May 23, 2023

NIH COVID-19 Therapy Panel

Dear Colleagues,

Thank you for meeting with us and the IDSA presidents on May 17th. We greatly appreciated the opportunity to discuss the clinical evidence on the efficacy of COVID-19 Convalescent Plasma (CCP). We found the meeting very helpful to our understanding of the panel's position on CCP.

During the discussion numerous issues were raised that could not be addressed in the limited time available. Hence, while our memory is still fresh, we thought we would write down some of these issues and address them. We do so in the spirit of continuing a line of communication and furthering understanding.

Dr. Tebas presentation.

Slide 2 states there is '*insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in hospitalized or ambulatory patients who are immunocompromised.*' The following points were made by Dr. Tebas to support this statement.

1. *Body of evidence regarding CCP efficacy is conflicting.*

This statement is true only if the data are analyzed without considering biological plausibility. In slide 5, Dr. Tebas showed the negative findings of three large inpatient trials performed outside the USA - RECOVERY, CONCOR-1 and REMAP.

As Dr. Tebas noted in his comments, the null results from each of these trials likely reflect CCP administration in late disease, when inflammatory tissue damage is rarely stemmed or reversed by antivirals, including specific antibodies. We agree. There is consensus on this point. These trials tested CCP in patients who were unlikely to benefit from antiviral therapy. However, the panel seems to have used these trials as evidence that CCP does not work. We do not understand the logic of this determination, particularly because COVID-19 guidelines stipulate defined stages of disease for other therapies. Specifically, corticosteroids benefit patients *only* in the inflammatory phase of the disease while remdesivir, like CPP and (previously) monoclonal antibodies (mAbs), do not.

In support of the conclusion that CCP treatment was administered too late in large inpatient RCTs, we note that participants who were seronegative, immunosuppressed or treated early in disease (with minimal or no oxygen supplementation) were key subgroups identifiable in RECOVERY, CONCOR-1 and REMAP (as well as in CONTAIN (1), which was conducted in the US) in which evidence of benefit was seen (2). These are exactly the participants in whom therapeutic efficacy of antibody therapy is biologically plausible. The literature on inpatient CCP treatment is now extensive and includes 39 RCTs, involving 11,303 CCP participants and 10,228 controls. Notwithstanding that many participants were in very advanced stages of illness; the aggregated data still reveal that the relative risk of mortality was

13% lower in CCP recipients than recipients of usual care (3). When the analysis are restricted to the early-use case the relative risk of mortality is reduced by about a third.

In slide 6, Dr. Tebas presented the findings of five outpatient RCTs, noting that two trials showed substantial and significant benefit, while three trials did not. As Dr. Tebas shows in his notes, if an imbalance in one of these three trials (SIREN C3PO) is corrected by removing participants who did not meet the trial's standard for entry, the findings favor CCP. CoV-Early showed a modest tendency to improvement (OR for highest symptom score = 0.86), leaving just one trial of the five that failed to find any effect at all (COnV-ert). That trial used plasma treated with methylene-blue, a known inactivator of antibody Fc function (4). A recent meta-analysis examining the combined data from these five trials concludes that CCP is effective in reducing the likelihood of hospitalization in outpatients (5).

2. *We recommend against use of current anti-SARS-CoV-2 mAbs (in vitro data suggest ineffective).*

We agree with this recommendation since all previously deployed mAbs were specific for a single viral determinant and no longer bind to newer omicron strains. We note that the problem of viral escape from mAbs does not apply to CCP, because it is a polyclonal antibody product that adapts to circulating variants. This is evident in a large sample of unselected contemporary plasma units from blood donors studied by Vitalant Labs, showing that the vast majority of potentially available CCP comes from donors with very high anti-SARS-CoV-2 titers to both legacy and currently circulating viral strains attributable to vaccine-elicited or hybrid (vaccine + infection) immunity. Antibody levels in this unselected sample of donors frequently exceeded the upper limit of detection for one of the FDA authorized assays used to qualify 'high titer' CCP and often required dilutions of 100-fold or more to obtain a reading (Dr. Michael Busch personal communication).

