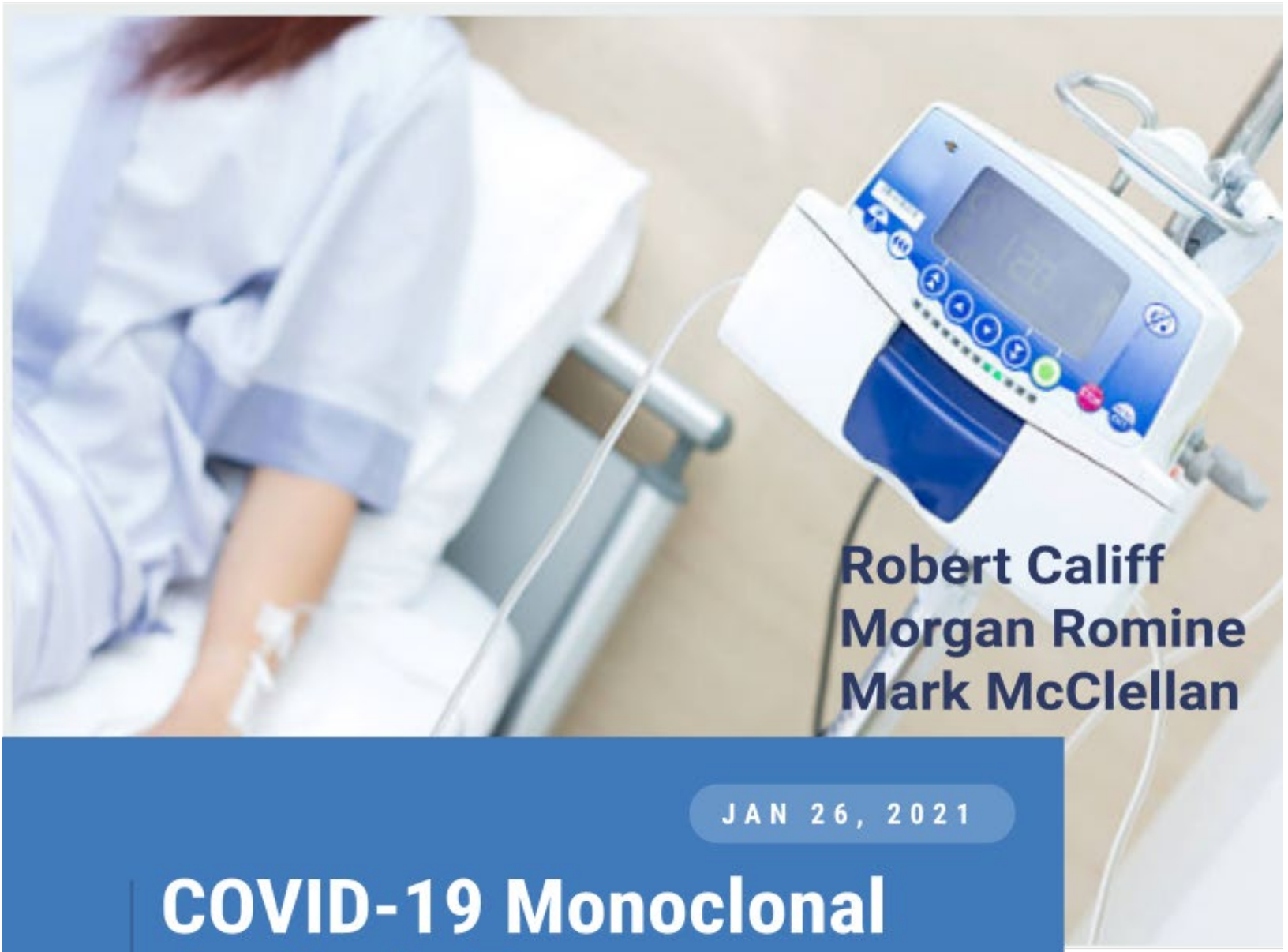
Duke | Robert J. Margolis, MD Center *for* Health Policy



Robert Califf
Morgan Romine
Mark McClellan

JAN 26, 2021

COVID-19 Monoclonal Antibody Treatments: Using Evolving Evidence to Improve Care in the Pandemic

Authors

Robert Califf, Verily Life Sciences and Google Health

Mark McClellan, Duke-Margolis Center

Morgan Romine, Duke-Margolis Center

Acknowledgements

The authors thank the following experts for their ongoing contributions to our work on monoclonal antibodies:

