COVID-19 Evidence Accelerator Collaborative

Lab Meeting 44

Thursday, November 4th, 2021, 3 - 4:00 pm ET

Call Summary

Overview of Lab Meeting 44

During the 44th lab meeting of the vaccines and therapeutics accelerator we heard from three groups about ongoing platform trials. First, Dr. Edward Mills of McMaster University discussed the TOGETHER Adaptive Platform Trial which is investigating a series of treatments for COVID. Next, we heard from Dr. Stacey Adam of the Foundation for the National Institutes of Health (FNIH) who provided an overview of the prioritization process used to select new and repurposed agents to be investigated in the ACTIV-6 Trial. Finally, Dr. Aaron Hernandez of Duke University School of Medicine presented on ACTIV-6, an outpatient platform trial investigating agents for treatment of mild-to-moderate COVID-19.

Highly Efficient Clinical Trials: The TOGETHER Adaptive Platform Trial

Edward Mills, PhD, McMaster University

What makes useful trials different?

- Platform Trials (e.g., Remap-Cap, Solidarity, Recovery, Principle, TOGETHER)
    - Multi-arm
    - Adaptive
    - Can add/ withdraw interventions from trial based on early data
    - Very efficient

TOGETHER Trial Overview

- **Trial Setting**
    - Primarily Brazil (Minas Gerais)
    - Began trial in South Africa and moved to Brazil because greater statistical power/ less competition for enrolling patients on trial
- **Inclusion Criteria**
    - Patients over the age of 18
    - Presenting to an outpatient setting with an acute clinical condition consistent with COVID-19 & symptoms beginning within 7 days of the screening date.
    - Positive rapid test for SARS-CoV-2 antigen
    - At least one additional criterion for high-risk
- **Statistical Approach**
    - Bayesian model for primary outcomes
    - Frequentist model for secondary outcomes
    - Decisions to stop, proceed, or make changes by a blinded data safety monitoring board (DSMB)

- **Composite Outcomes**
    - Admission to hospital care
- **Primary Outcomes**
    - COVID-19 emergency setting visits due to the clinical worsening of COVID (defined as participant remaining in observation for >6 hours, not including wait time).
        - Challenge defining "emergency setting" because of confusion around meaning of "mobile hospitals."
    - Hospitalization due to progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization.
- **Secondary Outcomes**
    - WHO clinical worsening scale
    - PROMIS global health scale
    - Mortality defined and all-cause mortality
    - Cause-specific hospitalization
    - Viral clearance and viral load
    - Respiratory symptoms
    - Adverse events
    - Adverse drug reactions
    - Adherence with medications

Intervention Timeline

- **June 2020** – Started trial with three arms: Placebo, Hydroxychloroquine (HCQ), & Lopinavir/ritonavir (LPV/r)
- **October 2020** – Discontinued HCQ & LPV/r after interim analysis in October 2020
- **January 2021** – Introduced Fluvoxamine, low dose Ivermectin (IVM), & Metformin
- **March 2021** – Discontinued low dose of IVM, switched to higher dose of IVM
- **June 2021** – Discontinued use of Metformin
- **July 2021**
    - Introduced Doxazosin & Interferon-Lambda (IFN-Lambda)
    - Discontinued high dose IVM & Fluvoxamine
- **September 2021 –** Discontinued Doxazosin (experiencing issues with low blood pressure, causing falls, etc.)
- **Today/Future** – Continuing to randomize to placebo & INF-Lambda (1:1), intention to begin looking into additive effect of combined Fluvoxamine + Budesonide

Results

- **Effect of Early Treatment with HCQ or LPV/r on Risk of Extended Care or Hospitalization Among Patients**
    - Similar rates of COVID-19-associated hospitalization between HCQ (3.7%), LPV/r (5.7%), and Placebo (4.8%) arm.
- **Effect of Early Treatment with Metformin on Risk of Emergency Care and Hospitalization Among Patients with COVID-19**
    - No difference in proportion of patients with extended ER observation or hospitalization between Metformin (17.2%) and Placebo (14.5%) arm

    - Placebo was slightly more protective than Metformin
- **Effect of Early Treatment with Ivermectin 3-day on Risk of Emergency Care and Hospitalization Among Patients with COVID-19**
    - No significant difference in proportion of patients with extended ER observation or hospitalization between IVM and placebo group.
        - Relative Risk = .91 (.69, 1.19)
        - Mortality Relative Risk = .82 (.44, 1.52)
- **Effect of Early Treatment with Fluvoxamine on Risk of Emergency Care and Hospitalization Among Patients with COVID-19: The TOGETHER Randomized Platform Clinical Trial**
    - Promising results showing a reduced proportion of patients with extended ER observation or hospitalization among Fluvoxamine group (10.7%) compared to placebo group (15.7%). (32% reduction on composite primary endpoint)