3. *There are very little data on the effectiveness of CCP in immunocompromised patients, making it difficult to make a recommendation for this patient group*.

We respectfully disagree. In addition to the numerous case series described in Dr. Joyner's presentation, several propensity-controlled studies and one RCT from Germany in cancer patients (19) provide evidence for efficacy in this population. A summary of these data was published in January 2023 (6).

Moreover, evidence of treatment effectiveness is seen in Dr. Tebas' Slide 7. Examining immunosuppressed patient subgroups in five trials, the slide shows two trials in which CCP was highly and significantly effective, two trials with evidence of effectiveness short of statistical significance (in one of these, the p value was between .05 and .10) and one trial in which the number of deaths was identical in both arms. Aggregating data from the 5 trials, mortality was 35% lower in CCP recipients (chi-square = 8.94, $p < .003$). Dr. Tebas's slide thus shows substantial evidence for CCP efficacy in immunocompromised patients.

The panel's neutral stance on CCP in immunocompromised patients is the crux of our concern. CCP is a logical and biologically plausible treatment for patients with B-cell defects that prevent them from producing endogenous or vaccine-elicited antibody. While the current FDA EUA authorizes CCP in this

population, including in outpatients, conducting RCTs in immunocompromised patients has logistical and ethical challenges because of disease heterogeneity and ethical concerns

However, the varicella vaccine experience illustrates that hard evidence can be obtained without an RCT. When fatal varicella was a dreadful complication for children who had been cured of leukemia, Dr. Anne Gershon, who attended our meeting, organized a study of varicella vaccine (then not yet approved by the FDA) to vaccinate children with leukemia. There was no control group. The vaccine turned out to be both effective and safe and is now standard of care (7).

4. *Paxlovid and remdesivir are highly effective treatments.*

The effectiveness of these treatments was established before widespread vaccination. The efficacy of Paxlovid in vaccinated people is uncertain. Similar to CCP, neither Paxlovid nor remdesivir has been tested in immunocompromised patients in an RCT, although there is some observational data supportive of Paxlovid efficacy in this population (8). Antibody deficiency in B-cell deficient patients often results in an inability to durably clear the virus even after one or more courses of small molecule antivirals and some patients end up receiving 'combination therapy' that includes CCP (9). We are all aware of patients who could not clear the virus until CCP was administered (for a notable case report see (10)).

Small molecule antivirals present distinctive risks and logistical challenges in immunocompromised patients that lead to reasonable hesitancy in their use on the part of clinicians in this patient population. For patients on anti-rejection medications, ritonavir drug interactions introduce risks for drug toxicities or organ rejection. Remdesivir requires multiple, sequential days of infusion. CCP, in contrast, has minimal drug interactions, and can be given in a single infusion, an important consideration in regard to access and equity.

Although head-to-head comparisons of the efficacy of CCP and antiviral drug efficacy have not been done, CCP is comparable to small molecule antivirals and mAbs in immunocompetent outpatients (11). We note that small molecule antivirals are a different type of antiviral therapy than specific immunoglobulins, with a fundamentally distinctive biological mechanism of action. Unlike small molecule antivirals, antiviral antibodies potentiate other beneficial human immune functions, including cellular effector clearance mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), complement activation and phagocytosis, in addition to their potential for viral neutralization. Fc-related activities correlated with CCP benefit in one RCT (12).

Additional concerns were raised by Dr. Tebas, including

1. Potential loss of plasma neutralization against XBB despite pre-XBB Omicron breakthrough infection (slide 8). We note that a recent study showed that CCP from individuals with hybrid immunity neutralizes omicron variants, even if the donor had not experienced an omicron infection (13), and a recent review of all available data revealed that plasma from individuals with hybrid immunity potently neutralizes BQ.1.1 and XBB.1 (14). Notably, hybrid plasma neutralization of XBB.1 is greater than the levels used for the outpatient trial that demonstrated CCP efficacy in largely antibody naïve individuals.

