Monoclonal Antibody Treatments Covid 19
Where We Were And Where We Are Now
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Disclosure/s

The following conflict of interest has been resolved and bias is not present in this presentation. Dr. Fiorini serves as a scientific advisor for Regeneron.

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Current EUA Criteria The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progressing to severe COVID-19:

- Older age (for example, age ≥65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m², or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy and Postpartum
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma
  - [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary
  - hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that
  - confer medical complexity (for example, genetic or metabolic syndromes and
  - severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy,
  - gastrostomy, or positive pressure ventilation (not related to COVID 19))
- Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progressing to severe COVID-19 and authorization of REGEN-COV under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progressing to severe COVID, see the CDC website:
- Healthcare providers should consider the benefit-risk for an individual patient.

St Peter’s Health Partners
EUA Changes to Criteria to Treat

- >25 BMI
- Multiple Medical Conditions
- Heart and lung disease for any age
- Pregnancy/postpartum
- Cancer
- Smoking history
- Race
- Ethnicity
- Systemic health and social inequities
- People with disabilities
- Pediatrics 12 and older
Where We Were and Where We Are Now

• mAb treatment for Covid 19 what is it?
• Data that let to emergency use authorization (EUA)
• mAb infusion Clinic at Albany Memorial Hospital (AMH)
  • Obstacles and triumphs
• Covid 19 Variants and their effect on mAb Tx
• Where we were and where we are now
What is a monoclonal antibody?
**Process**
- Source material

**Search**
- Screening for RBD-specific single B cells
  - Multiplexed bead-based assay
  - Live cell-based assay
  - Fluorescence-activated single-cell sorting

**Sequence and identity**
- Cloning and expression
  - High-confidence sequences clustered by sequence identity
  - Clonal families

**Analyze**
- Validate and characterize
  - Binding validation
  - Functional validation
  - Stability
  - Organization
  - Affinity

**Select**
- Antibodies
Monoclonal Antibody for Covid 19

• New for Covid

• Not new for Cancer, Rheumatology and ID

• 20 years

• Ebola Virus

• Given to the President under Compassionate use IND – with no other alternative; benefits outweigh risk

Protection With mAbs
Monoclonal antibody therapies are drugs that could provide a ‘bridge’ of immunity until vaccines are ready.

Without any antibodies, the coronavirus will bind to the ACE2 receptor on a human cell

SARS-CoV-2

Spike protein

Human cell

ACE2 Receptor

The antibody acts as a blocker, preventing the virus from attaching

Neutralizing antibody

Source: Siemens
11 volunteers

B cells

82 Monoclonal Antibodies

- Multiple epitopes
- Diverse V_H gene use
- Close to germline sequences
- High binding affinity

Curative Treatment

<table>
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<th>Days after virus infection</th>
<th>Percent survival</th>
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4 mAbs cocktail
PBS

Affinity constant KD (nM)

Published Protective Mabs from Convalescent donors
Mabs from Vaccinated donors
mAb specific for Covid 19

- **S protein/Spike protein** which targets the Ace2 receptor found in the respiratory system, GI tract and endothelium
- Specifically, mAb treatments targets the **receptor binding domain** (RBD) of the spike protein
- The exact point on the RBD that the mAb fuses to is what differentiates the treatments that we have available for us today.
  - **Bamlanivimab**
  - **Bamlanivimab/Etesevimab**
  - **Casirivimab/Imdevimab**
What is a mAb and how does it work?

• Neutralization of the Virion preventing target cell binding or fusion
• Opsonization of the virion marking the virion for phagocytosis
• Facilitation of target cell death via complement fixation and membrane attack complex MAC
Bamlanivimab

- 452 pts with mild to moderate disease
- Treated within 3 days of positive test
- Lower rate of hospitalizations/ED visits esp. in high-risk groups
- P 6%, mAb 2%; High risk P 10%, mAb 3%
- Bamlanivimab received Emergency Use Authorization (EUA) from the FDA on **November 9**th
Casirivimab/Imdevimab (Regn/Cov2)

- 799 pts with mild to moderate disease
- Treated within 3 days of positive test
- Lower rate of hospitalization/ED visits esp. in high-risk groups
  - P 4%, Mab 2%; High risk P 9%, 3%
- Casirivimab/Imdevimab received Emergency Use Authorization (EUA) from the FDA on **November 21**

**St Peter’s Health Partners**
Bamlanivimab/Etesevimab Blaze 1

• Same set up mild/mod illness within 3 days of obtaining sample for testing
  – 54% female
  – 29% Hispanic or Latino
  – 9% African American
  – Mean age 57
  – 37% > age 65
  – BMI - 34
  – Mild covid 77%
  – Mod covid 23%
  – Duration of sx – 4 days
Bamlanivimab/Etesevimab Blaze 1

- Rate of hospitalization or death
  - P 7%, N 517
  - Mab 2% N 518
  - Death P 10 (1.9%) mAb 0
  - 70% reduction in Hospitalization or any cause death by day 29
- Decrease in viral load, more rapid clearance
- Phase 3 trial N769 P 5.8%. Mab .8%, deaths 4,0
- 87% Risk Reduction
Casirivimab/Imdevimab Phase 3 Results

