IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 15, Issue 4 Ser. I (Jul. –Aug. 2020), PP 10-16
www.Iosrjournals.Org

Contingency of Monoclonal antibodies and Convalescent Plasma therapy as an effective Immunoprophylaxis against COVID- 19 in India

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Abstract: *COVID- 19 an evolved virus emerged as a threat to human life since December 2019, declared a pandemic on 20th January 2020; researchers worldwide are studying several drugs for enabling cure. Prophylaxis using vaccine is not available at present for prevention of COVID- 19. The treatment relies on use of anti- viral drugs; its failure has left no choice other than passive immunisation. The review article aggregates information on (a) Coronavirus case fatally compared to SERS and MERS. A survey on (b) present treatment using anti- viral drugs therapy and its failure (c) plasma therapy, its contingency in cure of COVID- 19 (d) monoclonal antibody therapy and (e) need for immunoprophylaxis (using convalescent plasma therapy or monoclonal antibody therapy) is done. Findings reveal that immunoprophylaxis along with drug treatment has worked successfully in China. The present study suggests that convalescent Plasma (CP) therapy and monoclonal antibody treatment must undergo human trial in India. It is encouraged since countries like Israel, China and USA has been benefited. Survey shows promising result of immunoprophylaxis as these agents shows potential efficacy against COVID- 19 cure where most of drug treatments failed to work single-handedly.*

Keywords: *COVID- 19, Anti- viral drug, Immunoprophylaxis, Plasma therapy, Convalesent plasma, monoclonal antibody.*

Date of Submission: 23-06-2020 Date of Acceptance: 11-07-2020

I. Introduction

The world is in midst of COVID 19 pandemic, <7.94 million cases of Coronavirus infection and < 4.35 lakh deaths cases has been reported so far. Recovery rate is only 29.1 %, accounting for 2.7 million recovery figures recorded until now. The world is struggling with the pandemic situation. This infection has been spreading at an alarming rate in most of the countries and continues to evolve because of its need of medical and pharmaceutical interventions [21 & 22].

Lockdown was imposed in India after as WHO declared COVID- 19 a pandemic. The first case in India was reported on 30th January 2020; a patient carried the infection and travelled to Kerela, India. Human Coronavirus (SARS- CoV- 2), first originated on December 2019 from Wuhan, Hubei province, China [8, 12]. Public health measures like use of face masks, washing hands with frothing soap and social distancing helped to contain the cases [20], in the first stage of COVID- 19 in India but now the numbers of infectious cases has increased to < 7.1 thousands (confirmed cases),< 2.3 thousands death cases has already been recorded [21 & 22]. The entire population in our country is struggling with the disease. The doubling rate in India is 12.2 days, much slower than that of developed countries like USA, Italy, France and Spain. In stage 2 of COVID- 19 infection (in India) the worrisome fact is its cure and treatment. As, India is high in terms of population; its control of COVID- 19 is definitely going to be complicated. Drugs, vaccines and immunoprophylaxis are surely needed for better treatment, prevention and cure of COVID-19 [21].

COVID-19 is caused by a beta- Coronavirus (CoV) that possess positive sense RNA as its genetic material. This virus is highly contagious and spreads through droplet nuclei, mainly transmitted through droplets generated when an infected person coughs, sneezes, or exhales. These droplets are too heavy to hang in the air, and quickly fall on floors or surfaces. Infection may be acquired by breathing in the virus within close proximity of someone infected with COVID-19, or by direct contact with a contaminated surface and then touching eyes, nose or mouth. Canadian scientist June Almeida in 1963 at the Ontario Cancer Institute in Toronto, Canada first observed Coronavirus using electron microscope techniques she developed. Coronaviridae comprises of alpha, beta, delta, and gamma Coronaviruses. It was proposed as a taxonomic family 30 years after Tyrrell and Bynoe discovered human CoV in 1965, from patients suffering from cold [1]. However, human Coronavirus came to

attention only in late 20th century after WHO declared a pandemic. A mortality rate (as on 3rd March) of 3.4% was estimated by World Health Organisation [21].

