USES OF PIPERIDINYL-INDOLE DERIVATIVES

FIELD OF THE INVENTION

The invention relates to the use of certain piperidinyl-indole derivatives in the treatment of patients suffering from conditions and diseases associated with complement alternative pathway activation such as renal diseases and in particular for the treatment of patients suffering from C3G (C3 glomerulopathy) and IgAN (immunoglobuline A nephropathy).

BACKGROUND OF THE INVENTION

The complement system is an important component of the innate immune system and comprises a cascade of proteases that are normally present in an inactive state. These proteases are organized in three activation pathways: the classical, the lectin, and the alternative pathways that all converge on C3 and C5 cleavage and a common terminal pathway (V. M. Holers, In Clinical Immunology: Principles and Practice, ed. R. R. Rich, Mosby Press; 1996, 363-391). Molecules from microorganisms, antibodies or cellular components can activate these pathways resulting in the formation of protease complexes known as the C3-convertases and the C5-convertases. The classical pathway is a calcium/magnesium-dependent cascade, which is normally activated by the formation of antigen-antibody complexes. It can also be activated in an antibody-independent manner by the binding of C-reactive protein complexed to ligand and by many pathogens including gram-negative bacteria. The lectin pathway is also calcium and magnesium dependent and is normally stimulated by lectins. The alternative pathway is a magnesium-dependent cascade which is activated by deposition and activation of C3 on certain susceptible surfaces (e.g., cell wall polysaccharides of yeast and bacteria, and certain biopolymer materials). In addition to alternative pathway-specific stimulation, the alternative pathway also serves as an amplification loop for the other complement pathways.

Factor B is a key protease of the alternative pathway and may be a suitable target for the inhibition of the alternative pathway as well as the amplification of the other complement pathways. Its plasma concentration in humans is typically about 300 μg/mL (or about 3 μM), and it has been shown to be a critical enzyme for activation of the alternative complement pathway (P. H. Lesavre and H. J. Müller-Eberhard. J. Exp. Med., 1978; 148: 1498-1510; J. E. Volanakis et al., New Eng. J. Med., 1985; 312:395-401).

WO2017/109208 discloses certain polypeptides for inhibiting complement activation and their use in disorders such as atypical hemolytic uremic syndrome (aHUS), C3G and IgA nephropathy. It describes a fusion construct in which multiple active domains from naturally occurring complement regulators (complement factor H (FH) and complement FH related protein 1 (FHR1)) were combined to a single molecule. The FH part of the molecule dissociates the C3 convertase of the AP, and at the same time acts as a cofactor of Complement factor I, which cleaves C3b to smaller, inactive fragments. In addition, the fusion construct also binds to C5 and inhibits the (AP) C5 convertase. Finally, the FHR1-part of the construct inhibits the classical complement pathway (CP), as shown in the Wieslab assay for classical pathway activity. Therefore this should result in a dual inhibition of the classical pathway and the alternative pathway/amplification loop. WO2015/009616 describes the synthesis and some utilities of the piperidinyl-indole derivatives. The said compounds are powerful factor B inhibitors and suppress the amplification of the complement system caused by C3 activation irrespective of the initial mechanism of activation (including for example activation of the classical, lectin or alternative pathways). WO2015/009616 discloses a wide variety of indications including the renal diseases atypicaly hemolytic uremic syndrome (aHUS) and glomerulonephritis including membrane proliferative glomerulonephritis. It is silent about the use of the piperidinyl-indole derivatives in other renal diseases which are separate conditions with a distinctly different causality from the above, in particular it does not describe the use in classical HUS (*E. coli* induced hemolytic uremic syndrome) and membranous nephropathy. In contrast to the polypeptide construct according to WO2017/109208, the low molecular weight compounds as disclosed in WO2015/009616 specifically inhibit the protease complement factor B, which is responsible for cleaving C3 and C5 of the AP. Thereby the direct generation of C3a, C5a and C5b-9 through the classical pathway is spared. In 2017, Konar and Dranoff (Konar M and Granoff D M 2017. Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. Blood. 130(7):891-899) have elegantly shown that selective inhibition of Factor D, the protease that activates FB, did not impair the protective immune response against *N. meningitidis* in vaccinated individuals, whereas inhibition at the level of C5 does.

SUMMARY OF THE INVENTION

Surprisingly, the present invention provides now a method of treating or preventing factor B mediated diseases, which consists of administering a compound of Formula (I) to a patient suffering from a renal disease or disorder selected from the complement-driven renal disease C3G (C3 glomerulopathy) and IgAN (immunoglobuline A nephropathy) and other nephropathies with evidence of glomerular C3 deposition such as MN (membranous nephropathy) and HUS (*E. coli* induced hemolytic uremic syndrome).

DETAILED DESCRIPTION OF THE INVENTION

In a first embodiment, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of the complement-driven renal diseases C3G (C3 glomerulopathy), IgAN (immunoglobuline A nephropathy) and other nephropathies with evidence of glomerular C3 deposition such as MN (membranous nephropathy) and HUS (*E. coli* induced hemolytic uremic syndrome). Compounds of Formula (I) or pharmaceutically acceptable salts thereof, are represented by the following structure:

(I)