• Mild/mod disease, +PCR, $\geq 1$ risk factor for severe disease

• N 1484 at 1200mg dose Hosp/death by day 29
  • P 3.2%, Mab 1%; 70% Risk Reduction
• N 2696 at 2400mg dose Hosp/death by day 29
  • P 4.6%, Mab 1.3%; 71% Risk Reduction
• Median age 50, 58% obese, 36% CAD(HTN) 3.4% immunosuppressed
• 3 days of symptoms at time of infusion
• Deaths P 5/1843, 1200mg 1/827, 2400mg 1/849
• Decrease in viral load, more rapid clearance
Hospitalized Patients with Covid 19

- BAM ACTIV-3 hospitalized pts. without end organ failure; stopped for futility, no evidence of efficacy
- Independent Data Monitoring Committee held Regn-Cov2 in hosp. pts on **high flow oxygen**; Harm?
  - What was high flow oxygen?
- Regeneron announces encouraging results on hospitalized patient on **low flow oxygen**.
  - Passed futility test able to show promise in reducing death or mechanical ventilation
  - What was low flow oxygen?
- **Recovery Trial (UK)** still evaluating the antibody cocktail in hospitalized patients
Covid 19 Monoclonal Antibody Infusion

- On **November 9th**, the FDA issued an emergency use authorization (EUA) for Bamlanivimab and on **November 21st** an EUA for Casirivimab/imdevimab (Regn-Cov2)

- On **November 12th**, an email was initiated between Drs. Hanks, Sanders and myself about the treatments

- On **December 3rd** we had our first day of clinic with 11 pts scheduled (most from NHs suffering an outbreak)
EUA Criteria for mAb Infusion

- High-risk individuals specified as those who meet at least one of the following criteria:
  - Aged ≥65 years
  - Body mass index (BMI) ≥35
  - Chronic kidney disease
  - Diabetes mellitus
  - Immunocompromising condition or Tx.
  - >55 years HTN, CAD or Pulmonary condition, COPD, not Asthma
EUA for mAb therapy for Covid 19

• Only to be given in patients who had symptoms for 10 days or less?
  • Fatigue?
  • Sniffles in allergy season?
  • LTC facilities do you wait for symptoms? Syncope?
  • Dementia? Disabilities?

• Was not for asymptomatic patients; Why?
mAb Therapy was **NOT** For

- Who are hospitalized due to COVID-19
- Who require oxygen therapy due to COVID-19
  - What was required oxygen? What were low levels? Determined by whom?
- Who require an increase in baseline oxygen due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity
SPHP ED Safe
Discharge 12/3/20

**Moderate illness**
Dyspnea or other evidence of LRTI, but RA SPO$_2$ $\geq$ 94%

**Moderate-Severe Illness**
RA SPO$_2$ < 94%
or RR > 24

- W/U: COVID panel
- Provide ED treatment
- D-Dimer for pleuritic CP, CTA if D-Dimer $>1000$ ng/mL
- CXR

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**Consider:**
- CXR, Lab testing
- Provide standard ED treatment
- Check Exertional O2 Sat

- **1 min walk in place:** Patient walks in place briskly for 1 min continuously.
  - Or
  - **1 min sit to stand:** Patient continuously performs a sit to stand for 1 min.
  - Inability to perform for 1 min is classified as a test failure.

- Exertional SPO$_2$ < 90% $\rightarrow$ admit*
- Exertional SPO$_2$ 90-92% and COVID symptoms $>7$ days $\rightarrow$ admit.

If symptoms 1-6 days $\rightarrow$ D/C with PMD F/U, O$_2$ monitoring and Coach program$^{1,2}$
- Exertional SPO$_2$ 92-94% $\rightarrow$ discharge with COACH program and O2 monitoring

*On selected patients it may be appropriate to send them home on $\leq$ 2L of oxygen $\rightarrow$ consult RT 24/7 to arrange

- Consider observation of high-risk patients

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Phases of Covid-19

- Presymptomatic phase
- Virus
- Viral phase
- Cytokine storm phase
- Coagulation phase
- Late hyperinflammatory phase

Days

- 0
- 7
- 14
- 21
- 28
**Clinical Symptoms**
- Mild constitutional symptoms
  - Fever >99.6°F
  - Dry Cough, diarrhea, headache

**Clinical Signs**
- Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)
- Shortness of Breath
- Hypoxia (PaO2/FiO2 ≤ 300 mmHg)
- Abnormal chest imaging
- Transaminitis
- Low-normal procalcitonin

**Potential Therapies**
- Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
- Reduce immunosuppression
- Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors

**Stage I** (Early Infection)
- Viral response phase

**Stage II** (Pulmonary Phase)
- IIA
- IIB

**Stage III** (Hyperinflammation Phase)
- Host inflammatory response phase

**Time course**
Phase I

SARS-COV2

Direct viral inoculation

Phase II

Hypoxia due to acute lung injury

Phase III

Cytokine storm

(Disease severity/Inflammatory cytokines/Cardiac troponin)

Switching from innate to adaptive immune response

~5 days

~10 days

Time course (days after symptoms appear)
Mild COVID

Symptoms onset

Virus shedding (Infectiousness)

Virus detection

Recovery

Infection

Days 20

Severe COVID

Symptoms onset

Virus shedding (Infectiousness)

Admission to ICU

Recovery or Death

Infection

Viral disease

Complications

Incubation

Stage I

Fever, dry cough, diarrhea, headache, loss of sense of smell and/or taste. Possible dermal, neurological, or cardiac disorders.