Coronavirus is a RNA virus with a un- segmented positive sense RNA genome of 26- 30 kb length. The COVID- 19 virus shares 88% sequence identity to two Coronaviruses found in bats, bat-SLCoVZC45 and bat-SL-CoVZXC21, (termed SARS-CoV-2), 79% identity with the Severe acute respiratory syndrome (SARS) Coronavirus and 50% identity with Middle eastern respiratory syndrome (MERS) Coronavirus [3,12 & 25]. The number of open reading frames (ORFs) differs species to species. More than two-thirds of the CoV genome is composed of an open reading code (ORF) coding for the replicase polyprotein 1a/ 1b, and the remainder contains ORFs that -encodes the structural proteins: spike protein (S), envelope (E), membrane (M), nucleoprotein (N), and a variable collection of accessory proteins (Kim et al). Protein S plays a key role in the control of pathogenicity. This glycoprotein (S) is an important factor in the species specificity, pathogenesis, and escape of immunity [7].

The review paper aims in aggregating information on (a) Coronavirus case fatally compared to its similar strains that caused earlier pandemics like SERS and MERS and consolidates a survey on (b) present therapies of COVID- 19 including classic therapy, by using anti- viral drugs (c) and plasma therapy. We studied contingency of plasma therapy in cure of COVID- 19 (d) Monoclonal antibody and use it as a therapy (e) critical requirement of immunoprophylaxis (using convalescent plasma therapy or monoclonal antibody therapy) and suggestion of its trial in our country for cure of COVID-19. India is a highly populous country; the risk of community break of COVID- 19 is much higher. There is no literature available at present that ensures concomitant hopeful treatment in our country using convalescent plasma therapy and monoclonal antibody. This study may be useful in terms of stipulations, an alternate treatment as the drug treatment is less effective.

COVID- 19 case fatality compared to SARS and MERS

Many researchers believe that COVID-19 is an evolved virus. Coronaviruses (CoVs) belongs to the family Coronaviridae, subfamily Orthocoronavirinae and the order Nidovirales. The COVID- 19 virus shares 88% sequence identity to two Coronaviruses found in bats, bat-SLCoVZC45 and bat-SL-CoVZXC21, (termed SARS-CoV-2), 79% of identity with the Severe acute respiratory syndrome (SARS) Coronavirus and 50% of identity with Middle eastern respiratory syndrome (MERS) Coronavirus. Researchers concluded that the virus is the product of natural evolution through selection in a non- human host that leaped on to human. The researchers proposed bats are the most likely reservoir for SARS-CoV-2 as it is very similar to a bat Coronavirus [25]. There are no documented cases of direct bat-human transmission.

The COVID-19 pandemic is generally a highly contagious disease with high reproductive number, a relatively long incubation period and short serial interval. COVID- 19 generally not so fatal but has high case fatality rates in patients with both morbidity and co- morbidity compared to SARS and MERS. Clinical representation and pathology of COVID-19 greatly resembled SARS and MERS [10, 11& 25]. Though, generally less fatal but the degree of pathogenicity, rate of transmission and rate of mortality is relatively high compared to both SARS and MERS. The different strains of Coronavirus are represented in table 1. The resembling symptoms are upper respiratory and gastrointestinal syndromes. COVID- 19 may be spread from asymptomatic carriers to a healthy individual through fecal- oral transmission [26, 27]. Table 2 represents origin, fatality and routes of transmission of COVID- 19, SARS, MERS and other pandemics.

Table 1 Human/ animal Coronaviruses (CoV) and Associated Disease

Group	Coronavirus Types	Acronym	Host	Associated Diseases
1. Alpha	Human CoV-229E	HCoV-229E	Human	Mild Respiratory tract infection
	Human CoV-NL63	HCoV-NL63	Human	Mild Respiratory tract infection
	Feline infectious peritonitis virus	FIPV	Cat	Hepatitis, respiratory tract, enteric, and neurologic infection
2. Beta	Human CoV-OC43	HCoV-OC43	Human	Respiratory tract infection
	Human CoV-HKU1	HCoV-HKU1	Human	Respiratory tract infection and possibly gastroenteritis
	Severe acute respiratory syndrome-CoV	SARS-CoV	Human	Severe acute respiratory syndrome (SARS)
	Middle- east respiratoy syndrome- CoV	MERS- CoV	Human	Middle- east respiratory syndrome (MERS)
	Severe acute respiratory syndrome 2- nCoV- 2*	SARS- CoV- 2* or COVID- 19*	Human*	Coronavirus disease- 19 associated with severe acute respiratory syndrome (COVID- 19*)
	Bat Coronavirus	SL-CoVZXC21	Bat	Respiratory tract infection

