Eculizumab

Not to be confused with ocrelizumab.

Eculizumab (INN and USAN; trade name **Soliris**) is a humanized monoclonal antibody that is a terminal complement inhibitor.[1] In people with paroxysmal nocturnal hemoglobinuria (PNH) it improves quality of life but does not appear to affect the risk of death.[2] Its safety is unclear as of 2014.[2] It is the first approved therapy for paroxysmal nocturnal hemoglobinuria.[1][3] Eculizumab is also the first agent approved treatment of atypical hemolytic uremic syndrome (aHUS) with likely benefit based on two small trials.[4]

Eculizumab was developed and is manufactured and marketed by Connecticut-based Alexion Pharmaceuticals. It was approved by the United States Food and Drug Administration (FDA) on March 16, 2007 for the treatment of PNH,[3] and on September 23, 2011 for the treatment of aHUS.[5] It was approved by the European Medicines Agency for the treatment of PNH on June 20, 2007, and on November 24, 2011 for the treatment of aHUS. Eculizumab is currently being investigated as a potential treatment for other rare disorders. Eculizumab has exclusivity rights until 2017 which protects it from competition from biosimilar applications until 2017.[6]:6

In 2010 Soliris was the most expensive drug in the world.[7] It costs £340,200 (approximately €430,000) per year for ongoing treatment in the UK[8][9] and $500,000 a year in Canada.[8][9][10] and US$409,500 a year in the United States (2010).[7] In the case of the rarest diseases that afflict fewer than 10,000 people, biotech companies who own the only approved drugs to treat those diseases "can charge pretty much whatever they want." "Before testing Soliris for PNH, Alexion tested the drug for rheumatoid arthritis, which afflicts 1 million Americans. The trials failed. But if it had worked for arthritis, Alexion would likely have had to charge a much lower price for this use, as it would have to compete against drugs that cost a mere $20,000." Alexion started selling Soliris in 2008 making $295 million in 2007 with its stock price rising 130% in 2010.[10]

1 Medical uses

1.1 Paroxysmal nocturnal hemoglobinuria

In people with paroxysmal nocturnal hemoglobinuria (PNH) it improves quality of life and decreases the need for blood transfusions but does not appear to affect the risk of death.[2] It does not appear to change the risk of blood clots, myelodysplastic syndrome, acute myelogenous leukemia, or aplastic anemia.[2]

1.2 Atypical hemolytic uremic syndrome

Eculizumab appears to be useful for atypical hemolytic uremic syndrome (aHUS).[4] In September 2011 the U.S. Food and Drug Administration (FDA) approved Soliris as an orphan drug to treat patients with aHUS.[5] This approval was based on two small prospective trials of 17 people and 20 people.[4]

Thrombotic microangiopathy (TMA) related endpoints in these trials included the following:[11][12]

- platelet count change from baseline
- hematologic normalization (maintenance of normal platelet counts and lactate dehydrogenase [LDH] levels for at least four weeks)
- complete TMA response (hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of four weeks)
- TMA-event free status (absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, PE/PI, and new dialysis requirement)
- daily TMA intervention rate (defined as the number of PE/PI interventions and the number of new dialyses required per patient per day)
- time course of changes in renal function as measured by estimated Glomerular Filtration rate (eGFR)
- proportion of patients with improvement by ≥ 1 Chronic kidney disease (CKD) stage, eGFR increase by ≥ 15 mL/min/1.73m2 or serum creatinine decrease by ≥25%

In Study 1, eculizumab inhibited complement-mediated TMA activity in all 17 patients through 26 weeks. Efficacy findings included a significant and sustained increase in platelet count through Week 26. Thirteen patients (76%) achieved hematologic normalization, and 15 patients (88%) achieved TMA event-free status. Renal function, as measured by eGFR, improved in nine patients (53%); the median duration of eGFR improvement

was 251 days. Additionally, four of the five patients requiring dialysis at study entry were able to discontinue dialysis for the duration of eculizumab treatment. Quality of life (QoL) was significantly improved, with 80% of patients achieving a clinically meaningful change through Week 26; this increased to 87% through 1 year.[11][12]

