to 80 more)	⨁⨁⨁◯ Moderate[e]	CRITICAL
Serious adverse events (assessed with: death, life-threatening AE, new/prolonged hospitalization, persistent/significant incapacity/substantial disruption of normal life functions, congenital anomaly/birth defect)												
1 [6]	randomized trials	not serious	not serious	not serious[i]	very serious[g]	none	128/509 (25.1%)	136/510 (26.7%)	**RR 0.94** (0.77 to 1.16)[h]	**16 fewer per 1,000** (from 61 fewer to 43 more)	⨁⨁◯◯ Low[g]	CRITICAL

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

Explanations

a. 95% CI cannot exclude the potential for no mortality benefit.
b. Events do not meet optimal information size and suggests fragility in the estimate.
c. OR in O'Halloran was 0.62 (0.41-0.94). Analyzed as binary endpoints using a logistic regression model with an indicator variable for treatment group, geographic region, baseline disease severity on the 8-point ordinal scale, age, and sex
d. Equivalent to categories 6, 7, or 8 on the study's 8-point ordinal scale.
e. 95% CI cannot exclude no meaningful difference in recovery.
f. Recovery rate ratio (RRR), similar to a hazard ratio.
g. 95% CI cannot exclude the potential for harms for total SAEs or SAEs related to abatacept.
h. All SAEs reported. SAEs reported by site PIs as related to the study drug: abatacept = 9/509, placebo = 7/510 (RR=1.29; 95% CI: 0.48, 3.43).
i. O'Halloran included patients 18 years or older

BENEFITS

Among hospitalized patients, abatacept showed a trend toward reduced mortality at 28 days compared to no abatacept treatment (RR: 0.73; 95% CI: 0.53, 1.01; low certainty of evidence). In addition, patients receiving abatacept trended toward improved recovery as measured by improvement to hospitalization without oxygen requirements or release from the hospital (HR: 1.12; 95% CI: 0.98, 1.28; moderate certainty of evidence).

HARMS

Serious adverse events among patients receiving abatacept did not differ from those receiving usual care (RR: 0.94; 95% CI: 0.77, 1.16; low certainty of evidence). The low certainty of evidence was due to very serious concerns with imprecision, reflecting both the wide confidence interval, which includes appreciable benefits and possible harms, and few reported events.

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 95% confidence intervals cannot exclude the potential for no meaningful difference in mortality, recovery, and serious adverse events. Regarding the definition of severe, rapidly progressing COVID-19, the panel recognizes that SpO_2 alone may not always correlate with disease severity, and the recommendation should be interpreted in the clinical context of the patient.

There is limited human data on the use of abatacept in pregnancy and its use in pregnancy has generally been avoided. However, in the small number of pregnancy exposures reported (n = 161), there is no indication that it increases the risk of miscarriage or birth defects [10]. The large size of the molecule and poor absorption in the gut suggests that there is minimal infant exposure via breastmilk ingestion [11]. Use of abatacept in the setting of COVID-19 for pregnant patients is reasonable if benefits clearly outweigh potential risks.

CONCLUSIONS AND RESEARCH NEEDS

Head-to-head comparisons of baricitinib, tocilizumab, abatacept, and infliximab in patients with severe, rapidly progressing COVID-19 and critical COVID-19 would be informative. It is also uncertain whether a combination of two or more immunomodulatory agents (i.e., baricitinib, tocilizumab, abatacept, infliximab) offers additional mortality or recovery benefits. Additionally, the efficacy of abatacept has not been evaluated in children or adolescents with severe or critical COVID-19. Future studies evaluating abatacept for COVID-19 should consider enrolling children and adolescents, particularly given the pediatric experience with abatacept and available pediatric dosing recommendations for non-COVID-19 indications.

The guideline panel suggests abatacept in hospitalized adults receiving systemic glucocorticoids who are experiencing severe, rapidly progressing COVID-19 or critical COVID-19, when baricitinib and tocilizumab are not available.

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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). No panelists had COIs directly related to abatacept. The following panelists have scientific advisory/consultant roles not related to the topic of COVID-19 with indicated companies: 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 related to COVID-19 but not severe/critical COVID-19 with indicated companies: 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 for critical COVID-19. 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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