Group	Coronavirus Types	Acronym	Host	Associated Diseases
		SLCoVZC45	Bat	Respiratory tract infection
	Mouse hepatitis virus	MHV	Mouse	Hepatitis, encephalitis, and enteric infection
3. Gamma	Infectious bronchitis virus	IBV	Chicken	Respiratory tract and enteric infection
4. Delta	Avian Coronavirus	Bu- CoV-HKU11	Birds	Respiratory tract and enteric infection

*SARS-CoV-2, now known as COVID- 19, phylogenetic analyses suggest it is the first member of a fourth group of beta- coronaviruses. COVID- 19 is responsible for the ongoing pandemic, globally spread across 210 countries.

Table 2 Viral pandemics, their route of transmission and severity

Virus/ Origin	Year/	Fatality Rate (%)	Pandemic	Contained	Transmission	Remarks
COVID-19, China	2019,	Yet Unknown*	Yes	Efforts ongoing	Human to human through droplet nuclei, contact. Fecal- oral transmission possible	No treatment available, Asymptomatic and symptomatic transmission seen
H1N1, 2009, USA		0.02–0.4	Yes	No, post-pandemic circulation and establishment in human population	Human to human through droplet nuclei and contact	---
H7N9, 2013, China		39	No	No, eradication efforts in poultry reservoir ongoing	Avian influenza, occasionally infect human	---
SARS CoV, 2002, China		9.5	Yes	Yes, eradicated from intermediate animal reservoir	Human to human through droplet nuclei, direct and indirect contact	58% of cases result from nosocomial transmission
MERS CoV, 2012, SaudiArabia		34.4	No	No, continuous circulation in animal reservoir and zoonotic spillover	Human to human through droplet nuclei, direct and indirect contact	70% of cases result from nosocomial transmission
Ebola, 1976, fatal in 2012, West Africa		63	No	Yes	Human to human through direct contact, body fluids, air, water food and insect bites	---

*Pandemic ongoing, number of cases most likely to increase every passing day

Present therapies of COVID- 19

There is no vaccine at present for the treatment of COVID- 19, identifying the drug for treatment is the available option. Hydroxychloroquine a well known drug used against treatment of malarial parasites was thought to ensure some relief from the severity of the fatal cases but it failed after series of clinical trials on patients [3]. Several other drugs like Remdesivir an antiviral drug was ensured for the treatment as it is a nucleotide analogue, specifically an adenosine analogue, which inserts into viral RNA chains, causing their premature termination. This drug showed an improvement in SARS and MERS patients and was thought to provide some relief against the novel COVID- 19 but Remdesivir also failed in the first randomised clinical trial against the disease [19]. Hence, a need for immunoprophylaxis with convalescent sera for immediate cure has become compulsory. There is no known vaccine against COVID at present. Vaccine against COVID- 19 is mandatory for prevention of this disease, but achieving this requires funding and time allocation since vaccine preparation and human trial is a time consuming process, required for enabling a successful and scheduled vaccine programme [9].

