A REVIEW OF siRNA THERAPEUTICS FOR THE THERAPY OF COVID 19 AND OTHER CORONAVIRUS

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ABSTRACT

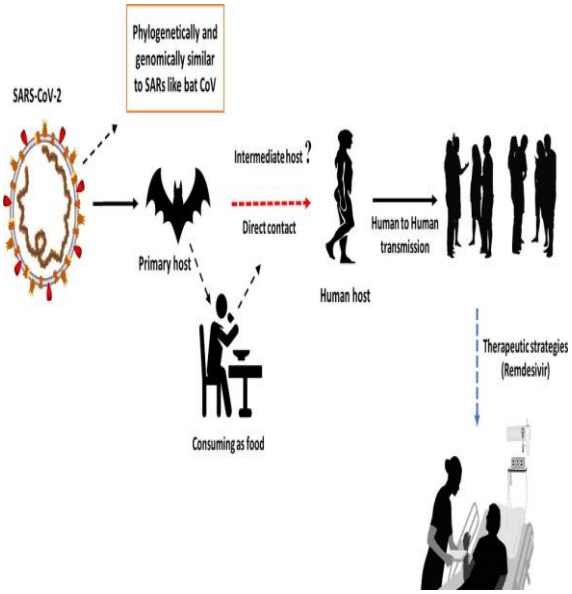
The enduring epidemic outbreak which started in Wuhan city of China, in December 2019 caused by the 2019 novel corona-virus (COVID- 19) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created a dangerous and dead-ly Public Health disaster of International apprehension, with cases confirmed in several countries. This novel community health trouble is frightening the universe with clinical, psycho-logical, emotional, collapse of health system and economical slowdown in each and every part of the world infecting nearly200 countries. A highly virulent and pathogenic COVID-19 viral infection with incubation period ranging from two to four teen days, transmitted by breathing of infected droplets or contact with infected droplets, belongs to the genus Coronavirus with its high mutation rate in the Corona viridae. The likely probable primary reservoir could be bats, because genomic analysis discovered thatSARSCoV-2 is phylogenetically interrelated to SARS-like bat viruses. The transitional resource of origin and transfer to human sis not known, however, the rapidly developing pandemic has con-firmed human to human transfer. Approximately 1,016,128reported cases, 211,615 recovered cases and 53,069 deaths ofCOVID-2019 have been reported to date (April 2, 2020). The symptoms vary from asymptomatic, low grade pyrexia, dry cough, sore throat, breathlessness, tiredness, body aches, fatigue, myalgia, nausea, vomiting, diarrhea, to severe consolidation and pneumonia, acute respiratory distress syndrome (ARDS) and multiple organ dysfunction leading to death with case fatality rate ranging from 2 to 3%. The most common diagnostic methods are molecular methods as RT-PCR (reverse transcription) or real-time PCR, which are prepared by means of RNA from respiratory samples such as oropharyngeal swabs, sputum, nasopharynx gealaspirate, deep tracheal aspirate, or bronchoalveolar lavage. Treatment is essentially supportive; as there is no documented clinically established and accepted antiviral remedy or vaccine existing, but some wide-ranging antiviral, anti-malarial and anti-parasitic drugs have been evaluated to be used in COVID-19.Prevention includes home segregation and quarantine of suspect-ed cases or those with mild illnesses and string ent infection con-trol measures should be taken at hospitals to contain contact and droplet infections. International health authorities are focusing on rapid diagnosis of cases, tracing of contacts, isolation of patients and searching for antiviral therapies to counter the deadliestCOVID-19 diseases.

1. INTRODUCTION

The human body is exposed to a variety of infectious microorganisms, such as viruses, bacteria, fungi, protozoa, and helminths, which cause tissue damage through different mechanisms. Viruses are unique among the sensitive types of infectious organisms in that they can manipulate the host-cell machinery in a unique way and continuously evolve to survive and prosper in all species[1].COVID-19 is the disease caused by a new corona virus called SARS-CoV-2. WHO learned of this new virus on31 December 2019, following a report of a cluster of cases of 'viral pneumonia' in Wuhan, People's Republic of China

