COVID-19 VACCINES CURRENTLY UNDER CONDITIONAL MARKETING AUTHORISATION IN THE EUROPEAN UNION

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Abstract

Summary

A total of four vaccine candidates for Corona Virus Disease – 19 have been granted conditional marketing authorisation by the European Medicines Agency. These new vaccines have been designed, developed, and tested in as little as eleven months. Novel vaccination strategies, such as mRNA vaccines, have been employed by various pharmaceutical companies to create vaccines with an impressive level of efficacy. Thus far, the conditionally approved vaccines all have a high vaccine efficacy and display a generally favourable safety profile. However, as different phases of clinical development have been performed within one protocol and phase III trial follow-up has been relatively short, long-term effects for neither safety nor efficacy have been observed yet. Different dosing regimens, storage conditions, and mechanisms of action show that each Corona Virus Disease – 19 vaccine currently under conditional marketing authorisation can fill its own niche. The current vaccine landscape is volatile, and vaccination policies are frequently changing. The vaccines that have been granted conditional marketing approval must still undergo the rest of the European Medicines Agency regular marketing approval process but have reported results of early clinical trials and interim results of their various phase III trials. These data show a generally favourable safety profile and remarkable efficacy.

In the past year, the world as we know it has been changed by the arrival of Severe Acute Respiratory Syndrome – Corona Virus 2 (SARS-CoV-2) and the associated Corona Virus Disease – 19 (COVID-19). Currently, there is no designated cure for COVID-19. However, vaccination is a promising strategy to reduce the burden of COVID-19 on the individual and on society. A multitude of companies has spent the last year developing and testing vaccines for COVID-19. As of March 23rd, the vaccines conditionally approved for use in the European Union by the European Medicines Agency (EMA) are Comirnaty (BNT162b2), developed by Pfizer, BioNTech, and Fosun Pharma; Moderna COVID-19 Vaccine (mRNA-1273), developed by Moderna, BARDS, and NIAID; AZD1222, developed by The University of Oxford and AstraZeneca; and COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S), developed by Janssen Vaccines [1, 2]. In total, thirteen vaccines have been granted (conditional) approval for emergency use in various countries around the world [1]. Next to this, a large number of other vaccine candidates are still in various stages of (pre-)clinical development [1].

The Netherlands has started to vaccinate various groups of the population on January 6th, 2021. As of March 28th, an estimated 1,688,490 people have received their first injection, and 690,062 people have received their second injection in The Netherlands [3]. So far, The Netherlands have only used the Comirnaty, Moderna, and AstraZeneca vaccines [3]. It is important to note that the policy regarding which vaccines are used and what dosing regimens are used may change in the future. The information included in this review is accurate as of April 2nd, 2021. The aim of this narrative review is to generate an overview of the mechanisms of action, safety and efficacy concerns, and general differences between the four COVID-19 vaccines currently in use in the European Union.

Current COVID-19 vaccines

BNT162b2/ Comirnaty

Comirnaty, or BNT162b2, is the COVID-19 vaccine developed by Pfizer, BioNTech, and Fosun Pharma and was the first COVID-19 vaccine administered outside of a study setting [4]. The vaccine uses a single strand, 5'-capped, non-replicating, nucleoside-modified mRNA, encoding the surface spike protein of SARS-CoV-2 that has been slightly modified to retain a prefusion conformation (structure of the protein before cell infection), which makes the first contact with the antigen easier (table 1) [4-7]. The mRNA is encapsulated in lipid nanoparticles to prevent RNA degradation and allow for cellular uptake [4, 5]. Once the vaccine is administered intramuscularly, the mRNA is taken up into host cells, where it is translated into the viral spike protein and incorporated into the cell membrane [4, 5]. Subsequently, the expression of the spike protein on the cell membrane will act as a pathogen-associated molecular pattern (PAMP) for immune cells, and an adaptive immune response is launched [4-6]. Successful vaccination with Comirnaty will result in circulating neutralising antibodies and cellular immunity against the spike protein [4-6]. As the spike protein is similar across multiple strains of coronaviruses, using the spike protein as a vaccination target may decrease the impact of random mutations or different variants of SARS-CoV-2 [4]. Finally, vaccination with Comirnaty resulted in higher neutralising antibodies than a normal immune response to SARS-CoV-2 would [4].

