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Eculizumab

Humanized Anti-C5 Monoclonal Antibody

Prop Inn; USAN

h5G1.1
5G1.1

Immunoglobulin, anti-(human complement C5 α-chain) (human-mouse monoclonal 5G1.1 heavy chain), disulfide with human-mouse monoclonal 5G1.1 light chain, dimer

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Abstract

Eculizumab (5G1.1) is a recombinant, fully humanized monoclonal antibody that inhibits the activation of terminal complement components. Eculizumab binds specifically to the terminal human complement protein C5, preventing the release of the inflammatory mediator C5a and the formation of C5b-9 by inhibiting the cleavage of human complement C5 to C5a and C5b. Preclinical studies have demonstrated that the antibody has high binding affinity for C5, blocks the formation of C5a and C5b-9, and protects mammalian cells from C5b-9-mediated damage. Favorable clinical results have been reported in patients with membranous nephritis, rheumatoid arthritis and paroxysmal nocturnal hemoglobinuria (PNH) and the antibody is in phase II clinical development for these disorders; phase I trials have also been conducted in dermatomyositis.

Introduction

There is increasing evidence that activated components of the complement system contribute significantly to the pathogenesis of a large number of acute and chronic inflammatory diseases including rheumatoid arthritis, atherosclerosis, acute myocardial infarction and vascular injury after cardiopulmonary bypass (1-5). Furthermore, complement plays a significant role in the pathogenesis of paroxysmal nocturnal hemoglobinuria (PNH), characterized by intravascular hemolysis and venous thrombosis, and associated with aplastic anemia. Patients with PNH have a deficiency in CD59 and CD55 proteins on the surface of erythrocytes, platelets and other blood cells, which normally protect cells from complement-mediated injury (6-8). Patients with PNH experience fatigue, dysphagia, pain and hemoglobinuria, and the disease is associated with about 50% mortality (9).

Strategies that inhibit the damaging effects of complement on disease pathogenesis have therefore become a major focus in pharmacological research. In particular, inhibition of the complement cascade at C5, the cleavage of which results in the generation of the potent inflammatory mediators C5a and C5b-9 (10), while allowing the upstream generation of C3b, essential for combatting infections and preventing the development of autoimmune diseases (11), would appear to represent a promising approach.

Eculizumab is a recombinant, fully humanized monoclonal antibody that inhibits the activation of terminal complement components. Eculizumab binds specifically to the terminal complement protein C5 and prevents the release of the inflammatory mediator C5a and the formation of C5b-9 by inhibiting the cleavage of human complement C5 to C5a and C5b (12). The antibody is being developed for chronic indications including rheumatoid arthritis, membranous nephritis, dermatomyositis, lupus nephritis and paroxysmal nocturnal hemoglobinuria (13).

Pharmacological Actions

Eculizumab, as well as Fab and scFv fragments thereof, was evaluated for binding to complement and inhibition of complement activation *in vitro*. Eculizumab had similar binding affinity for human C5 compared to the murine antibody (IC_{50} ~ 2 nM), as determined in an ELISA, and it inhibited human serum complement-induced lysis of porcine aortic endothelial cells (PAEC) at the same concentration as the murine antibody (12).

Pharmacokinetics

A double-blind, randomized, placebo-controlled study was conducted with eculizumab (8 mg/kg i.v. once or

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twice monthly) to evaluate the pharmacokinetics/pharmacodynamics in 117 patients with idiopathic membranous nephropathy (mean creatinine clearance = 111 ml/min; 24-h proteinuria = 9 g; protein/creatinine ratio = 5; serum cholesterol = 270 mg/dl; hemoglobin = 12.0 g/dl; serum albumin = 2.8 g/dl). Preliminary results were reported for 11 patients. Mean steady-state trough serum eculizumab levels were 18 μg/ml in the twice-monthly treatment group and 8 μg/ml in the monthly treatment group. Mean steady-state mid-dose interval levels (1 week postdose on day 119 of the study) were 47 μg/ml for patients treated twice monthly and 35 μg/ml for those treated once monthly. Urine levels of eculizumab at midtrial and at the end of the trial were below the level of quantification in 8 patients, and 3 patients excreted 65-400 μg/24 h of eculizumab. All eculizumab-treated patients demonstrated < 10% of the hemolytic activity of placebo-treated patients at 1 h postinfusion. Serum eculizumab levels > 38 μg/ml inhibited hemolysis in all patients. Treatment with eculizumab was found to be safe and well tolerated, with no hypersensitivity reactions noted (14).

