FDA Emergency Use Authorization: Glass Half Empty?

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Summary of main point:

Recent Food and Drug Administration emergency authorization of convalescent plasma for the treatment of COVID-19 sets a dangerous precedent. This premature action discourages health care providers from conducting randomized control trials that are essential for determining its efficacy and safety.

Abstract

Recently, the Food and Drug Administration (FDA) issued emergency use authorization (EUA) of convalescent plasma (CP) for the treatment of COVID-19 hospitalized patients based on a non-peer reviewed open label observational study. Issuance of an EUA without a proven randomized control trial (RCT) sets a dangerous precedent since the premature action drives health care providers and patients away from RCTs that are essential for determining the efficacy and safety of CP. More caution should have been taken based on what was learned from the recently rescinded EUA of hydroxychloroquine and chloroquine debacle which was approved initially based on an anecdotal report. The FDA approval process for determining efficacy and safety must be based solely on data from RCTs to sustain public and professional trust for future treatment or vaccine efforts to be successful.

Key words: Emergency use authorization, convalescent plasma, randomized control trial, public trust

The use of convalescent plasma (CP) for passive immunity against severe acute viral illness spanning from 1918 Spanish flu to hepatitis A and B, Ebola, SARS and influenza have worked with varying levels of success.[1,2] The majority of the studies were low or very low in quality, lacked control groups and were at risk of bias. The antibodies from CP are presumed to exert an antiviral effect, preventing virus replication before patients produce their own humoral immune responses.[3,4] Antibodies can neutralize virus infectivity directly or through Fc-mediated functions.[5,6] Despite early promising results from anecdotal reports and observational studies for the treatment of severe acute respiratory viral infections, CP failed to demonstrate a benefit for severe influenza A virus infection in randomized controlled trials.[1,2,7,8] A recent study reported that some patients not exposed to the COVID-19 virus already had T-cells against the virus in their system.[9] This may explain previous exposure to coronaviruses may provide a head start on fighting the new virus.

On August 23, 2020, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for the use of convalescent plasma (CP) for the treatment of COVID-19 hospitalized patients based on a non-peer reviewed report. [10,11] An open-label observational multi-center study with 35,322 transfused patients conducted by the Mayo Clinic, revealed that the seven-day mortality rate was 8.7% [95% CI 8.3%-9.2%] in patients who were transfused within 3 days of a COVID-19 diagnosis and 11.9% [11.4%-12.2%] if transfused 4 or more days after diagnosis ($p<0.001$).[11] Similar findings were observed in 30-day mortality (21.6% vs. 26.7%, $p<0.0001$). For patients who received high IgG plasma (>18.45 Signal-to-cut-off: S/Co ratio), seven-day mortality rate was 8.9% (6.8%, 11.7%); 11.6% for those on medium IgG plasma (4.62 to to 18.45 S/Co ratio) (10.3%, 13.1%); and 13.7% (11.1%, 16.8%) ($p=0.048$) for recipients of low IgG plasma (<4.62 S/Co ratio) .The pooled relative risk of

mortality among patients who received high IgG plasma was 0.65 [0.47-0.92] for 7 days and 0.77 [0.63-0.94] for 30 days versus those on low IgG plasma. Overall mortality was lower in patients who received CP within 3 days of diagnosis vs. ≥ 4 days post diagnosis. Although reduced mortality rate is a positive sign, no definitive conclusion can be drawn since there was no comparison against a control group demonstrating that the treatment works. Most of the patients also received other treatment options, including antibiotics, antivirals, antifungals, corticosteroids and hydroxychloroquine. The original intent of the trial was to determine safety of CP use, not efficacy.[12] As is common with observational trials, there were multiple issues with the study design including selection bias, comparison against a control group on standard of care or concomitant use of other treatments or comparison against same cohort like those who received early vs late CP. There may be confounding variables where those receiving CP early were treated more aggressively than those who received it late.

The FDA determined that CP "may be effective" and eligible for an EUA after the analysis of 4330 patients from the Mayo Clinic data that demonstrated no difference in 7-day mortality among patients who received high IgG-titer vs. low IgG titer plasma in the overall population or in the subset of intubated patients.[10,13,14] Among the non-intubated patients, death occurred within 7 days of transfusion in 11% patients in high titer vs. 14% on low titer plasma group (p=0.03).[13,14] 7-day mortality in non-intubated patients who were < 80 years old and treated within 72 hours of diagnosis was 6.3% in the high-titer group vs. 11.3% in the low-titer group (p=0.0008). While the EUA meets "may be effective" criteria, the analysis did not appear to establish the efficacy or safety of CP because of the lack of comparison against control group.