Stage II

Shortness of breath, Hypoxia

Stage III

ARDS, SIRS/shock, Cardiac failure

Coagulation disorder

Antiviral drugs?

Reduce immunosuppression

Reduce inflammation: anti IL6, GM-CSF, ...

Anti-clotting: heparin, ...
Covid 19 Monoclonal Antibody Infusion

- The impact of antibody treatments was very limited
- Treatment for over 1.2 million Americans were made available
- Potential preventing tens of thousands of COVID-19 hospitalizations
- January <20% of the nation's stockpile was being used

- New model of care for high-risk COVID-19 patients had to be adopted
A change in the care model for high-risk COVID-19 patients

Old Model
- Treatment options: Steroids not given until day 7-10; Remdesivir, convalescent plasma in hospital
- Stay home, isolate, nothing else to do, assume you have it; like the flu; quarantine
- Testing was scarce
- Turn-around time for results 5-7 days

New Model
- Tx meant to be given as early in disease as possible
- Get tested as soon as you have symptoms, exposure?
- PCP test high risk ASAP
- Need proof for treatment
- Patients were out of treatment window day 10
Covid-19 Monoclonal Antibody Infusion
Obstacles

- Time dependent
  - Education for earlier testing esp. for high-risk populations
  - Turn-around time for results
- Referral systems in place
  - Information and resources to make informed decision by patients and providers
- New payment models
  - CMS and private payments should encourage faster testing and referrals, and in-home access for antibody treatment
- Access
  - Lack of in-home or in SNF infusion capability/cost
  - Transportation to infusion center
  - Infusion time for mAb 1hr/ observation time 1hr
- The science was limited
  - but improving
mAb Clinic at Albany Memorial Hospital

• Our system
  – 700-bed hospital system under Trinity
  – Two acute care Hospitals; Samaritan and SPH
  – Two out-patient campuses; AMH and St. Mary’s
• Pool resources and medication allotment to serve the larger community out of one site
  – invited hospitals in our region
  – the supply of mAb would be consistent and continue for months
  – AMC broke off to start their own clinic, while Ellis continued to refer their patients
mAb Infusion for Covid 19
Full Hospital Support i.e., Dr. Hanks

• One department does not have the resources to carry out a feat of a free-standing clinic for infusion
• Following departments
  • Finance - Lori
  • Registration - Johan
  • Nursing – Chris, Shari, Allyson Mike
  • Pharmacy – Elma, Dario
  • Environmental and Janitorial – Staff at AMH
  • Later to add Emergency Medicine, IT, Security, Medical Group Practice, Corporate Communications, Courtney, Samantha
AMH: Hub for Covid 19 mAb Distribution

- Who will run the clinic?
  - EM/CC boarded actively working in urgent care, ER and have worked in our ICUs
- Finger on the pulse
  - Access to ER/UC covid + pts in a timely manner (IT Cavin)
  - Knowledge of testing, treatment and protocols
  - Encourage quicker testing (only admits)
  - Safe Discharge Protocols
- Standing orders
  - assume responsibility for hundreds of high-risk patients with a novel, deadly virus
- Partners: Dr. Sanders; CMO and ID; AMC ER/ERCC; vested interest Nephrology, Oncology, Pulmonary, Endocrinology, ID
mAb Infusion for Covid 19
Location, Location, Location

• Infusion Clinic
  • Separate from non-covid patients
  • Ideally separate entrance
  • Preferably first floor
  • Separate rooms with ventilation
  • Access to EMS or acute care
  • Monitors
  • Parking
• Infusion Capability
  • 3 hours of nursing services per patient
  • Pharmacist related clinical services
  • Infusion administration supplies; anaphylactic kits
AMH mAb Covid 19 Infusion Clinic
Location, Location, Location

• 8-bed fast track area of our outpatient campus
  • First floor
  • Separate entrance
  • equip with monitors
  • single bays with doors

• ED next door (Dr. Guzda, Kwok Tallman)
  • if there was an allergic reaction or anaphylaxis
  • Second pair of eyes
  • Comfort of sending the patients there for admission after their infusion
  • Back up for deteriorating patients or 9-day patients
  • Compassionate Care use patients
AMH-mAb Covid 19 Surge Scheduling and Referrals

- As close to 24/7 as possible during a surge

- Clinical provider
  - Confirm eligibility
  - Educate patients on treatment
  - EUA mandated that the pts receive materials on Tx
  - EUA mandated telling of other options available
  - Answer medical questions
  - 20-30 min/patient

- 10 days out or sick patients
  - ER will infuse the patients on off hours (7am Sat/Sun)
Monoclonal Antibodies Infusion Referral Form

Referring Provider Name: __________________________  Today's Date: ____________

Referring Provider Location: ______________________________________________________

☐ Provider has spoken to the patient and they agree to receive this treatment.

