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Letter to the Editor

Current vaccine strategies against SARS_CoV-2 only poorly protect kidney transplant recipients

In this Journal, early in the pandemic, Minotti and colleagues drew attention to the impact of COVID-19 on immunosuppressed patients[1]. Following studies reported that kidney transplant recipients (KTR) are at increased risk of severe COVID-19 infection[2]. Now that vaccines are available the urgent question is whether vulnerable patients such as renal transplant recipients can be protected, and if so, how.

We studied vaccine responses and effects of pre-exposition passive immunization in a single cohort of KTR. Kidney transplant recipients were included if they had received a complete vaccine scheme including 3 doses of mRNA antiSARS-coV-2 vaccine, they had available COVID-19 serology before vaccine and at least one month after the second and third injections, and they had negative pre-vaccine anti-SARS-CoV-2 serology. Humoral responses were closely monitored and guided medical strategy after three doses of vaccine. All the patients received three doses of either mRNA-1273 (Moderna) or BNT162b2 (Pfizer) vaccine. Anti-SARS-CoV-2 serology was performed before vaccine, one month after the second and third dose, and every three months thereafter (SARS-Cov-2 immunoassay, Abbott® designed to detect IgG antibodies to the receptor-binding domain (RBD) of the S1 subunit of the spike protein of SARS-CoV-2). Patients with antibody titers under 50 AU/ml were considered no responder (manufacturer threshold). In patients with detectable anti-RBD antibodies, those with titers between 50 and 3563 AU/ml (506 BAU/ml) were considered as low responders while those with anti-RBD antibodies >3563 UA/ml were high responders[3].

REGEN–CoV (a combination of two monoclonal antibodies, casirivimab and imdevimab, designed to attach to the spike protein of SARS-CoV-2 at two different sites) was used to prevent COVID-19 infection in patients without any antibody response after three doses of vaccine. The first dose of REGEN–Cov (1200 mg) was administered intravenously. The subsequent doses (600 mg) were administered subcutaneously every 4 weeks. Nasopharyngeal swabs were obtained for patients to test for SARS-Cov-2 by RT-qPCR before each administration of REGEN–Cov.

Four hundred and five patients were studied (Fig. 1). 286 patients exhibited anti-RBD antibodies (178 (44%) had a weak response (<3563 UA/ml), 108 (27%) had a strong response). A fourth dose slightly increased antibody levels and the rate of fully protected patients. Indeed, in patients with low humoral response after three doses, only 26% had strong antibody response one month after the fourth dose. Mean decrease in anti-RBD levels in the absence of subsequent vaccine boost was 17+/−9% each month. After three doses of vaccine, COVID 19 infection were only observed in low responders and non-responders not receiving passive immunization.

199 patients (29%) did not exhibit humoral response after three doses of vaccine and 91 of them received REGEN–COV. No adverse effect was observed in any patient. During treatment, anti-S antibody titers were > 40,000 AU in all patients. No patient treated with REGEN–Cov developed COVID infection. By contrast, in those without prevention, 5 (20%, $p<0.001$) experienced COVID infection and two of them required hospitalization in intensive care unit. One died three weeks after admission.

Humoral response to vaccine was especially impaired in patients receiving either Mycophenolic acid or Belatacept. Reduced renal function and CD4 lymphopenia were also associated with poor response to vaccine.

We show that after three doses of mRNA vaccine, only 27% of KTR exhibit a strong humoral response. The current strategy of prevention is mainly based on serology. A crucial question is about the correlation between antibody titers and protection. The immune system is by nature redundant and a single correlation cannot be given at an individual level. Both innate and cellular immunity may modify the association between anti-SARS-CoV-2 antibodies and global protection against COVID 19 infection. Therefore, our approach of serology-based strategy should be cautious. Nevertheless, anti-S IgG levels are related to neutralizing antibodies response in immunocompetent individuals[4]. Thus, it is reasonable to aim high anti-S antibodies levels that ensure high titers of neutralizing antibodies. A complementary approach is to search for thresholds protective against infection. Dimeglio et al. reported that total antibody titers above 1700 BAU/ml afford maximum protection[5]. A recent study[3] reported that an efficacy of 80% against alpha variant is obtained with anti-S antibody levels above 264 BAU/ml or anti-RBD antibody levels above 506 BAU/ml. It is possible that immunocompromized patients require higher antibody titers because of defective innate and/or cellular immunity. Furthermore, a relatively rapid decline in antibodies is well described that led to concordant recommendations for a booster dose in all populations[6]. Therefore, an antibody titer should be consider as a dynamic quantity. One should appreciate the delay between vaccine and serology, the actual value, and the anticipated decrease in concentrations.

