Research Article

Prevention of Symptomatic Covid-19 Infection by Personal Dendritic Cell Vaccine

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Abstract

Background: A meta-analysis revealed that for vaccines commercially available in the U.S., efficacy in preventing symptomatic Covid-19 infection was 64% five months after the first of two monthly vaccinations; efficacy in preventing hospitalization was 78%. Per previous report, personal Covid-19 dendritic cell vaccines are feasible to manufacture, cause minimal toxicity, and induce immunity against SARS-CoV-2 spike protein. The current study examined vaccine efficacy following a single injection of the dendritic cell vaccine in preventing symptomatic Covid-19 infection.

Methods: Healthy subjects without previous or active Covid-19 infection or anti-Covid-19 vaccination were injected subcutaneously during the last week of April 2021. Subjects were monitored for symptomatic infection for one year. Covid-19 Infections were confirmed by nasal swab PCR or blood antigen tests. Freedom from symptomatic Covid-19 infection was calculated from injection date.

Results: Of 145 vaccinated subjects, 139 with median age of 46.2 years participated in long-term follow-up with 138 assessed through six months, 127 through 12. 42 subjects experienced 44 episodes of symptomatic Covid-19 infection; six were hospitalized. Vaccine efficacy rates were 95.7% two months after vaccination, 84.9% during months three through eight, 83.4% at month nine, and 68.9% after 12 months. Rates of preventing hospitalization were 97.8% during months two through nine, and 95.5% by 12 months. Infections occurred at similar rates in subjects younger than 60 years of age and in those over 60.

Conclusions: Vaccine efficacy observed in this study is encouraging. The data supports additional studies of personal dendritic cell vaccines for the prevention of infectious diseases. (Funded by AIVITA Biomedical, Inc. and the Republic of Indonesia Ministry of Health) ClinicalTrials.gov number, NCT05007496.

Introduction

In April 2023 the World Health Organization estimated there were more than 760 million confirmed cases of Covid-19, about 7 millions deaths, and more than 13 billion vaccine doses administered. [1] There is no question that vaccines have decreased the morbidity and mortality caused by Covid-19, but the impact has been much less in middle- and low-income countries. [2] Despite the great public health benefit derived from existing anti-Covid vaccines, there are strong arguments for development of additional vaccines that may be more effective, associated with fewer adverse events, able to be manufactured more quickly, and easier to distribute [3].

The United States has produced the most successful anti-Covid vaccines including the mRNA vaccines BNT126b2 (Pfizer) [4] and mRNA-1273 (Moderna), [5] and the adenovirus vector Ad26.COV2.S (Janssen). [6] A key question is how long such vaccines are effective in preventing Covid-19 infection. To address this issue, a meta-analysis focused on data regarding about 2.67 million vaccinated individuals from 18 Covid-19 vaccine reports, including five randomized trials, five case-control studies, and eight cohort studies. [7] Loss of efficacy was defined by Covid-19 infections including asymptomatic diagnosis, confirmed symptomatic infection, and severe infection (hospitalization). From first injection, the median follow-up in these studies was only five months, and only four studies, three from Pfizer and one from Moderna, reported vaccine efficacy estimates beyond four months. For both mRNA vaccines, Covid-19 infections were reported only if they occurred at least one week after the second of two monthly injections. In relation to the date of first vaccine injection, prevention of symptomatic Covid-19 declined from 94% at two months, to 64% at five months, and to less than 50% at six months. [7] Such data contributed to recommendations for booster injections about six months after initial vaccination. [8] Vaccines that induce a longer period of vaccine efficacy could reduce costs and morbidity associated with infection.

Another approach to vaccination to prevent infectious disease is a personal dendritic cell (DC) vaccine in which antigen is incubated *ex vivo* with autologous DC which internalize and process antigens for presentation to lymphocytes to induce an immune response. [9-11] Proof of principle was shown in animal studies in which DC vaccines incubated with viral antigens *ex vivo* were effective in preventing viral infections with influenza, [12,13] and Herpes simplex. [14,15] In individuals infected with human immunodeficiency virus (HIV), subcutaneous injections of DC that had been incubated with HIV antigens were well-tolerated and decreased levels of detectable virus [16-18].

