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Review Article

Eculizumab: Pros and Cons

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Abstract

Eculizumab "Soliris", a recombinant, humanized, monoclonal, immunoglobulin G antibody that binds specifically to complement protein C5 and inhibits cleavage to C5a and C5b by C5 convertase, resulting in the prevention of terminal complex formation and therefore cell lysis.it has been authorized in treatment of some complement mediated disorders with good results. Eculizumab, the first agent to be approved by the Food and Drug Administration (FDA) for the treatment of patients with paroxysmal nocturnal hemoglobinuria "PNH" and atypical hemolytic uremic syndrome "aHUS", yet it has its drawbacks and some serious side effects. So, in terms of its use we must weight benefits against risks before giving to patients.

Keywords: *Eculizumab; Complement; PNH; aHUS; Side Effects*

Introduction

Eculizumab, a recombinant, humanized, monoclonal, immunoglobulin G antibody produced from murine myeloma cells works by inhibiting the complement cascade. It binds specifically to complement protein C5 and inhibits cleavage to C5a and C5b via C5 convertase, resulting in the prevention of terminal complex formation and therefore cell lysis [1].

Eculizumab is approved by Food and Drug Administration (FDA) and European Medicines Agency (EMEA) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and of atypical hemolytic-uremic syndrome (aHUS) and is considered a potential therapy for other complement-based diseases such as asthma, myasthenia gravis, autoimmune neuropathies and dense deposit disease (DDD) [2].

Despite this it can have serious side effects like life threatening meningitis and requires special precautions before use.

Chemical structure

Eculizumab (Soliris, Alexion Pharmaceuticals, Inc.) is a recombinant, humanized, monoclonal, immunoglobulin G antibody produced from murine myeloma cells that bind to complement protein C5. Composed of two 448-amino acid heavy chains and two 214-amino acid light chains, Eculizumab has a molecular weight of approximately 148 kDa [3].

Its heavy chains consist of portions derived from human IgG2 (constant region 1, the hinge and the very first part of constant region 2) and from human IgG4 (the remaining part of constant region 2 and the whole constant region 3) the light chains are derived from human a chains. The variable regions of heavy and light chains have a main human structure with transplanted murine sequences conferring substrate specificity [4].

Pharmacodynamics

Eculizumab binds to the complement protein C5, thus preventing its cleavage into C5a and C5b.

The three complement pathways, the classical pathway, which is activated by antigen/antibody complexes, the alternative pathway, which is activated by the deposition of C3b onto microbial and mammalian cell membranes and the lectin pathway, which is activated upon the binding of mannose binding lectin with mannose-containing carbohydrates, all converge onto C5 cleavage. C5 is split into C5a, a potent chemotactic factor and phagocytic cell activator, and C5b, which binds to C6 - C9 leading to the assembly of terminal complement complex (TCC) and to cell injury. Therefore, C5 blockade is expected to limit tissue damage both by suppressing inflammatory cell infiltration and activation, and by suppressing direct complement toxicity [1,5].

When C5 activation is prevented with Eculizumab, C3b can still be generated and exert its antimicrobial activity. This is an important argument for the choice of C5 as a target for anticomplement therapeutics as its blockade does not increase the susceptibility to potentially fatal bacterial infections.

Dosage forms and strengths

Eculizumab "Soliris" is supplied in 30-mL, single-use vials containing 300 mg (10 mg/mL) of sterile, and preservative-free solution per vial [6].

Therapeutics

Eculizumab is approved for the treatment of PNH and of hemolytic uremic syndrome. In addition, it could be helpful in other diseases in which tissue damage is dependent on complement activation such as such as asthma, myasthenia gravis and cold agglutinin disease (CAD). Eculizumab received orphan drug designation by the FDA in 2000 as a therapy for dermatomyositis and in 2003 for idiopathic membranous glomerular nephropathy [7].

Paroxysmal nocturnal hemoglobinuria [PNH]

Paroxysmal nocturnal hemoglobinuria is a rare acquired disorder of the hematopoietic stem cells. It is characterized by episodes of intravascular hemolysis, and chronic hemolytic anemia. The intravascular destruction of red blood cells involves clinical findings in gastrointestinal, cardiovascular, pulmonary, cerebral, and urogenital systems, as well as clotting disorders [8,9].

PNH results from a genetic mutation in the phosphatidylinositol glycan anchor biosynthesis, class A (PIGA) gene in a hematopoietic stem cell. The cells that contain the PIGA mutation are deficient in glycosyl phosphatidylinositol (GPI)-anchored proteins, leading to the production of abnormal erythrocytes that are more sensitive to complement activation and resulting intravascular hemolysis. The diagnosis of PNH is typically confirmed by flow cytometry of the peripheral blood, which identifies the absence of CD55 and CD59, two GPI-anchored proteins on the PNH clones [10].

Historically, PNH treatment has been primarily supportive, with transfusions, iron and folate supplementation as required. Medications, such as steroids, have been used successfully, although the adverse effects from long-term use are limiting. Allogeneic stem cell transplantation is the only potentially curative therapy, but it is considered only in severe cases because of high rates of treatment-associated morbidity and mortality [2,3]. Eculizumab, the first agent to be approved by the Food and Drug Administration (FDA) for the treatment of patients with PNH [6].