The vaccine is supplied in a frozen multiuse vial and must be thawed and diluted before a dose can be administered intramuscularly [7]. Each vial must be kept at -80°C and contains six vaccine doses after dilution; one dose contains 30 µg of mRNA [4-7]. Full immunisation requires two doses, spread at least 21 days apart [5-7]. Comirnaty reaches full effect seven days after the second injection [5, 6]. The second injection of Comirnaty can, thus far, not be substituted with a different vaccine, as data on combining vaccines are lacking [7].

Comirnaty is currently indicated for use in all adolescents and adults over the age of 16 unless one of the risk criteria, such as a suspected or proven allergy to one of the components of the vaccine, is present [7]. In December 2020, a publication of the largest clinical trial concerning the safety and efficacy of BNT162b2 was published, containing data of 42,448 participants, of which 18,556 received both doses of BNT162b2, and 18,530 received both doses of saline

placebo [5]. BNT162b2 recipients more often reported pain at the site of injection, while other local reactions such as redness and swelling were reported in similar frequency compared to placebo, after both the first and second dose [5, 6]. The local reactions were mostly mild-to-moderate in nature and were resolved in one to two days [5]. Systemic events, such as fatigue, headache, and muscle pain, increased in prevalence after the second dose in the vaccine groups [5]. BNT162b2 recipients reported more adverse events (AEs) overall: 27% versus 12% reported any AEs; 21% versus 5% reported treatment-related AEs (vaccine group versus placebo group, respectively) [5]. Most of these AEs are short-lasting, mild effects. In total, four treatment-related serious AEs were reported in the BNT162b2 group [5]. Overall, BNT162b2 displays an acceptable short-term safety profile, and safety monitoring will continue for two years after the administration of the second dose in the vaccine group [5].

For the efficacy of the vaccine, the trial observed the onset of COVID-19 in its participants seven days or more after the second dose of the regimen [5]. In those with no indication of a prior or current infection with SARS-CoV-2, only 8/18,556 cases of COVID-19 were observed in the vaccine group, compared to 162/18,530 among those in the placebo group, yielding a vaccine efficacy (VE) of 95.0% (95% Confidence Interval (CI): 90.0-97.9) [5]. This VE is comparable across age- and ethnic groups [5].

mRNA-1273/Moderna

The Moderna vaccine or mRNA-1273 is similar to the Comirnaty vaccine. mRNA-1273 is also a single strand, 5'-capped mRNA vaccine encapsulated in lipid nanoparticles, encoding the full-length spike protein of SARS-CoV-2 locked into the prefusion-stabilised position (table 1) [8, 9]. However, mRNA-1273 is dosed with 100 µg of mRNA per dose, is only indicated for persons above 18 years old, contains up to ten doses per supplied flask, and can be kept at a higher temperature of -25°C to -15°C [8, 9]. Similarly to Comirnaty, the vaccine is administered intramuscularly. The dosing regimen consists of two injections into the same arm, spread 28 days apart [9]. The second dose of mRNA-1273 can also not be substituted by a different vaccine due to the lack of data with combined schedules [8].

