cells), it conveys extra protection to complement-mediated injury.

Uncontrolled C3 activation occurs in C3 glomerulopathy (C3G), and treatment options for C3G are limited. Some progress has been made with the treatment of C3G with eculuzimab, an mAb against C5 that prevents the generation of the phlogistic fragment C5a from C5 and the formation of the MAC; however, the success of treatment is often uncertain.

In this issue of the *Journal of the American Society of Nephrology*, Wang *et al.*[1] explored the potential efficacy of an Fc fusion protein of complement receptor of the Ig superfamily (CRIg-Fc) in the treatment of mice with an experimental form of C3G, namely mice with a common CFH and properdin double deficiency. These mice develop an early onset of C3G with increased C3 catabolism, increased proteinuria, and lethal crescentic GN. Treatment of the double-deficient mice with CRIg-Fc but not the control Fc fusion protein reduced proteinuria, hematuria, BUN, C3 deposition, and GN scores. Additionally, treatment with CRIg-Fc improved complement pathology and survival. Treatment of these mice was started at 4 weeks of age, at which time the mice have a mild form of C3G. The question remains whether CRIg-Fc will prove to be efficient in reversal of a fully active disease. The findings, however, are promising, and combined with the fact that it down modulates the degree of C3 amplification, it adds a potential new approach to the treatment of C3G in patients.

Other promising approaches are being explored. Like the approach of using CRIg-Fc as a down modulator of C3 amplification, two other inhibitors have been developed. Both are on the basis of the regulatory domains of CFH itself.

Yang *et al.*[2] engineered two CFH miniconstructs consisting of specific domains of CFH, with a higher retention of the drug in the kidneys of mice. These mini-CFH constructs were fully able to regulate complement amplification in mice, and they were shown to be very effective in prevention of glomerular C3 deposition in CFH-deficient mice. The advantage of using these CFH miniconstructs is that they block complement activation in the affected organ directly, whereas the CRIg-Fc mainly down modulates circulating complement activation.

Another very promising agent to block the alternative pathway convertase was reported recently by Michelfelder *et al.*[3] They synthesized a fusion protein MFHR1 that contains the regulatory domains of CFH and the C5 convertase/C5b-9 inhibitory fragment of FH-related protein 1. MFHR1 has cofactor and decay accelerating activity and inhibits C5 convertase activation and MAC assembly, which prevent C3b deposition. Administration of MFHR1 to CFH−/− mice resulted in inhibition of C3 activation *in vivo* and reduced abnormal C3 deposition in the kidneys. The advantage of MFHR1 is that it not only controls alternative pathway C3 activation but that it also affects the C5 convertase and generation of MAC.

The idea to down modulate complement activation at the C3 level was introduced quite a number of years ago by the research group of Lambris and colleagues.[4] They developed a drug called Compstatin that prevents C3 activation by binding to C3 itself. Continuous development of the Compstatin scaffold for increased target affinity, inhibitory efficacy, and advantageous pharmacokinetic properties has resulted in the analog CP40, which also looks very promising in preclinical models of C3G and other complement-mediated diseases.

In summary, several potentially very promising drugs that control the degree of the activity of the alternative pathway are now in the pipeline. Most of these drugs are still in the preclinical stage, and much more work is ahead to bring these drugs to implementation in the clinic.

DISCLOSURES

None.

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See related article, "Prevention of Fatal C3 Glomerulopathy by Recombinant Complement Receptor of the Ig Superfamily," on pages 2053–2059.

Now or Later? Understanding Timing of Dialysis Initiation beyond IDEAL

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"When will I need dialysis?" For older patients with advanced CKD, the decision to start dialysis is one that is often fraught

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with uncertainty. For the physician approaching an individual clinic encounter, a complex set of variables goes into the clinical decision to start dialysis, including a constellation of symptoms, laboratory data, examination findings, comorbidities, and patient readiness and preferences. Virtually every practicing clinician can identify cases where he or she waited too long or started too early, having forecast the rate of progression incorrectly. Although waiting too long can lead to discrete, recognizable adverse events, starting too early is less likely to be clinically recognized as an error on an individual basis, and therefore, the natural desire to avoid harm pushes us toward preemptive action.