Table 3 Results of clinical trials of anti- viral drugs against COVID- 19

Si. No.	Name of anti- viral drugs	Mode of Action	Sponsors	Human trails and Efficacy	Reference
1.	Hydroxychloroquine (malarial drug, anti- viral effect on HIV)	Used for malaria parasite treatment. It increases lysosomal pH in antigen-presenting cells	Shanghai Jiao Tong University	Failure of trial phase 3 against COVID- 19	[12, 13, 14, 15 & 17]
2.	Remdesivir (Ebola virus drug)	Specifically an adenosine analogue inhibitor, insertion into viral RNA chains, causes their premature termination. Inhibits EBOV RNA-polymerase RNA-dependent (RdRp).	Capital medical university	Failure of trial phase 3 against COVID- 19	[2, 14&19]
3.	Arbidol or Umifenovir (Influenza virus drug)	Its intercalation into membrane lipids leading to the inhibition of membrane fusion between virus particles and plasma membranes	Wuhan University	Success of trial phase 1 against COVID- 19, when given in combination of Favipiravir	[2, 4, 14& 19]
4.	Favipiravir (braod-spectrum anti- viral drug)	Nucleoside analogue that is well-known as a broad spectrum antiviral drug; it has shown	Wuhan Jiangxia First People's hospital	Success of trial phase 1 against COVID- 19, when given in combination of Arbidol	[2, 4, 14 & 19]

*Details of COVID- 19 clinical trials, credit: Global Data. https://www.clinicaltrialsarena.com/comment/covid-19-clinical-trials-results/

Plasma therapy: it's contingency in cure of COVID- 19

Lack of vaccine for prevention of COVID- 19 has forged to use of only option that is immunoprophylaxis using Convalescent Plasma therapy [6]. Table 3 shows representation of success/ failure of therapy using anti- viral drugs. The pandemic is now in an exponential growth stage. No approved explicit anti-viral agents are present for treatment. The chances of convalescent plasma (CP) transfusion to rescue severe patients must be investigated in the present situation. Convalescent plasma (CP) therapy is a classic adaptive passive immunotherapy.

CP therapy is a classical immunotherapy that has been employed in treatment of many infectious diseases. Previously, CP has been used against viral diseases such as rabies, Hepatitis B, Polio, Measles, Influenza and Ebola. In the recent outbreaks of MERS and SARS-1, CP has been administered with satisfactory efficacy, safety and success. In a recent study related to Lassa fever and SARS-1 convalescent plasma worked best as prophylaxis to prevent the disease (before and after exposure to the virus). CP therapy provides passive immunisation to a patient, often lasting short, whereas vaccines produce active immunity lasting for years [6, 18 & 24].

CP therapy shows potential treatment option for COVID-19 rescue. In the present case, a patient who has recovered from COVID-19 containing a high neutralizing antibody titre(generally binding titre must be > 1:1000; neutralization titre > 40) in his blood fits the donor criteria. CP donation is a routine blood donation. Plasma is extracted from the blood. During this ongoing COVID-19 pandemic <6000 individuals in USA who has recovered from COVID- 19 donated their blood plasma, which was later transfused into 3000 patients as per their compatibility. Consequently, convalescent plasma (CP) provided short-term immunity against the disease by providing antibodies that neutralise the virus and prevent further damage. Recently, COVID-19 cases have also shown improvement to a certain degree after CP therapy in China [24 &27]. A research on SARS revealed specific IgG antibody titre started to increase around 3rd week after onset, and peaked at 12th week. On April 26, recent news sources revealed Max Hospital in Delhi, India had announced that a COVID-19 patient had shown progressive improvement after being administered convalescent plasma therapy. However, the Government has warned against its use until experimental study on the efficacy of plasma therapy has been a success in clinical trials.

Monoclonal antibody as therapy of COVID- 19

Convalescent plasma therapy is a crude approach. It may have some drawbacks when produced in non-human hosts like bovine, camel. For an instance anti- tetanus serum produced in bovine serum, once injected in human shows some allergic reaction like rash, irritation and often fever. It is recommended that the human host who recovered from COVID- 19 containing a good titre of neutralizing antibody should donate their plasma to avoid the side effects [5]. The blood compatibility should be kept in concern during CP therapy. The non-COVID- 19 infections may also be passed if improperly screened or contaminated during CP transfusion.

Generalised itching may develop to 1 - 3 % patients. Acute fever may occur in less than 0.1 – 1 % patient. Care should be taken during transfusion so that the transfusion related side effects do not occur.

Monoclonal antibody treatment is an immunotherapy employed to fight against several infections (viral infections). These are the most important bio-therapeutics used for passive immunization. Monoclonal antibody therapy is not associated with any risk as the antibodies are completely target specific against vulnerable sites on viral surface proteins. The efficacy and success rate is 100 %. The effect is immediate with no reactions.

