Passive Immunotherapy with Antibodies Against SARS CoV-2

- Single donor convalescent plasma
- Hyperimmune Intravenous Immunoglobulin (IVIg)
- Monoclonal antibodies

Single Donor Convalescent plasma

- Regulated by the FDA through clinical trials, single patient eINDs and an expanded access program (EAP) facilitated by the Mayo Clinic
- As of June 6, 2020, clinicaltrials.gov listed 87 studies administering COVID-19 convalescent plasma
  - 45 were open-label trials with no comparator
  - The remainder were randomized trials with a standard of care comparator (25); low-titer plasma comparator (8); crystalloid, IVIg or albumin comparator (8); or a comparator of packed red blood cells (1)

Mayo Clinic Expanded Access Program

- As of June 5, 2020 from https://www.uscovidplasma.org:
  - 2,467 sites
  - 7,887 physicians
  - 27,110 patients
  - 20,093 infusions

Data From the Expanded Access Program

- Cumulative data have been reported on the first 5000 patients
  - SAEs within 4 hours of transfusion were reported in 36 of 5000 (<1%) transfused patients
    - 15 deaths (4 possibly or probably related to plasma treatment)
    - 7 transfusion circulatory overload (TACO)
    - 11 transfusion related acute lung injury (TRALI)
    - 3 severe allergic reactions
  - Overall mortality was 14.9% at 7 days

Joyner et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. https://www.medrxiv.org/content/10.1101/2020.05.12.20099879v1

Additional Published Data on Convalescent Plasma

- Most open-label, case-control studies indicate some evidence of benefit
- A randomized, controlled trial of standard of care vs. standard of care + convalescent plasma in109 individuals found:
  - Clinical improvement within 28 days in 51.9% of the convalescent plasma group vs 43.1% in the control group; $P = 0.26$
  - No significant difference in 28-day mortality 15.7% vs 24.0%; OR = 0.65, $P = 0.30$

Ling Li, et al. JAMA June 3, 2020

Data Supporting the Efficacy of Convalescent Plasma in Other Infectious Diseases

- Open label, non-randomized trials
  - Ebola
  - Influenza
  - SARS

- Randomized, controlled trials
  - Argentine Hemorrhagic Fever (mortality of 16.5% vs. 1.1% in a cohort of 188 patients when treated within 8 days of symptoms)

JI Maiategui, NJ Fernandez and AJ de Damilano. Lancet December 8, 1979

Hyperimmune IVIg

- Licensed products for preventing post-transplant CMV disease (Ctyogam) and for post-exposure prophylaxis of varicella in high-risk individuals (VariZig)
- Two approaches are being taken to develop an anti-SARS-CoV-2 IVIg
  - Genetically modified cattle
  - Patients recovered from COVID-19

IVIg From Genetically Engineered Cattle

- SAB Biotherapeutics May 28 release:
  - Announced development of highly-potent neutralizing antibodies to SARS-CoV-2 that are four times higher than the most potent human convalescent plasma
  - Manufacturing of SAB-185 initiated on May 25

IVIg From Convalescent Donors

- Two randomized, placebo-controlled trials are being planned under the umbrella of ACTIV
  - Inpatient study in patients with ≤ 8 days of symptoms (+ remdesivir)
  - Outpatient study in patients at high risk of serious complications
  - Corporate partners include Emergent, Grifols and the Plasma Alliance (Takeda and CSL Behring providing products)

Monoclonal Antibodies to SARS-CoV-2

- At least 21 different products are in some stage of development
- Most target the spike protein
- Are undergoing pre-clinical evaluation as single agents and in combinations
- Clinical trials are being planned for both treatment and prophylaxis