Similar results were reported in Study 2, in which 16 patients (80%) achieved TMA event-free status and 18 (90%) achieved hematologic normalization. All patients discontinued PE/PI and no new dialysis was required. Eculizumab was associated with mean increases in platelet count and eGFR from baseline to 26 weeks. QoL was also improved, with 8 of 11 (73%) evaluable patients exceeding the clinically meaningful threshold through a median duration of 62 weeks.[11][13]

After completing the initial 26-week treatment period, most patients in each of the prospective studies continued to receive eculizumab by enrolling in an extension study. Two-year follow-up data from the extension studies suggest that eculizumab provides sustained inhibition of complement-mediated TMA and significant, continuous, time-dependent improvement in renal function. In the extension to Study 1, in which 13 patients were treated for a median duration of 100 weeks, chronic eculizumab treatment resulted in a continued increase in platelet counts and greater percentages of patients achieving key renal endpoints compared to those completing 26 weeks of therapy. Additionally, at a median duration of almost 2 years, all patients receiving chronic eculizumab therapy remain alive.[14] In the extension to Study 2, in which 20 patients were treated for a median duration of 114 weeks, 19 (95%) achieved TMA event-free status, and the percentages of patients reaching the key renal endpoints were also higher than at Week 26. No patient on chronic eculizumab therapy in the extension to Study 2 required PE/PI or progressed to ESRD or dialysis.[15]

Efficacy results from a single-arm retrospective study, in which 30 patients (including 19 pediatric patients aged 2 months to 17 years) were treated for a median of 16 weeks, were generally consistent with those from the two prospective studies. Among the pediatric patients, eculizumab reduced signs of TMA activity, as shown by an increase in mean platelet counts from baseline. Seventeen (89%) pediatric patients achieved platelet count normalization, 8 (42%) attained hematologic normalization, 8 (42%) had a complete TMA response, and 9 (47%) experienced improvement in eGFR from baseline. Four of 8 pediatric patients (50%) discontinued dialysis during the study period, and none required new dialysis while on eculizumab therapy.[11]

2 Adverse effects

In PNH clinical trials, the most frequently reported adverse events (AEs) were headache (44%), nasopharyngitis (23%), back pain (19%), nausea (16%), fatigue (12%), and cough (12%).[11] In two prospective clinical trials in aHUS, the most commonly reported AEs were hypertension (35%), upper respiratory infection (35%), diarrhea (32%), headache (30%), anemia (24%), vomiting (22%), and nausea (19%). Twenty of 37 patients (54%) in the aHUS trials experienced a serious adverse event (SAE); the most commonly reported SAEs were hypertension (16%) and infections (14%).[11]

Eculizumab inhibits terminal complement activation and therefore makes patients vulnerable to infection with encapsulated organisms. Life-threatening and fatal meningococcal infections have occurred in patients who received eculizumab.[11] Due to the increased risk of meningococcal infections, meningococcal vaccination is recommended at least 2 weeks prior to receiving eculizumab, unless the risks of delaying eculizumab therapy outweigh the risk of developing a meningococcal infection, in which case the meningococcal vaccine should be administered as soon as possible.[11] Both a serogroup A, C, W, Y conjugate meningococcal vaccine and a serogroup B meningococcal vaccine are recommended for people receiving eculizumab.[16]

Eculizumab treatment is recommended to continue for the patient's lifetime, unless discontinuation of therapy is clinically indicated.[17] In aHUS clinical studies, 18 patients (five in the prospective studies) discontinued eculizumab treatment; TMA complications occurred following a missed dose in five patients, and eculizumab was reinstated in four of these five patients.

3 Mechanism of action

Eculizumab is a recombinant humanized monoclonal IgG2/4 antibody[1] that selectively targets and inhibits the terminal portion of the complement cascade. The complement system is a branch of the body's immune system that destroys and removes foreign particles. When complement proteins are activated and bind to the surfaces of foreign particles, it triggers a cascade by which one complement protein induces the activation of the next protein in the sequence. The complement proteins then create holes or pores in the invading organisms, leading to their destruction. While complement plays an important role in protecting the body from foreign organisms, it can also destroy healthy cells and tissue.