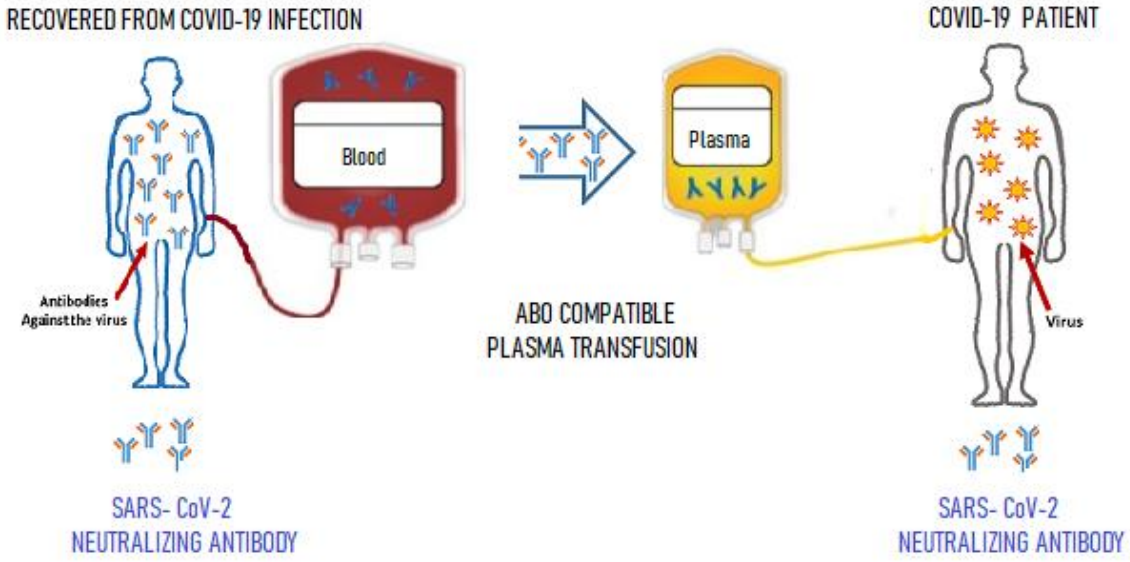

Fig. 1 Convalescent Plasma Therapy

The neutralizing antibodies against Coronavirus mainly targets trimeric spikes present on the surface of the virus known as (S) glycoproteins. It arbitrates entry into the host cell. The 'S' protein in the spikes on viral surface has two functional subunits that mediate attachment to cellular surface of the hosts (S1 subunit, active of four core domains $S1_A$ through $S1_D$) and fusion of the viral and cellular membrane (the S2 subunit). Effective neutralization by antibodies are often mediated by targeting receptor interaction sites in S1, immobilizing the receptor interactions [16, 23].COVID- 19 spike protein (1273 residues, strain Wuhan-Hu-1) and SARS (1255 residues, strain Urbani) are 78- 79% identical, the primary amino acid sequences, are structurally very alike, it usually binds to the human angiotensin converting enzyme 2 (ACE2) protein of the host receptor (mediated through their $S1_B$ domain). Once the receptor of virus and host cell interacts, an irreversible conformational change is activated in spike proteins of the virus that facilitate membrane fusion [5 & 23].

The sequences of monoclonal antibodies that are effective against SARS-CoV- 2 could be cloned and expressed in suitable expression method such as mammalian, yeast, plant and recombinant monoclonal antibodies. It may be tested against SARS-CoV-2. Plant expression system could be considered for the rapid production of monoclonal antibodies in a very short time with the affordable cost which is one of the major advantages to be considered especially during epidemic situation [5]. A noble method of preparing hybridoma, producing rat monoclonal antibodies by using cell fusion could be tested against SARS-CoV-2.This is a conventional method using mouse or rat spleen cells along with myeloma cells to produce hybridoma. This hybridoma may produce monoclonal antibodies against SARS-CoV-2.

