Covid-19 monoclonal antibodies (mAB) for treatment of high-risk patients with mild to moderate disease presented both opportunities and challenges for health systems. The ability to offer patients a treatment that reduces the likelihood of progression to severe disease, including the need for hospitalization, must be reconciled against limited available clinical evidence and logistical challenges inherent to delivering the therapy as authorized by the U.S. Food and Drug Administration (FDA). Houston Methodist was able to overcome these obstacles to rapidly establish and scale up treatment clinics, bringing mAB therapy to thousands of patients. They observed hospitalization rates in the high-risk group of treated patients that mirrored the positive findings of the initial clinical trials as well as high patient satisfaction with their treatment process. Their experience suggests that other health care systems can establish large mAB therapy infusion sites using this approach.

**KEY TAKEAWAYS**

» Emerging evidence continues to support that Covid-19 mAB therapy can reduce hospitalization when administered to high-risk outpatients.

» Provider education is key for ensuring patients are presented with the option for treatment, and patient education is critical for ensuring patients are aware of the benefits and risks of treatment and are empowered to make an informed decision.

» Offering patients virtual platforms for assessment and referral effectively augments traditional patient access points of care.
An accessible and simple referral process for providers that is supported by trained staff to manage referrals, screen criteria, educate patients, schedule appointments, and provide therapy once the patient arrives is key for scaling up capacity.

The Challenge

Treatments for high-risk Covid-19–positive patients that can prevent hospitalization, reduce hospital stay, and reduce mortality are urgently needed. Covid-19 monoclonal antibody (mAB) therapies that have been issued FDA Emergency Use Authorization (EUA) offer such an option. mAB therapy has been used throughout the 20th century with varied results to combat emerging viral diseases. Initial data suggest that mAB therapy reduces severity of illness in Covid-19 patients, but treatment outcomes are impacted by the illness severity when treatment is initiated. Notably, the mAB EUA was limited to patients who did not require hospitalization or additional oxygen, as research had shown this treatment was not beneficial for hospitalized patients. Difficulties in effectively bringing novel mAB therapies to Covid-19 patients have been discussed and include patient and provider education, infrastructure and supply challenges, and assessment of patient outcomes.

The Goal

Our goal was to safely and efficiently deliver mAB therapy to as many qualified Covid-19 patients as possible in order to prevent hospitalizations and mortality due to severe disease, while managing the uncertainties of product supply. We therefore needed to build the infrastructure to support this new service in the outpatient setting while simultaneously establishing provider and patient awareness of the therapy.

The Execution

Houston Methodist began clinical trials on therapeutics for Covid-19 on March 23, 2020, and has enrolled nearly 1,500 patients. On March 28, Houston Methodist became the first hospital in the United States to infuse a Covid-19 patient with convalescent plasma, demonstrating that antibodies from Covid-19 patients could save lives. We contributed significantly to the early understanding of plasma therapy, providing the foundation to advance mAB therapy investigations early in their development.

The Houston Methodist Research Institute formed early partnerships with industry to conduct mAB clinical trials, with infusions beginning in July 2020. Our scientists enrolled 127 patients across multiple trials conducted through outpatient visits. Crucial to the mAB program’s success at Houston Methodist was designing a protocol by which Covid-19–positive patients could return to the hospital for infusion and planned follow-ups. We designed a research clinic with separate entrances to eliminate contact between Covid-19–positive patients and other hospital patients. Because our mAB clinical trial data suggested a strong potential patient impact, we predicted an impending EUA, and began preparing approximately 4 weeks before it was ultimately issued.
As with many institutions, most established Houston Methodist infusion clinics were used primarily by immunocompromised cancer patients; therefore, treating Covid-19-infected patients required the de novo creation of clinics. Initially, just two infusion clinics were established. Patient demand ramped up very quickly, and we established six clinics in less than 6 weeks across greater Houston’s wide geographic footprint (Figure 1). While these clinics were being established, we utilized emergency departments for qualified patients to quickly bring them mAB therapy.

