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Editorial

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CONVALESCENT PLASMA for SARS-CoV-2 infection: Win or Learn

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At the end of the 19th century, Emili von Behring (Figure 1) demonstrated that serum from horses infected with diphtheria or tetanus was useful in treating people affected by these diseases, inaugurating the passive immunization as a new therapeutic strategy. He received the Medicine Nobel Prize in 1901.This finding opened the door to the use of plasma from convalescent patients to treat infectious diseases; and throughout history, convalescent plasma has been used to treat many diseases, such as Spanish flu, polio, Korean hemorrhagic fever and, more recently, Ebola virus disease, or Influenza A (Influenza H1N1 virus).

The first infusions of convalescent plasma to treat Coronavirus infections were performed more than 15 years ago. Along the Severe Acute Respiratory Syndrome (SARS) epidemics in Asia, the first published articles in 2004 and 2005 showed a reduction in mortality and hospital stay length in the group of patients receiving plasma compared with those receiving standard treatment [(1)(2)]

The first series of convalescent plasma treatment cases in SARS-CoV-2 patients were published in early 2020 by Asian groups. The first article[(3)] shows an improvement in clinical and biological parameters after plasma infusion in a series of 5 critical patients. A faster neutralization of viral load is also observed. [(3)] The second article includes 19 patients with similar results. [(4)]

In the light of these preliminary first results, and in view of the fact that COVID-19 did not have effective etiological treatment, the European Commission published a guide for obtaining, analyzing, processing, storing, distributing and monitoring the use of convalescent plasma [(5)]. The document covers the use of convalescent plasma exclusively as an experimental therapy and restricts its use to clinical trials or observational studies.

In the United States, the Food and Drug Administration (FDA) authorized, by an emergency procedure, the use of convalescent plasma in hospitalized COVID-19 patients, restricting its use only to high titers of anti-SARS-CoV-2 neutralizing antibodies plasma. This authorization received criticism, cataloguing it as premature and without a basis of scientific evidence. [(6)]

The first publications designed to assess the safety of convalescent plasma concluded that the risk is similar to that of conventional plasma transfusion.[(7)] Although some authors reported potential risks, such as

circulatory overload in critical patients, the effect of the complement and the coagulation factors in an inflammatory and prothrombotic environment and the potential worsening of COVID derived from the contribution of antibodies. [8]

The first systematic reviews were published and agree to highlight the lack of scientific evidence to recommend its use. [9] When clinical trial results were available, the use of convalescent plasma has disappeared from the standard treatment [10] and, simultaneously, recommendations for its non-use come out in particular groups of patients, for instance in critically ill COVID-19 patients [11][12]

Clinical trials such as PLACID [13], PLASMAR [14] or RECOVERY [15] agree to conclude that convalescent plasma treatment has no impact on mortality in COVID-19 patients. On the other hand, other clinical trials point to a reduction in the mortality and in the progression to severe disease with the use of convalescent plasma in specific subgroups of patients, provided that the plasma contains high titers of anti-SARS-CoV-2 neutralizing antibodies. [16]

A new clinical trial, DAWn-PLASMA[17], includes three important features: early plasma administration, high-dose plasma transfusion, and the high titer of neutralizing antibodies. Unfortunately, neither shows an impact on mortality or on the evolution to severe COVID-19. Thus, it contributes to reduce the role of convalescent plasma within the available therapeutic arsenal for treating COVID-19 patients. [17]

In addition, Sekine et al. [18] reported in an open label RCT that neutralizing antibodies were present in 83.1% of patients (66.3% critically ill) at baseline. There was no significant difference in pre-specified outcomes such as 28-day mortality, days alive and free of respiratory support, duration of invasive mechanical ventilation or clinical improvement (61.3% vs 65% with standard of care). Median days between onset and infusion was 10 days, no patients received remdesivir and steroids were prescribed in 65%. The results were similar in both the subgroups of severe and critically ill.

Whereas the current evidence does not support convalescent plasma use for standardized clinical use, there are an unmet clinical need to identify potential biomarkers and different immune-phenotypes towards a personalized management. It is needed to correlate the response depending levels of complement activation, patterns of ISG expression, viral load, steroids exposure, remdesivir use, monoclonal

antibodies use, immunocompomissed status or severity of respiratory failure.

Moreover, differences in time lapsed after symptoms infection onset to randomization are extremely important. Libster et al [16] reported that when administered within 72h after onset of mild-disease in older adults, convalescent plasma reduced the progression risk (RR: 0.52; 95%CI 0.21 to 0.94) to respiratory complications. These potential benefits did not translated in lower rates of patients who underwent mechanical ventilator support in the other trials (13-17) and it might be too late to obtain a meaningful clinical effect after 72h of symptoms onset, indeed. Interestingly, the DAWn-plasma trial (17) reflects a very short timeframe of only one day between hospital admission to randomization (two days in the RECOVERY trial (15)), illustrating that it is unlikely that convalescent plasma could have been administered earlier. Therefore, ongoing trials in high risk patients such as pregnant, vulnerable immune-compromised children or solid organ transplants should consider a pre-emptive start in very early infection (within 72h of onset) before hospitalization or in nosocomial acquisition. Comparing this early intervention with monoclonal antibodies administration is another unmet clinical need. Severely immunocompromised patients, with refractory infection and unable to do a seroconversion after three weeks of therapy, is another group to be assessed as salvage therapy.The evidence reported from current trials (Table 1) can help us to learn the complexity of SARS-CoV-2 infection and the difficulty towards a personalized management, indeed.