SARS-CoV-2 Spike Protein mAbs

REGENERON science to medicine® First in Human June 2020	Two SARS-CoV-2 spike directed mAbs from their humanized Ab mouse platform and isolated from human convalescent serum First in human in hospitalized patients June 2020; NIAID/Regeneron trial in July, 2020
AbCellera Lilly First in Human May 2020	One or two SARS-CoV-2 specific mAbs, convalescent plasma First in human hospitalized patients, May, 2020; NIAID/Lilly clinical trial late June, 2020.
VIR First in Human July 2020	Vir mAb, S309, isolated from a SARS1 patient, cross-reacts with SARS-CoV-2 Collaboration under active discussion for nursing home trial
AstraZeneca First in Human July 2020	AZ has selected a 2 mAb combination against the SARS-CoV-2 spike protein Plan Phase I single dose escalation study in normal volunteers, August 2020 (DARPA) Collaboration under active discussion (BARDA funding sought for Phase 3 trial)
The Rockefeller University 1901 SCIENCE FOR THE BENEFIT OF HUMANITY First in Human Fall 2020	Michel Nussenzweig developed cocktail of two mAbs isolated from convalescent plasma, target two non-overlapping epitopes of the receptor binding domain Bristol Myers Squibb will manufacture antibodies

Slide Courtesy of Mary Marovich, NIAID

ACTIV Clinical Trials with Monoclonal Antibodies in Planning

- ACTIV-2 is an outpatient study to be done by the NIAID AIDS Clinical Trials Network (ACTG)
- ACTIV-3 is an inpatient study to be done by the NIAID International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) + the NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) + the Veterans Administration Network
- Both trials combine classic Phase 2 and Phase 3 elements into a single study using an ordinal scale for outcomes