ACTIV Therapeutics Pre-Clinical & Clinical Working Groups: Repurposed Agents Prioritization
Stacey Adam, PhD, FNIH

- March 2020 – began developing agent prioritization process for repurposed and new agents
- ~1200 agents reviewed, in depth reviews of ~450 agents

Scoring Criteria

- Scoring criteria used for ACTIV 1-5 adapted for types of agents used in ACTIV-6 (widely available, easily distributable, etc. Because ACTIV-6 is an entirely remote trial)
- Scored on a scale of No Go OR 0 – 4
- **Triage & Must Have Criteria:** Safety & Route of Administration
- **Must Have Criteria:** Rationale for mechanism of action (MOA) to be relevant to COVID-19, Relevant Clinical Trial Data for Early COVID-19, Real World Evidence, Drug-drug Interaction
- **Nice-to-have Criteria**: Preclinical Data, PK/PD, Need for Scientific Clarity (I.e., strong public interest)

ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications
Adrian Hernandez, MD, MHS, Duke University School of Medicine

COVID Trends

- Recent decrease in cases but will continue to change
- Global & national COVID-19 hot spots changing over time
- Evolving trends illustrate why a fixed structure for a platform trial is not always the best approach
- Flexible platform trial allows research to "go where the pandemic is going"

Addressing Unmet Need

- >80% of COVID-19 cases diagnosed in outpatient setting
- No FDA approved standard of care for COVID-19 patients with mild-to-moderate disease
- Current therapeutic options under emergency use authorization (EUA) with complexities
- Testing "on the shelf" drugs has advantages during fast-paced pandemic:
    - Expedited timeline

- Existing knowledge of safety profile
- Possibly less expensive than newly developed drugs

Study Objectives

- Primary Objective
  - To evaluate whether repurposed medications can:
    - Make outpatient participants with mild-to-moderate COVID-19 symptoms feel better faster
    - Reduce death and hospitalization, with the following evaluated from baseline through 14-days: hospitalization, death, time to symptom freedom, symptom count
- Secondary Objectives
  - To evaluate clinical outcomes in a study drug arm versus placebo arm using modified COVID Ordinal Outcomes Scale on Day 1, 7, 14, 28, and 90
  - To describe symptom resolution (3 consecutive days without symptoms)
  - To describe participants' quality of life (QOL) using Patient-Reported Outcomes Measurement Information System (PROMIS)-29 at baseline, Day 7, 14, 28, and Day 90 follow-up.

Study Design

- Platform Protocol
  - Quickly test different medications using the same infrastructure
  - Used in a wide range of settings
  - Integrated into routine COVID-19 testing programs and treatment plans
- Remote Study Visits
  - Participants use online systems to complete study surveys and report adverse events or changes in clinical status
  - Unplanned in-person or remote study visits possible if deemed necessary by study investigator

Study Drug Selection & Study Arms

- Ivermectin in COVID-19
  - Retrospective cohort studies and randomized controlled trials (RCTs) comparing patients who received Ivermectin to patients who received comparator drug or placebo have reported:
    - Shorter time to resolution of disease
    - Greater reduction in inflammatory markers
    - Shorter time to viral clearance
    - Lower mortality rates
  - Existing studies have numerous limitations including research integrity
  - Still questions about the dose-dependent relationship between dose & clinical efficacy
    - Higher, multiple doses reported to reduce time to recovery and mortality

        - Higher-than-usual doses --> concentration-dependent relationship virologic response, reduced time to PCR viral positivity over standard doses, minimal associated toxicities
        - Doses from 30 mg/day to 120 mg/day given for 3 days shown to be safe & well tolerated
- Fluticasone Furoate
    - Synthetic trifluorinated inhaled corticosteroid (ICS) with inflammatory activity
    - FDA-approved for once-daily maintenance treatment of asthma (ages 5+)
    - Proposed activity of ICS for COVID-19 is both immunomodulatory and regulation of gene transcription including ACE2 and TMPRSS2
    - PRINCIPLE Trial reported superiority of ICS (budesonide) to standard of care (SOC) in preventing hospitalization and death
    - ACTIV-6 proposes a different high-dose high-potency ICS for 14 days

Conclusions

- COVID continues as a major public health problem
- Major unmet need for treating mild-to-moderate COVID-19
    - Easy to use
    - @ Home
    - Clear benefits > risks
- ACTIV-6 is an outpatient platform trial to generate answers for repurposed medications in addition to usual care.