Since December 2019, a novel coronavirus disease had rapidly spread throughout China, leading to a global outbreak, and causing considerable public health concern. World Health Organisation (WHO) announced the outbreak of COVID-19 as a global public health emergency on 30 January 2020. In India, the case of COVID-19was reported on January 27, 2020, in Kerala district. Since then, there is a wide variation in the reporting of cases across the country. The case reporting is based on theSARS-CoV-2 antigen testing by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-qPCR) or by Rapid Antigen Test (RAT) [3].Coronavirus (CoV) is clustered under the viral family group that causes disease in mammals and birds. A pandemic novel coronavirus was named as ''Corona Virus Disease 2019'' (2019-nCoV) by World Health Organization(WHO) in Geneva, Switzerland. As its RNA pattern is closer to SARS, the 2019 Coronavirus is renamed as SARS CoV- 2pandemic. It belongs to the subfamily Ortho corona virinae inside the family Corona viridae, order Nido virales, and the realm Ribo viria [4]. A two-dimensional view of Corona beneath a transmission electron microscopy reveals a characteristic look of ''paying homage to a crown'' around the virions. This lead to naming the virus ''Corona'', meaning ''crown'' or ''halo'' in Latin This is the deadly third-generation virus in Corona family preceded by severe acute respiratory syndrome (SARS) in2003, killed almost 10% of total affected patients (8429)across 29 international locations and Middle East Respiratory Syndrome (MERS) in 2012, even more lethal with a mortality rate of 30% of the infected patients.

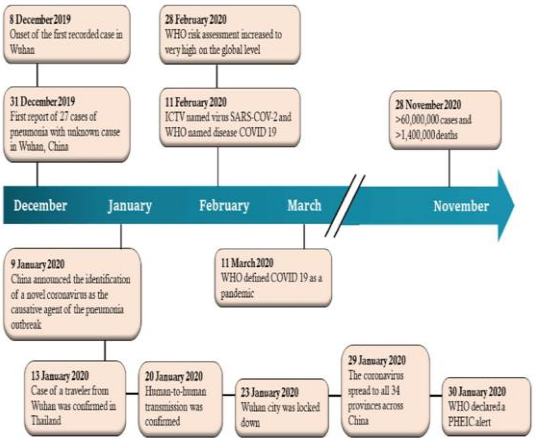
2. Origin and Spread of COVID-19 [1, 2, 6]



In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started pre-senting to local hospitals with severe pneumonia of unknown cause. Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animals. The surveillance system (put into place after the SARS outbreak) was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed. On 7th January the virus was identified as a coronavirus that had >95% homology with the bat coronavirus and > 70% similarity with the SARS-CoV. Environmental samples from the Huanan sea food market also tested positive, signifying that the virus originated from

there [7]. The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring [8]. The first fatal case was report-ed on 11th Jan 2020. The massive migration of Chinese during the Chinese New Year fuelled the epidemic. Cases in other provinces of China, other countries (Thailand, Japan and South Korea in quick succession) were reported in people who were returning from Wuhan. Transmission to health care workers caring for patients was described on 20th Jan, 2020.By 23rd January, the 11 million population of Wuhan was placed under lock down with restrictions of entry and exit from the region. Soon this lock down was extended to other cities of Hubei province. Cases of COVID-19 in countries outside China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries [9]. Airports in different countries including India put in screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19. Soon it was apparent that the infection could be transmitted from asymptomatic people and also before onset of symptoms. Therefore, countries including India who evacuated their citizens from Wuhan through special flights or had travellers returning from China, placed all people symptomatic or otherwise in isolation for 14 d and tested them for the virus. Cases continued to increase exponentially and modelling studies reported an epidemic doubling time of 1.8 d [10]. In fact on the 12th of February, China changed its definition of confirmed cases to include patients with negative/ pending molecular tests but with clinical, radiologic and epidermyologic features of COVID-19 leading to an increase in cases by15,000 in a single day [6]. As of 05/03/2020 96,000 cases worldwide (80,000 in China) and 87 other countries and 1international conveyance (696, in the cruise ship Diamond Princess parked off the coast of Japan) have been reported[2]. It is important to note that while the number of new cases has reduced in China lately, they have increased exponentially in other countries including South Korea, Italy and Iran. Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries)have died [2]. India, which had reported only 3 cases till 2/3/2020, has also seen a sudden spurt in cases. By 5/3/2020, 29cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an Indian who traveled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined. These numbers are possibly an underestimate of the infect-ed and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is un-certain. Pangolins and snakes are the current suspects.

3.HISTORY



Coronaviruses are enveloped positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like appearance

under the electron microscope; hence the name coronavirus [3]. Four corona viruses namely HKU1, NL63: 229E and OC43 have been in circulation in humans, and generally cause mild respiratory disease. There have been two events in the past two decades where in crossover of animal beta corona viruses to humans has resulted in severe disease. The 6□rst such instance was in 2002–2003 when a new coronavirus of the β genera and with origin in bats crossed over to humans via the intermediary host of palm civet cats in the Guangdong province of China. This virus, designated as severe acute respiratory syndrome corona virus affected 8422 people mostly in China and Hong Kong and caused 916 deaths (mortality rate 11%) before being contained. Almost a decade later in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of bat origin, emerged in Saudi Arabia with dromedary camels as the intermediate host and affected 2494 people and caused 858 deaths (fatality rate 34%) 229E and OC43 have been in circulation in humans, and generally cause mild respiratory disease. There have been two events in the past two decades where in crossover of animal beta corona viruses to humans has resulted in severe disease. The 6□rst such instance was in 2002–2003 when a new coronavirus of the β genera and with origin in bats crossed over to humans via the intermediary host of palm civet cats in the Guangdong province of China. This virus, designated as severe acute respiratory syndrome corona virus affected 8422 people mostly in China and Hong Kong and caused 916 deaths (mortality rate 11%) before being contained. Almost a decade later in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of bat origin, emerged in Saudi Arabia with dromedary camels as the intermediate host and affected 2494 people and caused 858 deaths (fatality rate 34%) [5].

