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Pexelizumab

Prop INN; USAN

Complement Inhibitor
Cardioprotectant

5G1.1-SC
h5G1.1-scFv

Immunoglobulin, anti-(human complement C5 α-chain) (human-mouse monoclonal 5G1.1-SC single chain)

CAS: 219685-93-5
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Abstract

Complement activation is greatly enhanced by several stimuli that take place during myocardial infarction and cardiopulmonary bypass surgery (CPB). Once activated, complement components initiate inflammatory responses that can lead to tissue destruction. Two activation pathways are involved in the complement system: the classical pathway involving binding of an antibody to its antigen and the alternative pathway involving activation by a variety of antigens and pathogens. Both pathways have a similar terminal sequence which creates the membrane attack complex (MAC), an enzyme complex that causes the lysis of the target cell. The cleavage of complement C5 protein into C5a and C5b is the key step in the formation of MAC, which ultimately leads to promotion of host immunity via induction of an inflammatory response. Because of the generally beneficial effects of complement components prior to C5 and the greater inflammatory disease-promoting effects of the cleavage products of C5, this protein has been identified as a potentially effective antiinflammatory drug target. Pexelizumab, a humanized single-chain monoclonal antibody, is a specific blocker of C5 cleavage that represents a promising therapy for reduction of cardiac damage, mortality reduction and other related sequelae associated with CPB and myocardial infarction.

Introduction

Activation of the complement system is greatly enhanced by several stimuli that take place during cardiopulmonary bypass surgery (CPB) such as contact of blood with artificial surfaces, ischemia and postoperative reperfusion. Once activated, complement components can initiate inflammatory responses associated with blood cell activation, changes in blood pressure, fluid leakage and changes in platelet activity. All these responses can lead to tissue destruction and excessive blood loss. Consequently, a significant proportion of patients undergoing CPB suffer serious morbidities to multiple organ systems, including the lung, kidney, gastrointestinal tract, heart and brain. Because of the important role of complement activation in myocardial infarction and CPB, a number of anticomplement therapeutic strategies are currently in clinical trials (1-4).

The complement system consists of several plasma proteins, the majority of which are inactive until cleaved by a protease which, in turn, converts them into a protease. Thus, when a complement protein is cleaved, two fragments are formed, generally referred to as “a” and “b” (*e.g.*, C5a and C5b in Fig. 1A), that can activate subsequent complement components (5). This pattern of sequential activation produces an expanding cascade of activity, analogous to some extent to that of blood coagulation. The complement system has 2 distinct activation pathways: the classical pathway involving binding of an antibody to its antigen and the alternative pathway which relies on a variety of antigens such as bacterial lipopolysaccharide and components of viruses and other pathogens for activation to occur. While the stimulating factors for each pathway are distinct, each one has a similar terminal sequence which creates the membrane attack complex (MAC), an enzyme complex which creates a transmembrane pore leading to the lysis of the target cell. Cleavage of C5 protein into C5a and C5b is the key step in the formation of MAC (Fig. 1A).

Cell lysis is not the only function of the complement system. Many of the enzymatic split products of both complement pathways promote host immunity via their induction of inflammatory responses. Thus, the split products C3a, C4a and C5a, low-molecular-weight peptides and anaphylatoxins, have the ability to bind to mast cells and basophils causing release of peptides such as histamine, a mediator of acute inflammation which can cause vascular dilatation and increased vascular

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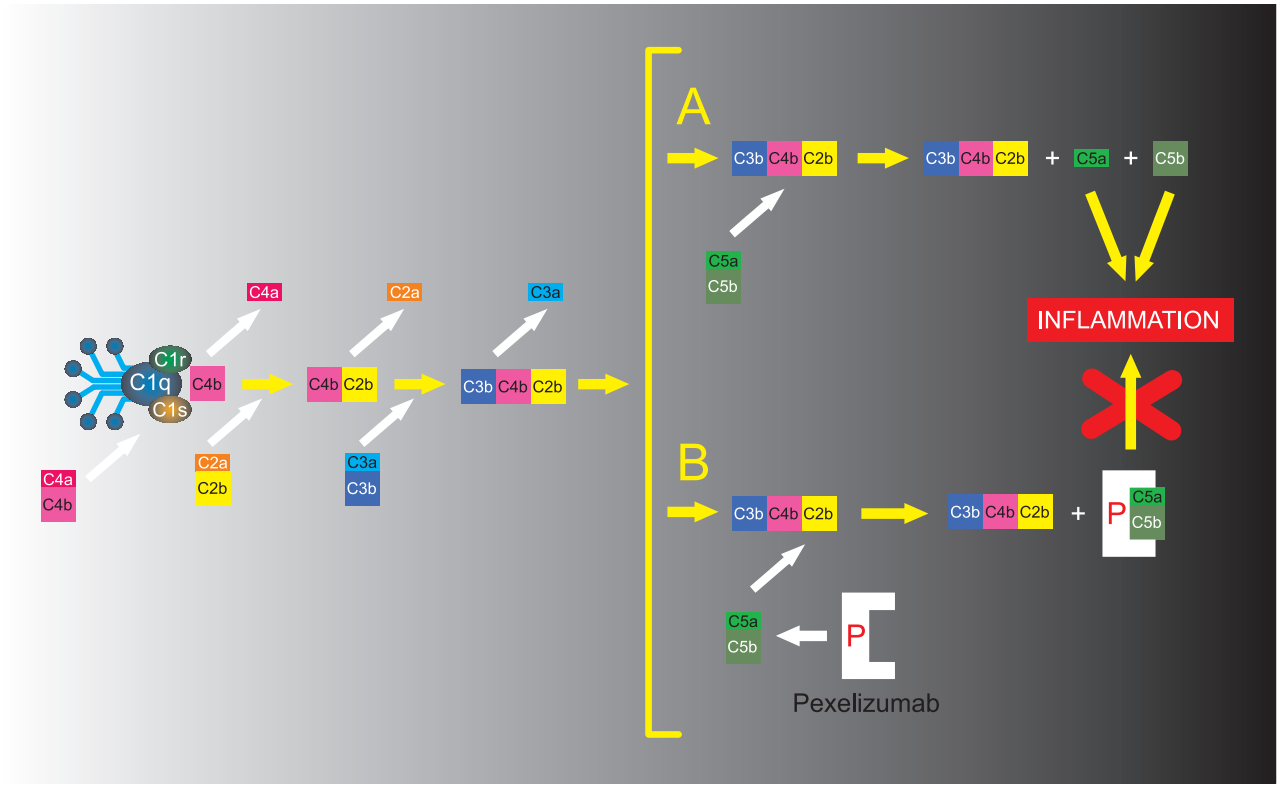