Patient Name ____________________________  Patient DOB ________________________

Patient Phone # __________________________

Patient E-mail: __________________________________________________________________

Length of Symptoms (Days) _______________________

*They are considered outside of the window if they have had symptoms for more than 10 days

BMI __________________________

Pertinent PMH (circle)

Diabetes  Imunosuppressive Therapy  CAD  Pulmonary Disease

Other:

Inclusion Criteria

Anyone meeting at least ONE of the below criteria AND within 7-10 days of symptom onset

- Are ≥65 years of age
- Have a body mass index (BMI) ≥35
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment

OR

Are ≥ 55 years of age AND have

- cardiovascular disease, OR
- hypertension, OR
- chronic obstructive pulmonary disease/other chronic respiratory disease.

This is not a guarantee that your patient will receive monoclonal antibodies. A physician will call the patient to assess if they are an appropriate candidate.
Holly
Monoclonal Antibodies Infusion Referral Form

Referring Provider Name: __________________________        Today’s Date: __________

Referring Provider Location: ______________________________________________________

☐ Provider has spoken to the patient and they agree to receive this treatment.

Patient Name ___________________________ Patient DOB ______________________

Patient Phone # ______________________

Patient E-mail: ________________________________________________________________

Length of Symptoms (Days) _______________________

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BMI _______________________

Pertinent PMH (circle)
- Diabetes
- Immunosuppressive Therapy
- CAD
- Pulmonary Disease
- Other:

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This is not a guarantee that your patient will receive monoclonal antibodies. A physician will call the patient to assess if they are an appropriate candidate.
For Patients

Only those patients who are eligible and have a referral from their physician can qualify to receive this treatment. If you do not have a primary care provider, but meet the eligibility requirement please acknowledge below.

I'm Eligible

If you believe that you meet the requirements above, please email MABReferrals@sphp.com requesting information about the clinic.

For Providers

If you are a provider and are looking to make a referral, please do so by visiting our provider referral application.

mab.sphp.com

St Peter’s Health Partners
AMH Covid 19 mAb Clinic Patients

- 920 patients were infused from 12/3/20 - 5/24/21
  - 526 Bamlanivimab
  - 20 Bamlanivimab/Etesevimab
  - 362 Casirivimab/Imdevimab
    - 12 under compassionate use

- Age 64
- BMI 33.5
- 41 patients were from skilled nursing facilities
- 89 had at least one dose of the vaccine
AMH Covid 19 mAb Clinic Patients

- Of 622 patients for which we have demographics
  - 25% DM
  - 5% CKD
  - 9% on Immunosuppressant Tx
  - 21% CAD
  - 42% HTN
  - 27% Pulmonary
AMH Covid 19 mAb Clinic Patients

Of 340 patients for which we have follow up for i.e. calls, surveys, LTC records

- 73% felt back to normal
- 83% felt the treatment helped
- 91% (297) would recommend Tx for others
380 mAb Clinic Patients

• 7% (29) required hospitalization
  • 3 pts sent from clinic
  • 8 were ER referrals to clinic; back to ER
  • 2 admitted >10d after infusion, unrelated

• 1.5% (6) deaths directly related to covid
  • 3 LTC pts died comfort that week
  • 73 yo died “massive stroke” family at home, 4d s/p infusion
  • 97 yo died after admission for hypoxia, then a wide complex tach, made comfort care 7d
  • 51 yo male no med hx, multiple referrals, 27 d

• 2 LTC patient died 46 and 77 days after infusion
  • Likely due to stroke
  • Not counted in mortality figures

St Peter’s Health Partners
AMH Covid 19 mAb Clinic Patients

- Average of first vital signs were (860N)
  - 128/75, 76, 96%
- 11% (96) $\leq$ 93%, 1% (9) $\leq$ 90%
- Blaze 1 - exclusion criteria of 93%, 125, 30
- 8% (73) patients had a sat $\leq$ 93%, or a HR $>$ 125 or RR $>$ 30
What is hypoxia requiring O2 in the world of Covid 19?

• 46 patients had a clinic saturation $\leq 92$
  • 3 deaths (86, 89, 92%), (100, 65, 102HR)
• Another 49 patients had a sat of 93%
  • 1 death in the NH population (93%, 81)
• Stable vital signs
  • 4 deaths (96,95,96,95%) (70,94,75,65HR)
One SNF Experience

- Summary:
- 47 Cases of Covid in our Frail multiple co-morbidity population most in 80’s and 90’s
- 10 deaths
- 23 received Monoclonal antibody
- Of the 23 who received the mAb there was one death (the patient was on comfort care at the time of death), a second 70 days later (CVA?)
- Two sisters who received monoclonal antibody were hospitalized with COVID related complications but ultimately survived. Cause of hospitalization not related to Monoclonal aby infusion.
- Almost all the 47 also received Ivermectin 15 mg dose on days 2 and 3 after being diagnosed with covid.(off label use of Broad-spectrum antiviral based on Article published in CHEST in October 2020).
- I believe the treatment was lifesaving and I am not sure why it has not been more widely promoted by the CDC and NYSDOH.
mAb Infusions and Covid-19 Variants