4.SYMPTOMS

A wide range of symptoms are found in COVID-19patients, ranging from mild/moderate to severe, rapidly progressive, and fulminant disease. Symptoms of COVID-19 are non Ğspec□6□c and disease presentation can range from asymptomatic to severe pneumonia. Incidence of asymptomatic cases ranges from 1.6% to51.7% and these people do not present typical clinical symptoms or signs and do not present apparent abnormalities in lung computed tomography. The most common symptoms of COVID-19 are fever, cough, myalgia, or fatigue and atypical symptoms include

sputum, headache, haemoptysis, vomiting, and diarrhoea. Some patients may present with sore throat, rhinorrhoea, headache, and confusion a few days before the onset off ever, indicating that fever is a critical symptom, but not the initial manifestation of infection. Furthermore, some patients experience loss of smell (hyposmia) or taste(hypogeusia), which are now being considered earlywarning signs and indications for self-isolation [6].

The most common symptoms of COVID-19 are

* Fever.

* Dry cough.

* Fatigue.

Other symptoms that are less common and may affect some patients include

* Loss of taste or smell.

* Nasal congestion.

* Conjunctivitis (also known as red eyes).

* Sore throat.

* Headache.

* Muscle or joint pain.

* Different types of skin rash.

* Nausea or vomiting.

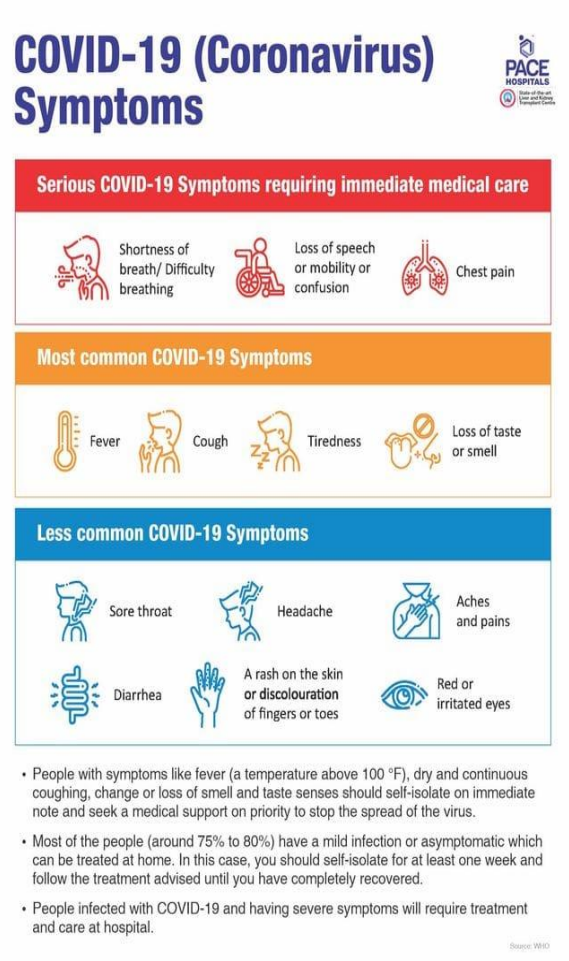
* Diarrhea.

* Chills or dizziness.

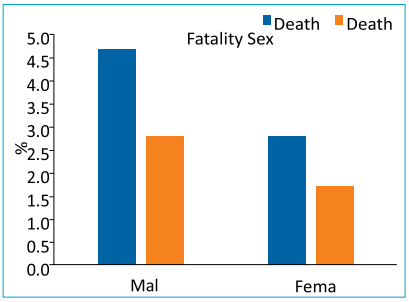
Symptoms of severe COVID-19 disease include:

* Shortness of breath.

* Loss of appetite.



5.Death Rate Varies by Age, Health and Sex



Covid-19 death Rate by Sex Ratio.

