mRNA-Based Vaccine and approach to treating COVID-19: Mini Review

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ABSTRACT
SARS-CoV-2, the causative agent of COVID-19, first appeared in late 2019 in China. Given its rapid spread and pathogenic potential, the world urgently needs a vaccine that is the only way to mitigate the impact of the pandemic on public health and the economy. Currently, scientists are trying to rapidly develop new candidate vaccines. A variety of vaccine approaches and formulations for targeting the SARS-CoV-2 S protein are being pursued, including nucleic acid vaccines (mARN). Here we give a reminder about vaccination in general and we report the results of some studies conducted on the evaluation of the mRNA Vaccine against SARS-CoV-2.

1. Introduction:
With the current rapidly spreading pandemic, no one will be safe until the whole world is safe. The development of a COVID-19 vaccine is the most urgent challenge of our time. The global pandemic has already caused hundreds of thousands of deaths and disrupted the lives of billions of people. In addition to reducing the tragic number of deaths and controlling the pandemic, the introduction of a vaccine will also help to avoid losses of US$375 billion in the global economy each month [1]. Global and equitable access to a vaccine, which will protect in particular health workers and those at greatest risk of contracting the disease, is the only way to mitigate the impact of the pandemic on public health and the economy.

2. Vaccination, a public health approach:
2.1. Definition:
The European Pharmacopoeia (2001) defines a vaccine as “a preparation containing antigenic substances that have the property of creating an active and specific immunity against the infecting agent, toxin, or antigen developed by it.” This active, specific immunoprophylaxis is in some cases very effective, constituting a very useful means of prevention in public health [2].

2.2. Characteristics of a vaccine:
There are three main characteristics of a vaccine:
- Be practical to administer in terms of intake or injection modality, number of administrations, conservation conditions or cost. Administration may be subcutaneous, intradermal, intramuscular or oral.
- Have an excellent tolerance by being free, at most, of serious adverse effects;
- Be effective, i.e. induce immune memory and provide lasting protection against infection.

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2.3. Principle of vaccination:
It involves introducing into the body all or part of a pathogen (virus, bacterium, toxin, etc.) that has been rendered harmless, but has retained its immunogenic power. The response to vaccinations is humoral (neutralizing antibodies produced by B lymphocytes) and/or cellular (CD4+ auxiliary T lymphocytes essential for the activation of B lymphocytes, CD8+).

Two types of responses are distinguished according to primary vaccination or recalls:
- The primary response occurs after the first injection. A latency period of 24-48 hours to 2 weeks, which depends on the patient’s characteristics as well as the immunogenic qualities of the vaccine, is observed. Then comes a rapid rise of antibodies (IgM) to reach a maximum at the latest after one month. The rate of anti-corps (Ac) then decreases rapidly;
- The secondary response is noted after the second injection (recall), in practice never less than one month after the first injection (immunological memory). The protective antibodies (IgG) secreted by the T and B lymphocytes are rapidly rising, with a significant and lasting effect.

Immunological memory persists for a very long time, even when the antibody level, which gradually decreases, becomes very low. With any new introduction of the antigen (vaccine or infective), these lymphocyte populations can again rapidly produce large amounts of antibodies. Some factors influence the immune response: age (immaturity of the newborn’s immune system and decline in response from the age of 40), congenital or acquired immune deficits, and genetic factors that are still poorly understood [3].

2.4. Compositions of vaccine preparations:
Different types of vaccines can be distinguished:
- Live or attenuated vaccines: whole infectious agents (viruses, bacteria) whose virulence is reduced after mutation; ex.: BCG, MMR, varicella vaccine.
- Killed or inactivated vaccines: whole infectious agents unfit for multiplication due to physical or chemical treatment; ex.: polio vaccine, hepatitis A.
- Subunit vaccines (purified vaccine antigens): antigens specific to the infectious agent after treatment or de novo manufacture; ex.: diphtheria and tetanus toxoids, polysaccharides (polysaccharides) capsularies of pneumococcus, meningococci and Haemophilus influenzae b, various and purified antigens of acellular pertussis vaccines, hepatitis B…

In addition, vaccine preparations most often contain an adjuvant (all inactivated vaccines except the seasonal injectable influenza vaccine), most often aluminum-based [4].