**FIGURE 1**

**Workflow for Bringing Patients to Houston Methodist Infusion Sites for mAB Treatment**

Source: The authors

NEJM Catalyst (catalyst.nejm.org) © Massachusetts Medical Society
However, with a dramatic increase in Covid-19–positive patients in December 2020, the EDs had difficulty meeting this additional patient demand. Separate infusion clinic sites were chosen based on the ability of Covid-19–positive patients to access the clinic without creating undue risk to other patients in the hospital. Underutilized clinical spaces were identified where multiple infusion chairs could be set up in a single room. Our experience in clinical trials showed that a single nurse could monitor multiple patients during their infusion. With the pandemic creating a strain on hospital staffing, this model was particularly advantageous.

With the goals of safety, efficiency, and efficacy, a multidisciplinary team created innovative workflows enabled by technology (Figure 1). Centralized patient scheduling optimized the time from referral until treatment by scheduling patients who may not have had an infusion time at one facility at another facility. The average time from referral to treatment was 1.2 days (including weekends and holidays), with 19% of patients infused on the day of referral.

“As the volume of patients treated increased rapidly, we came perilously close to running out of drug supply.”

Patient education materials designed during the clinical trials were then used as the infusion clinics opened to ensure patients understood the concept of an EUA and the treatment they would receive. Pharmacy staff in the centralized referral center called each patient to confirm this information was provided prior to scheduling. Misunderstanding EUA information can result in canceled appointments that reduce clinics’ effectiveness, so these educational activities prior to scheduling were critical. At Houston Methodist, approximately 3% of appointments were canceled on the day of the appointment, mostly due to symptom severity increases that disqualified the patient based on EUA criteria, indicating that patients sufficiently understood the therapy. An additional key to patients’ education is ensuring they understand the importance of seeking treatment while they are relatively well, as the EUA is for mild to moderate illness, and therefore this therapy will no longer be available if patients wait until they are severely ill.

One tool we used to educate patients was CareSense, which allows clinicians to send important information and reminders via text-messaging. Pre-procedure messages included Frequently Asked Questions, patient instructions, and directions to the clinic. Post-procedure texts were sent on days 1, 7, 8, and 26. The patients were asked how they were feeling, if they needed to speak to a nurse, if they had been hospitalized, and about the quality of the services they received. This technology allowed us to monitor our effectiveness and connect with patients who had questions.

As treatment availability increased, we quickly realized that Monday–Friday office hours were insufficient, especially given the rapid turnaround time needed to begin treatment. Our locations across Houston offered different hours, including evenings and weekends. With this process, since our first infusion on November 22, 2020, we have infused over 2,500 patients (Figure 2).
Hurdles

We faced three main hurdles in establishing clinics across the greater Houston area: (1) implementing protocols for safe facilities, (2) building a referral stream, and (3) ensuring the drug supply was sufficient to treat all patients.

Creating protocols to safely bring highly infectious patients into hospitals was the first hurdle to overcome. By working closely with clinical care teams, infection control and prevention, and hospital administration, we identified facilities that could treat multiple patients at the same time without contact between Covid-19–positive patients and the general hospital population. The protocols used for treatment had been refined during months of clinical trials in convalescent serum therapy and mAB therapy.

Establishing an accessible referral stream for patients was critical to treat large patient volumes. Referrals to the clinics were initially slow until multiple reliable referral sources were established, including affiliated health care providers and private physicians as well as our virtual urgent care, freestanding emergency centers, and hospital-based emergency room providers. We also created a direct patient line with an associated website; however, the line was overwhelmed, even after addition of automated screening. By routing patients through their providers instead, preliminary information could be gathered, streamlining the efforts of the referral center staff. Providers submitted referral orders through a simple referral pathway for patients they believed to be qualified for the EUA. The referral review process, patient education, medication order entry, and patient scheduling were centralized, maximizing efficiency and allowing visibility of available resources across our system.
As a mark of these infusion clinics’ success, patients have come from across Texas, traveling as many as 8 hours to receive mAB therapy."