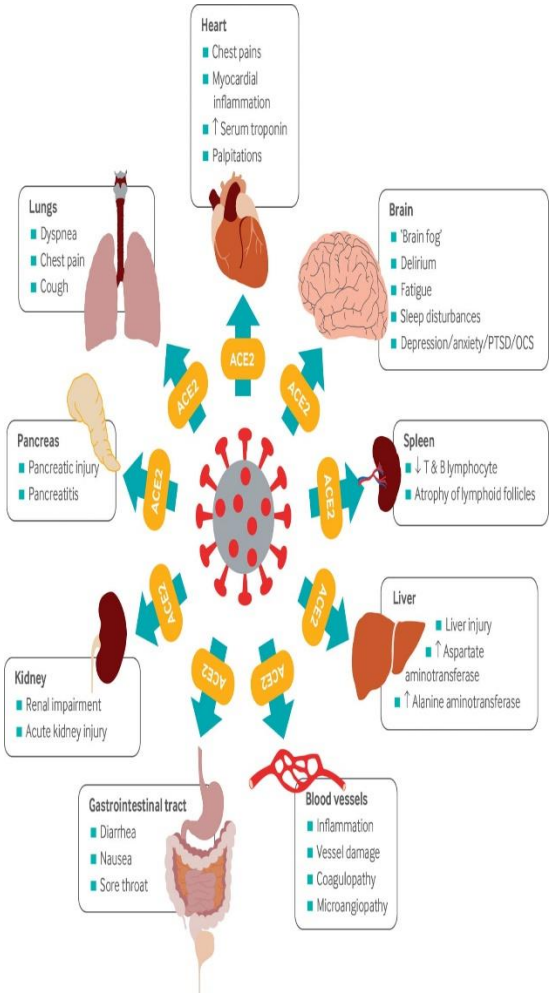
World Health Organizations Director-General, Tedros Adhanom Ghebreyesus, said that globally, about 3.4% of reported Covid-19 cases have died. Matt Hancock Health Secretary of UK governments said a

very best assessment was that the fatality rate was "2% or, likely, lower". However, it varies on a range of factors such as general health, age, sex, and the health system you are living in. In the first huge analysis of more than 44.000 cases from China, the death rate was ten times higher in the very elderly compared to the middle-aged. The death rates were lowest for under the 30s there have been eight deaths in 4.500 cases. And deaths were at least five times more common among individuals with d…from the coronavirus than women. yet its numbers slightly vary country to country. it doesn't necessarily reflect differences in biology. Scientists are still not completely sure but maybe on average, men more involve in health-damaging habits such as drinking and smoking than women (Fig. 4.) Show fatality sex difference.[8]COVID-19 death Rate by Health Conditions: Information made by Centres for Disease Control and Prevention (CDC) and lots of other studies increasingly clear that risk of se-vere illness and death increases with age. Adults who are both older and not have better medical conditions have a greater risk to become infected. Among adults age 60 or older, more than half also have a serious medical condition rising to nearly two-thirds of people age 80 and older.[2, 10]Older age people and younger adults with serious illness, such as diabetes, heart disease, and lungs disease, have a greater risk of becoming severely ill if they get infected with the coronavirus. The death rate for those who not have pre-existing conditions is approximately 1%. Centres for Disease Control and Prevention has issued specific guidance for people who fall into these categories. For those with cardiovascular (heart) disease the death rate is 10.5%, for diabetes death rate is 7.3%, for Chronic respiratory disease (such as asthma and chronic obstructive pulmonary disease) it is 6.3%, for hypertension (high blood pressure) it's 6.0% and the cancer death rate is 5.6% data summarised in. (8,9) Figure 5.

6.Mechanisms of action

The mechanisms of action of siRNA drugs are mainly through inhibition of expression of target genes by RNAi. The endogenous process of RNAi starts in the cytoplasm with the endoribonuclease Dicer, which produces mature siRNA by cleaving longer double-stranded RNA (dsRNA) or short hairpin RNA (shRNA) [10]. The resulting siRNA is 21-23 bases long and generally has 2 overhanging phosphorylated bases at the 3' end of each strand. Following processing, mature siRNA is incorporated into the RNA-induced silencing complex (RISC), which is made up of a collection of integral proteins, including Dicer and Ago-2 [11]. The siRNA is then separated into the sense and antisense strands. The sense strand is merely a passenger that is released from the complex, forming mature RISC. The antisense strand remains, serving as a guide that leads and aligns the complex to the target mRNA sequence. Complementary binding of the guide to the target triggers cleavage of the target sequence, mediated by Ago-2 endonucleases in RISC [12]. When utilizing RNAi pathways for therapeutic gain, one can bypass the initial Dicer-mediated step of processing mature siRNA by directly administering artificially prepared siRNAs. Since the activity of RISC is ultimately determined by the guide

strand, it is critical to synthesize an antisense strand that optimizes selectivity and potency. In addition to ensuring that the strand is complementary to the target mRNA, it is equally important to synthesize a strand that will not bind off-target, partially homologous mRNA sequences. Even a 7-base sequence complementary to the seed domain of the antisense strand can potentially trigger RISC [4]. Utilizing tools such as NCBI BLAST may allow for the determination of optimal target sequences that are unique within the human transcriptome.



