COVID Convalescent Plasma: What do we know and what do we still need to learn?

Jeffrey L Winters, M.D.
Division of Transfusion Medicine
Mayo Clinic and Mayo Foundation
Rochester MN

Disclosure

Relevant Financial Relationships

None

Relevant Non-Financial Relationships

Investigator and author for the Covid-19 Convalescent Plasma Expanded-Access Program (EAP)

Off Label Usage

None

MAYO CLINIC

Objectives

Following the presentation, the participant will be able to:

1) **Describe the EAP, why it was created, and what it has discovered to date.**
2) **Summarize the results of published, peer-reviewed randomized controlled trials utilizing CCP to treat SARS-C0V-2.**
3) **Describe the role of CCP in treating SARS-CoV-2 and what questions remain to be answered.**

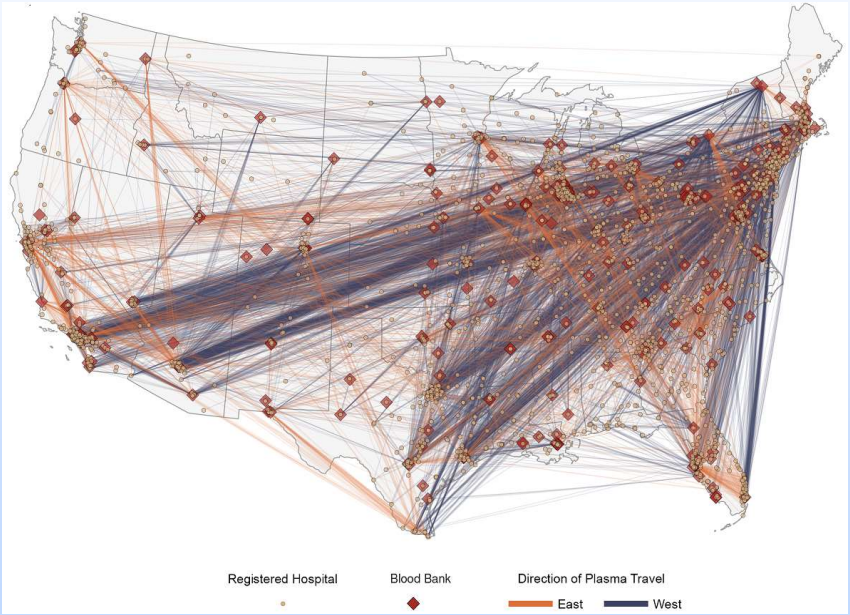
MAYO CLINIC

Expanded Access Program (EAP)

- Three potential pathways to obtain CCP
  - Single patient emergency use IND (eIND)
  - Traditional IND for clinical trial
  - Expanded Access Program
- Benefits of EAP
  - Central IRB which minimized administrative burden
  - Defined mechanism for CCP procurement with centralized funding through major blood centers
  - Structured reporting to facilitate data collection
- Goal of the EAP was to determine safety of CCP

Expanded Access Program (EAP)

- **EAP sought to improve access to CCP**
  - **All hospitals or acute care facilities in the US could participate.**
  - **Eligible patients were:**
    - **≥ 18 years of age**
    - **Severe or life threatening COVID-19**
    - **Hospitalized**
  - **Operated from April 7, 2020 to August 28, 2020.**
    - **112,654 units of CCP transfused to 94,287 patients**



Expanded Access Program (EAP)

- **Safety**
  - **First 5000 patients**
    - **Incidence of SAEs in first 4 hours after transfusion was <1%**
    - **25/36 felt to be related to transfusion**
      - **Death n=4**
      - **TACO n=7**
      - **TRALI n=11**
      - **Severe allergic n=3**
    - **Only 2/36 judged to be related**
    - **Seven-day mortality rate of 14.9%**
  - **First 20000 patients**
    - **Transfusion reactions n=78, <1%**
    - **Thromboembolic or thrombotic events n=113, <1%**
    - **Cardiac events n=677, 3%**
    - **The majority of thrombotic (n=75) and cardiac (n=597) classified as not related to transfusion**
    - **Seven-day mortality rate of 13%**

Expanded Access Program (EAP)

