New treatment options for the atypical hemolytic uremic syndrome

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The hemolytic uremic syndrome (HUS) is a rare and severe thrombotic microangiopathy characterized by hemolytic anemia, thrombocytopenia, and acute renal failure. HUS is characterized histologically by thrombotic microangiopathy (TMA): vascular abnormalities with glomerular endothelial damage , swelling of the endothelium, endothelial detachment of the basement membrane, intima fibrosis and thrombosis.

In more than 90% of the cases in childhood, the disease is triggered by an infection with Shiga-like toxin producing Escherichia coli (STEC). The most important causes seen in the remaining 5-10% of the HUS cases are dysregulation of the alternative pathway of the complement system due to genetic mutations (here called atypical HUS or aHUS) and a non-enteric infection with Streptococcus pneumoniae. The complement system is part of the innate immunity. It induces cell lysis by the incorporation of the membrane attack complex and activates and attracts leukocytes. The complement system, however, does not discriminate between pathogens and host cells. To protect our own cells the system is therefore tightly regulated on both the cell surface and in the fluid phase. Non-host surfaces that lack these regulators are attacked and damaged by the complement system. A mutation in one of the regulators will lead to uncontrolled activation of the complement system on host cells resulting in cell damage, especially to those in the microcirculation of the kidney. These mutations, mostly seen in the alternative pathway of the complement system, are identified in ~50-60% of the aHUS patients. It has been shown that both STEC and S. pneumoniae can protect themselves against complement activation. This knowledge, the fact that dysregulation of the alternative complement pathway due to mutations is believed to play an important role in the pathogenesis of aHUS, and the similarity of the clinical manifestations, let to questions if there is a general role of the complement system in the other forms of HUS.

For clinicians it is very important to recognize patients with aHUS in time. Without treatment, the prognosis of patients with aHUS is poor, up to 25% of patients may not survive the acute phase and up to 50% of the patients progress to end stage renal failure. The outcome is in general dependent on the underlying genetic aberrations. The diagnosis aHUS is made by excluding other forms of HUS. As soon as a suspicion of aHUS has raised, treatment for aHUS has to be started. In 2012, the recombinant, humanized, monoclonal anti-C5 antibody eculizumab has been registered for the treatment of aHUS patients by FDA and EMA. Eculizumab specifically binds to C5, thereby blocking the cleavage of C5 into C5a and C5b and the formation of the membrane attack complex C5b-9 is prevented. The use of this new unique complement inhibitor has clearly improved the treatment options for aHUS and will be here further discussed.