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mRNA Vaccines in the COVID-19 Pandemic: Production, Antibody Formation Mechanism and Advantages of mRNA Vaccines

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Abstract

Vaccines are antigens that are inactivated or attenuated to produce biological products that can stimulate the immune system. The mRNA vaccine is a new type of vaccine in an effort to deal with the coronavirus disease outbreak. An mRNA vaccine is a vaccine that carries the genetic information of a pathogen that is copied in mRNA This literature review uses an online-based literature study, the library sources selected for use are based on relevance to the topic. The stages of vaccine production include sequence cloning, purification, addition of cap structures, in the delivery of mRNA vaccines formulated in the form of lipid nanoparticles. mRNA vaccines are injected intramuscularly which will then trigger immune cells so that adaptive immune cells are formed. mRNA vaccines can be designed to synthesize quickly, mRNA vaccines do not interfere with cellular function or integrate into the host genome.
Keywords: Antibody; mRNA; Vaccine.

Abstrak

Vaksin merupakan antigen yang diinaktivasi atau dilemahkan menghasilkan produk biologis yang dapat merangsang sistem imun. Vaksin mRNA merupakan jenis vaksin baru dalam upaya penanganan wabah penyakit coronavirus. Vaksin mRNA merupakan vaksin yang membawa informasi genetik patogen yang disalin dalam mRNA Kajian literatur ini menggunakan studi literatur berbasis online, sumber Pustaka yang dipilih untuk digunakan berdasarkan relevansi dengan topik. Tahapan produksi vaksin meliputi kloning sekuens, purifikasi, penambahan struktur cap, dalam pengiriman vaksin mRNA diformulasikan dalam bentuk lipid nanopartikel. vaksin mRNA diinejksikan pada intramuscular yang kemudian akan memicu sel imun sehingga terbentuk sel imun adaptif. vaksin mRNA dapat dirancang sintesis dengan cepat, vaksin mRNA tidak menggangu fungsi seluler atau berintegrasi kedalam genom inang.
Kata Kunci: Antibodi; mRNA; Vaksin.

INTRODUCTION

Vaccines are inactivated or attenuated antigens that produce biological products that can stimulate the immune system and form a specific immune system that is active in certain diseases. Vaccines will elicit a specific adaptive immune response that provides effective protection against infectious diseases [1]. Vaccines continue to be developed by researchers for the development of better vaccines, in addition to the emergence of new infectious diseases, different types of vaccines emerge, one of which is the mRNA vaccine. Traditional vaccines are vaccines that contain a virus that has been weakened or inactivated or part of a virus that can trigger an immune response. Meanwhile, conventional vaccines in their way of working resemble pathogens that cause infectious diseases [2].

The mRNA vaccine is a new type of vaccine in an effort to handle the coronavirus disease outbreak. Coronavirus or commonly known as COVID-19 is a disease caused by the SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus 2*) virus which infects the human respiratory tract causing symptoms such as cough, runny nose, fever, and other symptoms [3]. COVID-19 (*corona virus disease-19*) was first discovered in Wuhan, China in early December 2019 which easily spread and infected humans almost all over the world until an outbreak (pandemic) occurred and spread to Indonesia in early March 2020. The coronavirus undergoes a spontaneous gene mutation over time and is hereditary to its offspring virus [4].

The mRNA vaccine is a vaccine that carries the genetic information of the pathogen copied in synthetic mRNA that will be received by the body's cells, then used to produce spike proteins on the cell surface where these proteins are harmless and this vaccine will induce cellular immune responses and humoral responses [5]. mRNA vaccines have the advantage of relatively fast production times, but the safety and side effects of mRNA vaccines need to be known. Therefore, the purpose of this literature review is to analyze the production of mRNA vaccines from the SARS-CoV-2 spike, explain the mechanism of action of mRNA vaccines from injection to the formation of an immune response, analyze the advantages of mRNA vaccines related to effectiveness, safety, and speed of production.

RESEARCH METHODS

This literature review uses an online-based literature study sourced from google scholar, pubmed and sciencedirect. This method is used to analyze various online literature sources with the topic of literature review, so that the library sources are chosen to be used based on relevance to the topic. The limitations in writing this literature review include the analysis of the production of mRNA vaccines from the SARS-CoV-2 spike, the mechanism of action of mRNA vaccines, and the analysis of the advantages of mRNA vaccines (effectiveness, safety, production speed).

