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Longitudinal study of the immune response after SARS-CoV-2 infection and vaccination in elderly care homes

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Background. The correlates of immune protection against severe COVID-19 in the elderly remain undescribed. Here we report a longitudinal follow-up study based on the evaluation of the different arms of the immune response (innate and adaptive, humoral and cellular) in the Branyas cohort of aged individuals from care homes, who were vaccinated against SARS-CoV-2, while monitoring for new SARS-CoV-2 infections and COVID-19 severity. Our goal is the identification of the correlates mediating immune protection in the vaccinated elderly and the establishment of risk profiles to identify vulnerable individuals.

Methods. A cohort of 196 individuals (median age 86, 73.5% Females, 98% vaccinated) housed in care homes were monitored for SARS-CoV-2 events since the COVID-19 pandemic outbreak, with the collaboration of the Branyas care home managers and residents. Immune responses were evaluated using plasma, serum and peripheral blood mononuclear cells (PBMC) isolated from fresh samples, collected at different time-points after vaccination. For innate immunity, the phenotype of monocytes and NK cells was analyzed by flow cytometry. Plasma antibodies against N and Mpro viral proteins were detected by ELISA. Anti-SARS-CoV-2 neutralizing antibody titers were determined in serum by flow cytometry using a GFP-expressing S-protein pseudotyped lentivirus. CD4+ and CD8+ T-cell responses were evaluated from PBMCs stimulated with SARS-CoV-2 peptide pools, soluble proteins and autologous cells infected with recombinant vaccinia viruses (rVACV) expressing S, N or M SARS-CoV-2 proteins. Soluble proteins and peptide pools were used to analyze activation- induced markers (AIM); cytokines and degranulation markers were analyzed following coculture with rVACV infections and peptide pools.

Results. From the onset of the COVID-19 pandemic until May 2021, 32% of the individuals had over- come SARS-CoV-2 infection according to the care homes. Of them, 21% showed undetectable antiN and antiMpro antibodies. Also, we detected 16 new positive individuals who were unnoticed, which account for 20% of the total SARS-CoV-2 cases. Concerning innate immunity, we observed altered percentages of monocyte and NK cell subpopulations and phenotypic changes over time after each vaccine dose. Regarding the neutralizing antibody titers, we observed a strong increase shortly after the third vaccine dose compared to samples extracted around 5 months after the second dose. CD8 responses were best detected using rVACV-infected autologous target cells. Up to 50% of vaccines showed CD8+ T-lymphocyte responses against S, which increased to 75% among those who were also infected. AIM assays were better for detecting CD4 T-cell responders. Overall, over 70% of the Branyas uninfected individuals showed cellular responses against S protein after the second dose.

Conclusions. Most of the vaccines developed adaptive immunity against SARS-CoV-2. We per- formed a thorough study including innate, humoral and cellular immune responses that will allow us to determine correlates of protection against severe COVID-19 and risk profiles in elderly vaccinated individuals. Remarkably, we developed a system based on rVACV that improves the capacity to detect anti-SARS-CoV-2 CD8 T-cells compared to the widely-used peptide pools. This allowed us to detect that a high fraction of the elderly individuals in our Branyas study developed cellular immune responses after vaccination.

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