Alpesh Amin, UC Irvine
Brian Anderson, MITRE
Tom Andriola, UC Irvine
Derek Asay, Eli Lilly and Company
Andrew Badley, Mayo Clinic
Maya Bermingham, Regeneron
Daniela Bota, UC Irvine
Sree Chaguturu, CVS Health
Daniel Chow, UC Irvine
William Fales, Michigan Department of Health and Human Services
Vicky Fraser, Washington University
Carl Garner, Eli Lilly and Company
John Halamka, Mayo Clinic
Adrian Hernandez, Duke University
Tricia Lacavich, Coram
Richard Migliori, UnitedHealth Group
Marion McCourt, Regeneron
Karla Miller, HCA
Steve Miller, Cigna
Brian Nyquist, National Infusion Center Association
Greg Paulsen, Intermountain Healthcare
Christian Ramers, Family Health Centers of San Diego
Saif Rathore, Evernorth
Kristin Russell, Humana
Kenneth Sands, HCA
Connie Sullivan, National Home Infusion Association
Will Shrank, Humana
Brandon Webb, Intermountain Healthcare
Janet Woodcock, FDA
Scott Wright, Mayo Clinic

Dr. McClellan, who directs the Duke-Margolis Center for Health Policy, was Commissioner of the Food and Drug Administration from 2002-04 and Administrator of the Centers for Medicare and Medicaid Services from 2004-06. He is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomIQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.

Duke | MARGOLIS CENTER for Health Policy

COVID-19 Monoclonal Antibodies: Using Evolving Evidence to Improve Care in the Pandemic

January 27, 2021

This Duke-Margolis resource on COVID-19 response policies is intended to inform and help guide policy makers addressing the evolving COVID-19 pandemic in the United States and around the globe, and will be updated as the pandemic and response capabilities change over time.

It contains recommendations for a U.S. Federal response as well as steps and resources for stakeholders across the health care ecosystem. We will add further resources to address a range of related, critical policy challenges.

We thank our many collaborators, co-authors, and reviewers who have contributed significant expertise and guidance on these rapidly evolving issues. Please reach out to us with additional suggestions for resources and effective policies at dukemargolis@duke.edu - we welcome your input.

Monoclonal antibodies (mAbs) for COVID-19 had shown promising results in limited trials, but new findings from ongoing trials in combination with previous data solidify the key role of therapeutic antibodies to reduce death and disability from COVID-19. Trials studying four mAbs manufactured by Eli Lilly and Regeneron show fewer complications leading to hospitalization or death for patients early in the course of illness and before they progress to breathing problems or other significant symptoms.

These mAbs have already been authorized by the U.S. Food and Drug Administration (FDA) for emergency use in early-stage, high-risk COVID-19 patients and the newest data are likely to merit adoption of therapeutic antibodies in high-risk patients as standard of care. Yet uptake has been slow, with more than 600,000 available doses remaining unused as of mid-January despite very high U.S. infection rates. Our previous work has highlighted two principal reasons for limited uptake: challenges in redesigning care pathways for timely mAb referral and infusion; and skepticism based on the quality of the evidence on mAb effectiveness and safety. Recent randomized trials confirming substantial benefits of early mAb treatment should help address early skepticism, and further trials are underway. But there are emerging concerns about the threat from viral mutations enabling SARS-CoV-2 to "escape" from currently available antibodies.

Here, we provide an update on the evidence and propose a feasible path forward to develop additional evidence, including timely evidence on adaptation to mutations, by establishing a registry network.

Evidence Supporting Emergency Use Authorization and Clinical Adoption

FDA's emergency use authorization (EUA) of two mAb products was based on a review of the evidence submitted to the agency in their EUA applications.

Eli Lilly's bamlanivimab was authorized for emergency use based primarily on a phase two randomized, double-blind, placebo-controlled trial of 465 non-hospitalized patients with mild-to-moderate COVID-19. Trial data demonstrated a reduction in risk of hospitalization or emergency room visits in a subset of 205 high-risk patients from 10% to 3%. While the reduction was substantial in absolute magnitude, it encompassed a total of only 11 events (7 in placebo, 4 in treatment arms). Further, frequency of hospitalization or emergency room visits was a predefined secondary endpoint. Bamlanivimab did not have a significant effect on the study's primary endpoint, reduction in viral load at 11 days versus placebo, as most patients generally achieved reductions in viral load by that date; bamlanivimab's impact appeared to be on accelerating viral load reduction earlier than 11 days into the course. A trial of bamlanivimab in hospitalized patients was terminated due to no evidence of benefit, and bamlanivimab is not authorized for patients who are hospitalized or receiving oxygen.