RESULTS AND DISCUSSION

Production of mRNA Vaccines from the SARS-CoV-2 spike

SARS-CoV-2 is an RNA virus that is divided into several segments with a helical nucleocapsid structure. The virus consists of *the Spike* (S) *glycoprotein* consisting of subunits 1 & 2, *Membrane* (M), *Nucleocapsid* (N), *Envelope* (E), *RNA Viral Genome* [6]. Infection caused by the SARS-CoV-2 virus will cause innate immune system activity and denritic cells that will promote the induction of T-cell and B-cell responses [7]. The production of mRNA vaccines involves a sequence cloning process using DNA plasmids that have a promoter RNA polymerase, after the process of amplifying the DNA of the plasmid is linearized and the impurities are removed, then the addition of a 5'cap structure is added. In vitro transcription is carried out followed by mRNA purification processes such as dsRNA removal. The mRNA vaccine modulates the untranslated 5' and 3' ends to optimize mRNA stability. To improve the stability of uridine is replaced by methylpseudouridine (m1Ψ). In delivery, the MRNA vaccine is formulated as a specific lipid complex in the form of lipid nanoparticles that provides protection from RNA degredation in tissues as well as facilitates the absorption and release of cells into the cytoplasm.[8]

The in vitro process is carried out by way of in vitro enzymatic reactions, the production process of mRNA vaccines must be in a cell-free system and not use raw materials of animal origin, with the aim of avoiding impurities or adventitious contamination. The first thing needs to be done is by making a DNA template first, making a DNA template can be done by linearizing the purified plasmid or using PCR [9]. The main component used is the enzyme RNA polymerase which plays a role in catalyzing the synthesis of target mRNA from the template. Another component in the in vitro enzymatic process is the nucleotide triphosphate (NTP) substrate, a pH buffer mgcl2 polymerase cofactor containing polyamines and antioxidants. The in vitro reaction takes only a few hours, with a short time allowing for a lower chance of contamination [9].

The capping process is no less important, the process can be done when enzymatic in vitro by substituting guanosine triphosphate (GTP) substrate or it can be done by carrying out a second enzymatic reaction by adding capping vaccinia (VCC) enzyme and dono methyl substrate [9]. After the in vitro enzymatic process is carried out, a purification process is carried out which aims to separate the mRNA from other components such as enzymes, NTP residues, DNA templates and also abnormal mRNA that is formed during the in vitro process. The best chromatography in mRNA purification is the reverse phase of *ion pair chromatography* (IPC). The back bone of the sugar-phosphate has a negative charge derived from oligonucleotides and will then bind to the quaternary ammonium compound which is in the silent phase. Then elution was carried out using compounds such as acetonitrile [9].

The mRNA-1237 vaccine produced by Moderna contains the S-2P antigen consisting of the sars-cov-2 glycoprotein. The vaccine is coated with a capsule of four lipid lipid nanoparticles. The vaccine is injected at a dose of 0.5mg/ml, the vaccine is injected into the deltoid muscle on days 1 and 29 [10]. The mRNA vaccine is in great demand as a COVID-19 vaccine because the mRNA vaccine has a fast development speed, after obtaining the antigen genetic sequence it only takes a few days. In the case of the Moderna vaccine, it takes only 2 days from receiving the genome sequence of the surface protein of the coronavirus [11].

Working Mechanism of mRNA Vaccines

Part of the COVID-19 mRNA is injected into the muscles of the individual so that it will process the formation of an adaptive immune system. mRNA encased with lipid nanoparticles enters the myocytes precisely in dendritic cells through endocytosis [12]. These lipid nanoparticles function to protect the mRNA structure from being damaged and help be absorbed by specialized cells from the cell dendritics. The mRNA in the lipid nanoparticles enters the myocytes by endocytosis and is released into the cytoplasm. mRNA is read by ribosomes to form a spike protein that is similar to one of the parts of the virus but not pathogenic [13]. The spike protein that has been formed will then leave the cell through the golgi body and break down into peptides [14]. It aims to provoke an immune response and form antibodies that are expected to be ready to fight the spike protein of the virus. The spike protein will appear on the surface of the cell, then the cell will travel to the lymph nodes and then present the spike protein to the immune cells. Then the protein will develop into two types, namely MHC-2 and MHC-1. Spike proteins produced massively by the immune cell system will later be recognized by MHC-1 and MHC-2 for activation of CD8+ and CD4+ T cells.

