CONTAIN COVID-19 – JAMA Internal Medicine Manuscript

Summary of Study and Resources for Study Team

What did our trial show?

1. COVID-19 convalescent plasma (CCP) was safe and well-tolerated.
2. Overall, over the 11 months of the trial, there was no difference in outcome that met pre-specified criteria for efficacy between CCP and placebo recipients of diverse racial-ethnic backgrounds in the US at 14 and 28 days (Figure 2).
3. Subgroup analyses were conducted because patient characteristics, treatment modalities, and possibly the virus changed over time. These analyses showed a heterogeneous treatment effect over time (eFigure 4 and 5).
    a) There was a likely benefit of CCP in the **first quarter of the trial** (Q2, April-June 2020) when remdesivir and corticosteroids were not in use (Figure 4). The effect may pertain to remdesivir more than corticosteroids. Patients on corticosteroids appeared to benefit from CCP at day 14, but when both medications were in use at randomization, CCP did not improve outcomes (rightward shift of the posterior distribution curve).
    b) The **participants changed over time**. Those in Q2 were older, less severely ill by WHO score (primarily WHO 5), had a longer symptom duration, and received high-neutralizing titer CCP (>1:160) (eTable 3).
    c) CCP that may have met FDA criteria for high-titer was used in Q2 (criteria were not in place at that time), high-titer CCP vetted by the NYBC per FDA criteria was used in Q5 (January-March 2021).

What are unanswered questions from the CONTAIN trial?

1. The relationship between patient serostatus and outcome. 66% of patients from whom sera were available was seropositive, but analysis was limited by missing samples (145) in Q2.
2. Given that CCP for the study at all sites originated from NYC, viral variants that emerged after Q2 may have affected CCP efficacy in later months and other states. NY area had alpha and iota. Florida had alpha and beta. Texas had alpha. Delta was likely present at all sites the end of the study.
3. The nature of optimally effective CCP - future studies should evaluate:
    a) The **timing** of CCP administration compared to other medications.
    b) **Characteristics** of optimally effective CCP, including titer, isotype, neutralizing activity, and non-neutralizing Fc mediated antibody functions.
    c) **Profile of patients** in whom it is most likely to be effective. A machine modeling paper addressing this is under review.

Any additional findings to point out?

1. The Bayesian analysis allowed frequent interim analysis based on an updated prior belief in a rapidly changing pandemic.
2. Symptom duration was a poor indicator of ‘early’ disease, those with shorter durations did worse, an indication of severe, rapidly progressive disease.
3. Disease severity marked by WHO score as opposed to symptom duration may be a more accurate tool to capture “early” disease.

4. Young people with rapidly progressive symptoms may have an overwhelming disease like influenza and other viral diseases.

How will our findings impact the care of future COVID-19 patients?

1. Convalescent plasma should be considered a validated treatment for a new infectious disease for which therapy is not available. Thus, it should be deployed immediately for the next pandemic.
2. CCP may be the only therapy available to patients in Lower/Middle-Income Countries. In settings of limited resources and/or where remdesivir is not available, its safety and availability (from survivors) make it a feasible option deserving of resource allocation.
3. CCP may be one of the few options for emerging variants resistant to MAbs and/or other antivirals.
4. The trial adds to evidence from observational and matched case-control studies that CCP is most likely to be effective when given in **high-titer**, **early in disease**, particularly to those who have not or cannot mount an adequate immune response to infection (e.g. **immunosuppressed)**. RCTs and observational studies independently provide important evidence for the use of CCP in specific populations.

Who should get CCP based on findings from CONTAIN and others?

1. Patients who are early in disease, prior to requiring corticosteroids.
2. Patients who do not meet criteria for remdesivir, or in settings where remdesivir is not available or contraindicated. Reminder: there is clinical equipoise with remdesivir, which also may be most effective when given early in the course of disease, but this has not been shown in an RCT.
3. Patients who are or have not or cannot mount an adequate immune response, such as those who are seronegative, immunosuppressed, including transplant recipients, those on B cell depleting agents, those with primary and acquired immunodeficiencies that affect B cell function and antibody production. The FDA CCP EUA notes this is a population in which CCP does not need to be given ‘early’. CONTAIN and other trials in which CCP appeared effective in older patients suggest that some elderly patients may be functionally immunosuppressed.
4. Patients with immune escape with variants and/or breakthrough infection after vaccination. What is needed is **VaxPlasma** (from people who were vaccinated after recovering from COVID-19). VaxPlasma is reliably high in titer, and unlikely to need tittering prior to transfusion.

How should I use plasma?

1. Administer immediately upon admission to the hospital.
2. Give two units (at least 400 mL) of high-titer CCP, if possible, obtained **recently and locally**.
3. Transfuse as soon as decision has been made to admit patient, ideally **before** initiating remdesivir.
4. Educate patients and their families, representatives about CCP safety and track record. FFP is used daily in every hospital in the world.

REFERENCES

NB: These are the main trials (RECOVERY (group), Begin), the small RCTs (Bar, McDonnell), observational studies (Salazar), use in oncology and immunocompromised (Thompson, Senefeld), HCA meta-analysis (Egloff), local source plasma (Kunze), Bayesian analysis of RECOVERY (Hamilton).

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