

Critical Analysis of the TSUNAMI Study(1)

Introduction

TSUNAMI was a multicenter randomized clinical trial of convalescent plasma for COVID-19 in hospitalized patients with moderate to severe disease. Results of the trial were initially reported in a press release posted on April 8, 2021 (<https://www.aifa.gov.it/en/-/covid-19-studio-tsunami-il-plasma-non-riduce-il-rischio-di-peggioramento-respiratorio-o-morte>) and were published on November 29, 2021(1). The authors concluded that COVID-19 Convalescent plasma (CCP) did not reduce progression of disease or death at 30 days in hospitalized patients with COVID-19.

However, we identify concerns that question whether such an absolute conclusion is justified. We are concerned that the positive signals of efficacy found in TSUNAMI - signals that were found in patient sub-groups where the biological plausibility for antibody efficacy was strongest - were either missed or not emphasized in the discussion.

Strengths

TSUNAMI was a prospective open label randomized clinical trial of moderate size that used plasma with high titer of neutralizing antibody that managed to achieve excellent balance of risk factors between experimental and control groups. Another strength was that CCP neutralizing capacity as measured with an authentic live virus neutralization assay.

Concerns

Center 02 mortality. This single site, which accounted for nearly 20% of study participants, had more than double the incidence of the study endpoint in the CP group than in the ST group, a finding that was highly significant ($p = .02$). This outlier site substantially skews the study's overall finding. In all other 26 centers combined, the net effect of CP was to reduce the study endpoint by 29% (RR = 0.71), a finding nearly significant at the level of .07. This lack of significance is largely due to underpowering – if all 27 centers had experienced the outcomes of the 26, the beneficial effect of convalescent plasma would have been statistically significant. No explanation has been provided for the discrepancy in findings for Center 02.

Too many participating centers contributed too few patients. TSUNAMI used 27 participating centers for a trial of 400 or so patients. Inter-center variability in delivery of care adds additional heterogeneity to the results, especially in pandemic conditions. Although this can be mitigated if all centers contributed sufficient patients, in TSUNAMI most centers contributed too few patients for meaningful across-center quality of care comparisons. Additionally, the centers had massively divergent findings for the effect of convalescent plasma, ranging from a protective odds ratio of 0.16 to a harmful odds ratio of 2.97.

Blood banking. It is not clear at all from the text how many different blood banks contributed which amounts of CP to which centers: while there was a minimum threshold, it cannot be excluded that several blood banks released CP with titers close to the minimum or with different pathogen inactivation technologies that could impact antibody functions, and this should be explored especially for Center 2, given that it was such a large outlier.

Duration of illness before receipt of convalescent plasma. 75% of patients in this trial had experienced symptoms for more than 5 days. The efficacy of convalescent plasma is maximal if administered soon after the onset of symptoms.

Safety. While the abstract reports that “Adverse events occurred more frequently in the CP group (12 of 241 [5.0%]) compared with the control group (4 of 246 [1.6%]; $P = .04$).”, at no point in the text is specified how many side effects were grade 3 or 4 or caused treatment discontinuation (either interruption of infusion or no repeated dose). Given the impressive amount of literature reporting CCP as a safe intervention, even within RCT, these findings are counterintuitive, unless the registered adverse events were very mild, and hence clinically not significant.

Viral Clearance. Inability to anticipate viral clearance is also a finding in TSUNAMI that goes against evidence from previous RCTs (2-7). It is not clear whether the reported differences in viral clearance was assessed at the end of the follow-up period (last NPS) or rather at specified NPS timepoints.

Signals of efficacy

Trend towards efficacy in mild pneumonia. While the median time from onset of symptoms to CP transfusion was quite long (median 8 days), signals of efficacy still emerged, possibly due to usage of high-titer units. The paper states:

“In the CP plus ST group, the primary end point occurred in 8 of 69 patients (11.6%) with a PaO₂/FiO₂ ratio of 300 mm Hg or greater at baseline and in 31 of 75 patients (41.3%) patients with a PaO₂/FiO₂ ratio from 200 to 249 mm Hg; conversely, in the ST group, the primary end point occurred in 16 of 75 patients (21.3%) with a PaO₂/FiO₂ ratio of at least 300 mm Hg at baseline and in 31 of 74 patients (41.9%) with a PaO₂/FiO₂ ratio from 200 to 249 mm Hg ($p = 0.06$).”

These results point to a clear trend towards efficacy in patients with milder disease (PaO₂/FiO₂ ratio of 300 mm Hg or greater at baseline). Although one must always be cautious in doing subgroup analysis because of the danger of cherry-picking data, this subgroup analysis is justified based on biological plausibility, whereby antibody (e.g., monoclonal antibody) is known to be most effective in early disease (8). Hypoxemia is caused by pulmonary inflammation that compromises gas exchange and CCP with high titer neutralizing antibody works primarily as an antiviral agent. There is no mechanistic plausibility for antibody to reverse life threatening pulmonary inflammation that occurs in late disease but viral neutralization early in the process can forestall the worsening of the inflammatory process thus producing a benefit in mild pneumonia. Hence, this subgroup analysis is precisely the group that would be expected to benefit from CCP, and the one where a modern RCT would focus nowadays, as it has happened for monoclonal antibodies. It is of concern that, despite growing amount of literature and late enrolment, the interim analyses (if any) were not able to readdress usage of CP towards early disease stages or focus on seronegative recipients, as happened for monoclonal antibodies trials.

Conclusions

TSUNAMI provides additional evidence, if any more was needed (9-11), that CCP administration to critically ill hypoxemic patients in the general patient population who have been ill for more than a week on average, is unlikely to be of benefit. More importantly, this trial also provides evidence for benefit in patients with milder disease with less severe hypoxia. Although a comparison of this sub-group in TSUNAMI barely missed statistical significance, this is more likely to be a Type II error from insufficient

power rather than reflect an inherent inefficacy of CCP in milder COVID disease. The trend towards CCP efficacy found in TSUNAMI in patients with milder disease is consistent with much other published data (12-15). Given biological plausibility for CCP efficacy in milder disease and consistency with other studies, the negative conclusions of Menichetti et al (1) are too absolute and do not allow for the possibility, found in their study as in several others, that CP may be effective if patients are treated while their disease is yet mild. Overall, the TSUNAMI study supports the notion that treatment of mild COVID-19 disease with CCP is effective at reducing both disease progression and mortality.

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