- **Efficacy**
  - **3082 patients received only one unit of plasma for which stored samples were available**
  - **Anti-SARS-CoV-2 neutralizing antibody titer retrospectively determined**
  - **Death occurred within 30 days after transfusion in:**
    - **115/515 (22.3%) high-titer group**
    - **549/2006 (27.4%) medium-titer group**
    - **166/561 (29.6%) low-titer group**
  - **Lower risk of death in high-titer vs. low-titer groups in those not receiving mechanical ventilation (RR 0.66; 95% confidence interval 0.48 to 0.91)**
  - **No difference in risk of death in high-titer vs. low-titer groups who received mechanical ventilation (RR 1.02; 95% confidence interval 0.78 to 1.32)**

Expanded Access Program (EAP)

- **References**
  - **Bloch et al. Development of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest* 2020;130:2757-2765**
  - **Joyner et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest* 2020;130:4791-4797.**
  - **Joyner et al. Safety update: COVID-19 convalescent plasma in 20000 hospitalized patients. *Mayo Clin Proc* 2020;95:1888-1897.**
  - **Andersen et al. Recruitment strategy for potential COVID-19 convalescent plasma donors. *Mayo Clin Proc* 2020;95:2343-2349.**
  - **Joyner et al. Convalescent plasma antibody levels and risk of death from Covid-19. *N Engl J Med* 2021;384:1015-1027.**

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-Threatening COVID-19. A Randomized Clinical Trial

- **Design**
  - **Wuhan China**
  - **Open-label multicenter RCT**
  - **Primary Outcome – time to clinical improvement within 28 days**
    - **Discharged alive or improvement by 2 points on a 6-point scale**
  - **Secondary Outcomes**
    - **28-day mortality**
    - **Time to discharge**
    - **Rate of viral PCR negativity from baseline**
  - **Severe or life-threatening clinical symptoms**
  - **Planned accrual of 100 patients in each arm**
  - **Plasma with titer >1:640 transfused at 4 to 13 ml/kg**

Li et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-threatening COVID-19. A Randomized Clinical Trial. *JAMA* 202;324:460-470.

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-Threatening COVID-19. A Randomized Clinical Trial

- **Results**
  - **103 patients randomized**
  - **Primary Outcome**
    - **Overall - 51.9% (27/52) CCP group and 43.1% (22/51) of control (difference 8.8%, [CI -10.4 to 28%]; Hazard ratio 1.40 [CI 0.79 to 2.49]; p=.26)**
    - **Severe Disease - 91.3% (21/23) CCP group and 68.2% (15/22) of control (Hazard ratio 2.15 [CI 1.07 to 4.32]; p=.03)**
    - **Life-threatening Disease – 20.7% (6/29) CCP group and 24.1% (7/29) of control (Hazard ratio 0.88 [CI 0.30 to 2.63]; p=.83)**
  - **Secondary Outcomes**
    - **No significant difference in mortality and time to discharge**
    - **CCP associated with negative PCR at 72 hours in 87.2% vs 37.5% (OR 11.39 [CI 3.91 to 33.18]; p<.001**
  - **Two patients experienced adverse events within hours after transfusion (allergic and TAD)**

Li et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-threatening COVID-19. A Randomized Clinical Trial. *JAMA* 202;324:460-470.

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-Threatening COVID-19. A Randomized Clinical Trial

- **Considerations**
  - **Trial closed before targeted recruitment leading to it being under-powered**
  - **Median interval between onset of symptoms and randomization was 30 days**
  - **Open –label**
  - **Care beyond CCP not protocolized**
  - **Short follow-up of 28 days**
  - **No placebo control**

Li et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-threatening COVID-19. A Randomized Clinical Trial. *JAMA* 202;324:460-470.

Convalescent plasma in the management of moderate covid-19 in adults in India Open label phase II mulicentre randomized controlled trial (PLACID Trial)

- **Design**
  - **India**
  - **Open-label multicenter RCT**
  - **Primary Outcome – composite of progression to severe disease and mortality at 28 days**
  - **Secondary Outcomes**
    - **Time to symptom resolution**
    - **Change in oxygen requirements**
    - **Duration of respiratory support**
    - **Proportion requiring ventilation**
    - **Sequential organ failure assessment score**
    - **Rate of viral PCR negativity from baseline**
  - **Moderate clinical symptoms**
  - **Two 200 ml doses of CCP transfused 24 hours apart**

Agarwal et al. Convalescent plasma in the management of moderate covid-19 in adults in India Open label phase II mulicentre randomized controlled trial (PLACID Trial). *BMJ* 2020;371:m3939