Of all of the clinical information that is synthesized into a decision to begin dialysis, the most quantifiable aspect of advanced kidney disease is measurement of glomerular filtration, most commonly through creatinine-based eGFR. In attempts to standardize the treatment of advanced CKD, eGFR became a driving factor in dialysis decision making and likely led to earlier initiation of dialysis at questionable patient benefit. Rigorous data-driven approaches to understanding the effects of early or late dialysis start as defined by eGFR had, until the Initiating Dialysis Early and Late (IDEAL) Study, been primarily on the basis of observational data.[1] The IDEAL Study showed little difference in outcomes between planned "early" and planned "late" dialysis initiation—although there was substantial crossover from one strategy to the other.[2] Although the IDEAL Study was a critical contribution to a field badly in need of randomized, controlled trial–level evidence, the inclusion criteria of the IDEAL Study did not encompass the older and more frail population of patients with CKD and needed to be supplemented with observational approaches investigating excluded populations.

Kurella Tamura *et al.*[3] add to our knowledge by examining data from the Veterans Affairs (VA) Healthcare System, one of the largest integrated systems for the care of patients with advanced kidney disease. They capture an older population of predominantly men with eGFRs$<$30 from before the IDEAL Study publication, many of whom are older than the IDEAL Study population, and follow them over an average of almost 4 years. Using models incorporating time-updated ages and eGFRs, they are able to delineate a set of "ideal" (maximal survival benefit) eGFRs for dialysis initiation at different ages and show the average life expectancy benefit of dialysis versus medical management at different ages and eGFRs. In sum, they find a slight upward shift in the eGFR range of best outcomes for dialysis initiation (benefit toward initiation at higher eGFRs up to 12 in the age range of 75 years old and older) but diminishing returns at older ages in terms of added life expectancy. As a complement to the IDEAL Study and to address the concerns of those who are wary of observational data on this topic, they re-create an IDEAL Study–like population within the VA cohort and almost exactly replicate the findings of that study, lending additional weight to their other findings.

For those of us who serve the hundreds of thousands of patients with CKD stage 4 and 5 seen by the VA system, one illuminating aspect of this study is to see the substantial number of patients, particularly at older ages, who did not start dialysis during the follow-up period (only 15% overall started dialysis; 5% of those over 85 years of age) and recognize that absolute life expectancy gains on dialysis were at best 17 months in those over 85 years old. Although the percentages of those starting dialysis and perhaps, the relative benefit of dialysis are different in those referred to a subspecialist, it is worth remembering, as noted in past work,[4] that most patients with advanced kidney disease will never get dialysis for a variety of reasons.

For those who do start dialysis, this work suggests that there is a measurable benefit in life expectancy but that benefit diminishes with age and is lower in those who start at higher eGFRs at any given age. Although we all understand that there are unmeasurable differences between those who do and those who do not start dialysis at eGFRs of $<$10, one would think that the benefit seen in an observational setting, such as this, is skewed toward the maximal end of the true benefit of dialysis—in other words, those choosing or being offered dialysis are those thought most likely to succeed.

A few significant caveats should be considered in evaluating the clinical applications of the data presented in this paper to our interactions with patients in nephrology clinic. First, the patients evaluated here were not necessarily followed by nephrologists, and it cannot be known whether they were seriously evaluated for dialysis at any given time point. Thus, there is likely a population of patients included here for whom decreasing eGFR was not considered a primary issue in the setting of some other life-limiting disease. These patients may or may not ultimately receive dialysis, but it seems probable that they are part of a later-start group or a group that does not start dialysis. This may make the findings difficult to apply to interactions with those referred to nephrology.

Second, a substantial fraction of participants had unknown eGFR at the time of dialysis initiation and that fraction increased with increasing age. Thus, the data that we have may not fully represent the patients who we see at the time of dialysis initiation—perhaps including those whose kidney disease has not been followed or appreciated before the point of failure.

Third, like all guidelines that suggest cutoff ranges for dialysis initiation and like the IDEAL Study itself, the focus here centers on eGFR. In the older adult, creatinine also is a marker of muscle mass, and therefore, higher eGFRs may reflect a frailer population with similar actual filtration rates if these were measured more accurately. Within any age stratum, there are robust and frail individuals, and therefore, adding age does not fully account for the different meanings of any given eGFR. Without an integrated clinical measure of "uremia," eGFR remains an incomplete picture of a complex disease.

In sum, the answer to the question "when will I need dialysis?" clearly involves more than just eGFR. This work helps us integrate age and eGFR together when attempting to quantify observed benefit or lack thereof of dialysis initiation, allows us to realistically forecast life expectancy on dialysis for groups with similar ages and eGFRs, and lets us move beyond the IDEAL Study when looking for evidence on the optimal time to start dialysis.

DISCLOSURES

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