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Review Article

TARGETING NOVEL APPROACH OF CORONA VIRUS -2019: BROAD VIEW IN PREDICTION OF POSSIBLE POTENTIAL DRUGS ETIOLOGY, INFLAMMATION INDICATORS OF SARS-COV-2

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ABSTRACT

Currently the world is facing the pandemic crisis due to COVID-19 (SARS-CoV-2).since the mutation of the spike protein in this virus occurs frequently; the pharmacy as well as biotech sector is facing lot of issues in the invention of its treatment. This study works on the finding of potential drug through broad view in the broad spectrum antiviral agents as well as in the various virus groups preferably those causing respiratory and gastric ailments.

Keywords: Pandemic crisis, Invention, Potential antiviral agent, Broad view.

INTRODUCTION

SARS-CoV-2 is communicable virus for the public and WHO designated as continue pandemic of COVID-19 a global emergency issue. The emergency of severe acute respiratory syndrome, initiated a global effort to identify effective treatments focusing on antiviral agents.[1] SARS-CoV-2 is positive stranded RNA viruses with spike glycoproteins on the envelope. The virus seems it belongs to beta CoVs category which has round or elliptic shape and often pleomorphic form with a diameter of approximately 60-140 nm, it is sensitive to UV rays and heat. Furthermore it is inactivated by lipid solvents like ether (75%), ethanol, chlorine containing disinfectant, polyoxyacetic acid & Chloroform except for chlorhexidine.[2]

Etiology and Inflammation Indicators

1. Virus isolation and culture is performed in laboratory qualified BSL-3 (Bio safety level-3), Samples are inoculated on Vero –E6 cells for viral culture, the cytopathic effect is observed after 96 hours. By using Plaque Forming Unit (PFU) for the determination of viral viability.
2. Detection of Serum Antibody is performed preferably by colloidal gold immunochromatography. ELISA, chemiluminescence immune-assay methods. Positive serum- specific IgM or specific IgG antibody titer in the recovery phase ≥ 4 times higher than that of the acute phase, can be used as diagnostic criteria for negative nucleic acid.

❖ IgM- Detectable 10 days after

symptom onset

- ❖ IgG- Detectable 12 days after symptom onset.

Viral load gradually decreases when serum antibody level increases.

3. Detecting indicator of inflammatory response provide the basis for the formulation of treatment strategies and it is performed by conducting tests of C- reactive protein, Procalcitonin, ferritin, D- dimer, total and sub populations of lymphocytes- IL-4, IL-6, IL-10, TNFα, TNFγ and other indicators of inflammation and immunestatus.
4. Increased IL-6, IL-10 indicates the high risk of progression to severe conditions.
5. Detection of secondary Bacterial or Fungal infection by collecting qualified specimens from the infection site, mostly severe and critically ill patients are vulnerable to secondary Bacterial or Fungal infections. In addition to fungal culture it is recommended to take blood G test and GM (Galactomannan) test at least twice a week.[3]

PATHOPHYSIOLOGY

The understanding the pathogenetic mechanism of COVID-19, its structure and genome must be considered. Here the genomic structure is organized in a +ssRNA of approximately 30 kb in length (the largest known RNA viruses) with 5" cap structure and 3"poly-A tail. From the viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in host is released. The transcription process works through the replication _transcription complex (RCT) organized in double membrane vesicles and via the synthesis of sub genomic RNAs (sgRNAs) sequences. Of note, transcription termination occurs at transcription regulatory sequences, located between the so - called Open Reading Frames (ORFs) that work as templates for the production of sub genomic mRNAs. In the atypical CoV genome at least 6 ORFs can be present. Among these, a frame shift between ORF1a and ORF1b guides the production of both pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin – like protease (3CLpro) or by main protease (Mpro), as well as one or two papain-like proteases for producing 16 non-structural proteins (nsps). Apart from ORF1a&ORF1b, other ORFs encode for structural proteins including spike membrane, envelope and nucleocapsid proteins.[4] and accessory proteic chains. Different CoVs present single structural and accessory proteins dedicated sgRNAs.