Convalescent plasma in the management of moderate covid-19 in adults in India Open label phase II mulicentre randomized controlled trial (PLACID Trial)

- **Results**
  - **464 patients randomized**
  - **Primary Outcome**
    - **19% (44/235) CCP arm versus 18% (41/229) (risk difference .008 [CI -0.062 to 0.078]; risk ratio 1.04 [CI 0.71 to 1.54]**
    - **Further examined outcomes in those with titers ≥1:80 versus best standard care with no differences.**

Agarwal et al. Convalescent plasma in the management of moderate covid-19 in adults in India Open label phase II mulicentre randomized controlled trial (PLACID Trial). *BMJ* 2020;371:m3939

Convalescent plasma in the management of moderate covid-19 in adults in India Open label phase II mulicentre randomized controlled trial (PLACID Trial)

- **Considerations**
  - **Trial achieved targeted enrollment**
  - **Median interval between onset of symptoms and randomization was 3 days**
  - **Open –label**
  - **Care beyond CCP not protocolized**
  - **Short follow-up of 28 days**
  - **No placebo control**
  - **Titers not determined on CCP prior to transfusion 2/3rds with neutralizing antibody titer > 1:20 with median of 1:40**

Agarwal et al. Convalescent plasma in the management of moderate covid-19 in adults in India Open label phase II mulicentre randomized controlled trial (PLACID Trial). *BMJ* 2020;371:m3939

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

- **Design**
  - **Argentina**
  - **Blinded multicenter RCT**
  - **Primary Outcome – development of severe respiratory disease**
  - **Secondary Outcomes**
    - **Life-threatening respiratory disease**
    - **Critical systemic illness**
    - **Death**
  - **75 years or older and 65 to 75 with at least one coexisting condition**
  - **250 ml of CCP with titer >1:1000 versus 250 ml saline**

Libster et al Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults.
N Engl J Med 2021:384:610-618.

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

- **Results**
  - **160 patients randomized**
  - **Primary outcome**
    - **16% (13/80) CCP arm versus 31% (25/80) in placebo arm developed severe respiratory disease (relative risk 0.52 [CI 0.29 to 0.94] p=0.03)**
  - **Dose-dependent effect seen with IgG titer of infused plasma**
  - **No adverse events were identified**

Libster et al Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults.
N Engl J Med 2021:384:610-618.

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

- **Considerations**
  - **Trial achieved 76% of targeted accrual**
  - **CCP or placebo administered within 72 hours of enrollment**
  - **Placebo controlled, double-blinded**
  - **Care beyond CCP not protocolized**
  - **Short follow-up of 28 days**
  - **High-titer units used**

Libster et al Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults.
N Engl J Med 2021:384:610-618.

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

- **Design**
  - **Argentina**
  - **Blinded multicenter RCT**
  - **Primary Outcome – clinical status at 30 days measured on a 6-point scale ranging from recovery to death**
  - **Secondary Outcomes**
    - **Time to discharge**
    - **Time to discharge from ICU**
    - **Time to improvement by 2 points**
    - **Time to death**
    - **Time to full recovery**
  - **Severe clinical symptoms**
  - **Single unit of CCP with a minimum titer of 1:400 versus saline**

Simonovich et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia *N Engl J Med* 2021;384:619-629.

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

- **Results**
  - **333 patients randomized (228 CCP versus 105 placebo)**
  - **Primary outcome**
    - **No significant difference seen in clinical outcome on ordinal scale (odds ratio 0.83 [CI 0.52 to 1.35] p=0.46)**
  - **Mortality 10.96% with CCP versus 11.43% with placebo (risk difference -0.46% [CI -7.8 to 6.8]**
  - **Total SARS-CoV-2 antibody titers tended to be higher at 48 hours in CCP group**
  - **Adverse events and serious adverse events were similar between the groups**

Simonovich et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia *N Engl J Med* 2021;384:619-629.

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

- **Considerations**
  - **Trial achieved targeted accrual**
  - **CCP or placebo administered within 8 days of onset of symptoms**
  - **Placebo controlled, double-blinded**
  - **Care beyond CCP not protocolized**
  - **Short follow-up of 30 days**
  - **High-titer units used**

Simonovich et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia *N Engl J Med* 2021;384:619-629.

Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial

- **Design**
  - **Chile**
  - **Open-label single center RCT**
  - **Primary Outcome – composite of mechanical ventilation, hospitalization > 4 days, or death**
  - **Secondary Outcomes**
    - **Days of mechanical ventilation**
    - **Time to respiratory failure**
    - **Hospital length of stay**
    - **Mortality at 30 days**
    - **SARS-CoV-2 PCR clearance rate**
  - **Patients with mild illness hospitalized within 7 days of symptom onset with risk factors for progression**
  - **Two 200 ml units of CCP 24 hours apart at enrollment or at prespecified worsening of respiratory function. Titer ≥ 1:400**

Balcells et al. Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial. *PLoS Med* 2021;18:e1003415.

Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial

- **Results**
  - **58 patients randomized with 57 completing the trial**
  - **43.3% (13) in the deferred group received CCP.**
  - **Primary outcome**
    - **No significant difference seen in composite outcome- 32.1% versus 33.3% (odds ratio 0,95 [CI 0.32 to 2.84] p>0.999)**
  - **Mortality was 17.9% vs 6.7%, mechanical ventilation 17.9% vs 6.7%, and prolonged hospitalization 21.4% vs 30.0%. Viral clearance was also not statistically different at day 3 and day 7.**
  - **Total number of days mechanical ventilation was higher in early CCP group**
  - **Two patients experienced serious adverse events within 6 hours of infusion**

Balcells et al. Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial. *PLoS Med* 2021;18:e1003415.

Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial

- **Considerations**
  - **Trial achieved targeted accrual**
  - **CCP administered within 3 days of enrollment in deferred group**
  - **Open-label**
  - **Care beyond CCP not protocolized**
  - **Short follow-up of 30 days**

Balcells et al. Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: A randomized phase II clinical trial. *PLoS Med* 2021;18:e1003415.

Other Randomized Controlled Trials

- **Recovery Trial**
  - **Closed due to futility**
  - **1873 deaths among 10406 randomized patients with no significant difference in endpoint of 28 day mortality (18% vs 18%; risk ration 1.04 [CI 0.95 to 1.14]; p=0.34**
- **Convalescent Plasma for Hospitalized Adults with Acute COVID-19 Respiratory Illness (CONCOR-1)**
  - **Closed due to futility**
  - **614 patients enrolled**
- **Convalescent Plasma in Outpatient with COVID-19 (C3PO)**
  - **Closed due to futility**

Association of Convalescent Plasma Treatment with Clinical Outcomes in Patients with COVID-19. A Systemic Review and Meta-analysis

- **Examined 4 peer reviewed RCTs and 6 publicly available RCTS involving 1060 patients**
  - **Most patients were from the Recovery Trial**
- **In the 4 published trials:**
  - **Risk ratio of mortality: 0.93 [95%CI 0.63 to 1.38]**
  - **Absolute risk difference: - 1.21% [95%CI -5.29% to 2.88%]**
  - **Hazard ratio for Length of Stay: 1.17 [95%CI 0.07 to 20.34]**
  - **Risk ratio of mechanical ventilation: 0.76 [95%CI 0.20 to 2.87]**

Janiaud et al. Association of Convalescent Plasma Treatment with Clinical Outcomes in Patients with COVID-19. A Systemic Review and Meta-analysis. JAMA 2021;325:1185-1195.

Association of Convalescent Plasma Treatment with Clinical Outcomes in Patients with COVID-19. A Systemic Review and Meta-analysis

- **In the 10 available trials:**
  - **Risk ratio of mortality: 1.02 [95%CI 0.92 to 1.12]**
  - **Absolute risk difference: -1.21% [95%CI -5.29% to 2.88%]**

Janiaud et al. Association of Convalescent Plasma Treatment with Clinical Outcomes in Patients with COVID-19. A Systemic Review and Meta-analysis. JAMA 2021;325:1185-1195.

Association of Convalescent Plasma Treatment with Clinical Outcomes in Patients with COVID-19. A Systemic Review and Meta-analysis

CCP compared to placebo was not significantly associated with decreased all cause mortality or with any benefit for other clinical outcomes

Janiaud et al. Association of Convalescent Plasma Treatment with Clinical Outcomes in Patients with COVID-19. A Systemic Review and Meta-analysis. JAMA 2021;325:1185-1195.

Conclusions

Evidence in support of use of CCP is currently lacking from randomized controlled trials

Questions & Discussion