We previously reported results for personal anti-Covid-19 Dendritic Cell-Lymphocyte (DCL) vaccines administered in a 31-subject phase 1 trial and a 145-subject phase 2 trial. [19] Anti-Covid-19 DCL vaccines were successfully manufactured for all subjects by incubating with a recombinant stabilized trimeric spike (S) protein of SARS-CoV-2 as antigen. The personal DCL vaccines were extremely well-tolerated. Mild to moderate, brief, self-limited, local injection site reactions were the most common Adverse Events (AE). In the phase 2 trial, 47.1% reported no AE, 46.4% reported grade-1 AE, 6.5% reported a highest toxicity rating of grade-2, and there were no grade-3 or grade-4 AEs, no acute allergic reactions, and no serious AE. [19] Antigen specific immune responses were detected in 97% of subjects within 28 days of vaccination. There were no differences among three formulations defined by the quantity of recombinant SARS-CoV-2 spike protein that was incubated for 36 to 40 hours with the autologous PBMC, after they first had been incubated for five days in interleukin-4 (IL-4) and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) to differentiate monocytes into DC. Herein we report the vaccine efficacy results for the subject-specific DCL anti-Covid-19 vaccines as defined by preventing symptomatic Covid-19 infection and hospitalization during the year following vaccination.

Methods

Trial Design

As previously reported, [19] a single-center, 3-arm randomized phase 2 trial was conducted, in which subjects were randomized to one of three different patient-specific anti-Covid-19 DCL vaccine formulations defined by the quantity of spike protein that was incubated with the autologous DCL. Each subject had a single DCL vaccine injection, underwent blood collection at baseline and two and four weeks after injection for immune testing, and was followed for 28 days for signs and symptoms of toxicity. Assessments were planned at 3-month intervals from the date of vaccination for signs or symptoms of delayed toxicity and manifestations of Covid-19 infection, which is the focus of this report.

Subjects

The phase 2 trial was performed at the Gatot Soebroto Army Hospital (RSPAD) in Jakarta, Indonesia, [19] but the trial was not conducted in military personnel; volunteer subjects were recruited from various parts of the country. Eligible subjects were 18 years of age or older, in good health without serious medical diagnoses that required ongoing care or medication, and non-pregnant. Subjects were ineligible if they had been previously vaccinated against Covid-19, if they had been diagnosed with Covid-19 in the previous three months, if they had symptoms suggestive of active Covid-19 infection, or if they had SARS-CoV-2 antibodies detected by a rapid lateral flow immunochromatography test.

Study Oversight

The protocol was approved by the Ethics Committee of Gatot Soebroto Army Hospital. The trial was conducted according to the principles of the Declaration of Helsinki and according to the International Council of Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All subjects participated voluntarily and provided written informed consent for participation. Oversight of the phase 2 trial was provided by Biometrik Riset Indonesia.

Vaccine

The subject-specific vaccines were manufactured by local laboratory technicians under the supervision of AIVITA employees who were experienced in manufacturing DC vaccines. As previously described, [19] PBMC from 40 ml blood samples were enriched by density-gradient centrifugation, incubated in

IL-4 and GM-CSF for five days to differentiate monocytes into DC, then incubated for 36 to 40 hours with 0.10, 0.33, or 1.0 mcg of recombinant stabilized trimeric spike (S) protein of SARS-CoV-2, alpha variant (Lake Pharma Biologicals, San Carlos, CA). Quality testing was performed on the seventh day, and vaccines were injected the following day, eight days after the initial 40 ml blood collection. The final DCL product contained an average of 2.1 million DC and 12.7 million lymphocytes. [19]

Assessments

After completing the day-28 safety assessment, subjects were monitored for symptomatic Covid-19 infection for the next 11 months; there was no monitoring for asymptomatic infection. Subjects were instructed to return to the clinic for free PCR testing in the event of symptoms suggestive of infection, and in addition they were contacted every three months from the date of injection for one year to capture any symptomatic Covid-19 infections that were diagnosed elsewhere by PCR or antigen test. At each three-month time-point, whether subjects had experienced Covid-19 infection and/or been hospitalized for Covid-19 infection was documented. Local clinical personnel who had been trained to perform data entry, entered specific dates of infection and/or hospitalization into the REDcap Cloud electronic data-capture system. [20]

Endpoints And Statistical Analysis

To determine vaccine efficacy, key endpoints were dates of documented symptomatic Covid-19 infections and any associated hospitalizations. Identification and documentation of Covid-19 infections began one month after vaccination. Freedom from symptomatic Covid-19 infection and freedom from hospitalization with Covid-19 infection were calculated from the date of vaccination and depicted on Kaplan-Meier plots. Curves were generated using GraphPad Prism 9 software. Proportions were compared using Fisher's exact test.

