# Current and Future Pharmacologic Complement Inhibitors

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**KEYWORDS**

• Eculizumab • Complement therapeutics • PNH • aHUS • C3 • C5 • Compstatin

**KEY POINTS**

- Eculizumab is the current anticomplement treatment agent approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.
- Emerging observations are suggesting that other strategies of complement inhibition/modulation may improve the clinical result of current anticomplement treatment.
- Novel complement therapeutics include inhibitors of the terminal effector complement as well as of early complement activation.
- Inhibitors of early complement inhibitors include broad C3 inhibitors as well as agents selectively targeting specific complement pathways.

## INTRODUCTION

The complement system is a key component of innate immunity, which is involved in several physiologic and pathologic processes. It was originally thought that complement merely represents the crudest sentinel for protection from microbes, with a possible additional role in inflammatory processes; however, its role in human homeostasis and disease is now widely recognized.[1–3] Indeed, dysregulated or impaired complement is involved in an increasing list of human diseases (eg, paroxysmal nocturnal hemoglobinuria [PNH], hemolytic uremic syndrome [HUS], kidney disorders, age-related macular degeneration [AMD]) as well as of clinical conditions (eg, sepsis, ischemia/reperfusion injury, allograft rejection).[4] The interest for complement-mediated pathophysiology has been strengthened by the recent availability of

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complement inhibitors.[5,6] Indeed, the clinical approval of the first complement-targeting drug, the anti-complement component 5 (C5) Eculizumab (Soliris), has drastically changed the natural history PNH and represents a novel treatment option for other complement-mediated diseases, such as atypical hemolytic uremic syndrome (aHUS). Subsequently, the introduction of the C1 inhibitor (C1-INH; Cinryze) for the treatment of hereditary angioedema has offered another compound in the armamentarium for the interception of specific component of the complement cascade.[7] All these observations have reignited the interest for a deeper investigation of complement-mediated pathophysiology in human diseases as well as the interest for the development of novel classes of complement inhibitors. Here, current and future agents are reviewed that intercept complement function in vivo and the rationale for targeted complement inhibition for optimizing the therapeutic effect in specific clinical conditions is discussed.

## CURRENT COMPLEMENT INHIBITORS: ECULIZUMAB

### *Eculizumab for the Treatment of Paroxysmal Nocturnal Hemoglobinuria*

PNH is a rare hematologic disease characterized by complement-mediated intravascular hemolysis, bone marrow failure, and propensity to thromboembolic events.[8–10] PNH is due to a somatic mutation in the phosphatidyl-inositol glycan class A (*PIG-A*) gene,[11,12] which impairs the biosynthesis of the glycosyl-phosphatidyl-inositol (GPI) anchor and the subsequent expression of a several surface proteins (GPI-linked proteins). The absence of 2 GPI-anchored complement regulatory proteins (CD55 and C59) is central to the pathophysiology of PNH. CD55 is a regulator of early complement activation,[13] which physiologically inhibits the formation of C3 convertase (both C3bBb and C4b2a) and also promotes its decay.[14] CD59 is a regulator of the terminal effector complement,[15] which interacts with C8 and C9, inhibiting the incorporation of this latter onto the C5b–C8 complex, eventually preventing the assembly of the membrane attack complex (MAC).[16] The concomitant lack of CD55 and CD59 accounts for the susceptibility of PNH erythrocytes to complement activation, which eventually leads to the chronic intravascular hemolysis typical of PNH.

Eculizumab (Soliris) is the first complement inhibitor available in the clinic; it is a humanized monoclonal antibody (mAb),[17] which binds the complement component 5 (C5) and inhibits its cleavage to C5a and C5b, eventually disabling the terminal effector complement (preventing the assembly of the MAC). Eculizumab has been extensively tested in different autoimmune disorders before changing the treatment paradigm of PNH; indeed, 2 large multinational phase III studies demonstrated the efficacy of eculizumab for the treatment of PNH.[18,19] In the first double-blind, placebo-controlled, multinational randomized trial (TRIUMPH), which enrolled 86 transfusion-dependent PNH patients, treatment with eculizumab resulted in a dramatic reduction of intravascular hemolysis, as measured by *lactate dehydrogenase* (LDH), leading to hemoglobin stabilization and transfusion independence in about half of the patients (and reduced transfusional need in the remaining ones).[18] These data were confirmed in the open-label phase III study, SHEPHERD, which included a broader PNH population[19]; this longer study also confirmed the excellent safety profile of eculizumab, with negligible side effects. A subsequent open-label extension study confirmed the efficacy and the safety of eculizumab with a longer follow-up, demonstrating a sustained control of intravascular hemolysis with all related signs and symptoms.[20] This study also demonstrated a remarkable (85%) reduction in the rate of thromboembolic complications,[20] possibly because of the pathogenic linkage between intravascular hemolysis and thrombosis (eg, nitric oxide consumption,[21] prothrombotic microvesicles) or to any