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Convalescent plasma to treat COVID-19: Following the Argentinian lead

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1. Treating COVID-19: current status and room for passive immunotherapy

As prolonged second waves as well as third waves for the COVID-19 pandemic strike a large number of nations world-wide, effective treatment of this viral pneumonia remains by and large an unmet need [1,2]. In addition to supportive care, dexamethasone provides relief to acutely ill patients [3]. In the most severely ill patients, further antagonism of inflammation with anti-IL-6 receptor monoclonal antibodies treatment may be useful [4,5]. Lastly, direct antiviral treatments, such as Remdesevir, is reportedly of limited efficacy [6].

In this context, passive immunotherapy, i.e. passive antibody administration to suppress viral replication, has been heralded as a potential treatment breakthrough [7]. Such immunotherapy encompasses polyclonal antibodies contained in plasma donations from COVID-19 convalescent patients to be transfused as such [8,9], or as hyperimmune globulin (hIVIG) after pooling and fractionation [10], and anti-SARS-CoV-2 monoclonal antibodies (MoAbs) of human or animal origin [11].

Several trials assessing the administration of anti-SARS-Cov-2 MoAbs very early after symptom initiation (less than 3 days) have demonstrated their ability to accelerate viral clearance and, more importantly, to reduce disease worsening to a point requiring hospitalization [12,13]. However, the emergence of SARS-CoV-2 variants raised the issues that such variants may resist these MoAbs (even in combined MoAb approaches) [14]. MoAb treatment in immunosuppressed patients with prolonged viral replication could also favor the selection of immune-resistant variants [15]. Further, MoAb availability and costs may limit accessibility, hampering wide-spread provision of this passive type of immunotherapy. Lastly, trials assessing MoAb in hospitalized patients, i.e. in acutely ill patients at a later time point in the disease, have been unsuccessful [16].

Anti-SARS-CoV-2 hyperimmune globulin (HyperIg) has been prepared in several locations worldwide and is currently undergoing clinical evaluation [10]. As with convalescent plasma, the polyclonal nature of antibodies in HyperIg may be advantageous with regard to variant immune-selection. Of note however, is the absence of IgM and IgA in HyperIg. Anti-SARS-CoV-2 IgM and IgA may be contributive to antiviral efficacy with the anti-SARS-CoV-2 IgG [10,17].

COVID-19 convalescent plasma (CCP) has been, and still is assessed in a large number of clinical trials, mainly in hospitalized patients [18]. By and large, most trials performed in hospitalized patients have so far been unable to demonstrate a beneficial effect of convalescent plasma [19,20], while often offering evidence that early to very early transfusion of high titer CCP may be advantageous [20,21]. Accordingly, a recent randomized study, detailed below, exhibited a favorable effect of very early administration of high-titer CCP in vulnerable patients [22]. Importantly, CCP may also benefit immunosuppressed patients unable to mount a humoral immune response to SARS-CoV-2 [23,24].

Highly heterogeneous antibody content in the transfused plasma units and limited ability to compare antibody content across trials or monitored access programs have hampered proper evaluations [25]. As

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an Ab dose effect has been reported in several instances [22,26,27], it appears essential to appropriately asses antibody content in convalescent plasma units. SARs-Co-V-2 variants, potentially resistant to antibodies present in convalescent plasma from patients having recovered from a different viral strain [28], may require adjusting donor selection criteria to include relevant convalescent donors, and possibly also vaccinated convalescent donors. Such donors may exhibit very high titer Ab with additionally, the ability to neutralize distinct viral strains [29].

2. Examining the Argentinian experience with convalescent plasma to enlighten future developments

Convalescent plasma treatment has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral aetiology [30]. Indeed, a number of studies, unfortunately all inadequately controlled for bias, have reported positive outcomes, including decreased mortality in the so-called Spanish influenza A (H1N1) infections in 1915–1917, the more recent influenza A (H1N1) infections in 2009/2010, and SARS-CoV infections in 2003. A systematic review and exploratory meta-analysis performed in 2014 revealed evidence for a consistent reduction in mortality with plasma therapy [30]. While inconclusive, such findings favored an administration of convalescent plasma as close as possible to the onset of the infectious course, at a time where pathology may be driven mainly by viral replication.

