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EDITORIAL

Convalescent Plasma the Old Warhorse First to be Inducted in Pandemics is not the Zippy Chippy of Derby

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Convalescent plasma (CP) therapy is one of the promising therapies used for COVID-19 patients, generated great enthusiasm in the earlier days of pandemic. In India, the permission was granted for use of CP under the ambit of ICMR trial (Placid trial) as early as April, 2020 and, it was authorized as an "off-label/emergency use authorization" therapy by the Drug Controller General, India. Subsequently it was incorporated in the "Clinical guidance for management of adult COVID-19 patients" AIIMS/ICMR-COVID-19 National Task Force/Joint Monitoring Group, MoHFW, GoI. However, in May, 2021, the therapy was excluded as an option [1].

The current issue of IJHBT, includes, a systematic review and meta-analysis on the efficacy CP in COVID-19. Author's report, that the "possible reduction in mortality, mechanical ventilation and rapid viral clearance is based on low certainty of evidence, and there is a need of high-quality evidence from RCTs" [2]. A living systematic review reports that CP offers "no benefits in treatment of patients having moderate or severe disease with certainty". CP has little to no impact on deaths from any cause, improvement in clinical condition, weaning from oxygen or mechanical ventilation" [3].

However, a systematic review, observes a 35% reduction in the odds of mortality in CP treated patients (after excluding 1 study from 10 RCTs). A lower aggregate mortality in patients transfused high titre CP (2 dose–response studies). A reduction in mortality with early administration of CP (3 days of hospital admission) based a subgroup analysis of RCTs and matched controlled studies. Notably, 11 (range, 8–16) patients need to be treated with CP to avoid 1 mortality. [4]. Further, an article with mathematical modelling, observed an "inverse correlation between CP usage and mortality per admission in the USA, and report that the population level evidence is consistent with the finding that CP reduces mortality in COVID-19. They extrapolate that the decline in use of CP may have resulted in excess deaths [5].

CP has a plausible biological therapeutic potential by the innate property of harbouring neutralizing antibodies (NAbs) against COVID-19. The response to eliminate viral infection depends on the infantry of the NAbs. The stoichiometry of these polyclonal NAbs recognize the specific viral epitopes, bind to them and thus block the entry, fusion and thus the multiplication of the virus inside the human host. The cavalry of non-neutralizing antibodies causes viral cell lysis, utilizing a variety of effector mechanism like antibody-dependant cellular cytotoxicity and or antibody-dependant cellular phagocytosis involving the natural killer cells, T-cells, macrophages and neutrophils. The antigen bound antibody can activate, complement and trigger the complement-dependant cytotoxicity. The immune modulation is articulated through signal pathways involving anti-inflammatory cytokines, anti-idiotype antibodies, compliment blocking antibodies and autoantibodies apart from influence on factors involved in homeostasis of haemostasis activating the naval and air defence [6–9].

The pathophysiology of COVID-19 involves rapid replication of the virus along with some chemokine's secretion in the initiation phase. The second phase of amplification signals rampant upscaling of inflammatory

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mediators. In the consummation phase the vicious cytokine release syndrome and the hemophagocytic lymphohistiocytosis and systemic inflammation leads to multi-organ dysfunction syndrome [6–9].

The mechanism of antibody generation as part of the host's response to the virus involves "state of the art" antibody hypermutation, isotype and class switching and selection of the most potent isotypes. This mechanism is aided by T-cells through IL-4, IL-21 and the CD40 surface activation. The B cells with maximum affinity for the antigen will continue to divide and differentiate into antibody producing cells, memory cells and plasmacytes that home into the bone marrow factory for long term propagative modelling [6–9].

Majority of COVID-19 patients will develop antibodies with in the first week, however adequate titres of may take 2 weeks. The Spike-specific (S) and Nucleocapsid-specific (N) antibodies and Receptor Binding Domain (RBD) specific antibodies titres, temporal switch etc., vary with disease severity, and antibodies wax and wane over different timelines [6–9].

The generation of a "racemic mixture of antibodies" appears just an apt response to the "quasi species existence" of the virus. Therefore, the recently collected CP is expected to have the armamentarium armed for the variants [10].

The complex interaction of CP in the host may have some undesirable influences in the host. Antibody dependant enhancement is a process in which antigen specific antibodies may actually enhance the entry of the virus in the host cells. The auto-antibodies in severe and critical patients with coagulopathy may be associated with enhanced neutrophil extracellular traps, exacerbating endothelial damage, thus supply of coagulant proteins in an already pro-coagulant pathology [11].

There are many challenges in CP therapy; the patients are past the viral phase, since it cannot be administered outside hospital settings in India. There is heterogeneity in patient profile and the viral dynamics in the host, leading to biological variability of the product, therefore, each CP unit is a unique "Batch" in itself. Further influenced by pre-analytical (such as donor selection timelines, mild/moderate/severe infection in the donor), analytical (such as neutralizing antibodies titres, surrogate antibodies detection), and post-analytical (such as apheresis, storage, thawing) variables.

To summarize—the timing, titre, dosage of CP and the end point for evaluation (correct patient profile, dose, titres, timeline relevant goal posts, for the proper evaluation of the desired action) may need to be critically reviewed for further evidence from the bench to the bedside.

To conclude—the holistic decision for CP usage should be based on individual patient's assessment, rather than an all or none dictum. The old war horse shall always be the first to be inducted in army in the wake of any pandemic. Subsequently, it may pass the baton in the relay race to monoclonal antibodies or other definitive treatment regimens. However, it may have to be relied upon again as a bridge therapy in the event of emergence of variants in the local demography.

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