Results

Subject Characteristics, Adherence, and Follow-Up

A complete table of subject characteristics was published previously. [19] The median age of the 139 patients who entered one-year follow-up was 46.2 years with a range from 19.5 to 82.8 years and interquartile range of 38.0 to 53.6 years. Twelve percent were age 60 or older. Gender distribution was 52.5% men and 47.5% women. Of 145 vaccinated subjects, 139 (95.9%) complied with follow-up assessments during the first month, and 139 (95.9%), 138 (95.2%), 137 (94.5.%), and 127 (87.6%) provided follow up information through months 3, 6, 9 and 12 respectively.

Vaccine Effectiveness

In the year following vaccination, 42 subjects experienced 44 confirmed cases of symptomatic Covid-19 infection; six subjects were hospitalized with more severe infections; there were no deaths. There were four subjects who had symptoms that were suspicious for possible Covid-19 infection, but they did not have a positive PCR or antigen test. Table 1 shows the distribution of symptomatic infections by the three vaccine formulations, and the timing of the infections relative to the injection date. There was no difference in the frequency or timing of symptomatic infections based on the quantity of SARS-CoV-2 spike protein that was incubated with DCL during manufacturing. Two patients injected with the 1.0 mcg antigen DCL formulation experienced two symptomatic infections. Each experienced an infection in June 2021; one had a second infection in February 2022; the other had a second infection in March 2022. There was no difference in the proportion of subjects who experienced symptomatic Covid-19 infections by age group: 36/122 (29.5%) in those less than 60 years of age, and 6/17 (35.3%) in those 60 years of age or older (p=0.78). Figure 1 shows that the timing of the symptomatic infections was synchronous with peaks in Covid-19 infection numbers in Indonesia during June 2021 through April 2022. [1]

Timing	0.1 mcg (n=48)	0.33 mcg (n=47)	1.0 mcg (n=44)	Total (139)
Jun-Jul 2021	6 (12.5%)	6 (12.8%)	9 (20.5%)	21 (15.1%)
Aug-Oct 2021	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nov-Jan 2021-2022	1 (2.1%)	0 (0%)	1 (2.3%)	2 (1.4%)
Feb-Apr 2022	7 (14.6%)	8 (17.0%)	4 (9.1%)	19 (13.7%)
Total	14 (29.2%)	14 (29.8%)	14 (31.9%)	42 (30.2%)
Hospitalized	1 (2.1%)	2 (4.3%)	3 (6.8%)	6 (4.3%)

Table 1: Distribution of symptomatic Covid-19 cases by vaccine formulation and time after vaccination.
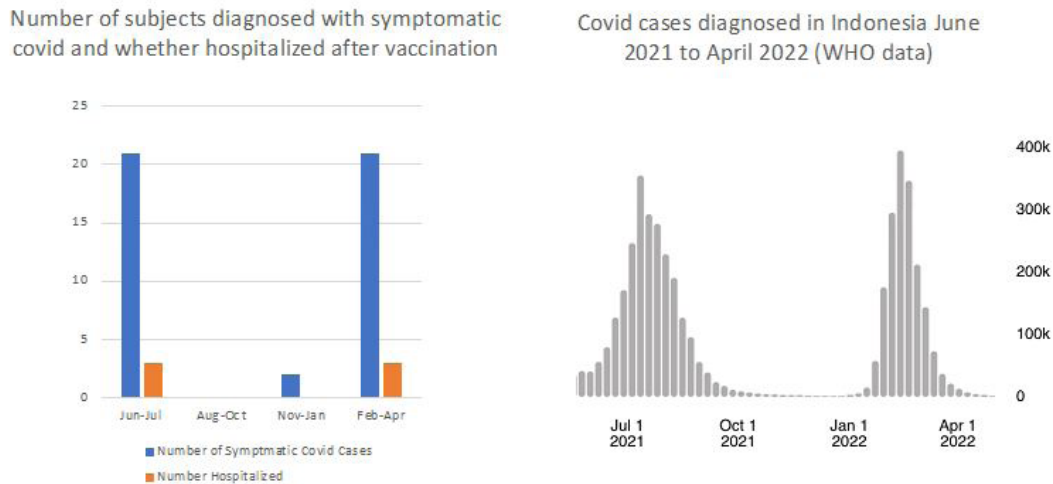
Figure 1: Timing of Covid-19 infections among 139 vaccinated subjects, and timing of Covid-19 infections in the general Indonesia population during June 2021 thru April 2022.

