bottom of the podocyte immediately under the slit diaphragm, which suggests that maybe it has some biologic role in the cell that we don't yet understand (10). The other good thing about that protein is that it is expressed in the mouse and rat podocyte, unlike PLA_2R. This allowed the Hamburg group to create the first mouse model, in which they injected a human anti-THSD7A in rodents and showed that it would localize in the mouse glomeruli and cause proteinuria.

Kidney News: *What makes THSD7A-linked IMN different from PLA2R-linked IMN?*

Dr. Beck: Some of THSD7A's unique features are really interesting. Initially, there was a suggestion that patients who had THSD7A were more likely to have underlying cancer that causes membranous nephropathy. This is supported by case reports from the Hamburg group showing that tumors in two different patients overexpressed THSD7A (11, 12). This suggests that the immune response to the tumor actually triggered the kidney disease by making THSD7A antibodies. Now, when someone receives a diagnosis of THSD7A-type membranous nephropathy, we look very closely to see whether they have any undetected cancers.

Kidney News: *What do you think the future holds in terms of treatments for IMN?*

Dr. Beck: In the future, treatments for autoimmune diseases like IMN will be more specific. Right now, we wipe out broad aspects of the immune system by targeting B cells or the bone marrow precursors. But there is a possibility you could create therapies targeting only the B cells that make antibodies to PLA_2R or THSD7A. Several groups are looking at ways to use CAR-T cell therapy, which is currently being used to treat certain forms of cancer, to destroy PLA_2R-targeting B cells. Another possibility would help a patient develop tolerance to PLA_2R or THSD7A.

Kidney News: *What are some of the key questions that remain to be answered about IMN?*

Dr. Beck: Have we found all the antigens? In the past year, workers at the Mayo Clinic have found two more antigens or biomarkers in certain types of membranous nephropathy. One is exostosin, which is also found in patients who have a systemic autoimmune disease, like lupus. Another is NELL-1. Those workers used new, less labor-intensive techniques that may help identify even more antigens in IMN. We need to learn more about each of the subtypes of the disease.

We also need to learn more about how environmental insults interact with genetic risk. Most cases of IMN emerge in middle age, and we don't know why. There's some evidence from China that air pollution is linked to an increased incidence of membranous nephropathy (13). So, one suspicion is that the increased PLA_2R expression in the lungs in response to air pollution could trigger IMN in susceptible individuals. We also need to learn more about why patients with IMN often experience a relapse.

Kidney News: *In the meantime, what can clinicians do to improve care for patients with IMN?*

Dr. Beck: A lot of people at academic centers are using antigen and autoantibody testing to guide patient care, but it is sometimes more difficult for community practitioners to access these tests. I'm hoping that even more nephrologists will gain familiarity with, and have access to, antibody testing for PLA_2R and THSD7A so they can better guide patient care. ■

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No Increase in COVID-19 Risks With ACE/ARB Use

Among patients with hypertension, previous treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) does not increase the risk of severe or fatal COVID-19, concludes a study in *The Journal of the American Medical Association*.

The retrospective analysis included data on 4480 patients with COVID-19, median age 54.7 years, drawn from Danish national registries. Patients were followed up from diagnosis until they reached a study outcome, or until early May 2020.

Twenty percent of patients had been using ACEI/ARBs, based on prescription fills within the previous 6 months. The primary outcome was death; secondary outcome was a composite of death or severe COVID-19, defined as severe acute respiratory syndrome or ICU admission.

COVID-19 patients with a history of ACEI/ARB use were older (mean age 72.8 versus 50.1 years) and more likely to be men (55.1% versus 46.1%), compared to non-ACEI/ARB users. The ACEI/ARB users also had higher rates of comorbid cardiovascular disease, including previous myocardial infarction and heart failure. About half of patients (49.6%) were hospitalized at the time of COVID-19 diagnosis.

Thirty-day mortality was 18.1% in patients with previous ACE/ARB use, compared to 7.3% in nonusers. On unadjusted analysis, mortality risk was more than twice as high in ACEI/ARB users with COVID-19, hazard ratio (HR) 2.65. However, the association became nonsignificant (HR 0.83) after adjustment for age and medical history. Standardized mortality was 8.8% in ACE/ARB users and 10.2% in nonusers.

Thirty-day rates of the composite outcome were 31.9% in ACEI/ARB users versus 14.2% in nonusers. Again, the association was not significant after adjustment for age and comorbidity. The same was true on analysis of severe COVID-19 (with 30-day rates of 22.6% and 10.4%, respectively).

A nested case-control analysis examined susceptibility in 571 COVID-19 patients with previous hypertension, compared to an age- and sex-matched group of 5710 hypertensive patients without COVID-19. Rates of ACEI/ARB use were approximately 85% in both groups.

Because angiotensin-converting enzyme 2 is the receptor for cell entry for SARS-CoV2, there have been concerns that ACE/ARB users might be more susceptible to infection, or might have worse outcomes of COVID-19. These registry data show no increase in the risk of death

or severe disease in COVID-19 patients with a history or ACEI/ARB use, nor any increase in the rate of COVID-19 diagnosis associated with these widely used antihypertensive drugs.

The investigators conclude: "These findings do not support discontinuation of ACEI/ARB medications that are clinically indicated in the context of the COVID-19 pandemic" [Fosbøl EL, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA*. 2020; doi: 10.1001/jama.2020.11301]. ■