SputnikV Vaccine

Subjects: Infectious Diseases

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Definition

SputnikV is a vaccine against SARS-CoV-2 developed by the Gamaleya National Research Centre for Epidemiology and Microbiology.

1. Introduction

The outbreak of acute pneumonia in Wuhan, China, in December 2019, spread rapidly throughout the world, prompting WHO to declare a pandemic by 11 March 2020 [1]. Sequence analysis identified a novel coronavirus as the cause of infection [2], which was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 11 February 2020, by the International Committee on Taxonomy of Viruses (ICTV) [1]. Soon after, WHO officially named the disease coronavirus disease 2019 (COVID-19) [1]. The disease rapidly spread from China, leading to a global health emergency. The disease quickly spread, and there are more than 213 million cases documented worldwide, with 4,459,381 deaths confirmed as of 27 August 2021 [3]. COVID-19 has been present in Russia since March 2020, where initially, all confirmed cases were imported, but local transmission was quickly observed and documented [4].

Initially, multiple approaches were suggested to control the disease using repurposed and novel drugs [5][6][7][8]. Some of the repurposed drugs had demonstrated efficacy in vitro [9], yet they failed to translate into patient treatment due to high mortality [10]. Lopinavir was used for COVID-19 treatment, although the drug's efficacy was inconsistent [11][12]. As a result, limited options remained to treat COVID-19, leading to high morbidity and mortality. With the increasing number of cases registered daily and the inefficacy of administrative measures to prevent virus spread, prevention of infection using vaccines appeared to be one of the most effective approaches to dealing with the pandemic. Several different methodologies have been developed including mRNA-based [13][14][15] and adenovirus-based vectors from gorilla [16] and chimpanzee [17][18] adenoviruses.

The SputnikV vaccine developed by Gamaleya National Research Centre for Epidemiology and Microbiology (GRCEM) demonstrating 91.6% efficacy in a clinical trial [19]. This vaccine is recombinant adenovirus (rAd) 26 and rAd5 vector-based, expressing SARS-CoV-2 Spike (S) protein. The selection of this protein is based on its essential role in virus entry as it binds to the receptor and allows for membrane fusion [20][21]. Currently, the vaccine is routinely used to immunize Russian citizens [22], where 22.9% of Russian citizens were fully vaccinated by August 2021 [23][24]. The vaccine is also authorized in over 60 countries worldwide as of 29 July 2021 [25]. Clinical trial studies have demonstrated that the vaccine is safe, and no adverse effects have been demonstrated [19]. There is currently limited knowledge on which immunogenic epitopes of SARS-CoV-2 S protein elicit an antibody response in immunized individuals and how these compare to antibodies produced in a natural infection.

2. Discussions on SputnikV Vaccine

Our data confirm the immunogenicity of the SputnikV vaccine, developed by GRCEM [19], where humoral and T cell immune responses were detected in vaccinated individuals. Our data corroborate the previous report by Logunov et al., where anti-SARS-CoV-2 antibodies and activated T cells were detected in immunized individuals [26]. In our study, we further advanced the understanding of the SputnikV vaccine by demonstrating the S protein epitopes involved in the induction of an immune response. We have identified several immunogenic epitopes located in NTD, RBD, FP, HR1 and HR2. Sixteen peptides were found in S1, and fourteen peptides were in S2 domains. S1 and S2 contain several domains and epitopes, ranging from binding to the receptor, membrane fusion and entry [20]. Therefore, by targeting multiple

regions, antibodies in immunized individuals can potentially interfere with the most important events in virus replication: entry to the target cell.

Interestingly, six peptides reacting with immunized serum were in the RBD of S1 responsible for binding to the ACE2 receptor [27]. It is the primary target for the most potent neutralizing antibodies [28][29]. Therefore, it is expected that antibodies induced by SputnikV could also be neutralizing, which was previously shown by Logunov et al. [26]. Additionally, RBD targeting vaccines were shown to be highly immunogenic [30][31] in part due to eliciting neutralizing antibodies against SARS-CoV. We also identified peptides in NTD, which were shown to contain epitopes producing neutralizing antibodies [32]. These antibodies appear to interfere with receptor binding or S protein conformation [33]. Our data suggest that neutralizing antibodies, previously detected in immunized individuals, could target RBD and NTD. Together, antibodies to RBD and NTD could provide broad coverage of epitopes in the RBD and FP of SARS-CoV-2, which will reduce the virus's potential to escape from a vaccine-induced immune response.

