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REVIEW ON TRADITIONAL TREATMENT METHODS OF ANTI-VIRAL AND m-RNA VACCINES

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ABSTRACT:

Widespread of any virus is due to the enhanced viral replication mechanism. In case of SARS-CoV2 the viral RNA genomic material enters the host cell and allow the replication of itself in the host cell, with the help of enzyme RNA-dependent-RNA-polymerase *(RdRp),* this helps in the encoding of required protein for the functionality purpose of the virus. Therefore, drugs like remdesivir, favipiravir and Paxlovid are used in the anti-viral therapy. The other traditional possibility of the anti-viral therapy includes, making the body immune against the viral spike protein binding interaction to the host. This method of therapy is achieved by the administration of m-RNA vaccines produced form Pfizer and moderna like company; constituting in intramuscular injection allowing the lipid nanovesicles containing the viral m-RNA entry into the host cell, thereby making the body immunized. All these traditional methods do reduce the virulence of the virus to certain extent with side effects of cardiovascular risk and many chronic lifestyle disorders. In this review we have focused on the possible methods that can be applied in order to reduce the possible risk of the drugs or the vaccines being administered.

INTRODUCTION:

SARS-CoV-2, the causative agent of COVID-19, escalated into a global pandemic in 2020. The molecular structure of the virus constitutes of single-stranded RNA β-coronavirus. RNA viruses are generally prone to mutation than DNA viruses due to the presence of OH in 2 positions in the RNA ribose nucleus, leading to significant changes in the viral genome, characterizing a new viral variant with varying transmission capacity, virulence trait, or different therapeutic susceptibility. [1]

STRUCTURE OF VIRUS:

The structure of the virion is made up of nucleocapsid (N), membrane (M) and envelope (E), and spike (S) protein, which interacts with the hACE2. It is observed to have a spherical or ellipsoidal shape in shape; and the diameter was 108 ± 8mm. [2] The $\sim 600 KDa$ trimeric S protein, one of the largest known class I fusion proteins, heavily glycosylated with 66 N-

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linked glycans. The S protein binds to the cellular surface receptor ACE2 through the **RBD receptor binding domain,** an essential step for membrane fusion. [2][3]
The genomic RNA of coronavirus is ~30,000 nucleotides in length with 5| cap structure and 3|- poly (A) tail and contain at least 6 open reading frames (ORFs). The first OFR (OFR1a/b) and about 2/3rd of the genome length directly translates 2 polyproteins, **pp1a and pp1ab**, so named because there is an a-1 frameshift between ORF1a and ORF1b [2]. these polyproteins are processed by a main protease, M^{pro} (also known as 3C-like protease *3CL^{pro}*), and by one or two papain-like proteases, into 16 non-structural proteins (NSPs). These NSPs engage in the production of subgenomic RNAs that encode four main structural proteins [envelope (E), membrane (M), spike (S), and nucleocapsid (N) proteins] and other accessory proteins. Therefore, these proteases, especially M^{pro}, play a vital role in the life cycle of coronaviruses. [2]

TREATMENT ALGORITHM FOR COVID:

The symptoms of COVID varied in people from mild illness to critical cases and even to death. For treating the mild symptoms of COVID, the patients were provided with OTC drugs like **acetaminophen or ibuprofen,** just to provide a short relief from the symptoms.
For severe constriction, oral antiviral drugs have been administered.

- Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) [4]
  - Adults and children (12 years of age)
  - Weighing at least 88 pounds (40kg)
  - Need to be administered to patients with high risk only, i.e., patients showing mild to moderate symptoms.
- Lagevrio
  - Adults 18 years and above.
  - Patients manifesting mild to moderate symptoms have not shown any clinical response to other therapies.
- Remdesivir (*Veklury*) [5]
  - FDA approved drug
  - Used on patients with either the risk of hospitalization or treated from home.
  - Route of administration involves intravenous (IV)
- Other FDA approved drugs
  - Baricitinib (*Olumiant*)
  - Tocilizumab (*Actemra*)

TREATMENT FOR COVID BASED ON ANTIVIRAL:

