The syndromes of thrombotic microangiopathy

11

New roads ahead (impact paragraph)

In the era of complement–specific drugs, the diagnostic approach of patients with thrombotic microangiopathy (TMA) should focus on the recognition of complement–mediated (C–)TMA in the earliest possible stage of disease. C–TMA, although considered a diagnosis of exclusion (i.e., primary atypical hemolytic uremic syndrome),[10,11] appeared prevalent along the spectrum of TMA and, in particular, among patients presenting with coexisting hypertensive emergency, pregnancy, and *de novo* TMA after kidney transplantation.[101,140] Our understanding of deregulated or excessive complement activation in patients with TMA and coexisting conditions highlights the need for a new and practical approach to diagnose C–TMA. Most patients with C–TMA, either with coexisting conditions or not, present with severe kidney disease not responding to standard of care and/or relapsing disease. It is important to stress that systemic hemolysis can be absent in up to 60% patients with coexisting conditions, requiring a kidney biopsy to detect the TMA.[140] *Ex vivo* C5b9 formation on the resting endothelium (i.e., HMEC–1 test), as described in this thesis, appears a promising method to diagnose C–TMA and thus, select patients for treatment with complement–specific drugs. Our data provide the background for the "*Complement Prospective Evaluation of TMA on the Endothelium*" (COMPETE; NCT04745195) study. The aim of this prospective observational cohort is to study the prevalence of C–TMA in patients with TMA and coexisting conditions. The application of the HMEC–1 test or other (high–throughput) methodologies is imperative to select patients for treatment. The COMPETE cohort will be used to assess the HMEC–1 test's performance for the diagnosis and monitoring of C–TMA.

Therapeutic C5 inhibition, that is, eculizumab[13-15] or ravulizumab,[224,225] revolutionized the treatment of C–TMA. None of the clinical trials, however, included patients with TMA and coexisting conditions. Observational cohorts, including those from Maastricht and Brussels,[140] indicate that patients with TMA and coexisting conditions may benefit from therapeutic C5 inhibition. Of note, many of the responding patients had C–TMA rather than secondary TMA. A randomized, placebo–controlled, trial (ALXN1210–TMA–315; NCT04743804) will evaluate ravulizumab's efficacy in 100 adult patients with TMA and coexisting conditions, including but not limited to hypertensive emergency and kidney transplantation. The results of this long–awaited trial will aid the discussion whether or not therapeutic C5 inhibition should be used for the treatment of secondary TMA. Newer complement–specific drugs targeting complement activities upstream of C5 (e.g., C3, Factor D, Factor B) are under development, providing a choice in therapeutic target, modality, and route of delivery in the next few years. I hope that with the advent of newer compounds on the horizon, there will be an opportunity to study complement–specific drugs more widely and that the cost of this class of drugs will be more affordable.

The optimal dosing and treatment duration remains to be established. Our

observations indicate that TMA recurrence is common in hereditary C–TMA. To date, the safety of eculizumab discontinuation has been studied in a single prospective cohort, including patients with C–TMA treated for at least 3–6 months who achieved a complete clinical response (i.e., estimated GFR >60 mL/min/1.73m^2).[226] TMA re–occurred in patients with hereditary C–TMA but not in those without a germline complement gene variant, confirming retrospective observations.[227-229] Thus, eculizumab discontinuation appears to be reasonable and safe in patients with normal complement genetics and no renal sequelae, while a subset of patients with hereditary C–TMA [11] and, in particular, those with chronic kidney disease, may require long–term treatment. Less–intensive treatment, such as prolongation of eculizumab's interdose interval as guided by the HMEC–1 test,[92,140] potentiates a lower (economic) burden of disease and warrants further evaluation. Also, it remains to be established whether or not less–intensive treatment is safe in kidney donor recipients because the allograft's capacity to recover is limited.[96]

Altogether, recent advances have clearly changed the landscape of TMAs. Knowledge on complement dysregulation has enabled breakthroughs in diagnosis and treatment of C–TMA. Further progress can be expected in the coming years and will pave the road to our ultimate goal of precision medicine.