Requirement of immunoprophylaxis in India

In India, the statistics for total confirmed cases of COVID- 19 are <70000 with <2400 deaths cases (3.2 % mortality rate), accounting for 1.8 % of global infections and 0.8 % of total deaths, although values for India and globally are changing daily, increasing exponentially in India. Currently no effective post- infection prophylaxis like convalescent plasma therapy or monoclonal antibody for the treatment of COVID-19is present in India. Some drugs are still in use. It is possible to construct monoclonal antibody against COVID- 19 and use it for a successful treatment after a clinical trial. It is expected to be months before antibodies emerge from clinical trials. CP, a post- infection treatment, has shown limited and moderate success, previously from SARS, MERS and COVID-19 in China [5, 10 & 18]. It may serve as an immediate solution to restrain the rate of mortality in our country India. Hopefully, recruitment of volunteers for clinical trial in our country may be able to see changes in the number of infectious cases.

The CP of infected patients could be donated or harvested for simultaneous treatment or future use until an effective monoclonal antibody is discovered in our country [16].It is easily available, unlike specific drugs or vaccines that takes time to develop, test and produce. The only cost involved is in extraction and storage. The antibodies are highly specific against the virus. The antibodies can have potential immune-modulator effect, reducing damage from the inflammatory response as the body mounts a severe response to the virus. Plasma treatment could help tone down the high immune response, which results in damage of normal tissue like those in the lungs, leading to lung injury and requiring the patient to be put on a ventilator. It's generally safe and well tolerated. It's as safe as a blood transfusion [16 & 18].

Table 4: Monoclonal antibodies targeted Eagainst SARS- CoV-1 and SARS- CoV- 2

Monoclonal antibody	Mechanism of action	References
80R	1) Binding to the conformational epitope (amino acid residues 426-492) on S1 fragment of SARS-CoV 2) Blocking the interaction of S1 subunit protein with cellular receptor ACE2 using 6 complementary determining regions (CDR) in vitro and in vivo (Mouse).	[16]
CR3014	1) Binding to the amino acid residues 318-510 and amino acid residue 565 with high affinity on S1 fragment of SARS-CoV 2) Blocking the interaction of S1 subunit protein with cellular receptor ACE2 in vitro and in vivo (Ferret).	[16]
201	1) Binding to the amino acid residues 490-510 on S1 fragment of SARS-CoV 2) Blocking the interaction of S1 subunit protein with cellular receptor ACE2 in vitro and in vivo (Mouse Syrian Hamster).	[16]
47D11*	1) Derived from immunized transgenic H2L2 mice that encode chimeric immunoglobulins with human variable heavy and light chains and constant regions of rat origin 2) The chimeric 47D11 H2L2 antibody was reformatted to a fully human immunoglobulin, by cloning of the human variable heavy and light chain regions into a human IgG1 iso-type backbone. The recombinant expressed human 47D11 was used for further characterization. 3) The 47D11 antibody was found to potently inhibit infection of VeroE6 cells with SARS-S and SARS2-S pseudo-typed VSV with IC_{50} values of 0.061 and 0.061 μg/ml Authentic infection of VeroE6 cells with SARS-CoV and SARS-CoV-2 was neutralized with IC_{50} values of 0.19 and 0.57 μg/ml.	[23]

*** Denotes SARS- CoV- 2 ongoing pandemic, the table represents some monoclonal antibodies directed against SARS- 1 and COVID- 19.**

II. Conclusion

Currently no effective immunoprophylaxis like convalescent plasma therapy or monoclonal antibody for the treatment of COVID-19 is present in India. Some drugs are still in use although most of the antiviral drugs were ineffective in clinical trials against COVID- 19. CP therapy shows potential treatment option for COVID-19 rescue but it is a crude approach and not so specific like monoclonal antibody therapy. Monoclonal antibody therapy is not associated with any risk as the antibodies are completely target specific against vulnerable sites on viral surface proteins. The efficacy and success rate are more effective along with drug treatment. The effect is immediate with no reactions. Recent advancements in clinical research may formulate the monoclonal antibody production at lower production costs. Monoclonal antibodies showed promising result in neutralizing SARS-CoV and MERS-CoV infection in the previous epidemics. The large-scale production of monoclonal antibodies against COVID- 19 may be a costly process but the success rate of therapy will be high. CP and monoclonal antibody therapy may be given more significance as the effect is immediate against COVID- 19 cure.

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