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Vaccinating hemodialysis patients against SARS-CoV-2

Yau et al. (Evaluation of the SARS-CoV-2 antibody response to the BNT162b2 vaccine in patients undergoing hemodialysis. JAMA Netw Open. 2021;4:e2123622.)

Ever since hepatitis B vaccines became available, we have known that patients on hemodialysis often do not respond or respond only weakly against vaccines. In the current pandemic, dialysis patients had been underrepresented in trials that led to the licensing of coronavirus disease 2019 (COVID-19) vaccines. In a study conducted in a dialysis center in Toronto, Canada, 142 patients on chronic hemodialysis and 35 health care workers were studied following 1 versus 2 doses of the BNT162b2 COVID-19 vaccine (Pfizer-BioNTech) in early 2021. This question was important because, in some countries, the second dose had been delayed to vaccinate as many persons as possible with at least a first dose. Outcome parameters of the present trial related to humoral immunity and included antibodies to the full-length spike protein (anti-spike) and its receptor-binding domain (anti-RBD), both of which can result from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination and/or natural infection. In addition, the investigators measured antibodies to the nucleocapsid protein (anti-NP) to detect natural SARS-CoV-2 infection. Despite extensive screening in the hemodialysis unit, 15 patients were detected to have either anti-NP antibodies or even COVID-19 (N = 3), suggesting subclinical or mild infections. In comparing patients receiving 1 versus 2 vaccinations, baseline demographics differed somewhat, and those receiving 1 injection only were somewhat younger and less likely diabetic but otherwise similar. The health care workers were markedly younger and mostly females.

Among the dialysis patients, 66 received 1 dose and 4 weeks later 80% had seroconverted but only 23% had an anti-spike antibody response exceeding the median relative ratio of convalescent individuals (defined as a “robust response”). Antibody responses to RBD, which correlate well with neutralizing antibodies, were much weaker at 55% seroconversion in the single vaccination group and only 6% mounted a robust anti-RBD response. In the 76 double vaccination patients at 2 weeks after the second dose, these numbers were considerably higher: anti-spike antibody seroconversion occurred in 96% (72% with a robust response) and 88% seroconverted for anti-RBD with a robust response in 60%. All of the health care workers exceeded the median level of anti-spike and anti-RBD detected in convalescent serum 2 to 4 weeks after the second dose.

The authors conclude that a single vaccination in hemodialysis patients is not sufficient to induce a reasonable immunogenic response to the BNT162b2 vaccine. In fact, several countries have now started to advocate third vaccination in these vulnerable patients.

—Jürgen Floege

Recessive, gain-of-function toxicity in an APOL1 BAC transgenic mouse model mirrors human APOL1 kidney disease

McCarthy GM et al. (Dis Model Mech. 2021;14:dmm048952.)

Risk allele variants of apolipoprotein L-1 (APOL1), G1, and G2 are prevalent in people of recent sub-Saharan African ancestry, and homozygosity or compound heterozygosity for these alleles is associated with increased non-diabetic kidney disease. However, many with risk alleles do not develop disease, and APOL1 is not required for normal kidney function. The mechanisms for this risk have been difficult to elucidate because mice do not carry the APOL1 gene. A second-hit mechanism of increased susceptibility to other injury has been proposed. The current studies created congenic bacterial artificial chromosome (BAC) transgenic mice with the full human APOL1 and flanking regulatory sequences with increased APOL1 protein levels in plasma, and low levels in liver and kidney, comparable to that seen in humans. More important, expression of G1, G2, or the nonrisk allele G0 did not per se cause any kidney damage, even up to 9 months of age. Sustained increased serum interferon-γ levels were then induced by injecting an interferon-γ expressing plasmid, resulting in increased APOL1 mostly in the podocytes, due to