The treatment for viral infections includes the targeting of the virus, or host of the specific symptoms. Antiviral treatments work by disrupting the viral life cycle. [6]
For SARS-CoV-2, the life cycle can be divided into three stages: [6][7][8]
Host cell entry and trafficking.
Replication of the viral genome.
Packaging and egress of new virions.
Entry of SARS-CoV-2 into host cells occurs through receptor-mediated endocytosis or virion fusion with the cell membrane. Once in the cell,
Two polyproteins, pp1a and pp1ab, are translated from the RNA genome. These polyproteins are **cleaved to generate non-structural protein 1 (nsp1) to nsp16**. [7]
The Nsps form the replication and transcription complex (RTC), which **transcribes the viral genomic and subgenomic RNA (sgRNA)**. [7]
The **sgRNAs encode structural and accessory proteins**. Structural proteins traffic through the endoplasmic reticulum–

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to–Golgi secretory pathway, where viral genomes are packaged to form budding vesicles, which are then released as new virions by exocytosis. [7][8]

A common class of antivirals being tested in clinical trials against SARS-CoV-2 is nucleoside and nucleotide analogues, which inhibit viral replication when incorporated into the RNA by the RTC, drug like Remdesivir belong to this class and approved by FDA for antiviral therapy.

ANTIVIRAL DRUGS:

The commonly used antiviral drug therapy involves the administration of remdesivir and a combination of lopinavir and ritonavir. The clinical effectiveness for the suppression of COVID symptoms was compared with each set; remdesivir was found to be **more effective than the combination of lopinavir/ritonavir.** Hence, remdesivir is classified as the gold standard of SARS-CoV-2 anti-viral therapy, also approved by the FDA. [8]

Remdesivir

PHARMACOKINETICS:

Remdesivir usage for the treatment of COVID-19 is a result of the **repurposing of an existing antiviral drug**. This drug was originally developed for the Ebola outbreak, but a study provided the effectiveness against COVID symptoms. [9]

It is an adenosine analogue prodrug that was first converted to alanine metabolites (GS-704277) and then to nucleoside core (GS-441524). Intracellularly, the nucleoside core is converted to nucleoside monophosphate and finally to a pharmacologically active nucleoside triphosphate metabolite (GS-443902). This active remdesivir triphosphate competes with endogenous adenosine triphosphate for incorporation into SARS-CoV-2 RNA chains and blocks the SARS-CoV-2 **RNA-dependent RNA polymerase enzymes**, leading to delayed chain termination during RNA replication. [10]

PHARMACOKINETIC PROPERTIES:

FORMULATION:

- solution: 5mg/ml in a vial of 100mg/20ml.
- lyophilized powder: 100mg single-dose vial with either 0.9% saline or 5% glucose. [10]

ABSORPTION:

In intravenous fusion, 30 mins to 120 mins, absorption enables 100% {*single loading dose of 200mg/day and maintenance dose of 100mg/day; for 5 to 10 days*}. **Oral route** undergoes high hydrolysis-mediated first-pass clearance in the GIT, leading to **limited absorption and systemic concentration.** [10]

The inhaled route of administration, mostly preferred for drug delivery for the COVID patients, allows the targeting of the lungs and enables proper absorption in the infected area. [11]

DISTRIBUTION:

The parent remdesivir has a higher affinity for human plasma protein with 88.0-93.6% binding, whereas **GS-441524 and GS-704277 have 2% and 1% protein binding**, respectively. The concentration of GS-441524 (nucleoside core) and GS-443902 (active triphosphate) in PBMCs (peripheral blood mononuclear cells) is used as a marker of the distribution of remdesivir in the cellular compartment. [10]

There are animal data of rats and monkeys, showing limited distribution of remdesivir to the tissues, but there is no evidence of

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remdesivir presence in the brain; therefore, it is concluded that it cannot cross the blood-brain barrier (BBB). [11]

Since it cannot cross the blood brain barrier it needs to be administer in higher dose and also in higher frequency to reach the infected organs. But if the dose administered exceeds 200mg then it can lead to **hepatotoxicity and renal dysfunction**. This led to the development of inhaled dosage form.

METABOLISM:

The conversion of remdesivir (parent drug) to its active metabolite is done by the action of various enzymes. The action of each enzyme constitutes a different active metabolite. For example, in the case of the hydrolysis via **carboxylesterase 1 (CES1)** results in remdesivir, this reaction constitutes like 80% of the metabolic reaction. Remdesivir metabolism via **cathepsin A** results in the production of active metabolite **GS-443902**, which constitutes of 10% of the metabolic product. the hydrolysis via **CYP3A** also results in the production of **GS-443902**, constituting 10% of the resultant. [10]

In vitro studies, the reaction of CYP2C8 and CYP2D6 was also evident for remdesivir metabolism reactions.

