UCSF COVID-19 Monoclonal Antibody Use Process

Background

The Federal Drug Administration (FDA) has now issued an Emergency Use Authorization (EUA) for the use of several neutralizing monoclonal antibodies (mAbs) that bind the receptor-binding domain of the SARS-CoV-2 spike protein for the treatment of outpatients with mild to moderate COVID-19. Published and unpublished data suggest that antibodies may help to augment decline in viral load and prevent a proportion of ED visits and hospitalizations. Current EUAs allows for the treatment of COVID-19 in ambulatory adults and adolescents ≥ 12 years old with mild to moderate disease.

The data on monoclonal antibodies remains new and evolving. Therapies through controlled trials should be considered as well as usual supportive care.

References:

1. Food and Drug Administration. Fact Sheet for Health Care Providers Emergency Use Authorization of Bamlanivimab: https://www.fda.gov/media/143603/download. Accessed 2.13.2021
2. Food and Drug Administration. Fact Sheet for Health Care Providers Emergency Use Authorization of Bamlanivimab+Etesevimab: https://www.fda.gov/media/145802/download. Accessed 2.13.2021
3. Food and Drug Administration. Fact Sheet for Health Care Providers Emergency Use Authorization of Casirivimab and Imdevimab: https://www.fda.gov/media/143892/download. Accessed 2.13.2021
4. Gottlieb RL, Nirula A, Chen P, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19. JAMA 2021: doi:10.1001/jama.2021.0202
5. Eli Lilly and Company Press Release: https://investor.lilly.com/news-releases/news-release-details/new-data-show-treatment-lillys-neutralizing-antibodies
6. Weinrich DM, Sivapalasingam S, Norton, T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. NEJM 2021; 384:238-251. DOI: 10.1056/NEJMoa2035002
7. Wolf J, et al. Initial guidance on use of monoclonal antibody therapy for treatment of COVID-19 in children and adolescents. J Pediatr Infect Dis Soc 2021
8. Chiotos K, et al. Multicenter interim guidance on the use of antivirals for children with COVID-19/SARS-CoV-2. J Pediat Infect Dis Soc 2020

Eligibility for Monoclonal Antibodies via EUA

Inclusion criteria: Meets all of these and no Exclusions
COVID-19 infection confirmed by PCR, NAAT, or Antigen testing
Symptomatic with time from symptom onset < 10 days
Mild-moderate disease*
Adult (≥18 yo) Criteria: Meets at least one of^: • Have a body mass index (BMI) ≥ 35 • Have ≥ stage 3b chronic kidney disease (eGFR < 45 mL/min per 1.73 m^2) • Have diabetes that is poorly controlled or requires medical treatment • Have immunocompromised condition# • Are currently receiving immunosuppressive treatment (see Appendix A) • Are ≥65 years of age • Are ≥55 years of age AND have cardiovascular disease (e.g. coronary artery disease, congestive heart failure, cerebrovascular accident), OR hypertension (poorly controlled or requiring medical treatment), OR chronic obstructive pulmonary disease/other chronic respiratory disease

Adolescent (>=12 yo to 17 yo) Criteria: Monoclonal antibody therapy is not recommended in any adolescent risk group due to lack of safety and efficacy data in this age group and low baseline risk for progression to severe COVID-19 infection in this age group regardless of comorbidities. Monoclonal antibody use may be considered in exceptional circumstances for patients based on the following criteria. *Note: UCSF Health criteria are more specific than those criteria defined in the EUAs.*

- BMI ≥35 or ≥99th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, OR
- Severely immune-compromised˜, OR
- Congenital or acquired heart disease considered high-risk by pediatric cardiologist, OR
- Neurodevelopmental disorders associated with significant respiratory impairment and/or prior hospitalizations for severe respiratory illness, OR
- Tracheostomy and/or ventilator and/or positive pressure ventilation (not related to COVID-19), OR
- Asthma, reactive airway or chronic respiratory disease with history of ICU admission or considered by pulmonologist to be at exceptionally high risk for decompensation
- Combination of multiple EUA risk criteria but no single risk factor meeting threshold

Exclusion criteria
Hospitalized for COVID-19
New O2 requirement
Worsening O2 requirement in those on supplemental O2

***Mild Illness:** Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging and who do not meet criteria for moderate, severe, or critical illness. **Moderate Illness:** Individuals who have evidence of lower respiratory disease by clinical assessment or imaging, and a saturation of oxygen (SpO2) ≥94% on room air at sea level.
^Pregnancy itself is not a criterion, but any pregnant woman meeting another criterion listed above will be eligible for administration of the drug. Any administration in pregnant patients must be discussed with Maternal Fetal Medicine

#For adult patients, the degree of immune-compromise for the patient is ultimately determined by the treating provider. Conditions include but are not limited to: (adapted from https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html#definitions)

1. Receiving current chemotherapy for malignancy
2. Having a hematologic malignancy that may be suppressing the immune system
3. HIV infection with CD4 T lymphocyte count < 200
4. Primary severe immunodeficiency disorder
5. Solid organ or hematopoietic stem cell (bone marrow) transplant recipient
6. Receipt of prednisone 20 mg/day or the equivalent for more than 14 days, or treatment with other high-risk immunosuppressive medications (see Table below for examples)