Thirty percent of patients had no antibody response after three doses of mRNA vaccine. A fourth dose is unlikely to boost humoral response and passive immunization with monoclonal antibodies is the strategy of choice. The first available antibody combination was REGEN–CoV. This treatment is well-tolerated and efficient on the delta variant. In our cohort, no COVID 19 infection was observed in patients treated with REGEN–CoV, whereas 20% of those not treated got the disease. Omicron is also partially resistant to EVUSHELD, a new antibody combination (Tixagevimab/Cilgavimab)[7]. Only, Sotrovimab seems to retain a strong neutralizing activity against Omicron[7].

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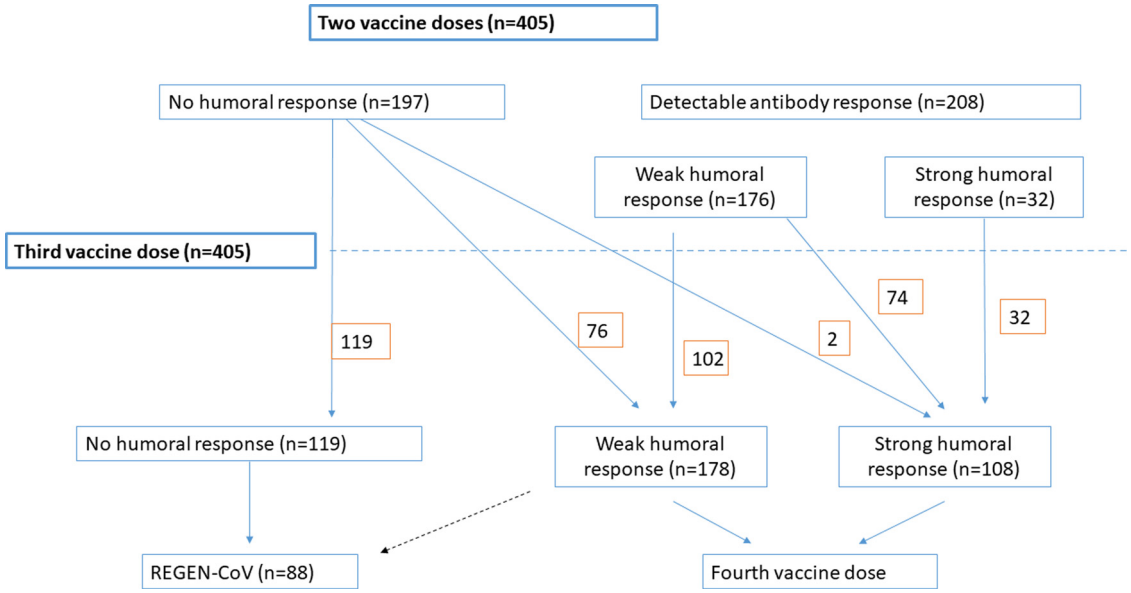

Fig. 1. Flowchart depicting the distribution of responders and non-responders after two and three doses of mRNA anti-SARS-CoV-2 vaccine.

Lower responses in MPA-treated patients have been reported after several types of vaccines including mRNA anti-SARS-Cov-2 vaccines[8]. Same observations are made in Belatacept-treated patients[9]. However, it does not seem reasonable today to recommend modulation of immunosuppression in KTR with no/low response to anti-SARS-Cov-2 vaccine. First, antibody combination are safe and effective against SARS-CoV-2. However, modification of maintenance immunosuppression exposes to acute rejection and subsequent increase in immunosuppression, which would be deleterious in the epidemic context.

Prevention of COVID 19 in transplant patients is an important and difficult challenge. Vaccine program must be rigorous and passive immunization should be considered in those with no or low response to vaccine. Whether modulation of immunosuppression is required remains a delicate issue.

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