Another active metabolite, GS-704277 formed via the action of the enzyme **HINT-1** histidine triad nucleotide-binding protein. This metabolite is particularly excreted of about 74% in urine and 18% in feces. [10]

The metabolite GS-441524 of remdesivir, excreted of about 10% via urine.

It is also noted that higher concentration of hepatic clearance of remdesivir drug is driven by hepatic blood flow rather than metabolic enzymes.

Elimination:

Nucleoside core **(GS441524) of remdesivir is the most abundant derivative** identified in urine, with remdesivir and other metabolites having moderate to low presence. [10]

Biotransformation is the primary path of parent remdesivir and GS-704277 (alanine metabolite) excretion, whereas.

- GS-441524, excreted by renal mechanisms such as GFR and active tubular secretion.
- Parent remdesivir an approximately 10% eliminated via urine.
- 49% of the dose GS-441524 is eliminated via urine.

TREATMENT OF COIVD BASED ON VACCINES:

The most common vaccine development approach was based on the spike protein of the virus as an antigen because it is the only surface protein on the microorganism and it is readily accessible by antibodies and immunological cells in the body. The spike protein seemed to be the best bet to get an effective vaccine ready fast. [12]

I) Pfizer-BioNTech (Comirnaty) BNT 162b2 and Moderna (1273)

This method utilizes **lipid nanoparticles (LNPs)** with a formulated mRNA vaccine. This work was fast-tracked at an unprecedented pace, even though **mRNA-based vaccines** have never been licensed before. RNA vaccines belong to a cutting-edge approach that uses genetically engineered RNA to generate a protein that safely prompts an immune response. Despite no mRNA vaccine having been previously approved, this technology was fast-tracked due to its adaptability and manufacturing efficiency. [13]

From the SARS-CoV-2 virus, the mRNA that codes for the spike protein is being isolated and included in a lipid

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nanoparticle. This nanoparticle (vaccine) is injected intramuscularly into the human body. Once attached to the host cells, it inserts its mRNA into the cytoplasm to reach the ribosomes and synthesize the **viral spike protein** (translation).

Protein achieves the cellular membrane and attracts the antibodies against the viral spike proteins and the cells of the immune system, in particular the T-helper (Th) cells which produce **cytokines (IL-2, IL-4, and IL-5)**. The interleukin also stimulates the T-cells to proliferate the memory T-cells and to kill the infected cells. [13] [14]

II) AstraZeneca Oxford

These vaccines are manufactured from the modified **chimpanzee DNA adenovirus**, which does not generate an immune response to the adenovirus itself, but only to the viral protein encoded in the host DNA. The DNA vector is used as a template in human cells to generate new chimpanzee adenovirus replicas and produce the viral protein that elicits an immune response. [12] [13] [14] [15]

The adenovirus is injected into humans, and it latches onto the host cells. The DNA gets released into the cytoplasm and later migrates into the cell nucleus without being incorporated into the cellular DNA. Through the enzymes of the host it will get converted into mRNA that migrates back into the cytoplasm and interacts with the cell ribosomes, resulting in translated proteins on the cell membranes, leading to the **activation of T-cells and antibodies.**

PROBLEMS INCORPORATED WITH TRADITIONAL TREATMENT METHODS:

Remdesivir is a prominently used antiviral drug for the treatment of COVID cases, due to its significance in interfering with the action of RNA-dependent RNA polymerase enzyme and preventing viral replication [16]. As a coin has its two faces, the same goes with this drug; firstly, it had to be given at a higher dose to achieve the reduction of infection, which also has the optional effect of leading to **respiratory failure and organ dysfunction, including lungs, liver and kidney**. [16] [17]

In case of the vaccines:

Pfizer vaccine consists of a constant structure of the mRNA coding for the spike protein; it doesn't count for the mutation occurring in the viral spike proteins. Also, this method of treatment provided sufficient evidence of increasing the **cardiovascular risk** in the individual administered with the 3rd booster dose. [18]

AstraZeneca vaccines constitute in the activation of T-cells and release of antibodies, by insertion of modified chimpanzee DNA adenovirus into the human host. Enabling the individual to fight the SARS-CoV2 if entered with readily available antibodies released in the body. But this method has a potential way of manifestation of severe immunological response against the vaccine, leading to **allergy and vaccine-induced immune thrombotic thrombocytopenia (VITT)**, leading to limitations in its usage and even temporary suspension in some regions. [19]

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