The structural elements of CoVs are spike glycoproteins with 2 subunits (S1&S2). Homotrimers of S- protein receptors. In the SARS-CoV-2, the S2 subunit with a fusion peptide, a transmembrane domain & cytoplasmic domain is highly conserved. The spike mutation occurred in late november 2019. In particular Angeletti et al compared the SARS-CoV-2 gene sequence with that of SARS-CoV-2. So far available data indicates that this viral infection is capable of producing an excessive immune reaction in host, labelled as "cytokine storm". The protagonist of this storm is interleukin 6(IL-6) produced by activated leucocytes and acts on a large number of cells and tissues. IL-6 has main role of pro-inflammatory, it can also have anti-inflammatory effects. It also implicated into the pathogenesis of cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.[5,6]

RESULTS AND DISCUSSION

The study of the etiology, inflammation indicators and pathophysiology of the SARS- CoV-2(novel corona virus-2) acts as a root work for the identification of various virus groups related to SARS-CoV-2.

Virus name with its abbreviation:

1. **HCoV-229E**-Human corona virus strain 229E
2. **HCoV-NL63**-Human corona virus strain NL63
3. **HCoV-OC43**-Human corona virus OC43
4. **HCV-**Hepatitis C virus
5. **HEV-**Hepatitis E virus
6. **HEV- A-**Enterovirus A
7. **HEV-B-**Enterovirus B
8. **HEV-C-**Enterovirus C
9. **HEV-D-**Enterovirus D
10. **HEV-J-**Enterovirus J

11. **MERS-CoV-**Middle east respiratory syndrome
12. **SARS-CoV-**Severe acute respiratory syndrome
13. **EBOV-**Ebola virus
14. **FLUAV-**Influenza A virus
15. **FLUBV-**Influenza B virus
16. **FLUCV-**Influenza C virus
17. **HENV-**Hendra virus
18. **NiV-**Nipah virus
19. **RSV-**Respiratory syncytial virus
20. **HIV-1-**Human immunodeficiency virus 1
21. **HIV-2 -**Human immunodeficiency virus 2

Table 1: Colour legend for various virus predictions

	Phase -II
	Approval
	Cell culture /co culture
	Phase -IV
	Animal Models
	Phase -I
	Phase -III
	Primary cells /organoids

Table 2: Shows the list of various broad spectrum antiviral agents and various virus groups related to SARS-CoV-2 and those various virus groups are related by their family-coronaviridae as well as by causative agents for various respiratory ailments and some causing the gastric ailments.(drugvirus.info) The development and approved stages of the various broad spectrum antiviral agents are also indicated as following colours –pink, light green, light blue, dark green, dark blue, orange, red.[7,8]

S.NO	*Drug Name*	*HCoV-229E*	*HCoV-NL63*	*HCoV-OC43*	*HCV*	*HEV*	*HEV-A*	*HEV-B*	*HEV-C*	*HEV-D*	*HEV-J*	*MERS-CoV*	*SARS-CoV*	*SARS-CoV-2*	*EBOV*	*FLUAV*	*FLUBV*	*FLUCV*	*HENV*	*NIV*	*RSV*	*HIV-1*	*HIV-2*
1	FAVIPIRAVIR																						
2	NITAZOXANIDE																						
3	MYCOPHENOLIC ACID																						
4	REMDESIVIR																						
5	CHLOROQUINE																						
6	NICLOSAMIDE																						
7	AMODIAQUINE																						
8	EIPA(Amiloride)																						
9	EMETINE																						
10	BDX4430(Galidesivir)																						
11	GEMCITABINE																						
12	RAPAMYCIN(Sirolimus)																						
13	ABT-263																						
14	CYCLOSPORINE																						
15	LUTEOLIN																						
16	RIBAVIRIN																						
17	TILORONE(Amixin)																						
18	GLYCYRRHIZIN																						
19	MONENSIN																						
20	ARBIDOL(Umifenovir)																						
21	SUNITINIB																						
22	SILVESTROL																						
23	EMODIN																						
24	AMIODARONE																						
25	AZITHROMYCIN																						
26	DASATINIB																						
27	CHLORPROMAZINE																						
28	HYDROXYCHLOROQUINE																						
29	NELFINAVIR																						
30	ORITAVANCIN																						
31	TAMOXIFEN																						
32	LOPINAVIR																						