We also identified multiple peptides in the S2 domain located in FP, HR1 and HR2. Upon attachment to the receptor, FP becomes embedded into the target cell membrane and installs an anchor inside to initiate fusion with the viral envelope [34][35]. HR1 and HR2 also contribute to fusion by bringing viral and cellular membranes proximal to each other [36]. Therefore, antibodies targeting these regions could potentially interfere with membrane fusion. As HR1 and HR2 are highly conserved among SARS-CoV viruses [37][38], including SARS-CoV-2, antibodies to these regions of S protein could prevent virus escape from immune response induced by the vaccine.

Convalescent plasma was shown to effectively treat critically ill COVID-19 patients [39][40]. This treatment is a polyclonal mix of antibodies developed to many viral proteins, including the S protein. It appears that among all antibodies, those recognizing the S protein are the most important in preventing a severe form of COVID-19. This assumption is based on the observation of Dispinseri et al., demonstrating that compromised immune responses to the S protein were major traits of critical COVID-19 conditions [41]. We have identified multiple peptides recognized by sera from both immunized and convalescent COVID-19 individuals. These data suggest that the SputnikV vaccine induces a humoral immune response similar to that occurring naturally after infection. Therefore, our data could explain the protective efficacy of the SputnikV vaccine demonstrated by Logunov et al. [26]. We believe that selection of epitopes similar to those in naturally infected and recovered individuals is the mechanism of SputnikV protection against COVID-19.

Studies have demonstrated that a single aa replacement could help the virus escape elimination by neutralizing antibodies [42][43]. Concerns have been presented that some mutations increase the infectivity of SARS-CoV-2 [44][45] and that new variants of SARS-CoV-2 may mutate to escape vaccine-induced immunity [46]. Our analysis demonstrated that several peptides recognized in vaccinated individuals remained 100% conserved in SARS-CoV-2 strains worldwide. Not surprisingly, three peptides were located in NTD, a highly conserved region [47][48]. We also identified four peptides in the RBD, which were 90–100% conserved in all SARS-CoV-2 strains included in the analysis. RBD region mutations could affect the neutralizing capacity of antibodies in the later waves of pandemics [21]. Our finding of conserved peptides in NTD and FP provides evidence that SputnikV induced antibodies should retain antiviral efficacy even in the case of a mutation in the S protein. We also did a detailed analysis of S protein mutations in one of the fastest spreading SARS-CoV-2 viruses, B.1.617.2 (Delta variant), which is currently detected in 78 countries [3][49]. This variant has shown moderate resistance to vaccine-induced immunity [50]. Only four peptides recognized by the immunized serum contained the aa positions mutated in the Delta variant of SARS-CoV-2. This is 11.1% out of all reacting peptides and represents a small fraction. Therefore, we suggested that the humoral immune response induced by SputnikV will be effective against the Delta variant of SARS-CoV-2.

We have identified multiple regions on S protein-containing immunogenic epitopes. These regions could be grouped as aa 137–309, 341–471, 579–812 and 1084–1188. Interestingly, these regions are within

those Grifoni A et al. predicted as associated with robust immune response [51]. A similar location of the peptides reacting to COVID-19 sera was demonstrated by Shrock et al. [52]. Many peptides that were recognized by convalescent COVID-19 sera were also recognized by vaccinated sera. These data provide strong evidence that the immune response induced by the vaccine is similar to that of a naturally developed response, after recovery from SARS-CoV-2 infection. Therefore, it could be suggested that the protective efficacies of convalescent and immunized sera are comparable.

