Complement activation and inhibition in autoimmune hemolytic anemia: Focus on cold agglutinin disease

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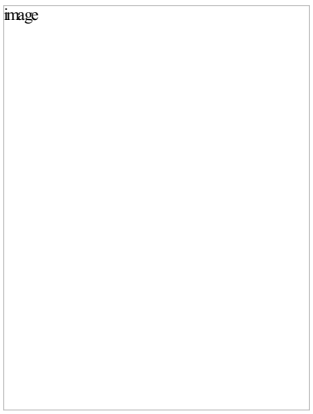

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Abstract

The classical complement pathway and, to some extent, the terminal pathway, are involved in the immune pathogenesis of autoimmune hemolytic anemia (AIHA). In primary cold agglutinin disease (CAD), secondary cold agglutinin syndrome and paroxysmal cold hemoglobinuria, the hemolytic process is entirely complement-dependent. Complement activation also plays an important pathogenetic role in some warm-antibody AIHAs, especially when IgM is involved. This review describes the complement-mediated hemolysis in AIHA with a major focus on CAD, in which activation of the classical pathway is essential and particularly relevant for complement-directed therapy. Several complement inhibitors are candidate therapeutic agents in CAD and other AIHAs, and some of these drugs seem very promising. The relevant *in vitro* findings, early clinical data and future perspectives are reviewed.

Keywords: autoimmune hemolytic anemia, cold agglutinin disease, complement, therapy, complement inhibitors.

1. Introduction

Autoimmune hemolytic anemia (AIHA) is a heterogeneous group of disorders, characterized by autoantibody-initiated destruction of red blood cells (RBCs). AIHAs can be classified according to the properties of the autoantibody as shown in **Table 1** [1-5]. Our knowledge of etiology and pathogenesis, including the role of complement for RBC breakdown in subgroups of AIHA, is rapidly growing [6, 7]. Although paroxysmal nocturnal hemoglobinuria (PNH) is not an autoimmune disease, lessons learnt from the entirely complement-mediated pathogenesis and the success of therapeutic complement inhibition in PNH have proved useful in understanding and treating AIHA [8, 9]. The fist examples of clinically effective complement modulation in subtypes of AIHA were published less than 10 years ago [10, 11] and, during the same period, several new complement inhibitors have been developed for potential clinical use [12-14].