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

Source: Simonovich VA, et al. N Engl J Med. 2020 Nov 24, 2020. DOI: 10.1056/NEJMoA2031304
A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia: Study Design

| Study Design |
|-------------|
| **Background**: Double-blind, placebo-controlled, multicenter trial using convalescent plasma for the treatment of COVID-19 in Argentina between May 28-August 27, 2020. |
| **Location**: 12 clinical sites in Argentina |
| **Inclusion Criteria** (n = 333) |
| - RT-PCR assay of a respiratory tract sample positive for SARS-CoV-2 |
| - Radiographically confirmed pneumonia |
| - At least of the following severity criteria: SaO₂ <93%, PaO₂/FiO₂ <300 mm Hg, SOFA score of two or more points above baseline status |
| - Age ≥18 years |
| **Exclusion Criteria** |
| - Pregnant or lactating; infectious cause for pneumonia other that SARS-CoV-2, requirement for mechanical ventilation, multiorgan failure |
| **Randomization**: 2:1 (convalescent plasma: control) |
| **Primary Endpoint** |
| - Clinical status at 30 days based on 6-point ordinal scale |

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**Treatment Groups**

- **Single administration of Covid-19 convalescent plasma plus standard of care** *
- **or**
- **Placebo plus standard of care** ‡

*Convalescent patients with a minimum SARS-CoV-2 total antibody titer of 1:400 were accepted as plasma donors. Convalescent plasma was from a single donor or from a pool of two to five donors. The total antibody titer goal in convalescent plasma pools before transfusion was above 1:800 in all cases.

‡ Patients were allowed to receive antiviral agents, glucocorticoids, or both according to the standard of care at the provider health care institution.

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

| Baseline Characteristics                  | Convalescent plasma (n = 228) | Placebo (n = 105) |
|------------------------------------------|--------------------------------|-------------------|
| Median age (IQR) – years                 | 62.5 (53–72.5)                 | 62 (49–71)        |
| Age category – no. (%)                   |                                |                   |
| <65 yr                                   | 126 (55.3)                     | 54 (51.4)         |
| ≥65 to <80 years                         | 75 (32.9)                      | 43 (41)           |
| ≥80 years                                | 27 (11.8)                      | 8 (7.6)           |
| Female sex – no. (%)                     | 67 (29.4)                      | 41 (39.0)         |
| Median time to onset of symptoms (IQR) – days | 8 (5–10)                      | 8 (5–10)          |
| Laboratory values                        |                                |                   |
| Median total SARS-CoV-2 antibody titer (IQR) | 150 (0–1:800)                 | 1:50 (0–1:1600)  |
| Negative total SARS-CoV-2 antibody titer – no./total no. (%) | 65/145 (44.8)                | 34/70 (48.6)      |
| Median d-dimer level (IQR) — ng/ml       | 697 (470–1150)                 | 797 (550–1224)    |
| Median ferritin level (IQR) — ng/ml      | 939 (441–1634)                 | 645 (362–1180)    |
| Severity inclusion criteria – no. (%)    |                                |                   |
| Oxygen saturation < 93% at FiO2 0.21     | 224 (98.2)                     | 100 (95.2)        |
| mSOFA or SOFA ≥2                         | 32 (14)                        | 17 (16.2)         |

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| Baseline Characteristics                     | Convalescent plasma (n = 228) | Placebo (n = 105) |
|----------------------------------------------|-------------------------------|------------------|
| Hospitalization area at enrollment — no. (%)|                               |                  |
| Emergency department                         | 11 (4.8)                      | 3 (2.9)          |
| General ward                                 | 150 (65.8)                    | 77 (73.3)        |
| Critical care unit                           | 67 (29.4)                     | 25 (23.8)        |
| Use of oxygen supplementation (n=299) — no. (%)|                               |                  |
| Low-flow nasal cannula                       | 146 (64.0)                    | 70 (66.7)        |
| Venturi or nonrebreather mask                | 49 (21.5)                     | 16 (15.2)        |
| High-flow nasal cannula                      | 11 (4.8)                      | 7 (6.7)          |
| Noninvasive ventilatory support              | 0                             | 0                |

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

| Baseline Characteristics                              | Convalescent plasma (n = 228) | Placebo (n = 105) |
|-------------------------------------------------------|-------------------------------|------------------|
| Coexisting conditions — no. (%)                       |                               |                  |
| No other conditions                                   | 80 (35.1)                     | 37 (35.2)        |
| Body-mass index >30                                   | 104 (45.6)                    | 52 (49.5)        |
| Hypertension                                          | 111 (48.7)                    | 48 (45.7)        |
| Diabetes                                              | 40 (17.5)                     | 21 (20)          |
| Chronic obstructive pulmonary disease                 | 23 (10.1)                     | 2 (1.9)          |
| Asthma                                                | 9 (3.9)                       | 5 (4.8)          |
| Chronic renal failure                                 | 10 (4.4)                      | 4 (3.8)          |
| Hematologic cancer                                    | 4 (1.8)                       | 3 (2.9)          |
| Solid tumors                                          | 23 (10.1)                     | 11 (10.5)        |
| Current tobacco use                                   | 6 (2.6)                       | 6 (5.7)          |
| Previous tobacco use                                  | 101 (44.3)                    | 37 (35.2)        |
| Congestive heart failure                              | 8 (3.5)                       | 3 (2.9)          |
| Thromboembolic disease                                | 5 (2.2)                       | 2 (1.9)          |