Regeneron's casirivimab and imdevimab combination treatment was authorized for emergency use based on a single randomized, double-blind, placebo-controlled phase one/two study in 799 patients with mild-to-moderate COVID-19. A sub-analysis of 229 patients at high risk of serious progression demonstrated a reduction in risk of hospitalization or emergency room visits from 9% to 3%. A total of 11 events occurred in this sub-analysis (7 in placebo, 4 in treatment arm). This outcome was also a predefined secondary endpoint. The trial's primary endpoint, a time-weighted average change in viral load versus baseline, showed significantly larger reduction in viral load at day seven in patients treated with casirivimab and imdevimab versus patients receiving placebo.

Based on the evidence from both mAb studies, as well as the apparent "class" effect of mAbs in early-stage patients, FDA concluded that both mAb products are reasonably likely to significantly reduce hospitalizations and downstream complications from COVID-19 – if administered early in the course of the disease before serious symptoms emerge. FDA authorized use of mAbs for high-risk patients, defined as meeting at least one of the criteria for adults and older children found on the following page.

Following FDA's action, the National Institutes of Health (NIH) and the Infectious Diseases Society of America (IDSA) both criticized the limited nature of the evidence underlying the EUAs. While acknowledging the potential for the treatment to benefit patients and urging the development of more evidence, both NIH and IDSA did not recommend routine use in the FDA-authorized populations.

Initial EUA Populations for bamlanivimab, casirivimab + imdevimab

Ages 18 and older	Ages 12-17

• Have a body mass index (BMI) ≥35
• Have chronic kidney disease
• Have diabetes
• Have immunosuppressive disease
• Are currently receiving immunosuppressive treatment
• Are ≥65 years of age
• Are ≥55 years of age AND have
  ○ cardiovascular disease, OR
  ○ hypertension, OR
  ○ chronic obstructive pulmonary disease/other chronic respiratory disease.
	• Are 12 – 17 years of age AND have
	  ○ BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
	  ○ sickle cell disease, OR
	  ○ congenital or acquired heart disease, OR
	  ○ neurodevelopmental disorders, for example, cerebral palsy, OR
	  ○ a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
	  ▪ asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Emerging Data and Evidence

Two trials of bamlanivimab were publicly reported ahead of peer review in late January. Early results announced from the trial most directly relevant to clinical use in COVID-19 positive patients, BLAZE-1, demonstrated that two therapeutic antibodies, bamlanivimab and etesevimab in combination, dramatically reduced (by approximately 70%) the need for hospitalization or death and found a substantial reduction in viral load in the first few days after treatment. The trial enrolled 1035 patients and recorded 36 events in the placebo group and 11 events in the treated group. These findings were supported by a significant reduction in viral load.

Second, a randomized, double-blind, placebo-controlled study of bamlanivimab for post-exposure prophylaxis for nursing home residents and workers has recently announced early topline findings. Analysis of that 965-participant (299 residents and 666 workers) BLAZE-3 trial demonstrates a significant reduction of symptomatic COVID-19 infection 8 weeks after receiving prophylactic mAb treatment. In the nursing home resident sub-population, results show an 80% reduction in risk of contracting COVID-19 compared to placebo arm residents within the same nursing home facility. While prophylactic use differs from early-stage use, the significant benefit in this ongoing study would add to the totality of evidence suggesting a beneficial effect for early-stage use. Moreover, an additional population of those infected in the nursing home outbreaks showed clinical benefits similar to those observed in the other trials.

The combined results from these two trials found 14 deaths in the placebo groups versus zero deaths in the treated groups. Eli Lilly is also testing a combination monoclonal product for early-stage and possible prophylactic use.

An update from Regeneron made public through a press release from an ongoing trial in patients requiring low flow oxygen administration demonstrated a trend towards lower risk of death or hospitalization. The virologic benefit (reduction in viral load) and clinically beneficial effects were limited to patients without their own intrinsic antibody response, regardless of whether they were hospitalized. In addition Regeneron reported an interim analysis of an ongoing trial of casirivimab and imdevimab in the first 400 participants in a prophylaxis trial enrolling people at risk because of exposure to a COVID-19 patient in the household. Symptomatic infection was completely blocked (8 cases versus zero) and asymptomatic infection was cut by 50% (23 versus 8 cases). Furthermore the viral load was cut by 100-fold, providing strong evidence for viral load as a surrogate.

