Advantages of the Use of Adjuvants against COVID-19

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During the COVID-19 pandemic, vaccination focused on mRNA-type and viral vector vaccines. Adjuvanted vaccines are capable of inducing potent responses, not only humoral but also cellular, in populations whose immune systems are weak or do not respond properly, such as the elderly.

Keywords: vaccines ; adjuvants ; COVID-19 ; immune response

1. Introduction

Modern vaccinology is a field in continuous evolution that is constantly subjected to the appearance of new challenges, which must be solved in the shortest possible time to transfer new improvements to the population. This was the case in the start of 2019 of the COVID-19 pandemic caused by SARS-CoV-2, which forced the scientific community to work in unison to design, test and administer new vaccines against this new pathogen in record time. In fact, since the appearance of the first cases of SARS-CoV-2 in December 2019 [1], only three months passed until the first clinical trials with the first vaccines against COVID-19 began, and one year until they began to be administered in people living in the European Union.

After three years of the pandemic, the number of vaccine designs against COVID-19, both approved and in clinical, pre-clinical and development trials, amounts to more than 370 [2]. The fact that, despite that great steps have been taken in the prevention of COVID-19, new vaccines against this disease continue to be so actively sought, shows that there is still a long way to go to, among other factors, protect the entire world population, democratize and make vaccines more accessible, adapt them to new variants of COVID-19 that appear in the future and, of course, make them more effective and to produce longer lasting protection.

Before the COVID-19 pandemic, there were already multiple vaccine designs against different microorganisms. Depending on the pathogen, inactivated vaccines are used if the microorganism is dead and not capable of producing infection [3], or, on the other hand, attenuated ones, if the microorganism has been subjected to different processes transforming it into a virulent, but leaving intact the capacity to replicate in the vaccinated host [4]. There are also vaccines that use only parts of the microorganism, such as vaccines based on antigen subunits or those that use toxoids. Additionally, and given that in certain groups of people a reinforcement of immunity is needed, there are also vaccines designed for increasing immunogenicity which, through different mechanisms, help to increase the vaccination response in those people who need it, mostly risk groups [5][6]. One of the vaccine designs that has the greatest interest in this aspect is one that includes adjuvants in its formulation. These vaccines have multiple advantages since they allow the immune response induced by the vaccine to be potentiated in different terms, either at the humoral or cellular level, being especially relevant in the elderly, or those whose ability to fight against infections is diminished.

Until the emergence of new designs in vaccinology during the pandemic, one of the main problems that has arisen with the evolution of vaccines since their origins is that, as the antigens became simpler and more purified, their immunostimulant capacity decreased in parallel. Many of the older inactivated vaccines were made up of the whole organism, which offered a moderate vaccine response (immunogenicity), but low tolerability due to frequent occurrence of side effects [7]. To avoid this reactogenicity, vaccines progressively evolved to designs that contained only parts of the microorganism, subunits, or even purified antigens [8]. However, this caused the immunogenicity to slowly decline compared to whole virus vaccines, which, for some risk groups such as people over 65 and those who are immunocompromised, is not acceptable. Due to their nature, purified protein antigen vaccines without adjuvants induce a modest antibody response with little or no T cell response [9]. The appearance of adjuvants made it possible to recover the immunogenicity of these kinds of vaccines, also demonstrating, in most cases, much better tolerability profiles than those of traditional whole inactivated organism vaccines [8].

Furthermore, inactivated vaccines require large and multiple doses to confer protective immunity [10] and, in contrast with live-attenuated vaccines, elicit primarily humoral immunity, with little to no induction of cell-mediated immunity [11]. However, these inactivated vaccines also act as their own adjuvant, as they elicit a robust protective immune response compared to subunit vaccines [11]. Some of the inactivated vaccines that traditionally had incorporated adjuvants are, for example, poliomyelitis, hepatitis A, Japanese encephalitis virus and tick-Borne encephalitis, most of them of the alum type [12].

2. Advantages and Reasons for the Use of Adjuvants in Vaccines against COVID-19

Adjuvants have been widely used in vaccines against many human infectious diseases, demonstrating their great utility in increasing the vaccine response. These vaccines have shown various advantages that must be considered for the design of future vaccines against COVID-19. The main reasons for the use of adjuvants are the following, but also, some of them have limitations that are worth comment [13][14].