7.Delivery systems

Delivery systems are critical for the drug discovery and development pipelines of siRNA drugs. Since siRNA molecules are fairly large (13-14 kDa) and hydrophilic, they are unable to passively cross the cell membrane. While chemical modifications and the addition of functional groups may increase stability and resistance to nucleases, they do not address permeability through lipid bilayers. To address this issue, two major delivery strategies are used: 1) formulation of the siRNA into nanocarriers that allow for transfection into target cells, and 2) conjugation of the siRNA to a targeting ligand that binds to a specific, high-capacity receptor on target cells. An ideal delivery system is biocompatible and non-immunogenic, allowing for specific cellular transport and entry [13, 18]. Lipid nanoparticles (LNPs) are the most successful formulation-based siRNA delivery strategy. They were used to deliver patis iran, the first approved siRNA drug [31]. LNPs are made up of cationic, ionizable, and helper lipids, such as cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-200, and D-Lin-MC3-DMA, which promote

RNA packing, increase stability, and allow for passage through the lipid bilayer [6, 16]. LNP surface sare PEGylated to reduce aggregation, opsonization, and RES clearance [16]. siRNA molecules are encapsulated within the LNP, protecting them from degradation. This greatly improves their pharmacokinetics and bioavailability, allowing for lower dose requirements [31]. LNPs are large, roughly

100-nm nanoparticles and can therefore only pass through fenestrated endothelium, making them optimal for targeting the liver [16, 25]. Due to the leaky vasculature at cancer sites, LNPs may also potentially be used to target certain tumors Other formulation-based strategies are currently in development, including complexes with cationic transfection agents, polymeric nanoparticles, liposomes, micelles, dendrimers, niosomes, metallic nanoparticles, human serum albumin-based nanoparticles, and oligonucleotide nanoparticles [32]. However, these all have various drawbacks and difficulties, rendering them at the present time as non-feasible pharmaceutical strategies. Although LNPs have demonstrated clinical utility, there are numerous drawbacks associated with their use. The main issue is the toxicity of its excipients [13, 18], which manifests as administration-associated inflammation. This can be so severe, that patients must be pre-treated with a cocktail of anti-inflammatory drugs. Additionally, LNP formulations must be administered by a medical professional through an intravenous infusion, which is an invasive and time-consuming method less favorable to patients [18]. Finally, due to the large size of LNPs, they predominantly target only fenestrated tissues, such as the liver. Their clinical utility to target other tissues is extremely limited [13]. Researchers are developing improved formulations that circumvent these issues, so LNPs may still have applications in the future [4]. However, the future of delivery seems to lie in bioconjugation to promising new ligands [27]. Bioconjugates are created by covalently conjugating siRNA molecules or their nanocarriers to specific molecules that enhance both delivery and uptake. The most promising conjugates are targeting ligands. In contrast to LNPs, these active targeting modifications allow for specific delivery by conjugating the drug to a cell-specific ligand, such as targeting peptides or antibodies [25]. This increases the concentration of the drug at the target site and often mediates internalization, resulting in increased bioavailability and efficacy and decreased off-target effects. Additionally, bioconjugates tend to be less toxic and less immunogenic, due to their relatively smaller size [27]. A typical example of bioconjugates is glycoproteins terminating with N-acetyl galactosamine (GalNAc) sugars with high binding affinity and specificity to asialoglyco protein (ASGPR), a receptor abundantly expressed in hepatocytes. Triantennary GalNAc (tri-GalNAc) has the highest affinity toward ASGPR [33]. Tri-GalNAc-conjugated antisense oligos display highly specific delivery to and internalization into hepatocytes [16, 25, 34]. Since ASGPR is an abundant, high-capacity receptor with rapid recycling and turnover, a single administration of GalNAc-siRNA conjugate yields very high siRNA uptake [35]. Tri-GalNAc was successfully used to deliver givosiran and lumasiran [36] and it has rapidly become the most popular platform for siRNA bioconjugation. Compared to LNPs, GalNAc-siRNA conjugates are much more straightforward to synthesize and refine [13]. Additionally, GalNAc conjugates are clinically convenient as they can be self-administered subcutaneously, resulting in rapid absorption, high uptake, and long half-life

