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Perspective

Commentary of the mRNA vaccines COVID-19

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The World Health Organization (WHO) declared global SARS-CoV-2 (COVID-19) pandemic status on March 11, 2020 [1]. To date, data record approximately 106 million infected individuals and 2.32 million deaths due to pandemic COVID-19, worldwide. The most common symptoms of SARS-CoV-2 infection reported are: elevation of body temperature, fatigue, cough, loss of smell. In a percentage of patients, especially elderly individuals with comorbidities, COVID-19 infection can cause severe organ injury [2]. Since the onset of the COVID-19 pandemic, numerous pharmacological treatments have been used off label, to treat the viral infection, with the primary aim of avoiding the most serious complications and organ injury. [3,4] Initially, the need and urgency for rapid action suggested the use of pharmacologic agents already on the market for other therapeutic indications, such as anti-inflammatory, antiviral, and anticoagulant agents. Remdesivir antivirals [5] have shown anti-COVID-19 efficacy in some studies [6], several immunomodulatory agents have been used to reduce the generalized hyperinflammatory state caused by cytokine storm [7]. Other experimental pharmacological approaches are directed to limit cardiac, pulmonary, and hepatic damage [8-10]. A few months ago, the first COVID-19 vaccines were licensed, initiating a worldwide vaccination campaign. The current licensed or investigational COVID-19 vaccines use different modes of action, mRNA, DNA, viral vector, protein subunits and with inactivated virus. The various vaccines differ in efficacy, safety profile, timing of administration, and mode of production. In particular, mRNA vaccines are the first vaccines licensed with this new method of action. With extraordinary rapidity, the first COVID-19 vaccines were produced and authorised. This speed of production was also made possible by a new vaccine method used, mRNA vaccines. The mRNA vaccines represent the beginning of a new era for preventive medicine.

The mRNA vaccines against COVID-19 are the first vaccines with this method of action to be authorised, representing the beginning of a new era for preventive medicine not only against SARS-CoV-2 but against all viral diseases. [11] The mRNA vaccines have several advantages over the traditional and conventional vaccines, in particular the development and production are carried out quickly and at low cost [12]. All this, has allowed to have available and authorized the first vaccines against COVID-19 in a very short time. In addition, early clinical data show excellent efficacy and safety. In these vaccines, the mRNA molecule is encapsulated in lipid nanoparticles, facilitating mRNA uptake and penetration into muscle cells, and protecting mRNA from degradation. Once the mRNA transits into the cytosol, ribosomes perform cellular translation by synthesizing spike (S) protein, which is released into the circulation stimulating the cell-mediated and antibody-mediated immune response. The spike protein (S) is critical for the endocellular entry of SARS-CoV-2, and is also responsible for the induction of neutralizing antibodies. Recent evidence, however, shows that the antibody response is not the only one produced by mRNA vaccines and argues that another important weapon of defense against Sars-Cov-2 is cellular immunity through the development of specific T lymphocytes [13]. New variants of SARS-CoV-2 have recently been identified in the United Kingdom and South Africa. These new variants share the N501Y substitution, which targets the spike (S) protein and the viral receptor binding site for cell entry. Early epidemiological evidence shows that mRNA vaccine-induced immune responses are equally effective in attacking these novel variants (Fig. 1).

The mRNA vaccine development and manufacturing process does not require toxic chemicals or cell culture, and the short production time presents a very low risk of microorganism contamination and to date are considered a

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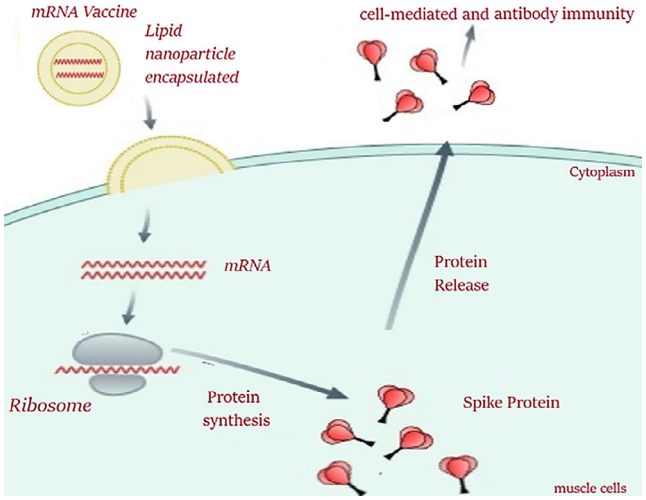

Fig. 1 – The mechanism of action of mRNA vaccines. The vaccine is administered at the level of the deltoid muscle. The mRNA molecule encapsulated in lipid nanoparticles penetrates the muscle cells, ribosomes translate the mRNA fragment into spike(S) protein. The externally released spike(S) protein stimulates antibody and cell-mediated immune cell responses.

safe vaccine method. Compared with traditional vaccines, the advantages of mRNA vaccines are features of rapid deployment, low cost, cell-free production, flexibility, safety, and power. A clinical study shows that the most commonly reported systemic events after administration of COVID-19 mRNA vaccine were fatigue and headache, although fatigue and headache were also reported in patients taking placebo. Serious systemic events were reported in less than 2% of vaccine recipients. Fever (temperature ≥38 °C) was reported after the second dose by 16% of vaccine recipients. No deaths were considered by the researchers to be related to the vaccine or placebo [14]. Anaphylaxis to COVID-19 mRNA vaccines is currently estimated at 2.5–11.1 cases per million doses, largely in individuals with a history of allergy. In one large study, the incidence of acute allergic reaction after more than 60 000 administrations of COVID-19 mRNA vaccine was examined. Acute allergic reactions were reported by 2.10%; anaphylaxis was confirmed in 0.025% of cases [15].

Efficacy data, including against new SARS-CoV-2 variants, and safety data of mRNA vaccines against COVID-19 are reassuring. However, some aspects need to be clarified and further investigated. The currently licensed COVID-19 mRNA vaccines involve two administrations a few weeks apart. But how long can dose administration be spaced in order to achieve a longer lasting response? Also, how long will the induced antibody response last? For individuals who have been infected and cured by antibody development, should only one dose be administered? Also, should certain categories of patients, such as cancer or organ transplant patients and those on immunosuppressive therapy, receive the same doses at the same interval as healthy individuals? Preventive vaccination is the safest and cheapest way to stop the COVID-19 pandemic; clinical data show good efficacy and safety for mRNA vaccines against COVID-19. However, further clinical data are urgently needed to clarify these important questions. The technical issues related to the production of billions of doses and the ethical issues associated with ensuring these vaccines even in the poorest countries are imminent and important challenges. mRNA vaccines represent a very valuable preventive medicine strategy, however, more vaccines are needed to ensure consistent global access and the highest immunity against viral variants.

The mRNA vaccines are safe and effective and represent a very valuable weapon to stop the global COVID-19 pandemic. RNA-based vaccines are a promising new approach to protect humans not only from SARS-CoV-2, but from infectious diseases, with the advantage of rapid production and sufficient resource investment. The development of RNA vaccines has been growing rapidly, the increasing number of trials will allow rational approaches to improve the efficacy and safety of this revolutionary class of preventive medicine.

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