An Evolving Ordinal Scale is Used to Classify Disease Progression in COVID-19

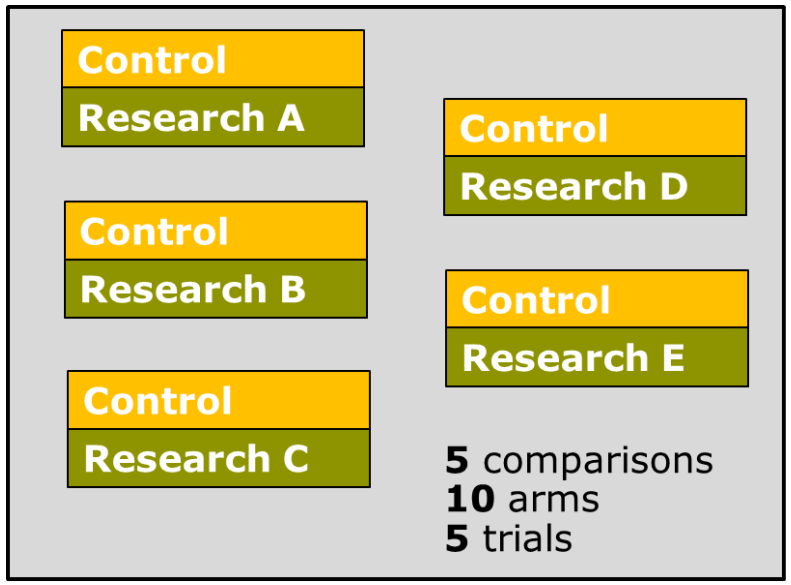
Better

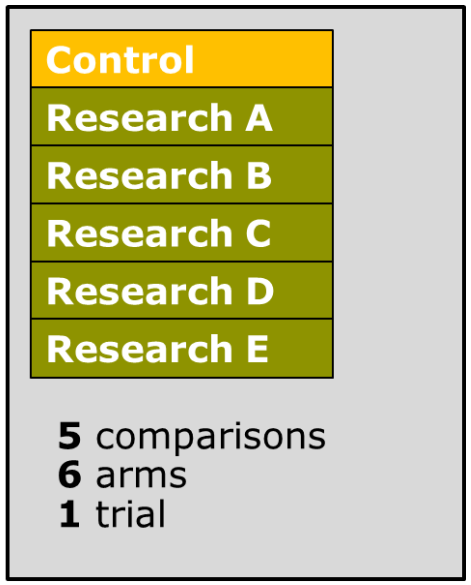
Worse

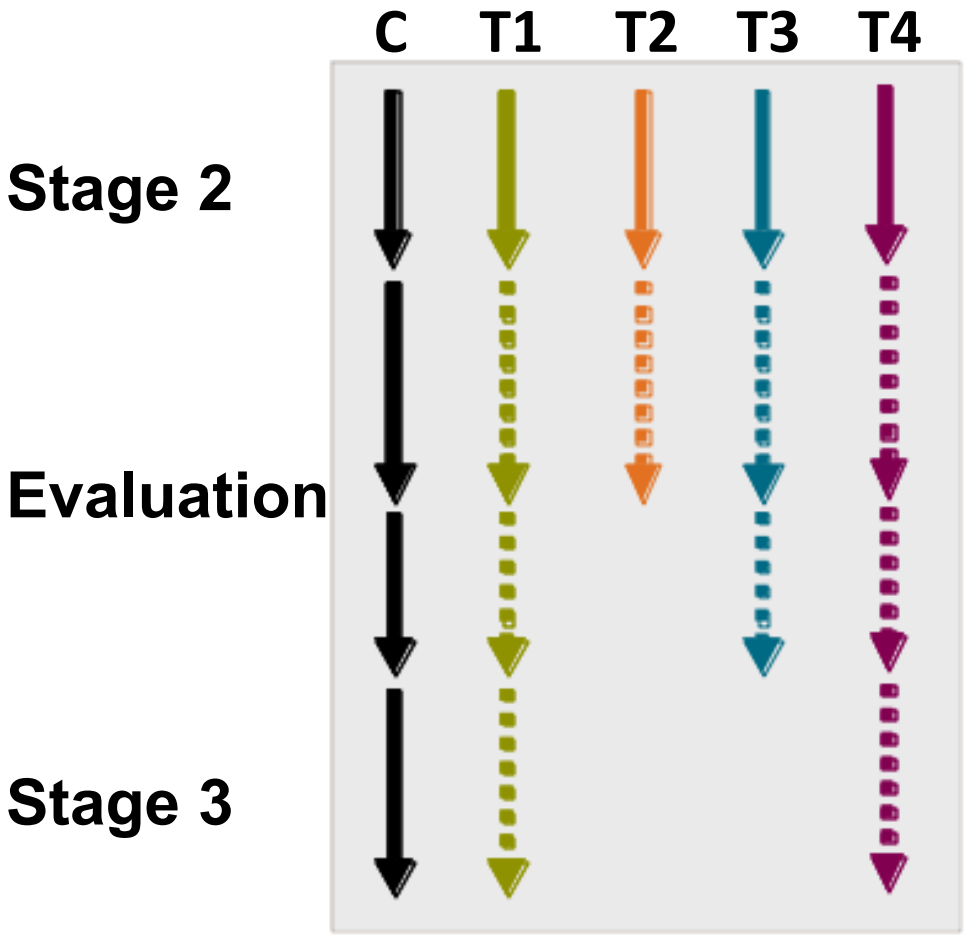
Category	
1	No limiting symptoms due to COVID-19
2	Limiting symptoms due to COVID-19
3	Moderate end-organ dysfunction
4	Serious end-organ dysfunction
5	Life-threatening end-organ dysfunction
6	End-organ failure
7	Death

Includes key non- respiratory elements of progression including thrombosis and dialysis

ACTIV-3; A Multi-Arm, Multi-Stage Trial







Mahesh Parmar, UK MRC, UCL

Summary

- A robust program examining the role of passive transfer of anti-SARS-CoV-2 antibodies is in place
- There is great enthusiasm for the use of convalescent plasma; the approach appears relatively safe; efficacy data are anxiously awaited
- Clinical trials of additional antibody products are slated to begin this summer; they include
  - Hyperimmune IVIg
  - Monoclonal Antibodies