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Anti-complement therapy of renal diseases

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The role of complement activation as a primary etiology and a secondary exacerbator of kidney disease have long been known. Recent advances in complement physiology have elucidated the central role of complement dysregulation as the root cause of hematologic, glomerular and systemic diseases. The recent development of therapeutic anti-complement antibody preparations has enabled the clinician to capitalize on these scientific advances by treating these disorders in a targeted fashion. Infection, surgery, autoimmune disease and pregnancy are the major activators of the complement pathway. The presence of intrinsic regulatory proteins brings about the physiologically appropriate down regulation of the system. There are currently known 4 counter-regulatory proteins (Factor H, Factor I, MCP, thrombomodulin) in which inactivating mutations lead to excessive complement activity. There are 2 proteins (Factor B, C3) that are integral complement component in which gain of function mutations lead to excessive complement activity. Acquired auto-antibodies resulting in excessive activity include: Inactivating Factor H antibodies, C3 nephritic factor stabilizing C3 convertase, and C4 nephritic factor stabilizing C4 convertase. Two renal disorders have been etiologically linked to complement regulatory pathology. C3 glomerulopathy (C3G) denotes primary glomerular diseases previously categorized as membranoproliferative glomerulonephritis. There is a predominance of C3 staining by immunofluorescence in the glomeruli. Usually evidence of complement activation can be detected by serologic testing. Biopsies demonstrating a proliferative component represent C3 glomerulonephritis as distinct from Dense Deposit Disease. A chronic relapsing course with progression to ESRD is typical. A typical Hemolytic-Uremic Syndrome (aHUS) is a multisystem disorder characterized by thrombotic microangiopathy (microangiopathic hemolytic anemia, thrombocytopenia and thrombi in the microcirculation resulting in end organ injury). The most frequent organ involvement is kidney, followed by the central nervous and the gastrointestinal systems. Autosomal recessive and dominant inheritance patterns have been identified. The long clinical course is characterized by flares and remissions, often with underlying indolent disease activity. Historically, approximately 70% of patients with Factor H deficiency (the first to be discovered and most prevalent mutation) will die or progress to ESRD in the first year of overt disease. C3G has been treated with various immunosuppressive regimens (steroids and cytotoxic agents) and aHUS has been treated with plasma therapies (infusion and exchange). These treatments have had variable and incomplete success. Eculizumab is a humanized anti-complement monoclonal antibody that has been utilized in the treatment of complement mediated diseases, including: Paroxysmal Nocturnal Hemoglobinuria (PNH), aHUS, C3G, and catastrophic anti-phospholipid syndrome. It is currently approved by the FDA and EDA for the treatment of PNH and aHUS. Eculizumab targets C5 and blocks its cleavage (activation) by C5 convertase. This leaves the proximal complement pathway intact while inactivating the terminal part of the pathway, thereby eliminating the production of the membrane attack complex. Data demonstrating the effectiveness of Eculizumab in the treatment of C3G is only anecdotal. There have been three pivotal clinical trials (two prospective adult and one retrospective pediatric), including a total of 67 patients, demonstrating efficacy and safety of Eculizumab in the treatment of aHUS. In all three trials terminal complement activity was totally blocked; 90% of patients had hematologic normalization (LDH and platelet count); the need for other interventions (plasma therapies and new dialysis) was eliminated; and 50% of patients experienced an eGFR increase of >15 ml/min/1.73M². 80% of patients in the shorter disease duration adult trial and 67% of patients in the pediatric trial who were on dialysis at study entry were able to discontinue dialysis. Eculizumab is a highly effective and well tolerated treatment for complement mediated renal diseases. An increased incidence of meningococcal disease (seen in the earlier, more extensive PNH experience) necessitates the administration of appropriate vaccination and antibiotic prophylaxis. All of the patients who remained on eculizumab during the extension studies remained free of disease manifestations. 8% of the nine patients, for whom follow-up data is available, who discontinued eculizumab experienced aHUS disease flares.

Biography

Kenneth Lieberman completed his undergraduate studies at Princeton University and then earned his MD from the Albert Einstein College of Medicine. He is currently the Chief of the Section of Pediatric Nephrology of the Joseph M Sanzari Children's Hospital of the Hackensack University Medical Center and a Professor of Pediatrics at Rutgers-New Jersey Medical School. He contributed to the identification of one of the complement component mutations causing aHUS and has been a Principal Investigator of the clinical trials of Eculizumab for the treatment of aHUS.

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