A focus on viral lung disease should not, however, refrain from examining other diseases treated by convalescent plasma and which may provide clues as to the best way to move forward regarding Covid-19. Hemorrhagic fevers are among these. While convalescent plasma to treat Ebola disease has been unable to demonstrate efficacy [31], convalescent plasma has demonstrated efficacy in another hemorrhagic fever, the Argentine Hemorrhagic Fever (AHF) [32]. As of today, convalescent plasma is a recognized treatment of this disease [33], with several features important to consider.

Argentine hemorrhagic fever is a severe viral hemorrhagic fever endemic to the pampa areas of central Argentina [34]. Junin virus (family *Arenaviridae)*, the etiologic agent of AHF, is a rodent-borne virus. *Calomys musculinus* has been identified as its principal reservoir. While an efficient attenuated vaccine manufactured in Argentina is used in high-risk individuals and reduces the incidence of AHF [35], cases continue to be observed [33]. Untreated, AHF has a mortality rate of 20%–30% resulting from hemorrhagic or neurological complications [36].

Early on, it was found that that mortality of experimental infections with arenaviruses could be reduced with immune (convalescent) plasma [37]. Clinical observations suggested that administration of such plasma early in the course of the disease was useful [38]. Evidence for the beneficial effects of this form of treatment remained inconclusive until a double-blind study in 1974–1978 comparing 500 mL convalescent plasma to 500 mL non-immune plasma to treat AHF early on (before the 9th day of symptoms) demonstrated a striking reduction of mortality associated with convalescent plasma (1/91: 1.1 %, vs 16/95: 16.5 %, ; $p < 0.05$) [32]. A retrospective study (1978–1981) further highlighted the importance of early treatment with the demonstration that convalescent plasma treatment later than after 8 days of illness was ineffective [39]. Also, standardization based on the amount of neutralizing Abs given to each patient allowed for the demonstration of an Ab dose effect with maximum efficacy (5/908: 0.55 % mortality) associated with a high dose (defined as 3,000–3,999 therapeutic units (TU)/kg) while lower doses 1,000–1,999 TU/kg and 2,000–2,999 TU/kg) were associated with increased mortality (7.7 % and 6.1 %) ($p = 0.002$) [39,40]. As a result, transfusion of convalescent plasma allowing for a dose of 3, 000–4,000 TU/kg was recommended [40]. Lastly, a late neurologic involvement associating encephalitic symptoms and fever, first described in the setting of the above-described randomized study [32], is observed 4–6 weeks after disease onset in ~10 % of patients treated with convalescent plasma, while more rarely in patients having recovered without Ab treatment. The pathophysiology of this late symptomatology, reported as generally benign and self-limited [41], remains not well understood [33].

Following these findings, a National Program for the control of AHF was developed and endorsed the early use of convalescent immune plasma in patients with AHF as the standard specific treatment [38]. Certified quality convalescent plasma banks were established in AHF endemic areas. Training programs for medical personnel of the endemic area were implemented to allow for early diagnosis and treatment. In parallel, health education for the general population was provided to promote immediate medical consultancy upon AHF symptoms initiation. Lastly but importantly, messaging toward patients having survived AHF to promote plasma donation was developed.

The availability of an effective live attenuated Junin virus vaccine resulted in a marked reduction in the incidence of AHF in the 1980's. However, this success combined with geographic extension of the endemic areas resulted in an AHF diagnosis being established more frequently late in the course of the illness in a smaller number of patients, resulting in an increase in the case-fatality rate in the early 2000's as well as potentially lesser availability in plasma donor [33]. Interestingly, the neutralizing antibody titers in vaccinees have been found to be lower than those in convalescent patients [42].