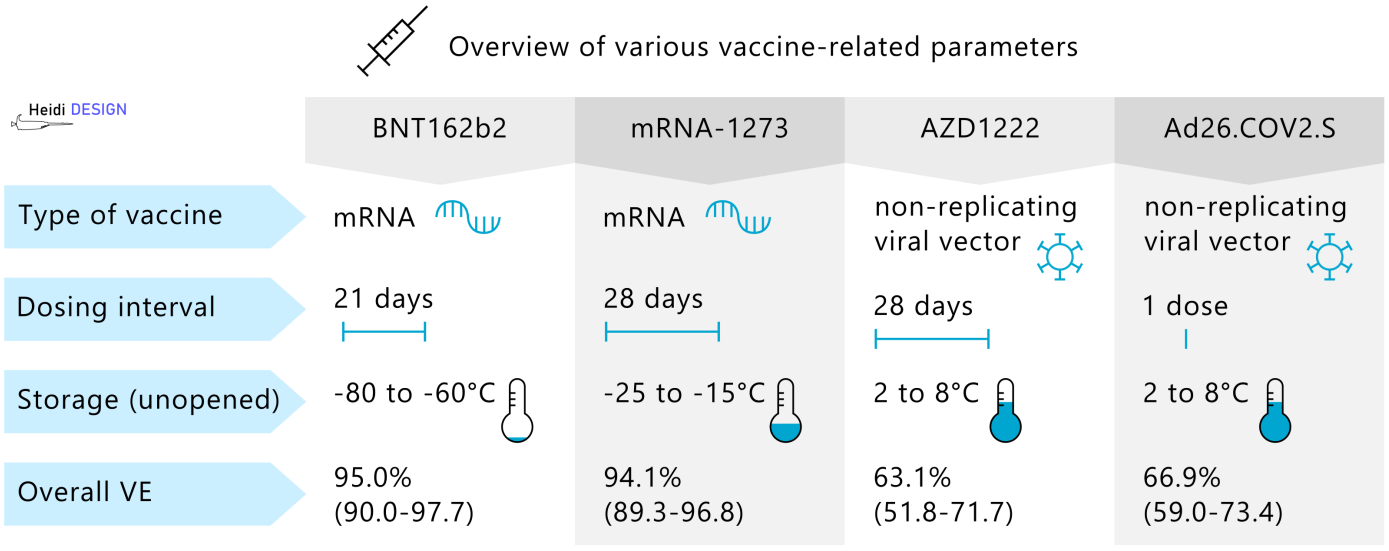
A large trial recruited adults over 18 years old with no known history of a SARS-CoV-2 infection but who were at risk of contracting a SARS-CoV-2 infection or its related disease COVID-19 [9]. A total of 30,420 participants were enrolled in the study and randomised at a 1:1 ratio between treatment and placebo groups. 14,134 and 14,073 participants in the treatment and saline placebo group, respectively, completed the full study thus far and were included in the analysis. AEs were recorded for 28 days following the injections. Local AEs were reported in 88.6% of the treatment group versus 18.8% in the placebo group after the second injection [9]. Pain at the site of the injection was reported as the main adverse event in the majority of the cases (86.0%) [9]. The incidence of solicited systemic AEs increased between the first and the second dose in the treatment group (54.9% vs 42.2% after the first compared to 79.4% vs 36.5% after the second, treatment vs placebo) [9]. The severity of the solicited adverse effects also increased after the second dose in the treatment group (16.5% to 38.1% grade II and 2.9% to 15.8% grade III of all reported solicited AEs) [9]. Any treatment-related AEs were reported in 8.2% and 4.5% of participants in the treatment group versus the placebo group, respectively [9]. Severe treatment-related AEs were reported in 0.5% of the treatment group versus 0.2% of the placebo group [9].

VE was analysed 14 days after the second dose. Only 11/14,134 cases of COVID-19 were reported in the treatment group, compared to 185/14,073 cases in the placebo group [9]. This yields a VE of 94.1% (95% CI: 89.3-96.8) for preventing symptomatic COVID-19 cases compared with placebo [9]. The vaccine also appears to prevent severe COVID-19; the 30 severe cases that were reported throughout the study were all in the placebo group [9]. According to these results, mRNA-1273 seems to be an excellent addition to the vaccination programme with a very similar efficacy profile to Comirnaty.

AZD1222/AstraZeneca

AZD1222 consists of a viral vector originating from a chimpanzee containing a monovalent, recombinant, non-replicating adenovirus (ChAdOx1), encoding the full-length spike protein (table 1) [10, 11]. Unlike the Cormirnaty and Moderna mRNAs, the AstraZeneca adenovirus was not modified to lock the resulting spike protein in the prefusion conformation [10]. Unopened flasks of AZD1222 contain ten doses of vaccine and can be kept in the refrigerator for six months between temperatures of 2°C and 8°C [12]. Once opened, the flask can be kept at the same conditions but must be fully used within two days [12]. The dosing regimen consists of two intramuscular injections, spread 28 days apart, in adults over 18 years old [10, 11]. Both a one-dose regimen, as well as a two-dose regimen

Table 1: *Overview of various vaccine-related parameters. IM: intramuscular; VE: vaccine efficacy*



have been tested [10, 11]. Two different dose strengths have been tested as well, being 2.2·1010 viral particles (low) and 5·1010 viral particles (regular) per dose [10, 11].

