ANTAGONISTS OF THE COMPLEMENT SYSTEM FOR USE IN METHODS OF TREATING PARAPROTEINEMIC NEUROPATHIES

FIELD OF THE INVENTION

The present invention relates to methods of treating paraproteinemic neuropathies using antagonists of the complement system. The antagonists block or inhibit the complement system upstream of complement factor C5. The paraproteinemic neuropathies that may be treated include, in particular, multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyneuropathy (CIDP), and Guillain-Barré syndrome (GBS).

BACKGROUND TO THE INVENTION

The complement system is an important facet of the innate immune system that enhances (complements) the ability of antibodies and phagocytic cells to clear microbial intruders and damaged cells from an organism. Complement therefore forms an essential line of defence against infection.

The response to infection has to be rapid and comprehensive enough to prevent risk to the host, but selective enough to avoid damage to healthy cells. Complement typically achieves this delicate balance by employing a tiered and closely regulated cascade system of more than 30 soluble and surface-expressed proteins. Complement factors circulate in the blood as inactive precursor proteins. Activation of the system leads to an activation cascade where one factor activates the subsequent one by specific proteolysis of a complement protein further downstream in the cascade. This cascade can ultimately result in: the production of anaphylatoxins that attract and activate macrophages and leukocytes; formation of the lytic membrane attack complex (MAC); and opsonization of targets for phagocytosis and destruction.

Activation of the complement system can occur via three pathways: the classical pathway; the lectin pathway; and the alternative pathway (see Fig. 1). Each pathway activates a central component, C3, which results in the activation of a common termination pathway leading to the formation of MAC (Muller-Eberhrd, *Annu Rev Biochem* 1988, 57:321). The classical pathway is often referred to as antibody-dependent because it is strongly initiated by IgM or IgG clusters. This pathway is usually activated when the hexameric C1q binds to the Fc regions of IgG or IgM molecules that are present in an antibody/antigen complex. Upon binding, C1s cleaves C4 to produce C4a and C4b. Next, C2 binds to surface-bound C4b (in the presence of Mg^{2+}) to form a C4bC2 complex, which is then cleaved by activated C1s into two fragments: a smaller 30 kDa