Eculizumab binds with high affinity to the C5 complement protein. In clinical studies, the effect of Eculizumab on hemolysis was measured by a reduction in serum lactate dehydrogenase (LDH) levels and reduced blood cell transfusion needs. In a Phase III trial, treatment with Eculizumab decreased the mean ± S.D. serum LDH level from 2199.7 ± 157.7 units/L at baseline to 327.3 ± 67.6 units/L after 26 weeks. The effect on hemolysis was evident after 1 week of treatment and led to an increase in mean ± S.D. circulating PNH type III erythrocytes from 28.1% ± 2.0% at baseline to 56.9% ± 3.6% after 26 weeks [11].

FDA's approved labeling of Eculizumab was based on three clinical trials that demonstrated its efficacy and safety in patients with PNH [4].

Several studies evaluated long term effect up to 4 years follow-up of Eculizumab therapy and showed an improvement in survival, a persistent decrease in LDH levels and reduction in thrombotic events [12]. Moreover, a progressive improvement in renal function was observed [13].

Atypical hemolytic-uremic syndrome (aHUS)

hemolytic uremic syndrome (HUS) is a clinical trial of Coombs-negative microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure [14]. In children, HUS is most commonly triggered by Shiga-like toxin (Stx)-producing bacteria . Approximately 10% of HUS cases are Stx negative. These atypical forms (aHUS) are often recurrent, and generally have a poor outcome [15].

aHUS is a genetic, chronic, and progressive inflammatory disease that affects patients of all ages. This syndrome is caused by defects in regulation of the complement system. These defects are inherited, acquired, or both, and they result in chronic, uncontrolled activation of the complement system which leads to platelet, leukocyte, and endothelial-cell activation and systemic thrombotic microangiopathy. Affected patients have a lifelong risk of systemic clinical complications of thrombotic microangiopathy, including damage to multiple organ systems (e.g., the central nervous system, kidneys, heart, and gastrointestinal tract) [16].

Although plasma exchange or infusion has been used to manage atypical hemolytic-uremic syndrome and may transiently maintain a normal platelet count and lactate dehydrogenase level in some patients, the underlying complement dysregulation and thrombotic microangiopathic processes are likely to persist. Indeed, end-stage renal disease (ESRD) or death occurs in approximately 33 to 40% of patients during the first clinical manifestation of atypical hemolytic-uremic syndrome. Within 1 year after a diagnosis of this syndrome, up to 65% of patients treated with plasma exchange or infusion sustain permanent renal damage, have progression to ESRD, or die [17].

Among patients with atypical hemolytic-uremic syndrome who undergo kidney transplantation, graft failure is reported in 60 to 90% of patients within 1 year. Combined liver and kidney transplantation may normalize complement regulation in patients with certain genetic defects, but it is associated with substantial morbidity and mortality, including a mortality of 14% in the short term [17].

In 2009, two case reports were published showing for the first time in humans that serious aHUS can be effectively managed with Eculizumab [18,19]. The results of phase 2 clinical trials showed both in adults and in adolescents with aHUS a substantial increase in renal function and platelet count, a decrease in the frequency of thrombotic events and an improvement in quality of life [20]. In September 2011, Eculizumab received fast track approval for aHUS and in 2014 the approval was converted to regular on the basis of further clinical evidence of efficacy in this disease.

Side effects

Serious meningococcal infection

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early so we need to immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitoring patients for early signs of meningococcal infections and evaluation immediately if infection is suspected is mandatory.

Other infections

Eculizumab blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria. Children treated with Eculizumab may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib).

Eculizumab resistances

A significant variability in clinical responsiveness to Eculizumab has been observed in PNH [21]. This variability could in part be due to the binding of C3 to the surface of red blood cells in Eculizumab-resistant but not in Eculizumab-sensitive patients, which causes red blood cell lysis despite C5 blockade [22]. C5 gene polymorphism may explain part of Eculizumab-resistant cases. Specifically, C5 gene polymorphisms 2654G! A and 2653C! T have been associated to Eculizumab refractoriness in people from China and Japan [23]. Eculizumab responsiveness also correlates with polymorphisms of the complement receptor 1 gene. The resistance to Eculizumab may be

also due to persistent activation of early phases of complement cascade leading to C3 accumulation on the surface of erythrocytes and to extravascular hemolysis. Therefore, the use of C1 esterase inhibitors or of synthetic C3 inhibitors has been suggested as possible pharmacological strategies in Eculizumab-resistant patients [22].

Expensive

Eculizumab is very expensive with an individual cost per patient per year that, in 2008, was estimated at around £250,000. Initial pharmacoeconomic evaluations suggest that Eculizumab could be economically sound because of the prolonged life expectancy of those treated with this drug and because of the high costs of the conventional treatment of the complications of the disease, such as thromboembolism pensive.

Others

The most frequently reported adverse reactions in clinical trials included headache, nasopharyngitis, back pain, and nausea [6,11].

Conclusion

Eculizumab is one promising drug in treatment of many difficult diseases that their treatment depends mainly on supportive measures only and so it can provide revolutional step in the way, however one must consider the risk of serious infection and the financial issue especially in developing countries.

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