Eculizumab specifically binds to the terminal Complement component 5, or C5, which acts at a late stage in the complement cascade. When activated, C5 is involved in activating host cells, thereby attracting pro-inflammatory immune cells, while also destroying cells by triggering pore formation. By inhibiting the complement cascade at this point, the normal, disease-preventing functions of proximal complement system are largely preserved, while the properties of

C5 that promote inflammation and cell destruction are impeded.[18]

Eculizumab inhibits the cleavage of C5 to C5a (a potent anaphylatoxin with prothrombotic and proinflammatory properties) and C5b by the C5 convertase, which prevents the generation of the terminal complement complex C5b-9 (which also has prothrombotic and proinflammatory effects). Both C5a and C5b-9 cause the terminal complement-mediated events that are characteristic of PNH and aHUS.[18]

4 Biochemistry

Eculizumab is a humanized monoclonal antibody against the complement protein C5. It is an immunoglobulin G-kappa (IgGκ) consisting of human constant regions and murine complementarity-determining regions grafted onto human framework light and heavy chain variable regions. The compound contains two 448-amino acid heavy chains and two 214-amino acid light chains, and has a molecular weight of approximately 148 kilodaltons (kDa).[3]

The metabolism of eculizumab is thought to occur via lysosomal enzymes that cleave the antibody to generate small peptides and amino acids. The volume of distribution of eculizumab in humans approximates that of plasma.[3]

5 Society and culture

5.1 Orphan drug

Main article: Orphan drug

Eculizumab was given the designation of orphan drug in 2011 when the FDA approved Soloris for treatment of aHUS.[5]

According to a 2014 report, the orphan drug market has become increasingly lucrative over recent years for a number of reasons. The cost of clinical trials for orphan drugs is substantially lower than for other diseases—trial sizes are naturally much smaller than for more common diseases with larger numbers of patients. Small clinical trials and little competition place these "orphan agents" at an advantage when they come up for regulatory review.[19] This approval was based on two small prospective trials of 17 people and 20 people.[4][11][12][20][21] and may get clinical trial tax incentives.[21]

There is a further reduction to the cost of development because of the tax incentives in the Orphan Drug Act 1983. On average the cost per patient for orphan drugs is "six times that of non-orphan drugs, a clear indication of their pricing power."[19] Although there are much smaller orphan disease populations are the smallest, the cost of per-patient outlays are the largest and are expected to increase with wider use of public subsidies.[19]

By 2015 industry analysts and academic researchers agree that the sky-high price of so-called orphan drugs, that treat these ultra-rare diseases, is no longer related to research, development and manufacturing costs.[20] The price is arbitrary and has become more profitable than traditional medicines.[20]

According to Sachdev Sidhu, a University of Toronto scientist who spent years researching monoclonal antibodies, "the underlying elements in Soliris, for a U.S. biotech company,"[20] claimed that 80 or 90 per cent of Soliris research and development was done by publicly funded university researchers working in academic laboratories.[20]

> "Public resources went into understanding the molecular basis of the disease, public resources went into the technology to make antibodies and finally, Alexion, to their credit, kind of picked up the pieces."
> — Sachdev Sidhu 2015

While Eculizumab is associated with greater life years (1.13) and it does provide benefits to PNH in terms of quality of life QALYs (2.45), there is a high incremental cost (CAN$5.24 million) and a substantial opportunity cost." "The incremental cost per life year and per QALY gained is CAN$4.62 million and CAN$2.13 million, respectively. Based on established thresholds, the opportunity cost of funding eculizumab is 102.3 discounted QALYs per patient funded."[22]

5.2 Price

Alexion prices Soliris, described by Forbes as the most expensive drug in the world,[7] at approximately US$409,500 a year in the United States (2010),[7] €430,000 per year for ongoing treatment in the UK[8][9] and $500,000 a year in Canada (2014) and.[10] The actual cost of manufacturing Soliris' monoclonal antibodies is less than "1 percent of the price of the drug."[20]

In the case of the rarest diseases that afflict fewer than 10,000 people, biotech companies who own the only approved drugs to treat those diseases "can charge pretty much whatever they want."[10] "Before testing Soliris for PNH, Alexion tested the drug for rheumatoid arthritis, which afflicts 1 million Americans. The trials failed. But if it had worked for arthritis, Alexion would likely have had to charge a much a lower price for this use, as would have to compete against drugs that cost a mere $20,000." Alexion started selling Soliris in 2008 making $295 million in 2007 with its stock price rising to 130% in 2010.[10]