Pharmacokinetics and pharmacodynamics were also examined in an open-label pilot study in 11 transfusion-dependent patients with PNH who received treatment with eculizumab (600 mg weekly for 4 weeks, then 900 mg every 2 weeks for 2 months). Peak and trough serum levels of eculizumab were measured 1 h after the initial dose and then at weeks 3, 4, 6, 10 and 12, and in 10 patients eculizumab levels were > 35 μg/ml from 1 h after the first dose to the end of the study period. In 1 patient, eculizumab levels were > 35 μg/ml for the initial 10 weeks but < 35 μg/ml at week 12. In 10 patients, serum hemolytic activity was 20% or less for the entire treatment period, representing complete blockade, with only 1 patient showing increased hemolytic activity at week 12, which corresponded with a decline in eculizumab levels to < 35 μg/ml (15).

Clinical Studies

The safety and biological activity of a single i.v. dose of eculizumab (0.1-8 mg/kg) were investigated in 40 patients with mild to moderate rheumatoid arthritis. Mean C-reactive protein (CRP) levels were significantly reduced at day 7 compared to baseline after the highest dose and returned to baseline by day 14. Patients treated at this dose showed a trend for reductions in the signs and symptoms of rheumatoid arthritis. Doses of 2 mg/kg and above resulted in > 80% inhibition of human complement C5 for at least 10 h, and a single dose of 8 mg/kg provided > 80% inhibition for 10 days, with a return to baseline levels after 17 days. Eculizumab was safe and well tolerated across patient groups (16).

Another study examined the safety, efficacy and pharmacokinetics of eculizumab following multiple doses in 209 patients with rheumatoid arthritis. Patients were randomized to receive placebo, eculizumab 8 mg/kg every 2 weeks, eculizumab 8 mg/kg every week x 5 weeks, then every 2 weeks, or eculizumab 8 mg/kg every week x 5 weeks, then monthly, and evaluated both after 3 months of treatment and 3 months after terminating treatment. After 3 months of treatment, the induction/monthly group met the primary endpoint of improvement in ACR20 score (44% *vs.* 18% on placebo), and both induction groups met the secondary endpoint of decrease in CRP. Baseline C5b-9 levels were correlated with increased CRP levels and therefore systemic inflammation. Baseline C5b-9 levels > 200 mg/ml were associated with clinical response to eculizumab. In cases of elevated C5b-9, an ACR20 response was obtained in 9% of patients in the placebo group, 33% of patients in the twice-monthly eculizumab treatment group, 57% of patients in the induction/monthly treatment group and 50% of patients in the induction/twice-monthly treatment group. The induction regimens completely suppressed complement-mediated serum hemolytic activity up to week 4. The half-life of eculizumab was 10-14 days (17-20).

A randomized, double-blind, placebo-controlled phase IIb clinical trial evaluated the efficacy and safety of eculizumab in 368 adult patients with mild to moderate active rheumatoid arthritis undergoing treatment with methotrexate and/or leflunomide. The patients were enrolled at 69 sites in the U.S. and Canada and were randomized to receive placebo, twice-monthly eculizumab (600 mg i.v. weekly for 5 weeks, then 600 mg once every 2 weeks) or monthly eculizumab (600 mg i.v. weekly for 5 weeks, then 600 mg monthly). The primary endpoint was improvement in ACR20 score after 6 months of treatment. Monthly administration of eculizumab following an induction period was associated with a statistically significant, moderate improvement in the ACR20 score compared to placebo at 6 months. The percentage of patients who achieved an ACR20 response was 34%, 24% and 22%, respectively, on monthly eculizumab, twice-monthly eculizumab and placebo. Monthly therapy was also associated with evidence of a long-term antiinflammatory effect, with a significant reduction in erythrocyte sedimentation rate at 6 months. The incidence of adverse events was slightly higher among patients given eculizumab every 2 weeks, although the incidence of injection-site reactions remained low (21).