2. Potential logistical issues including insufficient information on the neutralizing antibody capacity of units, preferential use of older and thus perhaps outdated units by blood banks, and some uncertainty as to number of units to use. We agree that these issues are important, but they are not insurmountable. Resolvable logistical issues cannot justify a neutral recommendation. In fact, it is likely that their resolution would be accelerated were the NIH Panel to recommend that the FDA and blood banking communities join together to resolve them.

   Regarding the dilutional effect of CCP antibody, Dr. Tebas mentioned that it was in the "25-30" range. Published data indicate that the actual dilutional effect is smaller, in the 15-20 range (15-17). While effective thresholds are not established, CCP from people with COVID-19 and boosted vaccinations is sufficiently high to provide recipients with considerable antibody even with dilutional effects.

Additional concerns raised by other panel members included

3. Heterogeneity and uncertain composition of CCP units. All blood products, including red cells and platelets, as well as organ and tissue transplants, differ from small molecule drugs in this characteristic. While physicians do not know the precise composition or extent of all cellular functions before provision to patients, their use and benefit is accepted. Uncertainty is managed after use by monitoring key clinical parameters such as post-transfusion hematocrit, degree of hemostasis, or organ function. The same is possible with CCP, as physicians can follow viral Ct and re-dose with CCP as needed.

4. Dr. Gulick expressed a concern that CCP would be used in lieu of effective small molecule antivirals. In our experience, CPP is rarely given to immunosuppressed patients alone without small molecule drugs. Indeed, we recognize that sometimes combination therapy may be necessary, providing antiviral activity from both chemotherapy and immunotherapy. Competition between these two modalities should not be a significant concern. We note that past IDSA presidents attending the meeting suggested several wording options that could be incorporated into the recommendations to emphasize small molecule antivirals if this remains a continuing concern of the panel.

We hope this letter is responsive to the concerns expressed by the panel. We also want to raise two other points that we hope the panel will consider.

First, there is an urgent need for antibody-based therapies for COVID-19 in immunocompromised patients who were very dependent on prophylactic and therapeutic mAbs that are now obsolete. Therefore, we would like to ask the panel to consider and perhaps opine on what type of data they would need to *fully* recommend CCP for this population. The FDA now provides guidance and works with researchers to outline the kind of studies that would lead to approval of a drug, and we believe they would welcome such guidance from guidelines committees such as yours. This could catalyze a new investigative effort.

Given than an RCT in immunocompromised patients cannot feasibly be completed in a short time period, and that CCP is in use now, we hope the panel will consider an *interim* recommendation other

than neutrality. As we have reviewed in this letter, we believe that such a recommendation is justified by the strong safety profile of CCP (18) and evidence of CCP benefit in immunocompromised patients from case reports, case studies, propensity-matched studies, positive subgroup analyses of large trials (6), an RCT in cancer patients (19), and the current FDA EUA which sanctions CCP use in immunocompromised patients.

Second, we note that CCP differs from the other antiviral therapies in that it lacks an industry sponsor. Studies of the safety and efficacy of Paxlovid and Remdesivir were supported, and the results delivered, by large pharmaceutical companies. By contrast, CCP trials lacked the infrastructure, messaging, and coordination provided by the pharmaceutical industry that enabled the antivirals and vaccines to be studied rapidly. As a result, information about CCP was mostly available to clinicians from the medical literature and guidelines documents. Your panel plays a critical role for informing clinicians and patients about the nuances of CCP as a therapeutic option.

Sincerely,

The CCPP19.org Leadership Team: Arturo Casadevall, Jeffrey Henderson, Michael Joyner, Brenda Grossman, Nigel Paneth, Liise-anne Pirofski, Shmuel Shoham

Cc: Past and current IDSA presidents. Barbara Alexander, Paul Auwaerter, Carlos Del Rio, Anne Gershon, Cindy Sears, Richard Whitley.

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