A pooled analysis of four clinical trials, totalling 24,422 participants, examined the safety and efficacy of AZD1222 [11]. 17,178 participants were included in the primary efficacy analysis, which examined the incidence of virologically confirmed, symptomatic COVID-19 cases, identified 14 days or later after the second dose as the outcome measure [11]. The other participants were dosed only once or were lost to follow-up. AZD1222 has a VE of 66.7% (95% CI: 57.4-74.0) overall for the previously mentioned primary efficacy analysis [11]. A low dose plus standard dose regimen appeared to provide more protection (VE: 80.7% (95% CI: 62.1-90.2)) than two times the standard dose regimen (VE 63.1% (95% CI: 51.8-71.7)) [11]. However, this may have been the result of uneven sample sizes, as the former condition was only explored in one trial in the United Kingdom [10, 11]. The safety data were comparable between the vaccine groups and the control groups [11]. 0.9% of all participants in the vaccine group reported any severe adverse event, compared to 1.1% of all participants in the saline control group; severe nausea and myalgia were more common in the vaccine group [11]. Overall, AZD1222 did not seem to induce more AEs than the control group.

In the first weeks of March 2021, several countries, among which the Netherlands, had shortly suspended the use of the AZD1222 vaccine after a few dozen case reports of severe blood clotting following vaccination with AZD1222 surfaced, known as thrombosis with thrombocytopenia [13]. However, an in-depth investigation by the EMA stated that there is no link between vaccination with AZD1222 and an increased risk of blood clots [14]. Most countries have since resumed using AZD1222 again, albeit with an adjusted schedule where only people over the age of 60 are vaccinated. However, the debate surrounding the safety of the AZD1222 vaccine intensified at the end of March and start of April 2021, when the EMA released a document stating the clotting problem must be listed as a very rare side effect, but that the advantages of vaccination with AZD1222 still outweigh the risks of rare side effects [15].

Ad26.COV2.S/Janssen Vaccine

The Janssen Vaccine consists of an adenovirus type 26, encoding the full-length spike protein of SARS-CoV-2 (table 1) [16]. It is supplied in multiuse vials, containing five doses of vaccine containing 5·1010 viral particles each. The vaccine must be administered intramuscularly and is indicated for adults over 18 [16]. Different from the previously described vaccines, Ad26.COV2.S only has to be injected once [16]. Similarly to AZD1222, Ad26.COV2.S can be stored at temperatures between 2°C and 8°C, although it must be fully used within 6 hours of opening [16].

Currently, Johnson & Johnson is running two phase III trials for Ad26.COV2.S. The ENSEMBLE (COV3001, NCT04505722) and ENSEMBLE 2 (NCT04614948) examine the safety and efficacy of one- and two-dose regimens, respectively. The ENSEMBLE trial is currently ongoing and has closed recruitment. Data from the ENSEMBLE trial, which entails 44,325 participants, was used for conditional marketing authorisation of the one-dose regimen by the EMA on March 11th, 2021 [1]. The ENSEMBLE 2 trial is currently still recruiting participants.

The preliminary data from the ENSEMBLE trial showed an overall VE of 66.9% (95% CI: 59.03-73.40) 14 days after vaccination and 66.1% (95% CI: 55.01-74.80) 28 days after vaccination against any severity of COVID-19 [17]. However, this VE is higher when examining the severe cases of COVID-19 [17]. Fourteen days after vaccination, Ad26.COV2.S had a VE of 76% (95% CI: 54.56-89.09), and 28 days after vaccination, the VE rose to 85.4% (95% CI: 54.15-96.90) against severe cases of COVID-19 [17].