Vaccine efficacy results in preventing symptomatic Covid-19 infections are depicted in Figure 2 and Table 2. Figure 2 shows the Kaplan-Meier plots for freedom from Covid-19 infection and freedom from hospitalization for symptomatic covid infection. Table 2 shows the efficacy percentages and 95% confidence intervals for each month of follow up. The efficacy rates for prevention of symptomatic infection were sustained at 85% for months three through eight; the efficacy rates for prevention of hospitalization due to symptomatic Covid-19 infection were sustained at 98% for months two through nine.
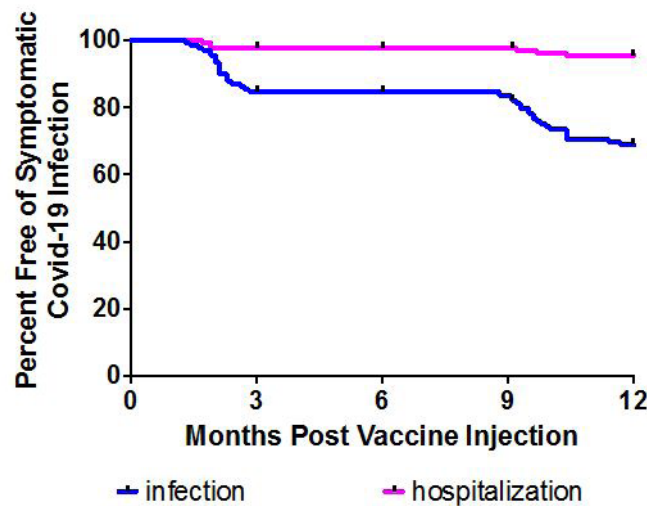

Figure 2: Percentage of subjects who remained free of symptomatic infection Covid-19 infection and from hospitalization for Covid-19 infection starting one month after single injection of personal dendritic cell anti-Covid-19 vaccine.

Months After Injection	Percent Free of Symptomatic Covid Infection & 95% CI	Percent Free of Hospitalization for Covid Infection & 95% CI
2	93.5 (96.1, 87.9)	97.8 (99.3, 93.4)
3	84.9 (89.9, 77.8)	97.8 (99.3, 93.4)
4	84.9 (89.9, 77.8)	97.8 (99.3, 93.4)
5	84.9 (89.9, 77.8)	97.8 (99.3, 93.4)
6	84.9 (89.9, 77.8)	97.8 (99.3, 93.4)
7	84.9 (89.9, 77.8)	97.8 (99.3, 93.4)
8	84.9 (89.9, 77.8)	97.8 (99.3, 93.4)
9	83.4 (88.6, 76.1	97.8 (99.3, 93.4)
10	73.5 (80.1, 65.2)	96.3 (98.5, 91.3)
11	70.5 (77.4, 62.0)	95.5 (97.9, 90.3)
12	68.9 (76.0, 60.3)	95.5 (97.9, 90.3)

Table 2: Freedom from symptomatic Covid-19 infection and from hospitalization for Covid-19 infection following a single subcutaneous injection of personal dendritic cell-lymphocyte anti-Covid-19 vaccine.

Discussion

The most noteworthy observation in this report is the 84.9% (95% CI: 89.9, 77.8) vaccine efficacy in preventing symptomatic Covid-19 infection that was sustained for up to nine months from the date of vaccination. Because there was no contemporary control group, in order to put these results into perspective, a recently published meta-analysis of vaccine efficacy following injection of commercially available anti-Covid vaccines, was used to provide a benchmark for historical comparison. [7] The median age of subjects was 46.2 years in our study and 46.1 years in the meta-analysis. The meta-analysis yielded mean vaccine efficacies for prevention of symptomatic infection of 94%, 71%, 78%, and 64% respectively at two, three, four, and five months after the initial vaccine injection; [7] there was no data provided at six months or beyond. As shown in Table 2, the data for the personal DCL vaccine at the same time points reveal that an 85% efficacy rate was sustained for up to nine months after vaccination. The meta-analysis estimated freedom from severe infection as 78% at 5 months. As shown in Table 2, for the DCL vaccine the freedom from hospitalization was 98% at 6 months and 96% at 12 months. Despite the apparent large improvement in preventing symptomatic Covid-19 infection, given the limitations of such historical published data, one should not conclude based on this comparison, that the DCL vaccine is definitely superior to the other vaccines in terms of preventing symptomatic Covid-19 infection.