2.5. From vaccine design to commercialization:
The practice of vaccination in a community or population allows the control, if not eradication, of certain contagious infections. Vaccines are an essential public health tool. But vaccine, antigenic preparation, adjuvants, preservatives, cold chain, adverse effects, contraindications, vaccine schedule and product availability. The pharmacist is a key point of contact on the subject.

In fact, it takes several years, often decades, to successfully manufacture and market a vaccine (Figure 1 and Table 1).

![Figure 1. Effects of Traditional Vaccine Development Pathway](image-url)
Table 1. Steps for marketing a vaccine [6].

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| Understanding of the disease | Knowing how to recognize the disease  
Establish valid and reliable diagnostic methods  
Identify the responsible officer and locate its presence in nature  
Knowledge of the physiopathology and immune defense mechanisms of the human body |
| Understanding the infectious agent | Understand its biochemical properties and characterize it well  
Know its ability to reproduce in cell culture  
Analyze its genetic properties and antigens  
Establish an animal model that will reproduce infection in humans |
| Manufacture of different vaccine candidates (preclinical studies) | Analyze the inactivation or attenuation capabilities of the infectious agent  
Select and purify the appropriate antigen that may stimulate the immune response  
If necessary, select the appropriate adjuvant  
Select the appropriate dosage and sequence  
Demonstrate vaccine stability, safety and immunogenicity in animal models  
Produce pilot batches |
| Clinical studies in humans | Conduct Phase I studies to determine the immunogenicity and safety of different doses in a limited number of healthy volunteers (usually between 10 and 100)  
Conduct Phase II studies to confirm immunogenicity and safety of the vaccine and determine optimal timing and doses in a larger number of healthy volunteers (usually between 50 and 500)  
Conduct phase III studies to determine the immunogenicity, safety and effectiveness of the vaccine in preventing the disease in a significant number of individuals (several thousand) in the target population |
| Approval by a regulatory body | In Canada: Health Canada  
United States: Food and Drug Administration  
In Europe: European Medicines Agency |
| Commercial production of the vaccine | Produce large-scale batches of vaccines |
| Post-marketing studies | Studies in other populations  
Studies of interactions with other vaccines  
Studies after implementation of programmes  
Studies to observe the safety and efficacy of the vaccine in the field (sometimes also called Phase IV studies). |

3. New and quickly type of vaccine:
Now the scientists are working on expediting a new type of vaccine for COVID-19, they are trying to expedite development of vaccines and antibody therapeutics. A vaccine trains the immune system to recognize a viral protein called antigen. SARS-CoV-2, like other coronaviruses, is named after the crown-shaped spikes on its surface. There are three proteins on the surface of these viruses: the shell, membrane and peak, which encapsulate a strand of RNA. This RNA molecule contains the genetic instructions that make up the virus. Researchers are using alternative approaches to make an effective vaccine more quickly against novel, rapidly spreading viruses such as SARS-CoV-2. In one approach, a new generation of vaccines, called mRNA vaccines, will carry molecular instructions to make the protein. An mRNA vaccine provides a synthetic mRNA of the virus, which the host body then uses to produce the viral proteins itself and can bypass the hassle of producing pure viral proteins, saving sometimes months or years to normalize and accelerate mass production (Figure 2).
The mRNA used in vaccination cannot be part of the person’s chromosomes. The mRNA vaccines basically mimic the virus’s natural infection, yet they contain only a short synthetic version of viral mRNA that codes only for antigenic protein. As a result, mRNA vaccines would be safer than viral or weakened protein vaccines since they do not involve the risk of the injected virus becoming active, or protein contamination [7].