Figure 1 | (a,b) Mice with expression of G0/G0 versus G1/G1 or G2/G2 at (a) 1 and (b) 3 weeks after additional induction of increased interferon-γ. No lesion was observed 1 week after injection, but sclerotic glomeruli were found in G1/G1 and G2/G2 mice 3 weeks after injection. Purple arrows mark normal glomeruli. CTRL, control. Adapted from McCarthy GM, Blasio A, Donovan OG, et al. Recessive, gain-of-function toxicity in an APOL BAC transgenic mouse model mirrors human APOL1 kidney disease. Dis Model Mech. 2021;14:dmm048952. Under a CC BY 4.0 license. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.
increased glomerular cell synthesis, confirmed by in situ hybridization. In this model system, mice with G0/G0 did not show albuminuria even after interferon-γ induction. However, G1/G1 and even more so G2/G2 mice had marked increase in albuminuria and died with increased serum creatinine of apparent kidney disease. They demonstrated early development of foot process effacement, and by 3 weeks after induction of interferon-γ, the risk allele variant mice had severe glomerulosclerosis, with some collapsing glomerulopathy features, with loss of podocyte staining markers nephrin and Wilms’ tumor antigen-1 (WT1; Figure 1). More important, adding the G0 allele did not protect mice against G1- or G2-associated toxicity. Taken together, these studies support that G1 and G2 are toxic gain-of-function mutations with a recessive mode. This model, mirroring key elements of human APOL-1–associated disease, thus provides a foundation for further studies to test specific mechanisms of injury and efficacy of therapeutic interventions.

—Agnes B. Fogo

Ultra-low-dose quadruple combination therapy for hypertension

Chow et al. (Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension [QUARTET]: a phase 3, randomised, double-blind, active-controlled trial. Lancet. 2021;398;1043–1052.)

A meta-analysis of quarter-dose blood pressure (BP)—lowering therapy of 2017 highlighted potential benefits in comparison to standard dose monotherapy. However, it remained inconclusive as regards to long-term efficacy and tolerability. Chow et al. conducted a multicenter, randomized, controlled phase 3 trial (QUARTET) among Australian adults with hypertension, who were untreated or receiving monotherapy. Participants were randomly assigned to either treatment that started with the quadpill (irbesartan, 37.5 mg; amlodipine, 1.25 mg; indapamide, 0.625 mg; and bisoprolol, 2.5 mg) or an indistinguishable monotherapy control (irbesartan, 150 mg). If BP was not at target, additional medications could be added in both groups, starting with amlodipine, 5 mg. The primary outcome was difference in unattended office systolic BP at 12 weeks. Secondary outcomes included BP control (standard office BP <140/90 mm Hg), safety, and tolerability. A subgroup continued randomly assigned allocation to 12 months to assess long-term effects. Analyses were per intention to treat. From 2017 to 2020, 300 participants were randomly assigned to quadpill treatment, and 291 to initial standard dose monotherapy treatment. Mean age was 59 years; male/female ratio was 60:40; White, Asian, and other ethnicity were 82%, 12%, and 6%, respectively. Baseline mean office BP was 141/85 mm Hg. By 12 weeks, 15% participants in the intervention group had additional BP medications compared with 40% in the control group. Systolic BP was lower by 6.9 mm Hg (95% confidence interval [CI], 4.9–8.9 mm Hg; P < 0.0001) (Figure 2), and BP control rates were higher in the intervention group (76%) versus control group (58%; relative risk, 1.30; 95% CI, 1.15–1.47; P < 0.0001). There was no difference in adverse event related treatment withdrawals at 12 weeks. Among the 417 patients who continued, up titration occurred more frequently among control participants than intervention participants (P < 0.0001). At 52 weeks, mean unattended systolic BP remained lower by 7.7 mm Hg (95% CI, 5.2–10.3 mm Hg) (Figure 2). Serious adverse events were low in both groups. In sum, early fixed-dose quadruple quarter-dose combination treatment achieved and maintained greater BP lowering than early standard monotherapy. The initial quadpill-based treatment strategy is attractive in terms of efficacy, tolerability, and simplicity. It holds promise for achieving better BP control in people with hypertension.

—Tilman B. Drüeke