There were only two underpowered unblinded RCT reports with a total of 189 hospitalized patients of whom 95 patients received CP at the time of the EUA approval.[15,16] In an open label RCT with 103 severe and life-threatening COVID-19 patients stratified by disease severity, 52 patients received CP and standard treatment vs. 51 patients on standard treatment.[15] There was no statistically significant difference in primary outcome of clinical improvement within 28 days where 51.9% of the CP recipients had clinical improvement versus 43.1% in the control group (OR 1.40 [95% CI 0.79-2.49], p = 0.26). Secondary outcomes did not demonstrate any significant difference among the two group; 28-day mortality (15.7% vs 24.0%; OR 0.59 [95% CI, 0.22-1.59]; p = .30) or the time from randomization to discharge (51.0% vs 36.0% discharged by day 28 (OR 1.61 [95% CI, 0.88-2.95]; p = .12). Two patients in the convalescent plasma group experienced adverse events within hours after transfusion that improved with supportive care. The trial was terminated early because of low enrollment secondary to containment of the epidemic at study locations. Another RCT (non-peer reviewed) that compared 43 patients on CP with standard care against same number of patients on standard care alone.[16] There were no differences in mortality (aOR 0.95 [CI 0.20 – 4.67], p=0.95), day-15 disease severity (aOR 1.30, [CI 0.52 – 3.33, p=0.58) or hospital length of stay (aOR 0.88, CI [0.49-1.60], p=0.68) observed between plasma-treated patients and those on standard of care. No serious adverse event was reported. The study was halted because of concerns about lack of benefit. In addition, majority of patients already had high titers of virus neutralizing antibodies at baseline. Interestingly, this may shine light as to why CP failed for the treatment of Ebola.[17,18] Future studies should consider testing patients for antibody titers prior to treatment with CP. To date, two other RCT has been reported (non-peer reviewed).[19,20] The only completed RCT was an open label parallel arm phase II trial (PLACID) in patients with moderate COVID-19

where 235 patients were enrolled in the intervention and 229 in the control group to assess composite outcome of progression to severity or all-cause mortality at 28 days.[19] Overall, CP did not improve either of the trial outcomes. Composite primary end point, progression to severe disease was achieved in 18.7% of patients in the intervention vs. 17.9% in the control arm (aOR 1.09; 95% CI 0.67-1.77). 14.5% deaths occurred in the intervention group vs. 13.5% in the control arm (aOR 1.06, 95% CI: 0.61-1.83). CP titers used in the study were low. The other underpowered open label RCT with 81 patients assessed the efficacy and safety of CP in preventing progression to severe disease or death in hospitalized patients with early COVID-19 (not peer reviewed).[20] The study was stopped early because of low enrollment. 38 patients assigned to CP had a lower rate of worsening at 15 days compared to 43 patients on standard of care at 15 days. There were no deaths or progression to mechanical ventilation in the CP arm compared to 6 patients in the control arm. Mortality rates were 0% vs 9.3% at days 15 and 29 for the active and control groups. Six serious adverse events were reported in the CP arm vs. 7 in the control. Similar to the other two underpowered RCTs, it is difficult to conclude whether CP was beneficial or not.

Serious adverse events such as lung damage, anaphylaxis and immune reactions are associated with CP use.[21] The Mayo Clinic study which was considered for the EUA reported a total of 868 serious adverse events among 20,000 patients.[12] 78 patients had transfusion reaction (<1%), thrombotic or thromboembolic events in 113 patients (<1%) and cardiac events in 677 patients (~3%). 96% of thromboembolic or thrombotic and 88% cardiac events were deemed to be unrelated to transfusion. The 7-day mortality rate was 13.0% (12.5%, 13.4%), and was higher among more critically ill patients relative to less ill counterparts, including patients admitted to the intensive care unit versus those not admitted (15.6 vs

9.3%), mechanically ventilated versus not ventilated (18.3% vs 9.9%), and with septic shock or multiple organ dysfunction/failure versus those without dysfunction/failure (21.7% vs 11.5%).