Helper T cells and B cells will work together to make antibodies suitable for the spike protein. The helper T cells will bind to the spike protein of the virus. Helper T cells also produce CD4+ which will interact with MHC-2 [15]. Helper T cells that have been strongly activated will produce cytokines (interleukins) where the interleukin functions to differentiate B cells which will turn into plasma cells that function to destroy spike proteins. Interleukin also functions to stimulate helper T cells to multiply memory T cells.

On the cell membrane, cytotoxic T cells that bind to the MHC-1 protein will produce CD8+ protein. This CD8+ protein is particularly dangerous because it will allow cytotoxic T cells to produce molecules that are pathogenic and can cause cells to die if infected with the resulting molecules [16]. Cytotoxic T cells can destroy virus-infected cells by strengthening the immune response.

The mRNA vaccine will produce a humoral (B cell) response and a cellular immune response (T cell) by: cytotoxic cd8+ T cell activation that can destroy cells infected by the virus, activation of CD4+ T cells to enhance the response of CD8+ T cells and B cells, memory T cells and B cells that can respond to cells infected by the virus quickly, as well as the production of antibodies against viruses with B cell activation.

Advantages of mRNA Vaccines

mRNA vaccines have advantages compared to conventional vaccines in that they can increase the immune response quickly and develop faster due to the absence of genome integration [17]. The mRNA vaccine will only express specific anigens and induce a targeted immune response. In addition, mRNA vaccines will induce humoral and cellular immune responses and induce the innate immune system. Zhu et al., 2020 said that mRNA vaccines have been proven to be safe because there is no effect on genetics and DNA in the body because the body's immune cells can destroy parts of the vaccine such as mRNA shortly after the vaccine works. mRNA vaccines can be self-reinforcing and due to the presence of lipid nanoparticles that protect the structure of the mRNA [12].

mRNA vaccines have several advantages compared to conventional vaccines such as:

a) Production speed, Once the genetic sequence of the antigen is known, mRNA vaccines can be designed and synthesized quickly, allowing for a faster response to infectious strains [19]. The production of mRNA is more advantageous because most biological products do not require the use of cell culture. So that the risk of contamination is lower. mRNA vaccines are precise, safe and flexible so they can be easily produced at scale for clinical-level applications.
b) Security, The mRNA vaccine does not contain infectious agents or other pathogenic components so it cannot cause disease. In addition, mRNA vaccines do not interfere with cellular function or integrate into the host genome. Due to the fast production time, the contamination rate is lower. In addition, its non-integrative properties and transient expression within cells support the safety of mRNA vaccines [9].
c) Effectiveness, Clinically tested mRNA vaccines have shown a high level of protection against viruses with a high level of efficacy with great value. In addition, mRNA vaccines trigger humoral immune responses but do not trigger antivector and cellular immune responses that are essential for long-term immunity and protection against new viruses [20].

Ulmer & Geall, 2016 said that the advantages of mRNA vaccines are in terms of safety and effectiveness because mRNA vaccines can reduce the potential risk of infection and reduce the risk of mutations due to mRNA degradation. Hoffman et al., 2020 said that mRNA-based vaccines are very effective so that they can increase the immunity of the mRNA structure due to the modified design of the mRNA structure for optimal translation and stability. According to [12] that mRNA vaccines with low doses but with high concentrations can neutralize immunoglobulins so that they can activate T cells to induce a strong immune response. According to [14] mRNA vaccines do not interfere with DNA components because immune cells in the body will form immunity to disease by separating parts of the mRNA vaccine after the vaccine works.

CONCLUSION

The stages of vaccine production include sequence cloning, purification, addition of cap structures, vaccine delivery is carried out by adding nanoparticles that function to protect RNA degredation in tissues and facilitate the absorption and release of cells into the cytoplasm. The mRNA vaccine will produce humoral (B cell) and cellular immune responses (T cells) by: cytotoxic cd8+ T cell activation that can destroy virus-infected cells, CD4+ T cell activation that enhances the response of CD8+ T cells and B cells, memory T cells and B cells that respond rapidly to viral infection, as well as B cell activation to produce antibodies against the virus.The production of mRNA vaccines is fast, and also the MRNA vaccine will only express specific anigens and induce a targeted immune response.

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