• Emergency use authorization (EUA) from FDA has changed
  – Bamlanivimab alone is no longer approved (4/16/21)
  – Bamlanivimab/etesevimab recommended unless regions with increased variants
  – Casirivimab/imdevimab recommended in regions with higher level of variants

• NIH Guidelines – In regions where SARS-CoV-2 variants with reduced invitro susceptibility to Bam/etes; Casirivimab/Imdevimab is preferred mAb to use from the panel.
Receptor Binding Domain
Bamlanivimab

- IS potent neutralizing mAb (IgG1 with an unmodified Fc region) to the S protein that was derived from the convalescent plasma of a patient who had COVID-19
- Binds the S protein’s RBD, engaging its cognate epitope in both up and down conformations, which makes this antibody useful as a monotherapy
- Bamlanivimab together with Etesevimab an S protein-binding IgG1 with a modified Fc region, resulting in null effector function
Receptor Binding Domain
Casirivimab/Imdevimab

- Reg-cov2, chosen from a pool of 200 neutralizing mAbs present in the initial isolation of thousands of antibodies and were derived from parallel efforts using humanized mice and the sera of patients recovering from COVID-19
- The antibodies bind two distinct and non-overlapping sites on the RBD3,67
- The rationale for this antibody combination is that it is unlikely that a mutation in the S protein of SAR-CoV-2 will simultaneously render both antibodies ineffective
Receptor Binding Domain Bamlanivimab

- For Bamlanivimab, non-clinical studies show a problem with (E484D/K/Q, F490S, Q493R and S494P, amino acid substitutions in the S protein RBD) that had increased resistance to this drug.
Casirivimab/Imdevimab Binding

- Variants with reduced susceptibility to casirivimab (K417E/N/R, Y453F, L455F, E484K, F486V and Q493K) or imdevimab (K444N/Q/T and V445A) each viral variant showing reduced susceptibility to one mAb remained susceptible to the other mAb; all identified variants retained susceptibility to the combination.

- The G476S, S494P and Q409E variants had reduced susceptibility (5-fold, 5-fold, and 4-fold, respectively) to casirivimab, and the N439K variant had reduced susceptibility (463-fold) to imdevimab. The casirivimab and imdevimab combination was active against all individual variants tested.
CDC Classification of Covid-19 Variants

- CDC 3 classifications of Variants
  - Interest
  - Concern
  - Consequence
CDC Classification of Covid-19 Variants

• Transmission
• Diagnostics
• Therapeutics
• Immune escape (vaccines)
• Increased proportions of illness or unique outbreak clusters
• Prevalence or expansion in the US or in other countries
mAb Infusions and Covid-19 Variants of Interest

- B.1.536 - New York variant of Interest; Nov2020
  - Sometimes E484K mutation
  - Reduced neutralization by convalescent and post vaccination sera
  - Marked in vitro reduction to Bam
  - Reduced in vitro susceptibility to Bam/Etes
  - Possible in vitro reduction to Casirivimab
  - Retains in vitro effectiveness of Imdevimab
- Recommended Casirivimab/imdevimab mAb infusion
mAb Infusions and Covid-19 Variants of Interest

- B.1.617;.1.2 - India variant of Interest; Dec 20; Feb 21
  - E484Q mutation
  - Reduced neutralization by convalescent and post vaccination sera
  - Pfizer/BioNTech vaccine were 3-fold to 6-fold less potent against the India variant than against the UK variant
  - The double mutant; contains both L452R mutation and the E484Q mutation
CDC Classification of Covid-19 Variants

Variants of Concern

*In addition to the possible attributes of a variant of interest*

- Widespread interference with diagnostic test targets
- Substantially decreased susceptibility to one or more class of therapies
- Significant decreased neutralization by antibodies generated during previous infection or vaccination
- Reduced vaccine-induced protection from severe disease
- Increased transmissibility
- Increased disease severity
mAb Infusions and Covid-19 Variants of Concern

- B.1.1.7 UK variant of concern
  - E484K mutation found is some but not all strains
  - 50% more transmissible
  - More serious illness; based on hospitalizations and fatality rates
  - Minimal impact on neutralization of convalescent and post vaccination sera
- **Recommended Bamlanivimab/etesevimab or Casirivimab/imdevimab mAb infusion**
mAb Infusions and Covid-19 Variants of Concern

- B1.427 and B.1.429 California variants of Concern
  - L452R mutation
  - 20% more transmissible; California, Arizona, Nevada,
  - More serious illness; 5x more likely to be admitted to ICU and 11x more likely to die (USCF 300 pts)
  - Reduced neutralization by convalescent and post vaccination sera
  - Marked in vitro reduction to Bam
  - Modest in vitro reduction to Bam/etes
  - Casi/imdev retains activity
  - **Recommended Casirivimab/imdevimab mAb infusion**
mAb Infusions and Covid-19 Variants of Concern

