Scientific considerations regarding the mRNA candidate vaccines against SARS-COV-2

Report to the Spanish Ministry of Health COVID-19 vaccines task force on behalf of the ad-hoc scientific expert group of the Spanish Agency for Medicines and Medical Devices (31-07-2020)

Introduction

Currently there are three mRNA candidates in different stages of development. The most advanced is the vaccine from Moderna that started phase III on Monday July 27th, followed by Pfizer-BioNTech and CureVac. The latest is just initiating phase I in Germany and Belgium.

The Spanish ad-hoc scientific expert group has reviewed papers from Moderna related to a preliminary Phase I report published on July 14 in the New England Journal of Medicine (NEJM)[1] as well as an evaluation of mRNA vaccine in non-human primates published on July, 28 also in the NEJM[2]. Furthermore, an interim phase I/II study from Pfizer-BioNTech available on a preprint publication was also reviewed[3]. The expert group have had also access to the materials provided by Moderna and Pfizer during ad-hoc meetings with the companies not related to regulatory purposes,

The Spanish ad-hoc scientific expert group would like to stress that only immunogenicity data are available so far in humans. Until a correlate of protection is universally accepted, it is very complicated to translate these parameters to clinical protection. Therefore, it is very premature to infer if any of the vaccines would show a higher vaccine efficacy in preventing COVID-19 than the others. The answer to this question would only be ascertained after Phase 3 trials are completed.

Our expert group want also to highlight that the antibody response elicited in vaccinated humans in some of the studies has been compared with those from convalescent sera. We acknowledge that this is the best option for the time being, but it should be noted that these comparisons might be biased. The reason is that the neutralizing capacity of convalescent sera can be different according to patient age, disease severity, time since disease onset and the number of samples tested Thus, based on these data, no firm conclusion can be reached on one vaccine being better than the others. Furthermore, as no standardisation exists, the only way to compare the antibody response elicited by the vaccines would be to obtain biological samples of the different studies and analysing them in an independent laboratory using the same technique across different vaccines.

Moderna

- The mRNA vaccine from Moderna uses a stabilized pre-fusion conformation of full-length spike protein.
- Humoral immunity in humans was measured by antibodies ELISA targeting the spike protein and receptor binding domain and neutralizing antibodies by means of pseudo-virus and live virus neutralization tests.
- It has an acceptable safety profile although 40% of participants experienced fever (≥38°) after the second dose. From a public health perspective, this adverse event can be a mild pitfall in order to achieve high vaccination uptake.

[1] DOI: 10.1056/NEJMoa2022483
[2] DOI: 10.1056/NEJMoa2024671
[3] https://www.medrxiv.org/content/10.1101/2020.06.30.20142570v1

- Good neutralizing responses (PRNT) after two 100-µg dose in people 18 to 55 years. In the elderly (>70 years) good responses, as well, after two doses (although in a limited number of subjects, so far).
- Good $CD4^+$ responses after two doses with a Th1 cytokine profile.
- A very important point regarding the vaccination impact on the epidemiology of the disease is that in a challenge non-human primate model, no viral replication of SARS-CoV-2 was detected in the nose of any of the eight vaccinated animals (in the 100-µg dose group by day 2 after challenge). This finding in non-human primates, if reproducible in humans, would suggest that the vaccine induces sterilizing immunity. This is very important from a public health perspective since it would increase vaccine effectiveness by providing herd immunity.
- From a massive immunization campaign point of view the short vaccine half-life after defrosting is a drawback when compared with other classical vaccines (e.g., protein subunit); however, the fact that this vaccine can be stored at -20° and that may have stability for at least 1 week after defrosting might be an advantage over other mRNA vaccines.
- Phase III with 30.000 participants in a two-dose scheme has started July 27, 2020.

Pfizer-BioNTech

- The data so far published correspond to an mRNA (BNT162b1) that express an antigen that includes only the receptor-binding domain (RBD) of the spike protein. Other mRNA construct expressing the full-length spike protein (BNT162b) is also in a Phase I clinical trial. The decision on what mRNA is going to be used to be taken shortly (or already taken but not known for us).
- High number of participants (75%) with temperatures over 38° after a 30-µg second dose (high systemic reactogenicity). We do not know the reactogenicity in the elderly.
- The increasing in neutralizing antibodies is observed only after second dose. To the best of our knowledge, there is no available data about cellular responses.
- For the time being, it has just started phase III with 30.000 participants aged 18 to 85 years in the United States, Germany and France. It is unknown if the mRNA to be used in this large trial will be the one including the RBD of the full length spike protein
- The storage conditions (-80°) as well as a very short half-life after defrosting (six hours) may be a serious inconvenient for the implementation of a huge vaccination campaign.

CureVac

- Data commented on CureVac are not based on published reports and/or meetings with companies but only on data shared by other experts in the ongoing negotiations with the companies. Data on good immunogenicity using the full-length spike protein as well as a very long half-life after defrosting seems to be the main points in favour CureVac. However, no data regarding safety nor immunogenicity in humans as Phase I started only last June. Doses are lower as compared with other mRNA candidates (2, 4 or 8-µg per dose).
- In summary, it looks as a very good candidate but more data are needed to provide a more precise assessment.

Therefore, the Spanish ad-hoc scientific expert group on COVID-19 vaccines **recommends:**

- All three vaccines have a similar mechanism of action to prevent COVID-19. In humans, both Moderna and Pfizer-BioNTech show a good immunogenicity

profile and a reasonable safety record, characterized by short-lived local and systemic reactions. CureVac appears to be a very promising vaccine but with a limited set of data available so far. None of the vaccines have yet clinical efficacy data in humans.

- Preliminary data from the animal model -at least in one vaccine- suggests the possibility to induce sterilizing immunity (indirect protection), a fact that can be crucial in order to protect the most vulnerable subjects and is indicative that the vaccine can provide herd immunity.
- At this moment, we do not have enough solid data to favour any of the two most advanced mRNA vaccines (Moderna or Pfizer-BioNTech vaccines), nor to discard the CureVac vaccine.