Other randomized trials are underway that will provide additional evidence relevant to early-stage use of mAbs; these studies are summarized in a table in the appendix. As noted, trials in hospitalized patients have generally been halted based on increasing evidence of futility. By the time COVID-19 patients are hospitalized, they have generally mounted an immune response and the primary clinical management challenge is avoiding the complications of an excessive response. An important trial to watch will be the RECOVERY Trial, which includes clinical arms that randomized hospitalized patients to mAbs or usual care and should be reporting out soon.

Augmenting Evidence Using Real-World Observational Studies

Ahead of the most recent randomized trial outcome data, mAb use had been rising. This use will provide real-world data about outcomes as well as characteristics of patients who do and do not receive treatment. While not randomized, these data can provide additional insights about use, and potentially safety and effectiveness, to augment the further clinical trials now in process.

The basic approach for efficiently treating patients with the mAb supply available, maximizing the impact of that supply, and generating further evidence to inform use should include several steps:

- **Prioritize access based on risk** of serious consequences of COVID-19 infection, utilizing risk models where available and appropriate to more accurately predict and further define patients who may benefit most
- **Establish or augment existing COVID-19 registries** to include data on treated and nontreated patients and to support observational studies to augment mAb evidence

- **Track key endpoints**, including allergic/other reactions, emergency room visits, hospitalization, mechanical ventilation (if available), and death (if available)
- **Conduct real-world analyses of key questions** related to use, safety, and effectiveness
- **Characterize the utility and limitations of such rapid observational analysis,** particularly for generating actionable insights that could help to refine clinical practice while additional randomized trials continue to add to the larger mAb evidence base
- **Explore the feasibility of conducting practical real-world randomized studies through health care organizations participating in the registries**, focusing on questions that reflect current standards of care and where placebo controls are not needed – for example, studies of alternative doses of mAbs

A successful effort that efficiently establishes a registry or linked registry could contribute even more to our understanding of the most effective approaches to provide access to mAbs, and of mAb impct, including a number of key topics where real-world evidence could be helpful:

- Characterizing events related to safety and effectiveness in subgroups of high-risk COVID-19 patients
- Identifying and assessing approaches to address disparities in access across demographic, geographic, and risk groups, as well as understanding the ability of alternative strategies to increase access to address these disparities
- Improving operational efficiency of rapid treatment programs and processes
- Assessing comparative effectiveness of mAbs, including in subgroups of patients infected with new genetic variant strains

Utilizing Risk Models for Clinical Care and mAb Access

Many health care organizations are reviewing the available clinical evidence, information from FDA's Emergency Use Authorization, and recommendations from NIH and professional societies to guide their clinical decision making and care pathways related to COVID-19 mAbs**.** Some of these organizations (e.g., Cleveland Clinic, UC Irvine) have developed risk prediction and stratification models based on data from their experience to-date with the COVID-19 pandemic, while others are using publicly available models like these and adapting them to the characteristics of their own patient populations and system capabilities.

These risk prediction models build on the basic concept, as described in the EUAs, that patients must be at elevated risk of serious outcomes from COVID-19 in order to justify the resource requirements and small risk associated with therapeutic antibody infusion. The prognosis of lower-age patients who also do not have major comorbidities is good enough that any potential benefit appears negligible. In contrast, the likely benefit for patients age-65 or older, or patients with significant comorbidities with a high risk of serious illness or death, justifies the burden, logistical difficulties, and the small risk associated with treatment. Health systems and providers

can use risk models, and further refinements based on their real-world use, to guide their treatment protocols based on local capabilities and circumstances.

The models use a range of approaches for gathering data. UC Irvine's published and externally validated model utilized manual chart review of EHRs to generate their dataset, whereas the Cleveland Clinic utilized an existing COVID-19 registry in which a combination of manual chart review and automated data feeds captured "[d]emographics, comorbidities, travel, and COVID-19 exposure history, medications, presenting symptoms, treatment, and disease outcomes." With increasing use of mAbs and data collection, these models can be refined on an ongoing basis to stay responsive to characteristics of the pandemic, emerging treatments, and patient outcomes. A registry network can facilitate this process. It could apply consistent methods to refine the risk models (e.g., the presence of rapid antibody response in infected individuals), use the risk models to set up observational comparison groups, and conduct practical, multisite studies.