Our results confirm that SputnikV induces a T cell immune response supporting findings by Logunov et al. [26]. We have found that the T cell immune response was active 42, 90 and 210 days after immunization, suggesting long term circulation of memory T lymphocytes. These lymphocytes are essential for protection against virus infection [53], providing long-lasting immunity. T cells were shown to be activated in convalescent COVID-19 patients [54]. The analysis also revealed that those activated lymphocytes contribute to the amelioration of clinical symptoms of the disease. Multiple studies have found activation of T cells in convalescent COVID-19, where the S protein appears to maintain this immune response [54][55][56]. Interestingly, several peptides (S10, S21, S23, S46 and S48) that activated T cells in SputnikV immunized individuals were similar to those described by Peng et al. in convalescent COVID-19 patients [54]. The immunogenic epitopes appear in aa 166–180, 351–365, 381–395, 751–765 and 801–815 regions on the S protein. Additionally, we have identified two peptides (S21 and S23) that activated T cell responses in SputnikV vaccinated individuals as located in the RBD of the S protein, suggesting that this domain also contains T cell epitopes similar to that described by Ni et al. in convalescent COVID-19 patients [56]. These data indicate that the T cell response in immunized individuals resembles that of individuals that recovered from a SARS-CoV-2 infection. Our data also show that the SputnikV vaccine-induced T cell and humoral immune responses to the S protein of SARS-CoV-2 lasted out to seven months after vaccination. This suggests the long-term efficacy of this vaccine, which is a significant consideration with all vaccine candidates [57][58].

There is limited real-life data on the duration of the immune response elicited by the Sputnik V vaccine. Our data, therefore, collected on samples from 90 and 210 days after the first dose of SputnikV vaccine demonstrating long-term activation of both the humoral and T cell immune responses is of importance. These long-term immune responses could explain the efficacy of the SputnikV vaccine reported by Gonzalez et al. in an Argentinian cohort [59]. Authors have also shown that receiving even a single dose of vaccine reduced the duration of hospitalization and fatality, after exposure to SARS-CoV-2. In another study by Rossi et al., eliciting anti-SARS-CoV-2 neutralizing antibodies was demonstrated in 288 volunteers 21 days after the first dose vaccine [60]. Additionally, the efficacy of SputnikV was demonstrated in a cohort from Venezuela, where even a single dose was shown sufficient to induce neutralizing antibodies in previously SARS-CoV-2 positive individuals [61]. A 100% seroconversion was found in a Venezuelan cohort 6 weeks after the second dose of SputnikV vaccine, confirming induction of long-term immune response.

Cytokines regulate immune responses during natural infection and vaccination [62][63]. These cytokines also contribute to developing clinical symptoms of COVID-19 and post-immunization side effects [64][65]. We have found fifteen cytokines that remain upregulated in convalescent COVID-19 individuals one month after infection (IL-1α, IL-3, IL-10, IL-12p70, CCL7, IFN-α2, bFGF, LIF, TRAIL, IL-2, IL-4, IL-5, IL-12p40, IL-17 and MIF) indicating a strong activation of the immune response. These cytokines are associated with inflammation, activation of T and B cell immune response, and regeneration [66]. A set of cytokines were upregulated in SputnikV immunized individuals (IL-1α, IL-3, IL-10, IL-12p70, CCL7, IFN-α2, bFGF, LIF and TRAIL), where nine of them were similar to that in convalescent COVID-19. These data suggest similarity in mechanisms of an immune response activation in vaccinated and convalescent individuals.

It should be noted that convalescent COVID-19 sera had more cytokines upregulated 42 days after infection than immunized, indicating that infection generates a more robust immune response. This could be explained by the exposure of the immune system to multiple viral antigens during infection compared to only the S protein used in SputnikV. Additionally, differences in cytokine activation could be explained

by the differing quantities of SARS-CoV-2 antigens encountered during infection and upon vaccination. Some findings support this suggestion where a higher viral load was closely related to severe COVID-19 [67][68]. Additionally, the simultaneous exposure to adenovirus antigens from the vector and SARS-CoV-2 antigens could affect cytokine activation in vaccinated individuals. The lesser number of cytokines activated in vaccinated compared to convalescent COVID-19 could also explain the lack of clinical symptoms of COVID-19, such as severe inflammation, high fever and tissue damage [64].

In summary, we have shown that vaccination with SputnikV induces a broad antibody response that recognizes a wide variety of epitopes on the S protein and excellent cellular response. Both of these responses are still measurable three months after vaccination, suggesting the long-term efficacy of this vaccine.

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Keywords

SARS-CoV-2;SputnikV;Spike protein;humoral immune response;cellular immunity