Overall, development of convalescent plasma to treat AHF highlights several important features for us to consider:

- Randomized clinical trials are essential to validate a therapeutic approach;
- When used appropriately, convalescent plasma may provide a valid therapeutic intervention to treat severe infectious disease;
- Standardized assessment of antibody content in convalescent plasma is required.
- Appropriate use entails very early intervention with standardized high Ab titer convalescent plasma;
- Such early intervention requires the set up of programs to facilitate early diagnosis and treatment as well as to ensure timely availability of convalescent plasma;
- Continuous implementation of such programs in a changing epidemiological environment, including the availability of a successful vaccine, may be a challenge;
- Such passive immunotherapy may be associated with adverse events that require reporting and careful assessment.

3. Convalescent plasma to treat COVID-19: the Argentinian studies

Building on this impressive background, our Argentinian colleagues have successfully engaged in the evaluation of COVID-19 convalescent plasma to treat COVID-19 with—notably—two clinical trials assessing the efficacy of convalescent plasma in hospitalized acutely ill patients or in less ill vulnerable patients earlier in the disease [19,22].

Simonovitch et al. randomly assigned patients hospitalized adult patients with severe Covid-19 pneumonia to receive convalescent plasma or placebo [19]. The primary outcome was the patient's clinical status 30 days after the intervention. A total of 228 patients were assigned to receive convalescent plasma and 105 to receive placebo. The median time from the onset of symptoms to enrollment in the trial was 8 days (interquartile range, 5–10), and hypoxemia was the most frequent severity criterion for enrollment. The infused convalescent plasma had a median titer of 1:3200 of total SARS-CoV-2 Ab (interquartile range, 1:800 to 1:3200]. At day 30, no significant difference was noted between the convalescent plasma group and the placebo group in the distribution of clinical outcomes (odds ratio, 0.83 (95 % confidence interval [CI], 0.52–1.35; $P = 0.46$). Overall mortality was 10.96 % in the convalescent plasma group and 11.43 % in the placebo group. Adverse events and serious adverse events were similar in the two groups. Overall, this trial confirmed the limited efficacy, if any, of convalescent plasma in patients in hospitalized acutely ill patients.

On the other hand, Libster et al. randomized vulnerable older adult patients within 72 h after onset of mild COVID-19 symptoms to receive convalescent plasma with high IgG titers against SARS-CoV-2 or placebo [22]. The primary end-point was the occurrence of severe respiratory disease. A total of 160 patients underwent randomization. In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16 %) who received convalescent plasma and 25 of 80 patients (31 %) who received placebo (relative risk, 0.52; 95 % confidence interval [CI], 0.29 to 0.94; P = 0.03), with a relative risk reduction of 48 %. A modified intention-to-treat analysis that excluded 6 patients who had a primary end-point event before infusion of convalescent plasma or placebo showed a greater effect size (relative risk, 0.40; 95 % CI, 0.20 to 0.81). Importantly, an Ab dose effect was observed with a 73 % reduction in disease worsening in recipients of CCP with a titer above the median concentration versus 31,4% in recipients of CCP with a titer below the median concentration. No adverse events were reported. In a striking contrast to findings in patients treated later in the course of the disease, this trial demonstrated that very early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults could reduce the progression of Covid-19. Such results are in agreement with earlier suggestions regarding CCP treatment of COVID-19 as well as with the earlier findings with respect to convalescent plasma to treat the Argentinian hemorrhagic fever.

Taken together, these last findings as well as the earlier findings with regard to AHF treatment clearly establish the way to move forward with regard to clinical evaluation of CCP. Early outpatient intervention to reduce COVID-19 worsening and the burden on hospital means is today's priority [43]. Studies to further assess the ability of PCC to achieve this goal are very much in need. Congratulations and many thanks to our Argentinian colleagues for showing the way!

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