The employ of (mRNA) is a promise approach for Covid-19 vaccination, as it combines rapid manufacturing and prompt modification of the encoded immunogenic, both of which speed up vaccine development [9]. Indeed, the idea of using mRNA to ask the human body to read instructions and make viral proteins is not new. For two decades, the researchers have shown that the externally supplied mRNA translates into the encoded protein. However, mRNA is not a very stable molecule, which has prevented these mRNA vaccines from becoming a reality. In the other hand; RNA vaccines encoding viral antigens have been revealed to be secure and immunogenic in some clinical trials [10-11].

On February 24, 2020, the biotech company Moderna Inc. announced that it had rapidly developed an experimental vaccine against COVID-19 called mRNA-1273. It codes for a stable form of the transient SARS-CoV-2 protein and ready for clinical trials in humans to assess the safety and reactogenicity of a 2-dose immunization schedule of mRNA-1273. The mRNA-1273 vaccine developed today uses chemical modifications to stabilize mRNA and packs it in injectable form using liquid nanoparticles [12].

In a preliminary report on a phase 1 open-label trial conducted at an increased dose level, including 45 healthy adults aged 18 to 55, and who received two vaccinations, 28 days apart, with mRNA-1273 at a dose of 25 μg, 100 μg or 250 μg, the mRNA-1273 vaccine induced anti immune responses – SARS-CoV-2 in all participants, and no safety issues limiting testing were identified. The mRNA-1273 vaccine induced anti immune responses – SARS-CoV-2 in all participants, and no safety issues limiting testing were identified. In addition, more than half of the participants had solicited adverse events that included fatigue, chills, headaches, myalgia, and pain at the injection site. Systemic adverse events were more common after the second vaccination, especially at the highest dose, and three participants (21%) in the 250 μg group reported one or more serious adverse events [13].

A study was conducted on non-human primates that offer several benefits for clinical translation by evaluating immunogenicity and vaccine protection in preclinical animal models. They have a greater similarity with humans than rodents in innate immune responses and directories of B and T cells, and allow the use of clinically relevant vaccine doses. In addition, recent studies have shown that SARS-CoV-2 targets similar replication sites and summarizes some aspects of COVID-19-like disease in non-human primates [9,14].

They have transient viral replication in the upper and lower respiratory tract and mild inflammation in the lungs that resolves within 14 days [14]. As a result, they represent a useful animal model for evaluating vaccine protection against early viral replication. The results of this study show that the vaccination of non-human primates with mRNA-1273 induced robust SARS-CoV-2 neutralizing activity, quick protection in the upper and lower airways, and no pathological changes in the lungs [15].

BNT162b1 is a lipid-nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes the the trimerized receptor binding domain (RBD) of the advanced glycoprotein of SARS-CoV-2. The Phase II/II study of this RNA vaccine shows encouraging clinical results and strongly supports accelerated clinical development, including efficacy testing, and at-risk manufacturing to maximize opportunities for rapid production of a SARS-CoV-2 vaccine to prevent COVID-19 [16]. And on safety and immunogenicity data for BNT162b1 in younger adults from trials conducted in Germany and the

Figure 2. The central dogma of molecular biology, stated by Crick in 1960. It describes the expression of genetic information from its support, DNA, to proteins [8].
United States, are added safety and immunogenicity data from a Phase 1 study conducted in the United States on two vaccine candidates (BNT162b1, which encodes a secreted trimerized SARS-CoV-2 receptor–binding domain and BNT162b2, which encodes a membrane-anchored SARS-CoV-2 full-length spike, stabilized in the prefusion conformation) in younger and older adults, to assess the safety and efficacy of Phases 2-3 [17].

4. Conclusion:
Clinical trials are carefully put in place, and this is good news that could potentially bring the world back to something more normal, but it is possible that the virus has evolved sufficiently since the vaccines were designed to offer fewer benefits. Therefore, it is not possible to say with certainty that the outbreak will end once the vaccine is available for public use. In addition, it will also take time to manufacture and administer enough vaccine for the population to reach collective immunity.

References:

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