• P1 Brazilian variant of concern
  • E484K mutation
  • Reduced neutralization by post vaccination sera
  • Marked in vitro reduction to Bam alone and Bam/etes
  • Retained in vitro activity to Casi/imdev
  • If in addition found to have K417T with E484K mutation, K417T reduces Casi activity in vitro
  • Casi/imdev appears to retain activity b/c Imdevimab is unaffected

• Recommend Casirivimab/imdevimab mAb infusion
mAb Infusions and Covid-19 Variants of Concern

- B.1.351 South African variant of concern
  - E484K mutation
  - 50% more transmissible
  - Reduced neutralization by convalescent and post vaccination sera
  - Marked in vitro reduction to Bam alone and Bam/etes
  - Retained in vitro activity to Casi/imdev
  - If in addition found to have K417N with E484K mutation, K417N reduces Casi activity in vitro
  - Casi/imdev appears to retain activity b/c Imdevimab is unaffected
  - **Recommended Casirivimab/imdevimab mAb infusion**
mAb Infusions and Covid-19 Variants

Variants of High Consequence

Currently there are no SARS-CoV-2 variants that rise to the level of high consequence.

In addition to the possible attributes of a variant of concern

• Impact on Medical Countermeasures (MCM)
• Demonstrated failure of diagnostics
• Significant reduction in vaccine effectiveness
• Significantly reduced susceptibility to multiple Emergency Use Authorization (EUA) or approved therapeutics
• More severe clinical disease and increased hospitalizations
• Requires notification to WHO under the International Health Regulations, reporting to CDC, an announcement of strategies to prevent or contain transmission, and recommendations to update treatments and vaccines.
mAb Infusions and Covid-19 Variants

In Summary

• B117 (UK Variant)
  – Susceptible to both mAbs
  – Some have E484K and may become a problem

• B1351, P1 (South African and Brazilian)
  – E484K; marked reduction to Bam/etes and Bam
  – K417N and E484K; reduce casi activity
  – Casi/imd appears to retain activity b/c of imdev unaffected

• B1429/B1427 (Calif Variant)
  – L452R; marked reduction to Bam; modest reduction to Bam/ete

• B1526 (NY Variant)
  – sometime has E484K; marked reduction in Bam/ete and Bam may reduce casi; casi/imd retains effectiveness
mAb Infusions and Covid-19 Variants In Summary

• mAb may be less effective for treating cases of variants with the L452R or E484K substitution in the spike protein

• L452R is present in B.1.526.1, B.1.427, and B.1.429.

• E484K is present in B.1.525, P.2, P.1, and B.1.351, but only some strains of B.1.526 and B.1.1.7.

• L452R and E484K both are present in B.1.617.;1.2
### Neutralization for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

<table>
<thead>
<tr>
<th>Lineage with Spike Protein Substitution</th>
<th>Key Substitutions Tested</th>
<th>Fold Reduction in Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7 (UK origin)</td>
<td>N501Y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.351 (South Africa origin)</td>
<td>K417N, E484K, N501Y&lt;sup&gt;b&lt;/sup&gt;</td>
<td>no change</td>
</tr>
<tr>
<td>P.1 (Brazil origin)</td>
<td>K417T + E484K</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.427/B.1.429 (California origin)</td>
<td>L452R</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.526 (New York origin)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>E484K</td>
<td>no change</td>
</tr>
</tbody>
</table>
Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

<table>
<thead>
<tr>
<th>Lineage with Spike Protein Substitution</th>
<th>Key Substitutions Tested</th>
<th>Fold Reduction in Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7 (UK origin)</td>
<td>N501Y</td>
<td>no change</td>
</tr>
<tr>
<td>B.1.351 (South Africa origin)</td>
<td>K417N + E484K + N501Y</td>
<td>&gt;45(^c)</td>
</tr>
<tr>
<td>P.1 (Brazil origin)</td>
<td>K417T + E484K + N501Y</td>
<td>&gt;511(^c)</td>
</tr>
<tr>
<td>B.1.427/B.1.429 (California origin)</td>
<td>L452R</td>
<td>7.4</td>
</tr>
<tr>
<td>B.1.526 (New York origin)(^d)</td>
<td>E484K</td>
<td>17</td>
</tr>
</tbody>
</table>
SARS-CoV-2 Variants Circulating in the United as of 5/8/21

