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Review

# Therapeutic complement inhibition in complement-mediated hemolytic anemias: Past, present and future

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ABSTRACT

The introduction in the clinic of anti-complement agents represented a major achievement which gave to physicians a novel etiologic treatment for different human diseases. Indeed, the first anti-complement agent eculizumab has changed the treatment paradigm of paroxysmal nocturnal hemoglobinuria (PNH), dramatically impacting its severe clinical course. In addition, eculizumab is the first agent approved for atypical Hemolytic Uremic Syndrome (aHUS), a life-threatening inherited thrombotic microangiopathy. Nevertheless, such remarkable milestone in medicine has brought to the fore additional challenges for the scientific community. Indeed, the list of complement-mediated anemias is not limited to PNH and aHUS, and other human diseases can be considered for anti-complement treatment. They include other thrombotic microangiopathies, as well as some antibody-mediated hemolytic anemias. Furthermore, more than ten years of experience with eculizumab led to a better understanding of the individual steps of the complement cascade involved in the pathophysiology of different human diseases. Based on this, new unmet clinical needs are emerging; a number of different strategies are currently under development to improve current anti-complement treatment, trying to address these specific clinical needs. They include: (i) alternative anti-C5 agents, which may improve the heaviness of eculizumab treatment; (ii) broad-spectrum anti-C3 agents, which may improve the efficacy of anti-C5 treatment by intercepting the complement cascade upstream (i.e., preventing C3-mediated extravascular hemolysis in PNH); (iii) targeted inhibitors of selective complement activating pathways, which may prevent early pathogenic events of specific human diseases (e.g., anti-classical pathway for antibody-mediated anemias, or anti-alternative pathway for PNH and aHUS). Here we briefly summarize the status of art of current and future complement inhibition for different complement-mediated anemias, trying to identify the most promising approaches for each individual disease.



**Contents**



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## 1. Introduction

The complement system is a key component of the innate immunity which is finely regulated in humans. As for the adaptive immunity, the physiologic role of complement includes protection from foreign dangers, mostly infectious agents, as well as from self-triggers, like damaged tissues [1,2]. The complement system also represents a broad effector mechanism which may play a role in several human diseases (e.g., paroxysmal nocturnal hemoglobinuria [PNH], hemolytic-uremic syndrome [HUS], kidney disorders, age-related macular degeneration) and conditions (e.g., sepsis, ischemia/reperfusion injury, allograft rejection) [2–4]. These diseases may affect basically all human organs or systems; here we focus on disorders characterized by a common hematological presentation, which is hemolysis. Hemolytic anemias are a heterogeneous group of disorders which may have completely different causes; nevertheless, the complement system has been implicated as possible pathogenic mechanism in many of them. However, since the possible involvement of complement encompasses diseases which traditionally have been considered largely independent, a systematic classification of complement-mediated hemolytic anemia is missing. A tentative classification (see Table 1) may discriminate between forms caused by a primary impairment of endogenous complement regulation (primary forms), as compared with forms characterized by hyperactivation of complement secondary to other pathogenic events (secondary forms). Sometimes this distinction is not easy, because primary and secondary complement derangements may lead to similar disorders (see for instance the broad chapter of thrombotic microangiopathies, TMA), as well as primary dysregulation may work as a permissive environment where further secondary events are needed for the development of the disease. Primary forms include the most typical complement-mediated hemolytic anemia – namely PNH – as well as inherited diseases such as atypical HUS (aHUS) and a rare congenital deficiency of CD59. While in PNH the impairment of complement regulation is restricted to affected blood cells, eventually accounting for the typical hemolysis (see below), in aHUS such impairment is systemic, mostly in the fluid phase, and it results in possible microangiopathy (aHUS can be considered a primary, inherited microangiopathy). Secondary forms can be divided in two subgroups with different pathophysiology, according to the event triggering complement: (i) auto-immune antibody-mediated hemolytic anemia (AIHA), and (ii) secondary thrombotic microangiopathies. Antibody-mediated hemolytic anemia include cold agglutinine disease (CAD), cold paroxysmal hemoglobinuria (CPH) and other warm or mixed auto-immune hemolytic anemias; these conditions differ for the intrinsic features of the pathogenic immunoglobulin (e.g., antigen specificity, thermal range and mostly capability of activating the complement cascade), which eventually account for the contribution of the complement system to the mechanisms of hemolysis. TMAs are even more heterogeneous, and include the typical form of HUS (driven by bacterial toxins activating complement), as well as thrombotic thrombocytopenic purpura (TTP) and transplant-associated microangiopathies (TA-TMA), two conditions where the pathogenic role of complement has not yet been elucidated.

Here we briefly review the use of therapeutic complement inhibition in complement-mediated anemias, aiming to highlight how clinical interventions contribute to elucidate complement-mediated pathophysiology. Based on these finding we will also review the novel strategies of complement modulations which are currently under development, that eventually aim to improve the treatment of different complement-mediated anemias.

## 2. The history of complement inhibition in hemolytic anemias

Eculizumab (Soliris®, Alexion) [5] is the first complement inhibitor approved for clinical use in humans, initially for PNH and subsequently for aHUS. The experience with this anti-C5 humanized monoclonal antibody (mAb), which intercepts the complement cascade at the level of its terminal effector pathway, is extremely informative.

### 2.1. Eculizumab and paroxysmal nocturnal hemoglobinuria

PNH is a rare hematological disease characterized by three major clinical manifestations: complement-mediated intravascular hemolysis, bone marrow failure and propensity to thrombosis [6–8]. The cause of PNH is an inactivating somatic mutation in a gene called *phosphatidyl-inositol glycan class A* (*PIG-A*) [9,10], which eventually disables the biosynthesis of the glycosyl-phosphatidyl-inositol (GPI) anchor. Since the mutation occurs in a hematopoietic stem cells, all blood progeny cells carry the same aberrant phenotype characterized by the lack from the cell surface of all GPI-linked proteins, including the two major endogenous complement regula-