In conclusion, the available evidence, reinforced with the publication of the DAWn-PLASMA and Sekine's clinical trials, does not support the use of convalescent plasma in the standard treatment of COVID-19. It is likely that, in the near future, more data will appear to help determine whether convalescent plasma transfusion, administered within 72 hours of symptoms onset, may benefit some subgroups of patients, with very specific clinical and biological characteristics. These findings also reinforce the need to limit compasionate use of therapies [19], performing well designed randomized clinical trials and restricting therapeutic interventions to those documented on evidences.

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Figure Legend

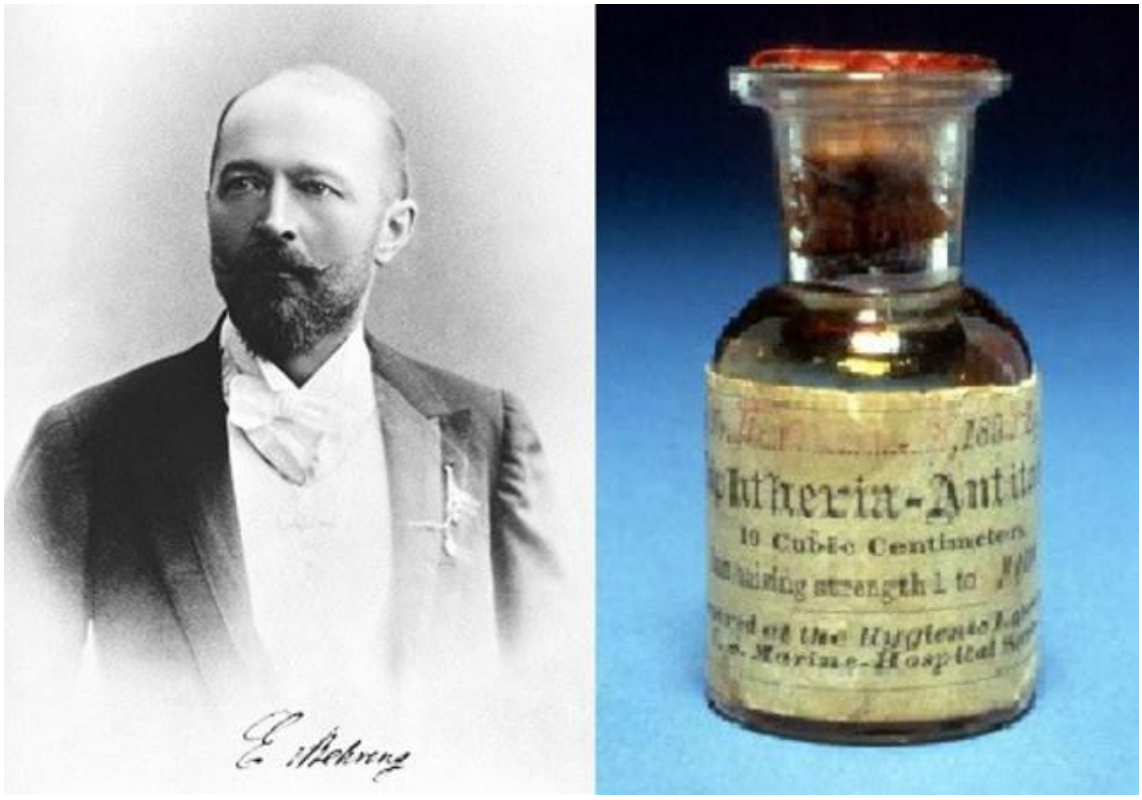

Figure 1. Emili Adolf von Behring and anti-Diphtheria serum

Table 1- Effects on mortality from randomized clinical trials of convalescent plasma vs Standard of Care for SARS-CoV-2 infection.

Trial (ref)	Country	N	Time from symptoms onset (median)	Mortality plasma	Mortality control	Comments
PLACID (13)	India	464	4 days	19%	18%	10% dexamethasone. 3% remdesivir
PLASMAR (14)	Argentina	333	8 days	10.9%	11.4%	91.7% steroids. 29.4% ICU
RECOVERY (15)	UK	16287	9 days	24%	24%	93% steroids. 5% mechanical ventilation
DAWn-PLASMA (17)	Belgium	483	7 days	16.2%	15.9%	65% steroids. 14% Remdesivir. Progression to mechanical ventilation: 15% vs 13.5%
NCT04547660 (18)	Brazil	160	10 days	22.5%	16.3%	98.8% with steroids. 61.3% vs 65% improvement