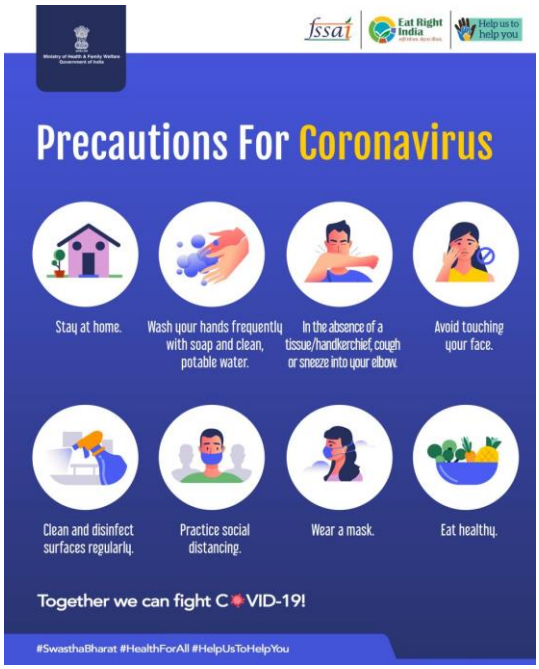
[35]. Unlike LNPs, GalNAc conjugates have a very favorable toxicity profile and therefore do not require the pre-infusion anti-inflammatory treatment that LNPs formulations do. GalNAc conjugates have been so successful that up to 2/3 of all RNAi drugs in clinical trials are GalNAc conjugates, including givosiran, vutrisiran, nedosiran, inclisiran, and fitusiran It is likely that these will far outpace and overshadow the use of LNPs, which has only been us din patisiran (Fig. 2). Other ligand-receptor pairs in development include glucagon-like peptide-1 and its receptor in pancreatic beta cells, transferrin and its receptor protein 1 in skeletal and cardiac muscle, cyclic arginyl-glycyl-aspartic acid and integrins on cancer cells, folate and folate receptors on cancer cells, and antibodies and their cell-specific receptors [16, 25, 27]. siRNA drugs may also be conjugated to cationic peptide moieties, such as penetratin and Endo-Porter, which effectively penetrate tissue barriers and cell membranes [16]. Conjugation to lipophilic moieties, such as cholesterol, improves pharmacokinetic properties and increases serum stability [27, 37]. With recent advances in the development and/or adoption of novel chemical modifications and delivery systems to overcome these barriers, siRNA-based therapy is now a reality for two FDA-approved drugs and nearly a dozen others on late stages of clinical trials. For the remainder of this review, we will discuss three FDA-approved drugs (patisiran, givosiran, and lumasiran) and seven candidates in Phase 3 trials (vutrisiran, nedosiran, inclisiran, fitusiran, teprasiran, cosdosiran, and tivanisiran).

8.Diagnosis of COVID-19

Diagnosis allows suspected people to understand that they are infected or not. Diagnosis can help them receive the care they need and it can help them take measures to cut back the probability of infecting others. People who don't know they are infected may not occupy at home and thereby risk infecting others. If the person develops symptoms of coronavirus disease 2019 and they have been ex-posed to the virus, he should consult to doctor. The doctor may decide whether to conduct tests for COVID-19 based on individual signs and symptoms. The doctor may also consider whether an individual had close contact with someone diagnosed with COVID-19 or travelled to or lived in any areas with ongoing community spread of COVID-19 within last 14 days.[18]Coronavirus Disease-2019 tracking and diagnostic testing are critical and also critical to understanding epidemiology, informing case management, and to suppressing trans-mission. The Coronavirus disease outbreak is additionally typical to prevent virus community transmission, including how testing might be rationalized when lack of reagents/testing kit or testing capacity necessitates prioritization of certain populations group or individuals for testing." (MA 3) To test for COVID-19, doctor or health practitioner may take samples, including a sample of saliva (sputum), a nasal swab and a throat swab, to send to a lab for testing or fol-low the directions of your local health authority.

9.Prevention & Precaution of COVID-19

People should stay aware of the latest information on the COVID-19 outbreak provided by WHO and Follow the directions of your local health authority and prevent secondary infections, interrupt human-to-human transmission to your close contacts, health care workers and prevent further international spread. most of the people who infected, experience mild illness and recover it, but its infection can be more severe for other individuals. To take care of your health and protect others take the subsequent steps:[30, 31



9.1.Take steps to protect yourself

* Wash your hands regularly and thoroughly with soap and water for at least 20 seconds or with an alcohol-based hand rub (hand sanitizer that contains at least 60% alcohol) completely cover your hands and rub them together until they do not dry especially after you have been visited a public place, or after blowing your nose, sneezing or coughing.

* Hands touch many surfaces and pick up viruses and these contaminated hands, can transfer the virus to your nose, eyes or mouth So, avoid touching these organs with unwashed hands. Because from there, the virus can enter the body and may cause persons to sick.

* Maintain social distancing (maintain at least 1 metre or 3 feet distance between yourself and anyone) and avoid close contact with people who are sick (who is coughing or sneezing). When infected individuals cough or sneezes, they spray small droplets from their nose or mouth which may contain COVID-19 virus. The person can breathe in these droplets.[31, 32]

* Avoid large events and mass gatherings Take steps to protect others

9.2.Take steps to protect others

* Stay home if you are feeling unwell, unless you're going to get medical care.