Strengths of this study include: the subject population was representative of the Indonesian population, a high proportion of subjects complied with follow up, and there was laboratory confirmation and documentation of symptomatic Covid-19 infections. Weaknesses of the study are the lack of a contemporary control group, and the relatively small sample size. Although the median age was 46 years for both Indonesian subjects and the subjects included in the meta-analysis, there may be factors among the healthy subject populations other than the vaccine products and age that could affect vaccine efficacy rates.

The effort to utilize DC vaccines to prevent infectious diseases such as Covid-19 is a relatively recent development, [11-18,21] but DC vaccines have been tested in cancer patients for more than two decades with variable success. [22-24] The feasibility and safety of our DC vaccine approach was established during treatment of over 190 cancer patients with more than 1300 subcutaneous injections of one to 30 million DC per injection over the years 2001-2022. [25,26] These cancer trials provided some suggestion of clinical efficacy including delayed but durable objective tumor regressions, [27,28] prolonged progression-free survival, [29,30] and increased overall survival [31-33].

The major differences between the Covid-19 DCL products and cancer DC products were: (1) using a single 40 ml blood collection to obtain PBMC, rather than a leukapheresis, (2) manufacturing of vaccine at the point of care in local Indonesian hospitals rather than in a biotechnology manufacturing facility in southern California, and (3) immediate incubation of PBMC with IL-4 and GM-CSF to generate DC without a monocyte enrichment procedure, which resulted in vaccine products that consisted of an

average of 85% lymphocytes and 15% DC as opposed to a product that is 98 to 100% DC. [19] Differences in vaccine administration in Indonesia included omission of GM-CSF as an adjuvant, and administration of a single subcutaneous vaccine injection rather than up to eight injections over six months.

Direct injection of antigen and in vivo manufacturing of antigen rely on endogenous antigen presenting cells, especially DC, to initiate the immune response. Immune adjuvants are typically co-administered to insure a local inflammatory response that includes DC. *Ex vivo* incubation of autologous DC with antigens or pathogens of interest may offer advantages as a vaccination strategy, since it circumvents the need to create local inflammation to facilitate immunization, and may greatly increase the number of DC that take up antigen. [9-11,21] In terms of inducing a desired immune response, animal and human anti-cancer studies suggest that immunization via DC may be more effective than directly injecting antigen, [33-36] and this may be true for infectious diseases as well. While all infections and vaccines induce both humoral and cellular immunity, the commercially available vaccines were designed to produce neutralizing antibodies. The data from the two Indonesian trials suggest that the DCL vaccine produced a stronger cellular response than humoral; [19] this may be an explanation for the apparent longer duration of effective immunity against symptomatic infection.

In terms of infectious disease application, a potential advantage of this approach is how quickly a personal vaccine can be made available for clinical use. The rate limiting component is the antigen source. As new virulent SARS-CoV-2 variants emerge, the subject-specific vaccines can be quickly modified once the mRNA of the new spike protein has been sequenced, and recombinant spike protein manufactured that can be incubated with subject DC. In terms of exposure to antigen presenting cells, the quantities of recombinant proteins necessary for ex-vivo immunization are a fraction of classic vaccine requirements and there is no need for adjuvants in the final dose composition. The additional substances used in the manufacturing (media components, GM-CSF, IL4, and antigen) are removed at the end of the process, and for the final product, the autologous cells are resuspended in autologous plasma. Because the antigen source is completely consumed by DC during ingestion and processing of antigen, [19] the only substance being injected into the subject is his/her own immune cells and autologous plasma. In the absence of adjuvants, once the quantity of antigen for incubating with DC has been established by in-vitro mixed lymphocyte reaction assay, individual blood samples can be collected, and one week is needed to manufacture a subject-specific DCL vaccine at the point of care. [19]

At least four studies have shown that vaccination can reduce the infection spread and mortality caused by Covid-19 with low cost-benefit ratios. [37] However, it is estimated that the Covid-19 death rate is two to four times higher in low-income countries than in high-income countries. [38] This is likely related to estimates suggesting that at least one-third of the world's population in low-income countries remain unvaccinated. [38] DCL may be useful to help address the issue of access to effective vaccines in many countries around the world, and potentially shorten the time of vaccine development and field deployment for a novel pathogen.

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