In December 2014 the provincial government of Ontario, Canada was in ongoing price negotiations with the Soliris manufacturer, the only drug approved by Health Canada to treat aHUS. Patients who require the apply for it on "compassionate grounds" "on a case-by-case basis for individuals who have been urgently hospitalized due to an immediate life-, limb-, or organ-threatening complication." Soliris is already "funded by the Ontario government for the treatment of another rare illness, paroxysmal nocturnal hemoglobinuria (PNH), through a bulk-buy deal reached by the provincial premiers in 2011."[10]

In February 2015, Canada's drug-price regulator took the rare step of calling a hearing into Soliris, accusing Alexion of exceeding the permissible price cap under the Highest International Price Comparison (HIPC).[23] In June 2015, the Patented Medicine Prices Review Board (PMPRB) under the Canadian Patent Act, held a preliminary hearing in Ottawa, Ontario to examine allegations. John Haslam, President and General Manager of Vaughan, Ontario-based Alexion Canada, was named as one of the respondents.[24] Alexion charges Canada $700,000 per patient per year—more than anywhere else in the world.[20] Alexion denies the claim. In Canada "provincial drug plans have already negotiated secret discounts on Soliris for many of the patients they cover."[23]

> "This drug is forcing us to have to rethink how we say yes and how we say no when it comes to prescription drugs."
> — Michael Law, University of British Columbia

Because there is insufficient evidence to show that eculizumab therapy results improvement in life expectancy, statistical calculations have shown poor cost-effectiveness. For example, a 2014 Canadian study calculated the cost per life-year-gained with treatment as CAD$4,618,561 (US $4571564) and cost per quality-adjusted-life-year as $2,134,156 (US $2,112,398).[25] New Zealand's government pharmaceutical buyer Pharmac declined a proposal to subsidize the drug in December 2013, after Alexion refused to budge on a NZ$670,000 (US$590,000) per patient per year price and Pharmac's economic analysis determined the price would need to be halved before the drug was cost-effective enough to subsidize.[26] Pharmac's decision upset many New Zealand PNH patients,[27] although Pharmac has not ruled out reviewing the decision at a later date, should the drug be made available at a lower price.[26]

5.3 Biosimilar competition

Main article: Biosimilar

While The FDA will not approve biosimilar applications for Eculizumab before 16 March 2019,[6]:6 there is an ongoing debate over the length of exclusivity periods. While national regulators protect orphan drug producers from competition with biosimilar products, through a multi-year exclusivity period, as markets open and new international trade deals are negotiated—such as the Trans-Pacific Partnership (TPP), a free trade agreement between the US, Australia, Chile, and Singapore and a number of other nations—the exclusivity is being challenged.[6]

6 Research

6.1 STEC-HUS

There are case reports of eculizumab being used to treat Shiga-toxin-producing Escherichia coli hemolytic-uremic syndrome (STEC-HUS),[28] such as occurred during the May 2011 outbreak of enteroaggretative E. coli infections in Germany (the STEC-HUS commonly seen in North America is of the enterohemorrhagic type). Eculizumab was given to block complement activation, which plays a role in the pathogenesis of both STEC-HUS and aHUS. Specifically, Shiga-toxin has been shown to trigger uncontrolled complement activity through direct activation of the alternative complement pathway[29][30] as well as by binding to and inactivating the regulatory protein complement factor H.[31]

6.2 Acute humoral rejection (AHR)/ antibody-mediated rejection (AMR)

Preliminary results from a Mayo Clinic research study show that eculizumab prevents acute humoral rejection (AHR, also known as antibody-mediated rejection (AMR)) of kidney allografts by inhibiting activation of the complement system by antigen-antibody complexes.[32] Specifically, eculizumab treatment led to a significant decrease in the incidence of early AHR, compared to a historical control group that received no eculizumab. Eculizumab also reportedly maintained stable allograft function and simplified the management of kidney transplant patients by decreasing the need for post-transplant plasma exchange and splenectomy.[33] Researchers at Johns Hopkins University have also reported a case in which eculizumab was combined with plasmapheresis and intravenous immunoglobulin to salvage a kidney undergoing severe AMR. In this case, eculizumab, by inhibiting the cleavage of complement protein C5 to the C5a and C5b receptors, was associated with a marked decrease in membrane attack complex (C5b-9) deposition in the kidney.[34]