* If you have a cough, fever and difficulty breathing, seek

medical attention consult online to your doctor.

* If you're sick avoid taking public transportation.

* Whenever you cough or sneeze cover your mouth and nose with a tissue paper.

* Throw used tissues in the trash and wash your hands immediately with antiseptic soap and water.

* If possible, stay isolated in a separate room from fam-ily and pets and wear a facemask when you are around other people

(e.g., sharing a room or vehicle). If you are unable to wear a facemask (due to its causes trouble breathing or other reason) then you should cover your coughs and sneezes, and but when the people who are caring for you enter your room they should wear a facemask (Facemasks may be in short supply and they should be saved for caregivers).

* Stay home for a duration of time and follow your doc-tor's instructions.

* If you're sick, avoid sharing bedding, dishes, glasses and other household items

* If possible, use a separate bathroom and toilets from the family.

* If surfaces are dirty, clean them, and use detergent or antiseptic soap & water before disinfection apply,

* Apply disinfectant daily on frequently touched surfaces. This includes desks, phones, keyboards, toilets, faucets, tables, doorknobs, light switches, countertops, handles,

and sinks.[32, 33]

* Identify and Isolate Suspected Cases

* Before clinical care is started, Identify the potential cases as soon as possible and isolate the suspected people separately from those who confirmed cases of the virus COVID-19, to Prevent the potential transmission of infection to other patients and health care staff.

* Avoid direct physical contact (including physical examination and exposure) to respiratory and other body secretions. For instance, move potentially infectious people to isolation rooms and close the doors. In a working place, make the distance in workers, customers, and other visitors, especially from potentially infectious individuals location

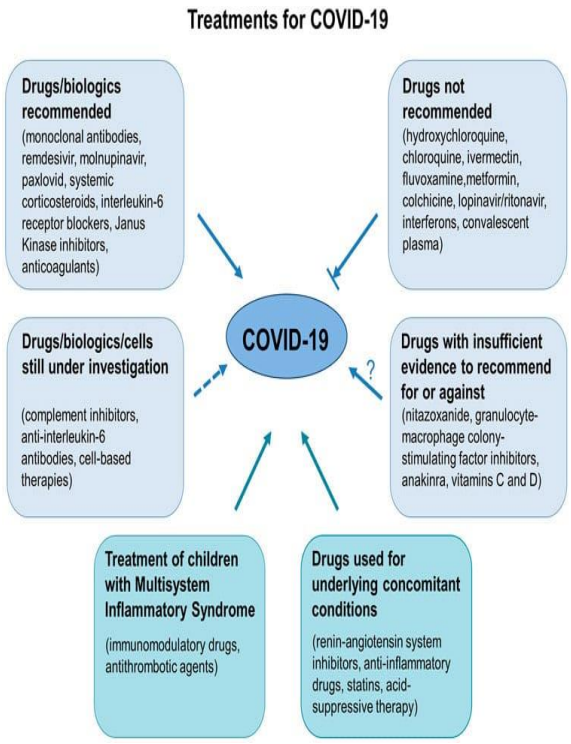
* In case of need to isolate a patient or patient group, pharmacies should designate and prepare a suitable space

* Most patients presenting in community pharmacies are unlikely to have COVID-19. If they have coughs, colds or flu-like symptoms but not relevant to COVID-19, travel or contact history, pharmacies should proceed in line with their best practice and routine management of the cross-infection risks to staff and other patients.

* Restrict the number of individuals entering isolation areas, including the room of a patient with suspected and confirmed COVID-19.

* For safe work practice, protect workers to close contact with the infected person by using additional engineering and administrative control.

10.Treatment



No specific treatment, drugs, monoclonal antibodies (mAbs) or vaccines exist for SARS-CoV-2 till the end of March 2020 [47].Concerted efforts are required to effect rapid diagnosis, quarantine infected cases to ensure adequate isolation to prevent transmission to other contacts, patients and healthcare workers and provide effective essential supportive and symptomatic treatment. Patients with mild illness, while maintaining good hydration and nutrition and controlling fever and cough, should be asked to manage at home with proper counselling about danger signs. Patients with hypoxia, can be managed with provision of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC) or non invasive ventilation. In severe pulmonary dysfunction cases mechanical ventilation or an extra corporeal membrane oxygen (ECMO)support may be required. Patients with renal dysfunction may require renal replacement therapy. If any patient is having suspicious or proven co-infections; antibiotics and antifungals may be required (Figure 1). Chinese guidelines do propose short term steroid therapy with low-to-moderate dose corticosteroids inCOVID-19 ARDS but it is unproven and against their use according to current international consensus and WHO [48,49]. Comprehensive guidelines have been published by the WHO for the management of critically ill COVID-19 patients [50]. At this time as there is no existence of specific antiviral therapies for SARS-2-CoV, the combination of the protease inhibitors, ritonavir, and lopinavir, or a triple combination of these anti viral agents with the addition of ribavirin, showed some success in the treatment of SARS, and early reports suggested similar efficacy in the treatment of COVID-19 [51]. However, a more recent randomized controlled open-label trial failed to demonstrate any added benefit of lopinavir-ritonavir combination therapy [52]. Initially, interferons-α nebulization, broad-spectrum antibiotics, and anti-viral drugs were used to reduce the viral load [53,54], however, only remdesivir has shown promising impact against the virus[55]. Remdesivir alone or in combination with chloroquine or Interferon beta, a drug originally developed to treat Ebola virus