As the volume of patients treated increased rapidly, we came perilously close to running out of drug supply. We overcame this barrier by ensuring that Texas Health Department officials understood our plans to increase capacity. In addition, our system’s Pharmacy and Therapeutics Committee reviewed the available clinical data and EUAs issued by the FDA and approved both the Lilly and Regeneron drugs to formulary as interchangeable. This simplified the process by which we moved between products depending on our product blend of allocations. By working with federal and state government partners, we were granted a special waiver that allowed a generous increase in our weekly allocation and direct ordering from the distributor. This ensured a consistent and adequate supply, solving the greatest challenge in establishing a large mAB therapy clinic. Centers with a demonstrated capacity for mAB infusion may be able to apply for a similar waiver.

The Team

Our core team comprised nursing and pharmacy leadership from across the health system, physician champions, and Research Institute leadership. Executive leadership, including Chief Nursing Officers, was key in prioritizing resources. Houston Methodist Research Institute researchers performed the early studies on convalescent serum therapy and mABs, and a clinical trials team led early mAB therapy initiatives. Pharmacy clinical specialists received referrals, educated patients, and ensured drug availability. An operations manager created the patient access processes and oversaw the centralized infusion schedulers. Nursing leaders established each site and staffed the infusion centers. Registered nurses administered the mAB, performed infusion related monitoring, and reinforced education. Operations and inventory pharmacy teams managed timely medication delivery and navigated supply chain issues, respectively. System patient safety nurses performed post-treatment phone calls.

Metrics

We have identified a hospitalization rate of 4.2% after mAB infusion, consistent with mAB treatment groups in clinical trials and at other large centers tracking mAB-treated patient outcomes, and lower than the 9–14.6% hospitalization rates reported for untreated, high-risk patients. As of January 24, 2021, there have been only three Covid-19–related deaths among our treated patients and no significant infusion-related reactions. From November 22, 2020, to January 28, 2021, using only those aged over 60 as a qualifying high-risk criterion for comparison, Houston Methodist admitted 2,701 patients to our hospitals for severe Covid-19 disease and had an average hospital length of stay of 6.7 days with a mortality rate of 13.3%. Applying an absolute risk reduction of approximately 10% observed in the mAB clinical trials for high-risk populations, and having treated over 2,500 high-risk patients, we estimate we have avoided nearly 250 Covid-19–related hospitalizations. Although the investment to establish and manage the outpatient mAB infusion program was substantial, keeping 250 patients out of the inpatient hospital setting during a period
of stretched acute care and ICU bed resources was important for our system, and we believe can be of value to other centers.

In addition to preventing hospitalizations, the patient’s experience is another important outcome measure of success. Utilizing an automated platform for continued patient engagement, instruction, and surveys post-treatment, nearly 99% of patients would recommend the treatment to their family and friends, and 95% of patients were confident in the communication between providers. Only 13% of patients felt that their symptoms progressed after therapy.

As a mark of these infusion clinics’ success, patients have come from across Texas, traveling as many as 8 hours to receive mAB therapy (Figure 3). This indicates the need for other health systems to invest heavily in creating or expanding mAB infusion clinics to improve availability for patients who are not able to travel.
Where to Start

mAB therapy is being used to varying extents around the world. By applying our model, medical systems can expand their offerings and improve patient access to this critical therapy. Institutions looking to establish large mAB infusion clinics should:

- Identify medical staff leaders to champion the therapeutic approach who understand the role of mAB therapy in practice.
Enlist nursing, pharmacy, and scheduling staff early in the process to ensure proper staffing and smooth operations at infusion sites.

Work with state agencies responsible for drug allocation to understand mAB availability and opportunities for expanded supply to meet program demands.

Identify facilities that can be modified to ensure Covid-19 patients do not come into contact with other hospital patients or visitors.

Develop educational materials and dissemination plans to ensure patients are informed about mAB therapy and EUAs.

Establish follow-up procedures to track patient outcomes.

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