33	BENZTROPINE																						
34	DALBAVANCIN																						
35	TEICOPLANIN																						
36	HOMOHARRINGTONINE																						
37	ALISPORIVIR																						
38	CEPHARANTHINE																						
39	RITONAVIR																						
40	MEFLOQUINE																						
41	HEXACHLOROPHENE																						
42	IMATINIB																						
43	NAFAMOSTAT																						
44	CAMOSTAT																						
45	TENOFOVIR																						
46	INDOMETHACIN																						
47	CLOMIPRAMINE																						
48	TELAVANCIN																						
49	TOREMIFENE																						
50	PROMETHAZINE																						
51	TRAMETINIB																						
52	ZANAMIVIR																						
53	LAMIVUDINE																						

Table 3: Indicate the broad spectrum antiviral agents under development as well as some of the approved agents for the treatment of three different virus groups namely middle east respiratory syndrome causing agent as MERS-CoV, severe acute respiratory syndrome-1 causing agent as SARS- CoV-1 and severe acute respiratory syndrome-2 causing agent as SARS-CoV-2 which is commercially called as COVID-19.

S.NO	Drug Name	MERS-CoV	SARS-CoV-1	SARS-CoV-2
1	FAVIPIRAVIR			+
2	NITAZOXANIDE	+		
3	MYCOPHENOLIC ACID	+		
4	REMDESIVIR	+	+	+
5	CHLOROQUINE	+	+	+
6	NICLOSAMIDE		+	
7	AMODIAQUINE	+	+	
8	EIPA(Amiloride)	+	+	
9	EMETINE	+	+	
10	BDX4430(Galidesivir)	+	+	
11	GEMCITABINE	+		
12	RAPAMYCIN(Sirolimus)	+		
13	ABT-263	+		
14	CYCLOSPORINE		+	
15	LUTEOLIN			+
16	RIBAVIRIN	+		
17	TILORONE(Amixin)		+	
18	GLYCYRRHIZIN	+		
19	MONENSIN			+
20	ARBIDOL(Umifenovir)	+		
21	SUNITINIB		+	
22	SILVESTROL		+	
23	EMODIN	+	+	
24	AMIODARONE	+	+	
25	AZITHROMYCIN	+	+	
26	DASATINIB		+	
27	CHLORPROMAZINE	+	+	
28	HYDROXYCHLOROQUINE	+	+	
29	NELFINAVIR	+		+
30	ORITAVANCIN	+	+	
31	TAMOXIFEN	+	+	
32	LOPINAVIR	+	+	
33	BENZTROPINE	+		
34	DALBAVANCIN	+	+	
35	TEICOPLANIN		+	+
36	HOMOHARRINGTONINE	+		+
37	ALISPORIVIR	+	+	
38	CEPHARANTHINE	+		
39	RITONAVIR	+	+	
40	MEFLOQUINE	+		
41	HEXACHLOROPHENE	+	+	
42	IMATINIB		+	
43	NAFAMOSTAT	+	+	
44	CAMOSTAT	+	+	
45	TENOFOVIR	+	+	
46	INDOMETHACIN	+	+	
47	CLOMIPRAMINE	+		

Since the identification of the potential drug plays a crucial role in the treatment of the SARS-CoV-2.The table 1 which is generated as the result of prediction of possible potential drug used for the treatment of various virus groups from the drugvirus.info, which is further acts as a root for the table-2 which contains the potential drug for the treatment of various infection caused by two different virus groups(SARS-CoV-1 and MERS-CoV) and this leads to the easy and effective prediction of the potential drugs for the treatment of SARS-CoV-2. [9,10]

CONCLUSION

So for analysed various broad spectrum antiviral drug candidates along with the two most closely resembling virus group to SARS-CoV-2 gave the result for the prediction of possible potential 47 drug candidates. The SARS-CoV-1 and MERS-CoV virus group are compared with the SARS-CoV-2 their pathophysiology and etiology which made to take these two groups for the prediction of some possible potential drug candidates against SARS-CoV-2.those predicted broad spectrum antiviral agents can be used for undertaking computational techniques used in the drug discovery called virtual screening by any of these following three method namely –Structure Based Method, Ligand Based Method and Hybrid Methods.

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