A recent updated Cochran systematic review of 19 published trials with 36,081 hospitalized patients concluded that "efficacy and safety benefits of CP cannot be determined in the absence of comparison against control group".[22] The recent National Institute of Health (NIH) updated guidelines for the treatment of COVID-19 concluded that "there are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19."[23,24] The Infectious Diseases Society of America (IDSA) issued guidelines for managing COVID-19 that recommended the use of CP in the context of a clinical trial.[25] The chief scientist of the World Health Organization stated that current data on convalescent plasma are inconclusive, lack quality evidence and should be evaluated in well designed, randomized, clinical trials.[26]

This is the second time in just seven months that the FDA's decision making has come into question. The EUA regarding hydroxychloroquine (HCQ), issued on March 28, 2020, was based solely on an anecdotal report.[27,28] The authorization resulted in confusion prompting many health systems to include HCQ in their treatment protocols. After numerous reports of adverse events and lack of meaningful benefit, the FDA was forced to withdraw the EUA on June 15, 2020.[29] It is worth noting that the FDA authorized an EUA during the 2009-2010 swine flu outbreak to allow the use of peramivir, an investigational agent, in 1,200 to 1,500 severely ill hospitalized patients with H1N1 influenza. Later, the FDA approved peramivir for

treatment of uncomplicated influenza after a randomized clinical trial failed to show any benefit of peramivir use in severely ill hospitalized patients.[30]

Issuance of an EUA without proven clinical efficacy establishes a questionable precedent since the premature authorization may drive health care providers and patients away from participating in properly designed RCTs which are essential in determining the efficacy and safety of CP. While lack of access to RCTs at many hospitals during the pandemic is a challenge, a balance between availability and scientific evidence on safety and effectiveness of promising therapies is imperative in ensuring that clinicians are not deprived from the compassionate use of CP outside of an RCT. Under the current Federal Food, Drug and Cosmetic Act (FD&C act) patients with serious or immediately life threatening diseases or conditions are permitted access to investigational drugs outside of clinical trials.[31]

Premature HCQ and CP use without evidence was a missed opportunity. The pandemic which has affected over 8 million cases in the US and 39 million worldwide (as of October 18, 2020) offers the unique opportunity to complete prospective adequately powered rigorous RCTs within a very short time.[32,33] RECOVERY (Randomized Evaluation of COVID-19 Therapy), ACTT (Adaptive COVID-19 Treatment Trial) and WHO-SOLIDARITY trials have taught us that well controlled adequately powered RCTs are possible during the challenges of the pandemic.[34-36]

The FDA's repeated failure to adhere to scientific rigor has compromised the agency's reputation for independence and science at a critical time when we are facing the public health crisis of contemporary history. The FDA's credibility is critical to ensure public confidence that key decisions are made independently and based on science. Despite years of public education and clinician efforts, vaccine hesitancy remains a major problem in the

US. Only 45.6% of adults and 62.6% among 6 month though 17 years were vaccinated against influenza during the 2018-19 season.[37] Due to the highly contagious nature of the virus, a high level of compliance with COVID-19 vaccines, when available is absolutely necessary to 'flatten the curve'. In a recent Pew research poll among 10,093 adults found only 21% would take a vaccine if it were available immediately compared to 42% in a similar poll in May.[38] The implications of such failing trust during the middle of a pandemic are concerning.

Public trust in the FDA's mission to approve safe and effective medications was built by the highly capable scientists of the FDA over the years. Moving forward, the FDA needs to establish a clear, transparent and rigorous scientific process for future emergent therapies to maintain scientific integrity and sustain public trust. The decisions should be based on evidence from well-controlled, adequately powered randomized trials and input from both internal and external subject matter experts. The data should be available to both public and clinicians throughout the process. The new process also needs to include specific terms for adequate monitoring and reporting of safety and outcomes by the providers to achieve robust post-EUA surveillance. Such improvements will help the FDA to meet its mission to deliver safe and effective access to lifesaving products during public health crises.

The FDA approval process for determining efficacy and safety must be based solely on data from the RCTs. Anything else has the potential to erode the trust of the public and thus would be a public-health tragedy. If we have learned anything from the pandemic, we need public and professional trust for future treatment and vaccine efforts to be successful. The only exception to RCT based evidence should be compassionate use when deemed absolutely necessary.

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