Planning for Evidence Needs Based on Variant Strains of COVID-19

Alongside progress on population-wide vaccination and continued public health mitigation measures, the virus has already mutated in ways that increase infection transmission and may increase risk of serious illness and death. Continued mutation is inevitable. Such mutations create risk that the treatments and vaccines designed so far will become less effective. Indeed there is already some concern that variants originally found in Britain, South Africa, and elsewhere may require modifications of the current set of mAb products given mutations in the receptor-binding domain of the virus' spike protein – the same receptor-binding protein that serves as the target of many mAbs and some vaccine development programs

This likely means that, in addition to an expansion of public health genomic surveillance measures to track potential spread of these more-transmissible variants, additional evidence development is needed to assess whether current mAbs and potential modified mAb treatments continue to work against the virus in practice, and the association between use of mAbs modified to be more effective against mutations and actual patient outcomes.

Depending on the pace and magnitude of viral mutations, it may not be feasible to conduct full, randomized clinical trials to confirm impact on clinical outcomes ahead of the need to deploy updated mAbs. The evidence emerging from Lilly and Regeneron's trials may provide enough evidence for the FDA to consider moving to a surrogate measure such as viral load for emergency authorization. This designation will require independent assessment of the data by FDA and clear demonstration that in multiple trials the effect on viral load predicted the effect on clinical outcomes – a relationship supported by current trials. In addition to developing evidence related to effective strategies for access and additional insights related to safety, effectiveness, and comparative effectiveness, an ongoing registry or network of registries would be particularly

helpful as a digital backbone for real-world studies to strengthen the evidence on timely mAb modifications in response to genetic variants. This could enable both trials assessing viral load and post-market studies assessing real-world comparative effectiveness of antibodies already under EUA or new antibodies against the new variants, ideally using practical randomization methods in addition to observational comparisons.

Conclusion

The growing evidence on mAbs demonstrates that if administered to the right patients early in the course of disease, these drugs are highly effective in keeping high-risk patients out of the hospital – helping them to avoid serious downstream complications and death while also alleviating burden on health systems buckling under the current spread of COVID-19**.** More randomized evidence in heterogenous clinical circumstances (hospitalization, long-term care facility, etc.) will be forthcoming and should facilitate more effective use**.** Registry approaches can provide a digital backbone for analyses of process and outcomes and hypothesis generation using real world data and analysis. Furthermore, a stable network could rapidly assess the impact of new antibodies designed to counteract mutant variants coupled with post-market clinical outcomes observational studies and trials. In the meantime, stakeholder-developed playbooks, supplemented by the learning and evidence emerging from trials and shared analyses, will be needed to further optimize the efficiency and impacts of mAb treatment.

Appendix: Snapshot of Select Ongoing mAb Trials

mAb	Sponsors	Setting	Phase	Enrollment Progress	Study Sites	Status	Completion Milestone
bamlanivimab	Eli Lilly + AbCellera	Inpatient	1	24 Actual	11	Completed	8/26/20
	Eli Lilly + NIAID + AbCellera	Nursing Home + Outpatient	3	Part 1: 1175 Actual Part 2: 2000 Target Part 3: 500 Target	26	Recruiting Part 3	Part 1: week 8 public disclosure 1/20/21
	NIAID + Others	Inpatient	3	314 Actual	61	Halted - Not Recruiting	
	NIAID + Eli Lilly + AIDS Clinical Trials Group	Outpatient	2/3	2000 Target	84	Lilly Arms Completed Recruiting	
bamlanivimab + etesevimab	Eli Lilly + AbCellera + Shanghai Junshi	Outpatient	2/3	2370 Actual / 3300 Target	131	Recruiting	Mono Ph2: public disclosure 9/16/20 Combo Ph2: public disclosure 10/7/21 Combo Ph3 (2800/2800 mg): public disclosure 1/26/21 Estimated completion 5/31/21
		Outpatient	2	700 Target	107	Recruiting	
casirivimab + imdevimab	Regeneron	Outpatient	1/2/3	275 Actual / 6240 Target	97	Recruiting	
		Inpatient	1/2/3	2970 Target	97	Recruiting	
		Outpatient	3	2000 Target	127	Recruiting	
		Outpatient	1	974 Actual	7	Halted – Not Recruiting	
sotrovimab	Vir + GSK	Outpatient	2/3	1360 Target	91	Recruiting	

This information was adapted from an earlier table published by Robert Califf and Deborah Zarin based on information found at clinicaltrials.gov and in journal publications, and has been updated where possible with public information shared by Eli Lilly and Regeneron. The snapshot represents trials with at least one US site.