A double-blind, placebo-controlled phase I pilot study was performed to determine the safety and tolerability of eculizumab (8 mg/kg weekly for 5 weeks, then once every 2 weeks) in 10 patients with dermatomyositis compared with placebo (n=3). After 2 months of treatment, results showed moderate improvements in skin score, physician global score and manual muscle test in the eculizumab group compared with controls. The placebo group showed deterioration of physician global score, but improvements in skin score and manual muscle test compared to baseline. Disease intensity measured by magnetic resonance imaging (MRI) and various parameters on skin biopsy were also improved in the treatment group compared with placebo. Eculizumab was safe and well

tolerated, with no significant differences in adverse events between treatment groups (22).

Alexion has sponsored phase II trials in patients with membranous nephritis, with results showing good tolerance. One trial did not reach the primary clinical efficacy endpoint of reduction in proteinuria after 4 months, while in the other trial an increase in remission rate and significant improvements in proteinuria, hyperlipidemia, hypertriglyceridemia and hypoalbuminemia were obtained after 12 months. The company also began a phase II study in lupus nephritis several years ago following the observation of positive effects on proteinuria in a study in patients with systemic lupus erythematosus (13, 23).

Further results regarding efficacy and safety were reported from the open-label pilot study in 11 transfusion-dependent patients with PNH treated with eculizumab (600 mg weekly for 4 weeks, then 900 mg every 2 weeks for 2 months). After 3 months of initial treatment, all patients were enrolled into an open-label extension study and went on to receive eculizumab 900 mg every 2 weeks for over a year. In the 12 months prior to entrance into the study, patients had received over 4 red blood cell transfusions, had detectable glycosylphosphatidylinositol (GPI)-deficient hematopoietic clone, and had a negative throat culture for *Neisseria meningitidis* and *Neisseria gonorrhoeae*. After the first 3 months of treatment, serum hemolytic activity was completely inhibited in the 10 patients who showed serum trough levels of eculizumab above 35 μg/ml; quality-of-life markers were also significantly improved, transfusion rates decreased and serum levels of lactate dehydrogenase (LDH), an indicator of hemolysis, were significantly reduced. Increased levels of PNH type III erythrocytes were thought to be due to prolongation of PNH red cell survival and confirmed that treatment with eculizumab inhibits complement-mediated hemolysis. The proportion of PNH neutrophils, monocytes and platelets did not change. The reduction in transfusions was greatest for patients (n=7) without thrombocytopenia. Biochemical markers of hemolysis showed dramatic improvement 1 week after beginning treatment with eculizumab. The most common adverse events were headache and upper respiratory tract infections, followed by influenza-like symptoms, rigors, dizziness, nausea, nasal congestion and joint aches. No episodes of thrombosis were reported. No adverse events were considered to be drug-related and although 2 patients had serious adverse events, all patients completed the 12-week study (15, 24-26).

Reports of the cumulative results after 6 and 12 months of eculizumab treatment showed that patients with purely hemolytic disease (macroscopic hemoglobinuria with a normal platelet count; n=6) had the best response to treatment, with type III erythrocytes increased from 39% to 67%, median transfusions reduced from 2.0 units/patient/month to 0 units/patient/month, and suppression of hemolysis. Four patients who did not become transfusion-independent were treated with additional subcutaneous erythropoietin with some improvement. Two patients reported breakthroughs in complement activity, demonstrated by increased lactate dehydrogenase levels, hemoglobinuria and symptoms. These symptoms resolved immediately after the next dose of eculizumab and patients were managed by reducing the dosing interval. The most commonly reported adverse events after 12 months of eculizumab treatment were flu-like symptoms, sore throat, headache and upper respiratory infection. Four serious adverse events were reported, but there were no study discontinuations as a result of adverse events and all patients elected to continue eculizumab treatment. It was concluded that eculizumab was well tolerated, decreased hemolysis and transfusion requirements, and improved symptoms of PNH for over 12 months (27, 28).

Conclusions

Eculizumab is a promising new monoclonal antibody that binds to human complement C5 and inhibits its cleavage by C5 convertase. Eculizumab has been granted orphan drug status for the treatment of PNH in both the U.S. and Europe. A pilot program has been completed in patients with PNH and plans are being finalized with the FDA for the next stage of development. Pilot programs have also been completed in patients with dermatomyositis and eculizumab is in phase II trials for rheumatoid arthritis and membranous nephritis.

Source

Alexion Pharmaceuticals, Inc. (US).

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