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Feature Article

Considerations for Treating Corona Virus (Sars-Cov-2) Infection with Passive Immunotherapy

Abraham Karpas,[1]* Douglas Bainbridge,[2] Stephen Ash[3]

[1] *formerly Assistant Director of Research, Department of Haematology, Cambridge University Clinical School*
[2] *Emeritus Consultant in Immunology, Royal London Hospital*
[3] *Associate Dean and Emeritus Professor of Infectious Diseases, AUC School of Medicine*

*Corresponding author: karpasa@hotmail.com

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For many disease-causing viruses in man such as the polio viruses, measles, rubella and mumps, vaccination in childhood gives protection and confers life-long immunity. Other viruses such as influenza continuously mutate and need new vaccinations as fresh strains emerge each year.

Among relatively recently discovered disease-causing viruses some are not easily transmissible, like the retro-oncovirus HTLV/ATLV. This was found to cause Adult T-cell leukaemia (ATL) in Japan [1] and subsequently in some people of African origin;[2] and although not easily transmissible, it is present in a significant percentage of the population in some villages in south-west Japan. Most transmission has been found to occur shortly after birth through breast-feeding, by HTLV-infected cells in the milk of infected mothers. Thus testing pregnant women for HTLV and stopping positive mothers from breast-feeding their newborn babies has effectively reduced the spread of the virus in Japan significantly.[3]

In contrast, despite enormous efforts and the expenditure of vast sums over the past 35 years, the primate retro-lentiviruses HIV-1 and its minor variant HIV-2, which are responsible for the globally important disease of AIDS, have resisted all attempts to develop an effective vaccine. The reason: HIV is a retrovirus. Through its reverse transcriptase HIV makes a DNA copy of its RNA genome; and this, integrating into the DNA of infected cells, does not kill them but maintains an infectious state througout life.[2] During the 80s and into the 90s there were no effective anti-HIV drugs, but early on we were able to establish that although both AIDS patients and healthy HIV-infected individuals tested positive for anti-HIV antibodies, AIDS patients had a far lower level of antibodies and more significantly, were devoid of antibodies that were capable of neutralising the virus. We were therefore encouraged to initiate a trial of passive immunotherapy in Cambridge in 1985[4] and later in London.

Plasma from healthy HIV-positive individuals who still had a high number of CD4+ T-cells (which we found correlated with high levels of neutralising antibody) was collected by plasmapheresis and given by infusion to patients with advanced AIDS. [5-6] Right from the beginning, infusion of the plasma improved their well-being. Subsequent double-blind controlled studies from the USA[7] and France[8] confirmed the long-term benefit.

As far as the donors were concerned, we had only a limited number, which meant many were required to donate repeatedly at monthly or bi-monthly intervals in order to provide long-term treatment for the AIDS patients. Plasmapheresis avoids depleting red and white blood cells, but we were concerned whether repeated donation might have other detrimental effects on the donors. In the event detailed study of their various lymphocyte populations showed no ill-effects.[9] Over several years passive immunotherapy for AIDS patients was given both at the Royal London Hospital by DB and at Ealing General Hospital by SA. We learned from this experience that collection of plasma by plasmapheresis machine is readily achievable on a substantial scale, even if somewhat labour-intensive.

Several reports have appeared of successful passive immunotherapy (PIT) following a single infusion after Ebola infections in Africa;[10] but here it was of restricted scope, because most Ebola-infected individuals die of the infection, greatly limiting the supply of blood/plasma available to use in treatment.

In the absence of generally effective drugs to treat corona-infected individuals, or the prospect of a vaccine in the near future, is there a place for PIT in order to save life and relieve some of the enormous amount of medical and nursing time that it takes to care for the sick?

The corona viruses are transient RNA viruses; once an infected individual recovers he or she becomes virus-free and immune. One could expect that in SARS-Covid-19 also, infected individuals who recover will have developed some form of protective immunity. Very little is yet known about its development, when and for how long it might last, and though it is very likely to involve virus-neutralising antibodies, to what extent it might depend on the appearance of such antibodies. However in a recent report 10 very advanced corona patients were treated with a single 200 ml dose of plasma obtained from individuals recovered from the infection. There was impressive clinical improvement.[11] We have been told of a similar outcome from passive immunotherapy in Germany.[12]

There are some ten times more individuals recovered from infection than deaths. This argues that the majority are likely to be making or to have made effective antibody responses to the virus. It would then not be unreasonable to ask those among the younger recovered individuals to donate blood. Since blood can be stored for a month medical centres could collect such donations and create a bank of blood/plasma (presumed hyperimmune), to be provided firstly to the severely ill patients as a blood or plasma transfusion with a matching blood group, and thereafter to newly infected individuals developing clinical symptoms. Hopefully the majority of the sick patients receiving PIT would recover and those in the early phase of the disease would recover more quickly.

Caveats:
Passive immunotherapy will not necessarily help:
(1) if the donated plasma contains little antibody. In plasma collected some time after recovery the donor's antibodies could have waned too far, due to their normal half-life; and this would be particularly important if the normal immune response to SARS-Covid19 is in any case usually short-lived. We are just beginning to know something of the dynamics of the response [13];
(2) if the donor's antibodies are not effective in neutralising the virus. Detection of antibodies to the coronavirus is critical to the epidemiology of the infection but will say little about the immunity of the individual unless the antibody test is a functional one, measuring anti-viral activity.
(3) if a donor's recovery occurs principally by mechanisms other than neutralising antibody, probably cellular responses mediated through, for example, T- and NK-like lymphocyte responses.

At this stage of our knowledge of Covid-19 our guide to the use of PIT and the choice of donors can only be empirical – if one person's plasma does not work, try somebody else's. This consideration argues that it is of major importance to create, and expand the availability of, reliable tests for virus-neutralising activity of anti-corona antibodies. Then one will be able to decide with confidence which plasmas will work and which won't; and, thus, who can donate and when.[14]

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14. Interestingly, a recent Italian scheme by blood transfusion services in the localities of Lombardy most severely affected by Covid-19 proposes to screen all regular normal blood donations and test for viral neutralising antibody on the grounds that most individuals in the area will have had to face the virus. Those who did not succumb will have either been unusually lucky enough to escape entirely, or will have been able to resist infection and, as asymptomatics, are probably more strongly immune than individuals recovering from the disease. By screening and selecting plasma with proven neutralising activity it is hoped to build up a bank of hyperimmune plasma for use in emergency. Details of the scheme and the test methods are not known to the authors.