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The new generation of complement inhibitors and implications for clinical practice and vaccination policy

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The complement system is a key actor of innate immunity that plays a central role in tissue homeostasis and in defence against infection. It is composed of several components (C) that are activated in cascade through different pathways (alternative, classical or lectin pathway). The activation and the control of complement occur around the key component, C3. Subsequently, the formation of the Membrane Attack Complex (MAC), a structure formed by the late components (C5b, C6, C7, C8 and C9), on cell surface disrupts the cell membrane leading to cell lysis. The complement is under a tight control through several negative regulators (CD35, CD46, CD55, CD59, Factor I, Factor H C4BP) to protect host cells from self-complement activation.

Deficiencies in complement negative regulators enhances complement activation on the surface of host cells such as erythrocytes with subsequent hemolysis. This uncontrolled complement activation is a hallmark in the pathogenesis of several devastating disorders such as paroxysmal nocturnal haemoglobinuria (PNH), atypical haemolytic uraemic syndrome (aHUS) and age-related macular degeneration (AMD). Activation of complement via the alternative pathway on foreign cells contributes to hyperacute rejection of xenografts. The outcome of these diseases may benefit from drugs (such as monoclonal antibodies, Mab, against complement components) that inhibit complement activation. Mab against factor D can prolong the survival of xenografts. Eculizumab, the first licensed anti-C5 Mab (licensed in 2007), has provided a major advance in the treatment of PNH by reducing the amount of MAC but it does not completely prevent haemolysis due to C3-mediated extravascular haemolysis. Improvement of these anti-complement strategies is need. New inhibitors can be against the terminal complement pathway and/or against the key component, the C3.

At the opposite, complement activation eliminates pathogens, dying host cells and abnormal molecular structures. The complement system and in particular the components C5 to C9 that constitute the terminal complement pathway, plays a major role in defences against invasive meningococcal disease (IMD). Patients with terminal pathway deficiencies (TPD) are highly predisposed to invasive, often recurrent meningococcal infections that are provoked by isolates belonging to several serogroups and particularly serogroup Y. Deficiencies in components of the alternative pathway of complement (properdin and factor D) also predispose to IMD. Inhibition of terminal pathway increases therefore the risk of IMD in patients treated with anti-C5. New inhibitors can also increase IMD risk to a variable extent.

Anti-meningococcal vaccination is already recommended in subjects receiving eculizumab in some countries (e.g., UK and France). The protection should be wide as isolates belong to several serogroups (against ACWY and B serogroups). Vaccination scheme (number of doses) needs to be adapted as immunogenicity of these vaccines may be less optimal in these subjects. Boosters may be also required in addition to, antibiotic treatment (penicillin V). However, resistance to penicillin may jeopardise this use. Vaccination can also target household and close contacts of subjects with inherited or acquired complement deficiencies (cocooning strategy).