11. World Health Organization list of vaccines under evaluation

Manufacturer	Vaccine name	Platform	Approval body

BioNTech Manufacturing GmbH	BNT162b2/COMIRNATY Tozinameran (INN)	Nucleoside modified mNRA	EMA and USFDA
AstraZeneca, AB	AZD1222 Vaxzevria	Recombinant ChAdOx1 adenoviral vector	EMA, MFDS KOREA, Japan MHLW/PMDA, Australia TGA
Serum Institute of India Pvt. Ltd	Covishield (ChAdOx1_nCoV-19)	Recombinant ChAdOx1 adenoviral vector	DCGI
Janssen–Cilag International NV	Ad26.COV2.S	Recombinant, replication incompetent adenovirus type 26 (Ad26)	EMA
Moderna Biotech	mRNA-1273	mNRA-based vaccine encapsulated in lipid nanoparticle (LNP)	USFDA
Beijing Institute of Biological Products Co., Ltd. (BIBP)	SARS-CoV-2 Vaccine (Vero Cell), Inactivated (lnCoV)	Inactivated, produced in Vero cells	NMPA
Sinovac Life Sciences Co., Ltd	COVID-19 Vaccine (Vero Cell), Inactivated/ CoronavacTM	Inactivated, produced in Vero cells	NMPA
Gamaleya National Centre	Sputnik V	Human Adenovirus Vector-based	Russian NRA

Bharat Biotech, India	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)/ COVAXIN	Whole-Virion Inactivated Vero Cel	DCGI
Sinopharm / WIBP	Inactivated SARS-CoV-2 Vaccine (Vero Cell)	Inactivated, produced in Vero cells	NMPA
CanSinoBio	Ad5-nCoV	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)	NMPA
Novavax	NVX-CoV2373/Covovax	Recombinant nanoparticle prefusion spike protein formulated with Matrix-M™ adjuvant.	EMA
Sanofi	CoV2 preSdTM-AS03 vaccine	Recombinant, adjuvanted	EMA
Serum institute of India PYT LTD	NVX-CoV2373/Covovax	Recombinant nanoparticle prefusion spike protein formulated with Matrix-M™ adjuvant.	DCGI
Clover Biopharmaceuticals	SCB-2019	Novel recombinant SARS-CoV-2 Spike (S)-Trimer fusion protein	NMPA

Urevac	Zorecimeran (INN)	mNRA-based vaccine encapsulated in lipid nanoparticle (LNP)	EMA

12. Conclusion

Although only three siRNA therapeutics have been approved by the FDA to date, more are sure to follow in the coming years. With the refinement of GalNAc and the development of other novel strategies for targeting and delivery of siRNAs to other organs than liver, researchers have largely overcome the barriers of clinical utility of siRNA molecules, which are the main rate-limiting step in commercializing siRNA therapeutics. Besides siRNA products, other oligonucleotide-based therapies like miRNAs and antisense oligonucleotides are gaining prominence as well. In today's post-genome era, such products are becoming increasingly feasible and utile. Additionally, compared to other novel therapeutic classes, such as monoclonal antibodies, siRNA products have several advantages. First of all, they are relatively less expensive to synthesize and manufacture than their antibody rivals, so they can theoretically be priced at a more competitive rate [77]. Secondly, most late-stage products offer convenient dosing with regimens as infrequent as bi-annual treatments (e.g. inclisiran) and are potentially self-administrable (e.g. subcutaneous and topical products). Factors like these will become increasingly important as novel therapies are developed for rare indications and patients gain consumer power and choice as to which treatment they utilize.

Fortunately for the pharmaceutical companies that have invested so much time into siRNA development, the payoff promises to be high. Inclisiran was included on Cortellis' shortlist of Drugs to Watch in 2020. It is projected to generate $1.16 billion in sales by 2024. Givosiran is forecasted to reach $560 million by 2025 [104]. Patisiran's 2019 revenue was $166.4 million, its estimated 2020 revenue is $280 - $300 million, and sales are estimated to peak at $1 billion. Shares in Alnylam gained 41.9% in 2019, contrary to a 1.2% industry-wide decline. Only time will tell if these RNAi therapies are deserving of their new blockbuster status.

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