The American Food and Drug Administration (FDA) Emergency Use Authorisation (EUA) contains some information about the safety of Ad26.COV2.S. Solicited local AEs, such as injection site pain (58.6% vs 17.4%), injection site erythema (9.0% vs 4.3%), and injection site swelling (7.0% vs 1.6%) were reported more often in the vaccine group compared to the placebo group in the population aged 18-59, in the seven days following vaccine administration. The individuals aged 60 and up had a smaller discrepancy between the vaccine group and the placebo group for all local AEs: 33.3% vs 15.6% for injection site pain; 4.6% vs 3.2% for injection site erythema; and 2.7% vs 1.6% for injection site swelling in the vaccine group and control group, respectively. The vaccine group also scored higher in all categories of solicited systemic AEs, consisting of headache (reported by 44.4% vs 24.8%), fatigue (43.8% vs 22.0%), myalgia (39.1% vs 12.1%), nausea (15.5% vs 8.9%), fever (12.8% vs 0.7%), and use of antipyretic drugs or pain medication (26.4% vs 6.0%). The proportion of participants reporting unsolicited AEs was similar in both groups (13.1% in the vaccine group, 12.0% in the placebo group). Serious AEs, such as urticaria, blood clots, and seizures, were more common in the vaccine group but were so rare that this could thus far not be linked to the use of the Ad26.COV2.S vaccine. The safety profile was similar to a phase I and phase IIa trial, which had its data published in January 2021 [18]. Overall, the safety profile of Ad26.COV2.S was deemed sufficient, and Ad26.COV2.S was granted conditional marketing authorisation by the EMA.

Discussion

It is important to note that this review is based on short-term data, and the efficacy and safety profile of the vaccines may change over time. New, long-term safety concerns may arise after a longer time of observation. Additionally, it is known that the efficacy of other vaccines, such as influenza vaccines, wanes over time [19]. The median time since the final dose was about two months at the time of publishing of most phase III trials included here [5, 6, 9-11]. Next to this, there are no approved vaccines or medications for COVID-19 at the moment. The vaccines currently in use have only been granted conditional marketing authorisation. The companies behind the vaccines currently in use must continue submitting data on the process of manufacturing, safety, and efficacy of their product until the requirement for regular approval by the EMA is met. If serious side effects were to surface after a longer observation time, the regular approval could be denied, or the conditional marketing authorisation status can be revoked.

That being said, it is astonishing to realise that some of these novel vaccines have been designed, developed, and (partially) tested in as little as eleven months. This was made possible by the collaboration of health organisations, pharmaceutical companies, and universities. Major time was gained by blending clinical trial phases using multi-phase protocols (i.e., phase I and phase II, phase II and phase III) and the fast-tracked publishing of study results [20, 21]. Although the possibility of mRNA vaccines has been studied since the 1990s, COVID-19 is the first high profile case in which an mRNA vaccine was used [20-22]. The phase III trials of BNT162b2, mRNA-1273, and AZD1222 reported findings of early protection after the first dose [5, 6, 9-11]. As some countries are investigating a change in their dosing regimen by changing the second dose to 12 weeks after the first, instead of three to four weeks, this early protection may prove to be favourable.

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CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1:
A. Acetylcholinesterase inhibitor

Myasthenia gravis is caused by the blockage of the postsynaptic receptors, which are activated by acetylcholin (Ach). Acetylcholinesterase is responsible for the hydrolisation of Ach. Thus, acetylcholinesterase inhibitors limit the destruction of Ach, increasing the availability of Ach. This will alleviate the patients' symptoms.

For further reading:
Siegel, A., Sapru, H. Chapter 7: Neurotransmitters in Essential Neuroscience, 4th edition (Wolters Kluwer, Philadelphia, 2019).

During the exam, 28% of the participants answered this question correctly.

Answer question 2:
D. Refer the partner to the urologist

The low amount of proper functioning sperm cells in the semen suggests that there is a male factor involved; something is causing the abnormally low number of sperm cells. Therefore, it is important to firstly establish the reason for this by referring the partner to the urologist.

For further reading:
Smeenk, J., Broer, S. Chapter 13: Infertility in Textbook of Obstetrics and Gynaecology, 1st edition (Bohn Safleu van Loghum, Houten, 2019).

During the exam, 43% of the participants answered this question correctly.

The exam questions can be found back on page 25 in this journal.