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## A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia: Baseline Characteristics

| Baseline Characteristics                  | Convalescent plasma (n = 228) | Placebo (n = 105) |
|------------------------------------------|-------------------------------|-------------------|
| **Previous medications used — no. (%)** |                               |                   |
| ACEI or ARB                              | 269 (30.3)                    | 32 (30.5)         |
| Frequent or recent use of NSAID          | 37 (16.2)                     | 13 (12.4)         |
| Anticoagulation                          | 14 (6.1)                      | 6 (5.7)           |
| Corticosteroids                          | 7 (3.1)                       | 2 (1.9)           |
| Immunosuppressants                       | 6 (2.6)                       | 3 (2.9)           |
| Statins                                  | 61 (26.8)                     | 21 (20)           |
| **Treatments during trial† — no. (%)**   |                               |                   |
| Supplemental oxygen                      | 206 (90.4)                    | 93 (88.6)         |
| Glucocorticoids†                         | 209 (91.7)                    | 101 (96.2)        |
| Lopinavir–ritonavir                      | 7 (3.1)                       | 3 (2.9)           |
| Tocilizumab                              | 6 (2.6)                       | 8 (7.6)           |
| Ivermectin                               | 4 (1.8)                       | 1 (1)             |
| Hydroxychloroquine                       | 1 (0.4)                       | 0                 |

† Remdesivir was not available in Argentina during the trial.
‡ Glucocorticoids included low-dose dexamethasone or equivalent doses of other glucocorticoids.

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

| Outcome                                           | Convalescent Plasma (n = 228) | Placebo (n = 105) |
|---------------------------------------------------|-------------------------------|-------------------|
| Primary outcome, clinical status at 30 days — no. of patients (%)* |                               |                   |
| Death                                             | 25 (11)                       | 12 (11.4)         |
| Invasive ventilatory support                      | 19 (8.3)                      | 10 (9.5)          |
| Hospitalized with supplemental oxygen requirement | 5 (2.2)                       | 2 (1.9)           |
| Hospitalized without supplemental oxygen requirement | 8 (3.5)                       | 1 (1)             |
| Discharged without full return to baseline physical function | 30 (13.2)                     | 8 (7.6)           |
| Discharged with full return to baseline physical function | 141 (61.8)                    | 72 (68.6)         |

* Odds ratio or hazard ratio (95% CI) = 0.81 (0.50-1.31); p = 0.396

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

| Outcome                                                                 | Convalescent Plasma (n = 228) | Placebo (n= 105) | Odds Ratio or Hazard Ratio (95% CI) |
|------------------------------------------------------------------------|------------------------------|------------------|-----------------------------------|
| Secondary Outcomes                                                     |                              |                  |                                   |
| Median time from intervention (IQR) — days                            |                              |                  |                                   |
| To hospital discharge                                                  | 13 (8–30)                    | 12 (7–ND)        | Subhazard ratio, 1 (0.76–1.32)    |
| To discharge from the ICU                                              | ND (8–ND)                    | ND (6–ND))       | Subhazard ratio, 0.94 (0.48–1.82) |
| To complete restoration of physical functions†                         | 15 (9–ND))                   | 15 (7–ND)        | Subhazard ratio, 0.89 (0.66–1.18) |
| To death                                                               | ND                            | ND               | Hazard ratio, 0.93                 |
| To improvement of 2 categories in the ordinal outcome or hospital discharge within 30 days | 12 (7–29)                    | 12 (6–ND)        | Hazard ratio, 1 (0.76–1.32)       |
| Adverse Events — no (%)                                               |                              |                  |                                   |
| Any event                                                              | 153 (67.1)                   | 66 (62.9)        | Odds ratio, 1.21 (0.74–1.95)      |
| Serious event                                                          | 54 (23.7)                    | 19 (18.1))       | Odds ratio, 1.40 (0.78–2.51)      |
| Infusion-related event                                                 | 13 (5.7)                     | 2 (1.9)          | Odds ratio, 3.13 (0.69–14.11)     |

* ND denotes could not be determined. † Restitution refers to the patient’s status at baseline.

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A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia: Results—Death Rates

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A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia: Results—Invasive Ventilatory Support

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

• All enrolled patients have severe Covid-19 pneumonia

• Median time from onset of symptoms to enrollment in trial was 7 days. Thus, no firm conclusion can be made regarding the potential efficacy of passive immune therapy earlier in the course of disease

• Postinfusion reactions such as TACO and TRALI were difficult to assess and differentiate from Covid-19 progression*

• Convalescent plasma therapy is intrinsically heterogeneous.

* TACO = transfusion-associated cardiac overload, TRALI = transfusion-related acute lung injury
Conclusions: “No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo.”