A. They increase the response to the vaccine in the general population, and especially in those risk groups that show a reduced response due to age or different diseases:

Vaccines do not generate homogeneous protection in the population because there are multiple factors that condition the response to them. The most common are age, the existence of different diseases that can impact immunity, or the use of immunosuppressive medication, among others. These factors limit the response to old and new vaccines, directly impacting the ability to counteract an infection despite being vaccinated. Adjuvants are capable of increasing the response compared to antigen alone vaccines both in high-risk individuals and in the general population through, for example, an increase in seroconversion, an increase in the mean titers of antibodies detected, or stimulation of the cellular response [15][16][17]. Additionally, some works have also shown that vaccines with adjuvants are not only capable of increasing the amount of antibodies generated, but that this increase occurs specifically in those that have greater affinity for the antigens against which they are directed [18][19]. However, there are different types of adjuvants, and not all induce an optimal protection, so precision adjuvants may be used to avoid this issue.

B. They make it possible to reduce the amount of antigen needed for each vaccine dose:

One of the main advantages of using adjuvants is that, due to their immunostimulation-enhancing effect, a smaller amount of antigen is required to produce a vaccine dose [9][20][21][22]. This makes it possible to manufacture a greater number of doses and, therefore, to vaccinate a larger population in less time, which is especially important in situations of increased demand such as a pandemic. During the first months of the COVID-19 pandemic, the main need was to vaccinate as many people as possible, and for this it was necessary to increase the number of doses produced. Using adjuvants for protein COVID-19 vaccines may have been useful during the first months of pandemic. However, some manufacturing issues made the production of this kind of adjuvants longer in this emergency, so prioritization of other vaccine platforms may be more suitable. However, this is a topic that may be revised for the next pandemic, in order to be ready to develop adjuvanted vaccines using an antigenic ready-to-use platform.

C. They allow immunization with a smaller number of vaccine doses:

Another of the disadvantages of the use of traditional vaccines, and some of the current ones such as RNAm, is that they require multiple doses to achieve optimal responses [13]. At a logistical level, it is much more cost-effective for a person to acquire protection with the smallest number of doses possible, since, if they must get vaccinated several times, it supposes or implies different logistical challenges, in addition to the possibility of not attending future appointments. This can be detrimental because it implies a deficient vaccination, and does not ensure complete protection in the individual. Adjuvants allow the number of doses a person must be given to achieve protection to be reduced [20][21][23], which is also advantageous for faster immunization during a pandemic. The addition, for example, of the AS04 adjuvant to the hepatitis B antigen in the Fendrix (GSK) vaccine allowed a reduction from three to two doses in the vaccination regimen [24][25]. In the case of the emergence of a new virus, although adjuvants may require less doses than other vaccines, the population may need more than one vaccine dose to reach optimal protection. For that, the advantage of adjuvanted vaccines may be the need for fewer doses than other platforms for a more durable protection.

D. They stimulate the immune response beyond antibodies:

As previously mentioned, generally the vaccine response to purified protein antigens is moderate/low in the production of antibodies, but very limited or absent in the stimulation of the T cell response. With the development of new adjuvants, researchers can achieve vaccines which can stimulate the helper T cell response by optimizing the quality and durability of the antibody response, as well as the induction of effector CD4 and CD8 cells to clear intracellular pathogens [9]. Indeed, for some intracellular antigens, activation of CD8+ T cells is essential because cytotoxic functions can help restrict infection and progression of these types of diseases [26]. However, not all the adjuvants are able to induce broad T-cell responses to the same extent. For example, there are some adjuvants such as ISCOMATRIX (Toll-like receptor 3 agonist) [27], some saponins derived from the tree *Quillaja brasiliensis* [28] and the Matrix-M adjuvant [29], that can stimulate both the CD8 and CD4 response [30]. However, there are other adjuvants that only stimulate one part of the cell-mediated immunity, such as alum-based adjuvants, which preferentially stimulate CD4 cells [31].

Moreover, the T-cell-stimulated response depends not only on the type of adjuvant, but also on the type of antigen and the carrier of this antigen [15]. For example, the use of liposomes and nanoparticles can stimulate CD8 and CD4 cells depending on their specific composition, causing the antigen to be processed by pathways located in the cytosol rather than the lysosomes, resulting in MHC class I presentation [32][33]. Antigen load is also a critical issue for the robustness of the CD8 response, as a higher antigen load trigger better responses [34].

E. They stimulate heterotypic responses to different antigens:

Another of the advantages of adjuvants is that they are capable of producing heterotypic responses against antigens that have a phylogenetic relationship with the vaccine antigen, either due to the appearance of escape mutants, minor variants of a microorganism, etc. This has been previously demonstrated against influenza and HPV [35][36][37], and is especially important against SARS-CoV-2, since the continued evolution of the virus during the pandemic with the appearance of new variants has shown that the vaccines must be prepared to adapt easily and quickly to the variability of the virus.

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