˜For pediatric patients, the severely immune-compromised conditions include but are not limited to (Reference #8):

1. **HCT**: < 100 days post-allogeneic HCT, <30 days post-autologous HCT, Absolute lymphocyte count < 300/mm3, Recent anti-lymphocyte therapy or HCT with ex vivo T-cell depletion in < 6 months, GvHD requiring systemic immunosuppressive therapy
2. **SOT**: Recent SOT or high-level immunosuppression (e.g. ATG < 3 months or alemtuzumab < 6 months), Recent immunosuppressive treatment for transplant rejection (< 3 months)

3. **Receiving chemotherapy for cancer treatment**: ALL in induction or receiving therapy for relapsed or refractory disease, especially if ALC < 100/mm3. Other cancers including AML, ALL In remission, B and T cell lymphomas, and solid/brain tumors and receiving chemotherapy with ALC < 100/mm3
4. **Primary immunodeficiency**: Severe combined immunodeficiency or other congenital disorder associated with profound T-cell dysfunction or deficiency or history of prior opportunistic infections, hypogammaglobulinemia requiring IVIG replacement
5. **HIV** with CD4 count < 5% or <200/mm3
6. **Other medications and conditions:** Alemtuzumab (< 6 months), ATG (< 3 months), Co-stimulation inhibitors (e.g. belatacept, abatacept) for maintenance immunosuppression, High dose corticosteroids (>=2 mg/kg/day prednisone-equivalent for > 2 weeks), Expected profound T-cell dysfunction or ALC < 100/mm3

Pediatrics: While mAb treatment is an option for adolescents meeting the EUA criteria, the Pediatric COVID-19 Clinical Working Group does not recommend routine use of this therapy for our pediatric patients with risk factors as defined per the EUA but it is available on a case-by-case basis for patients evaluated and judged to be at exceptionally high risk for severe COVID-19 (see criteria in blue table above). Individual patients should be discussed with a Pediatric Infectious Diseases physician. At BCHO, individual patients should be discussed with a Pediatric Infectious Diseases physician.

Pregnancy: Monoclonal antibodies can be considered on a case-by-case basis in consultation with Maternal Fetal Medicine for pregnant patients otherwise meeting criteria.

Breastfeeding mothers: Given limited data, the manufacturer recommends that monoclonal antibodies be used with caution in breastfeeding patients. However, because of the antibody molecule's large size, it is unlikely to be present in large quantity in breast milk and unlikely to be absorbed from the infant gut. Additionally the anticipated effect on infant health from possible absorption is minimal.

Vaccine: Due to limited data on the safety and efficacy of mRNA COVID-19 vaccines in persons receiving mAb therapy, the CDC recommends deferring vaccination (either first or second dose) for 90 days after the treatment, in order to avoid interference with vaccine immune response.

High Risk Immunosuppressive Medications (Examples, not all-inclusive)

High Risk Immunosuppression		
Class	**Generic**	**Trade**
Steroids	Prednisone > 20 mg/day (adults) or > 1mg/kg/day (children) for >14 days or the equivalent for other steroid agents	
Purine analog	Azathioprine > 3mg/kg/day 6-Mercaptopurine > 1.5 mg/kg/day	Imuran Purinethol
	Methotrexate > 0.4 mg/kg/week	
Alkylating agents	Cyclophosphamide Chlorambucil	Cytoxan
TNF inhibitor	Etanercept Infliximab Adalimumab Certolizumab pegol Golimumab	Enbrel Remicade Humira Cimzia Simponi/Simponi Aria
CTLA-4 Ig	Abatacept	Orencia

B-cell inhibitor	Rituximab Belimumab Ocrelizumab	Rituxan Benlysta Ocrevus
Anti-IL 12/23	Ustekinumab	Stelara
Anti-IL 17/23	Secukinumab Ixekizumab Broadlumab	Cosentyx Taltz Siliq
Anti-IL-1	Anakinra Rilonacept Canakinumab	Kineret Arcalyst Ilaris
Phosphodiesterase 4	Apremilast	Otezla
Jak/Stat inhibitors	Tofacitinib Baracitinib Ocalacitinib	Xelijanz Olumiant Apoquel
Anti-IL-5	Tocilizumab Resilizumab Benralizumab	Actemra Cinquair Fasnera

Distribution plan:

Guiding principles

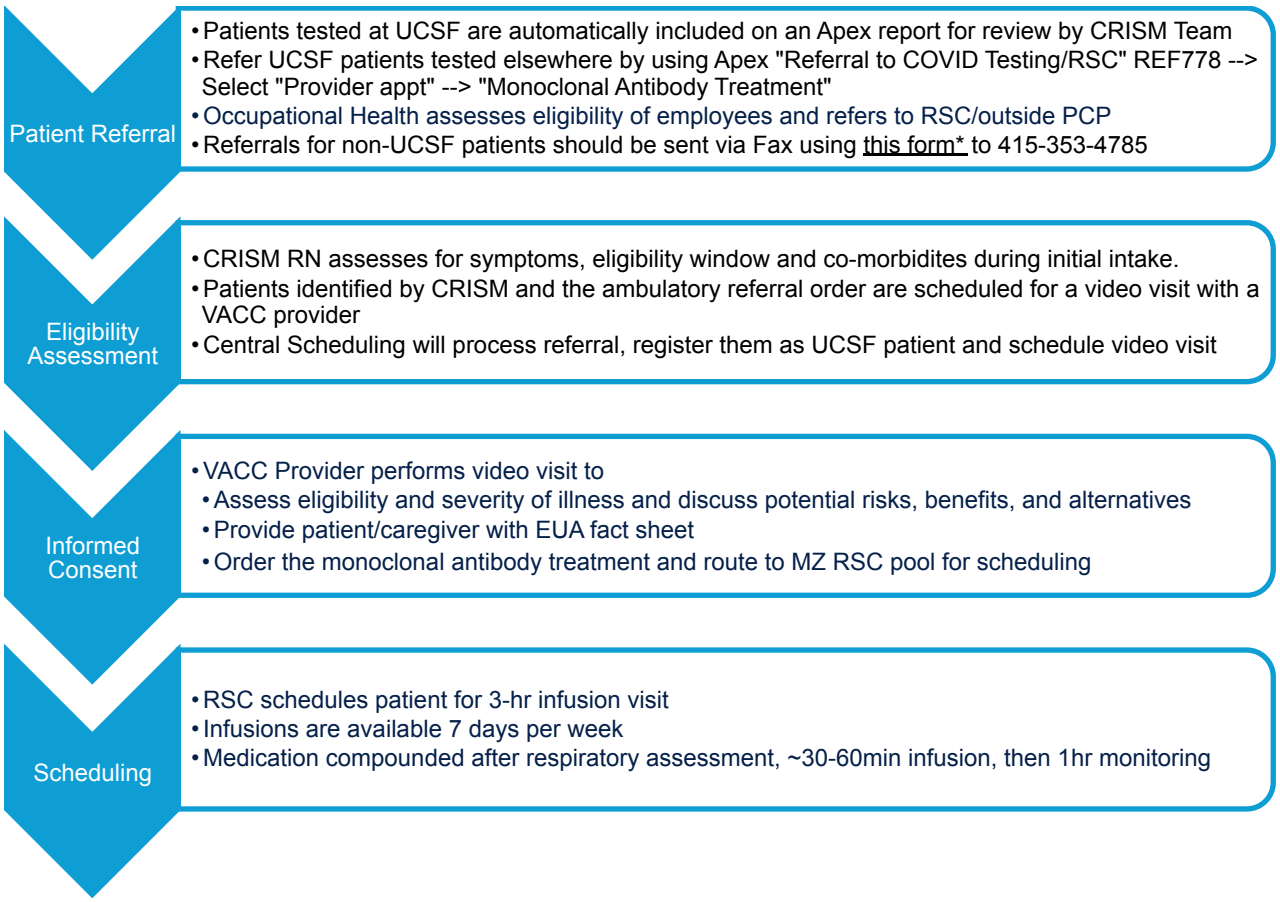
- No patient should be denied access to mAbs based on age, disability, religion, race, ethnicity, national origin, immigration status, gender/gender identity, perceived quality of life, or sexual orientation
- To maximize distribution of drug, the medication should not be stockpiled for future use
- Patients eligible for mAbs via clinical trials should be offered participation in the trials but should not be compelled to participate in trials for the sole purpose of accessing the drug. Patients who opt not to participate in trials shall be offered mAb via the EUA if eligible.

Responsibilities

- RSC, ED:
    - Reviews eligible patients in each location for mAb eligibility
    - RSC may receive referrals from subspecialty groups who become aware of patients tested elsewhere
    - Contacts the patient/caregiver and educates on bamlanivimab EUA and alternative options
    - Provides EUA fact sheet when patient arrives in clinic (all available in English, Spanish, Russian, Traditional and Simplified Chinese: bamlinivimab-etesevimab, casirivimab-imdevimab)
    - Orders drug via orderset
    - Picks up drug from pharmacy
    - Administers drug
    - Monitors for adverse events
- RSC Schedulers:
    - Place the patient on the schedule
- COVID-ID attending
    - Available as a resource if questions arise
    - Approves drug given outside of adult RSCs and ED
    - Reviews administrations weekly

- Study teams
  - Review patient eligibility for clinical trials
  - Inform patients of alternatives to trials
- Pharmacy
  - Prepares the drug
  - Medication Safety: reports to FDA Medwatch as needed
  - Notifies RSC or ED RN when drug is available for pick-up
- ID Pharmacist
  - Maintains list of mAb supply

MAB WORKFLOW:



*https://infectioncontrol.ucsfmedicalcenter.org/sites/g/files/tkssra4681/f/Monoclonal_Antibody_Outpatient_Treatment.pdf

Reviewed by representation from:

- Respiratory Screening Clinic
- Emergency Department
- Infectious Diseases
- Pediatric Infectious Diseases
- Care Delivery
- Nursing
- Pharmacy
- Ethics
- Occupational Health