- **The B.1.2 variant**
- **UK Variant**
- **Calif Variant**
- **P1 Variant**
- **NY Variant**
<table>
<thead>
<tr>
<th>State</th>
<th>B.1.1.7</th>
<th>B.1.351</th>
<th>B.1.427 / B.1.429</th>
<th>P.1</th>
<th>Other lineages</th>
<th>Total Available Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona</td>
<td>66.3%</td>
<td>1.1%</td>
<td>7.2%</td>
<td>8.9%</td>
<td>16.5%</td>
<td>732</td>
</tr>
<tr>
<td>California</td>
<td>54.5%</td>
<td>1.1%</td>
<td>9.3%</td>
<td>10.1%</td>
<td>25.1%</td>
<td>5,792</td>
</tr>
<tr>
<td>Colorado</td>
<td>68.3%</td>
<td>0.5%</td>
<td>7.4%</td>
<td>4.6%</td>
<td>19.3%</td>
<td>2,429</td>
</tr>
<tr>
<td>Connecticut</td>
<td>54.6%</td>
<td>0.8%</td>
<td>0.9%</td>
<td>3.1%</td>
<td>40.5%</td>
<td>1,115</td>
</tr>
<tr>
<td>Florida</td>
<td>69.0%</td>
<td>0.4%</td>
<td>1.4%</td>
<td>9.8%</td>
<td>19.4%</td>
<td>9,255</td>
</tr>
<tr>
<td>Georgia</td>
<td>79.3%</td>
<td>1.4%</td>
<td>1.1%</td>
<td>4.4%</td>
<td>13.7%</td>
<td>1,398</td>
</tr>
<tr>
<td>Illinois</td>
<td>61.1%</td>
<td>1.0%</td>
<td>2.3%</td>
<td>22.4%</td>
<td>13.2%</td>
<td>3,854</td>
</tr>
<tr>
<td>Indiana</td>
<td>72.9%</td>
<td>0.7%</td>
<td>1.4%</td>
<td>10.8%</td>
<td>14.2%</td>
<td>1,682</td>
</tr>
<tr>
<td>Kentucky</td>
<td>76.4%</td>
<td>0.8%</td>
<td>1.9%</td>
<td>3.6%</td>
<td>18.3%</td>
<td>382</td>
</tr>
<tr>
<td>Maine</td>
<td>37.5%</td>
<td>0.8%</td>
<td>1.9%</td>
<td>3.6%</td>
<td>56.2%</td>
<td>363</td>
</tr>
<tr>
<td>Maryland</td>
<td>72.8%</td>
<td>1.1%</td>
<td>0.4%</td>
<td>0.6%</td>
<td>25.0%</td>
<td>1,167</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>51.6%</td>
<td>0.1%</td>
<td>1.2%</td>
<td>13.6%</td>
<td>33.5%</td>
<td>7,307</td>
</tr>
<tr>
<td>Michigan</td>
<td>81.3%</td>
<td>0.4%</td>
<td>1.1%</td>
<td>2.4%</td>
<td>14.9%</td>
<td>4,892</td>
</tr>
<tr>
<td>Minnesota</td>
<td>79.3%</td>
<td>1.0%</td>
<td>5.0%</td>
<td>2.0%</td>
<td>12.7%</td>
<td>7,780</td>
</tr>
<tr>
<td>Missouri</td>
<td>79.3%</td>
<td>1.2%</td>
<td>1.0%</td>
<td>6.0%</td>
<td>12.4%</td>
<td>483</td>
</tr>
<tr>
<td>Nevada</td>
<td>63.8%</td>
<td>2.1%</td>
<td>7.9%</td>
<td>3.3%</td>
<td>22.8%</td>
<td>329</td>
</tr>
<tr>
<td>New Hampshire</td>
<td>48.9%</td>
<td>2.9%</td>
<td>6.2%</td>
<td>42.1%</td>
<td>763</td>
<td></td>
</tr>
<tr>
<td>New Jersey</td>
<td>50.6%</td>
<td>0.2%</td>
<td>0.8%</td>
<td>3.2%</td>
<td>45.3%</td>
<td>2,925</td>
</tr>
<tr>
<td>New Mexico</td>
<td>68.9%</td>
<td>0.3%</td>
<td>3.6%</td>
<td>1.1%</td>
<td>26.2%</td>
<td>366</td>
</tr>
<tr>
<td>New York</td>
<td>53.8%</td>
<td>0.9%</td>
<td>1.2%</td>
<td>4.4%</td>
<td>39.7%</td>
<td>1,607</td>
</tr>
<tr>
<td>North Carolina</td>
<td>63.3%</td>
<td>1.2%</td>
<td>0.7%</td>
<td>2.4%</td>
<td>32.5%</td>
<td>2,243</td>
</tr>
<tr>
<td>Ohio</td>
<td>75.2%</td>
<td>0.7%</td>
<td>0.9%</td>
<td>5.6%</td>
<td>17.6%</td>
<td>1,095</td>
</tr>
<tr>
<td>Oregon</td>
<td>47.3%</td>
<td>3.3%</td>
<td>15.9%</td>
<td>9.4%</td>
<td>24.2%</td>
<td>736</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>64.6%</td>
<td>0.8%</td>
<td>0.9%</td>
<td>2.5%</td>
<td>31.2%</td>
<td>4,503</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>72.5%</td>
<td>2.3%</td>
<td>2.3%</td>
<td>2.9%</td>
<td>22.3%</td>
<td>345</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>44.7%</td>
<td>0.1%</td>
<td>1.9%</td>
<td>9.5%</td>
<td>43.9%</td>
<td>1,269</td>
</tr>
<tr>
<td>Tennessee</td>
<td>85.3%</td>
<td>0.1%</td>
<td>1.0%</td>
<td>3.4%</td>
<td>10.2%</td>
<td>1,152</td>
</tr>
<tr>
<td>Texas</td>
<td>75.4%</td>
<td>0.3%</td>
<td>1.6%</td>
<td>5.7%</td>
<td>17.1%</td>
<td>4,021</td>
</tr>
<tr>
<td>Vermont</td>
<td>71.0%</td>
<td>2.2%</td>
<td>2.5%</td>
<td>2.8%</td>
<td>21.8%</td>
<td>899</td>
</tr>
<tr>
<td>Virginia</td>
<td>74.2%</td>
<td>1.2%</td>
<td>2.8%</td>
<td>2.8%</td>
<td>21.8%</td>
<td>899</td>
</tr>
<tr>
<td>Washington</td>
<td>59.6%</td>
<td>1.9%</td>
<td>13.9%</td>
<td>8.8%</td>
<td>15.8%</td>
<td>1,372</td>
</tr>
<tr>
<td>West Virginia</td>
<td>60.5%</td>
<td>0.1%</td>
<td>0.6%</td>
<td>0.2%</td>
<td>38.5%</td>
<td>821</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>65.5%</td>
<td>0.1%</td>
<td>4.4%</td>
<td>6.2%</td>
<td>23.8%</td>
<td>844</td>
</tr>
</tbody>
</table>
What's New Now