6.3 Myasthenia gravis

Main article: myasthenia gravis

Eculizumab has been shown to produce a clinically meaningful benefit in patients with severe and refractory generalized myasthenia gravis, a rare neurological disorder caused by uncontrolled complement activation resulting from auto-antibodies that recognize a specific target in the nerve-muscle junction.[35] In a Phase II study involving 14 patients, eculizumab was superior to placebo in improving disease severity scores, and the improvement was achieved more rapidly with eculizumab than with placebo.[36]

6.4 Neuromyelitis optica

Main article: neuromyelitis optica

An open-label study is investigating the effects of eculizumab in patients with neuromyelitis optica, a complement-mediated inflammatory disease of the brain tissues that can potentiate immune attack on the brain, optic nerves (leading to Optic neuritis), spinal cord (causing Transverse myelitis).[37]

6.5 Membranoproliferative glomerulonephritis (MPGN)

Main article: Membranoproliferative glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN, previously known as mesangiocapillary glomerulonephritis) is an uncommon cause of chronic nephritis that primarily affects children but can occur at any age. Its clinical presentation and course can range from benign and slowly progressive to rapidly progressive. Patients may thus present with hematuria (blood in the urine), proteinuria (excess protein in the urine), renal impairment, and hypertension. MPGN frequently progresses to end-stage renal disease (ESRD) and disease recurrence following kidney transplantation.[38] Some cases of the disease are thought to result from complement dysregulation.[38][39][40][41] Canadian researchers have reported a case in which eculizumab produced "a dramatic response" in a 16-year-old girl with MPGN, as evidenced by amelioration of neurologic complications, normalization of kidney function, and improvements in thrombocytopenia, anemia, proteinuria, and hypoalbuminemia.[40][41]

6.6 Dense-deposit disease (DDD)

Main article: Dense deposit disease

Dense-deposit disease (DDD), previously considered a subtype of MPGN (sometimes known as MPGN II), is characterized by dense deposits of immunoglobulins, complement factors, or both in the basement membrane of the glomerulus.[38] DDD frequently progresses to ESRD and disease recurrence after kidney transplantation.[42] In a March 22, 2012 letter to the New England Journal of Medicine, a group of Italian researchers reported a case involving an 11-year-old girl with DDD who was treated with eculizumab, which led to normalization of serum total protein and albumin, decreased creatinine, and decline of proteinuria to below the nephrotic range.[43] The same issue of the New England Journal of Medicine also featured a letter from another group of Italian researchers, who reported a case in which a 17-year-old patient with DDD experienced improvements in proteinuria, plasma protein levels, and renal function, along with reductions in the size of dense deposits, after treatment with eculizumab. After treatment was interrupted after 18 months, proteinuria rapidly increased; eculizumab therapy was resumed 6 months later, and was associated with a reduction in proteinuria.[42] In a Phase I trial involving three patients with DDD and three with C3 glomerulonephritis who were treated with eculizumab every other week for 1 year, two patients showed significantly reduced serum creatinine, one achieved a marked reduction in proteinuria, and one had stable laboratory parameters but histopathologic improvements. The investigators surmised that pre-treatment elevation of serum membrane attack complex may predict response to eculizumab in DDD and C3 glomerulonephritis, both of which comprise C3 glomerulopathy.[44]

6.7 Cold agglutinin disease

Main article: cold agglutinin disease

There are also reports of eculizumab being used to treat cold agglutinin disease. In one patient case report, eculizumab led to a sustained reduction of hemolysis, disappearance of further exacerbations, complete elimination of transfusion requirements, and improvement of symptoms and quality of life.[45]

6.8 Catastrophic antiphospholipid syndrome (CAPS)

Main article: Catastrophic antiphospholipid syndrome

Catastrophic antiphospholipid syndrome (CAPS) is a rare condition in which blood clots form in multiple organs simultaneously, possibly leading to multi-organ system failure and death. The kidneys are the most frequently affected organ system in CAPS, and patients who survive a CAPS episode commonly experience permanent

kidney failure.[46] There are reports in the literature suggesting that eculizumab therapy may be useful in CAPS by virtue of its blockade of complement activity, prevention of acute progressive thrombotic events, reversal of thrombocytopenia, and control of serum antiphospholipid antibody levels.[47][48]

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8 External links

- Flash animation of eculizumab mechanism of action
- US homepage

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9.1 Text

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