• Shorter infusion times for both cocktails
  • Regn-cov2 - 23 minutes for a 100ml bag
  • Bam/Etes - 31 minutes for a 100ml bag
• Easier for ED to accomplish
• Observation of one hour remains the same
### EUA Criteria: Then and Now

<table>
<thead>
<tr>
<th>Old EUA Criteria</th>
<th>New EUA Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• BMI &gt; 35</td>
<td>• BMI &gt; 25</td>
</tr>
<tr>
<td>• Age &gt; 65</td>
<td>• Age &gt; 65</td>
</tr>
<tr>
<td>• Age ≥55 years and have: Cardiovascular disease, or Hypertension, or Chronic obstructive pulmonary disease</td>
<td>• Cardiovascular disease, or Hypertension, or Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>• Cancer on immusupp tx</td>
<td>• Cancer</td>
</tr>
<tr>
<td>• DM, Renal, Im tx etc.</td>
<td>• Almost every medical dx</td>
</tr>
<tr>
<td></td>
<td>• Ethnicity and Race</td>
</tr>
</tbody>
</table>
mAb Treatments for Covid 19

ON THE HORIZON
Blaze 2 Bamlanivimab for prevention

• Phase 3 trial of residents and staff in LTC facilities
  – Initially negative pts were assigned to groups and followed 80% risk reduction in contracting covid
  – Deaths P 4/139, Mab 0/161
  – 72% reduction of symptomatic covid in high-risk pts
  – 76% reduction in detection of covid by PCR
  – For those who contracted covid, mAb resulted in lower viral load and cleared more quickly
Casirivimab/Imdevimab for Prevention

• Phase 3 trial 600mg Subcutaneous injection
  – 4 injections
  – Household contacts within 96 hrs. of positive test
  – Symptomatic PCR + infection P 3.6% 8/223; Mab 0/186 0%
  – Viral load in PCR + P 6.1%; mAb 0% (10 copies/ml)
  – Any PCR + infection P 10.3%; mAb 5.4%
  – Duration of PCR positivity shorter with mAb
Covid-19 Monoclonal Antibody Infusion
Obstacles

- Time dependent
  - Education for earlier testing (high-risk populations)
  - Turn-around time for results improved
  - Infusion time for medication improved
- Referral systems in place
  - Information and resources to make informed decision by patients and providers - better known, computer-based referrals; more needs to be done
- New payment models
  - CMS - payment $450 increased from 310; 750$ for in home
- Access
  - Transportation to infusion center – grant
  - Lack of in-home infusion capability/cost – above sub-Q injection
- Limited evidence 70-80% decrease in hosp/deaths
Summary

• mAb infusions reduce hospitalizations/deaths in outpatients with mild/moderate Covid
• Given variants use combination medicines
• mAb not authorized for people hospitalized unless they are admitted for another reason
• mAb infusions are promising for prevention
• Sub-Q injections like shorter infusion times will be game changers.
Event ID#:

Link to claim credits:
https://cmetracker.net/THLMI/Publisher?page=pubOpen#/getCertificate

Reminder: You have 30 days from the date of this activity to complete your evaluation and claim your continuing Education Credits.
Hypoxia

• 66 yo male htn, hyperlipidemia, DM, CVA, CRI, CHF with EF 20%, on o2 at home 3 L; arrived at clinic at 70%, states walked around a bit to find it.
  – Sat inc to 92 percent; we infused then sent to ER for admission. Pt had sx for 5 days at time of infusion. Pt admitted from 1/21-2/14, placed on apixaban for 3 wks, thrombosis work up negative.
  – Breathing returned to baseline
mAb vs Convalescent Plasma

- Convalescent plasma, a grab bag, not knowing the effective titers of ab that you may have
- Dosing with mAbs more precise
- Less risk of blood borne illness
- Polyclonal nature of CPT different ab targeting multiple epitopes may be useful with variants