Fig. 1. (A) Depiction of the classical complement activation pathway up to generation of C5a and C5b. Most proteins are inactive until they are cleaved by a protease and in turn converted into proteases. (B) Pexelizumab binds to the protein C5 preventing cleavage to C5a and C5b and subsequent generation of MAC and inflammation-promoting proteins. An animated version of this figure can be seen in Prous Science Drug R&D Backgrounders: *Dermatomyositis (online publication)* Updated April 22, 2003.

permeability (6). In addition, these low-molecular-weight peptides increase the permeability of the vascular walls, allowing neutrophils to migrate into the area. Neutrophils are further encouraged to migrate to the site of complement activation due to the potent chemotactic effect of C5a. The neutrophils phagocytose invading pathogens and also release mediators which attract macrophages to the site of infection. These cells also have the ability to phagocytose invading cells and further promote the inflammatory response (7).

Certain complement components such as C4b and C5b act as opsonins (8). Many phagocytic cells have receptors for these complement split products. Antigens coated with either of these molecules are said to be opsonized, meaning that they are more likely to be ingested by phagocytes. Early complement components are also important for solubilizing antigen-antibody complexes, assisting in their catabolism and elimination from the body. Failure of this function can lead to immune complex disorders.

Because of the generally beneficial effects of the components of the complement cascade upstream of C5 and the greater inflammatory disease-promoting effects of the cleavage products of C5, this protein has been identified as a potentially effective antiinflammatory drug target. Selective suppression of this immune response could provide a significant therapeutic advantage relative to existing therapies. Pexelizumab (5G1.1-SC, h5G1-1scFv) is a humanized single-chain monoclonal antibody that selectively and tightly binds to the complement protein C5, preventing its cleavage to C5a and C5b and the subsequent generation of inflammatory proteins (Fig. 1B) (5). Pexelizumab is currently under development to reduce cardiac damage and other related sequelae associated with CPB procedures and to reduce mortality in myocardial infarct patients receiving reperfusion therapy (PTCA or thrombolytic).

Pharmacological Actions

The pharmacodynamics of pexelizumab were investigated *in vitro* and *in vivo*. Pexelizumab was shown to concentration-dependently block C5b-9-mediated lysis of chicken erythrocytes *in vitro*, with complete inhibition observed at a concentration of 25 µg/ml in 20% rat serum. In addition, pexelizumab concentration-dependently inhibited zymosan-activated serum (a source of rat C5a/C5a des Arg)-induced rat polymorphonuclear leukocyte (PMN) chemotaxis. Results indicate that the

monoclonal antibody (MAb) binds to rat C5, resulting in inhibition of both C5a and C5b-9 (9).

The duration of pexelizumab-induced complement inhibition was determined from hemolytic assays using serum from rats treated with a single dose (20 mg/kg i.v.) of the agent. Treatment with pexelizumab significantly blocked complement activation by more than 80% for more than 4 h postdosing. Significant complement inhibition (> 70%) was also seen at 8 h postdosing, with levels of serum complement hemolytic activity returning to normal by 12 h after dosing (9).

The inhibitory effects of pexelizumab on terminal C5 complement components were further examined *in vivo* in a rat model of myocardial ischemia/reperfusion injury. Treatment with pexelizumab (20 mg/kg i.v.) 60 min before myocardial ischemia (30 min) and reperfusion (4 h) resulted in significant 91% reductions in left ventricular free wall PMN infiltration as compared to control rats and rats treated with a nonblocking MAb. When animals were administered the MAb 60 min before ischemia or 5 min before reperfusion, infarct size was significantly reduced. Moreover, significant 42% reductions in infarct size were observed when animals were treated after 30 min of ischemia and 7 days of reperfusion. The cardioprotective effects of pexelizumab were concluded not to be due to effects on myocardial oxygen since administration of a single dose to rats had no significant effects on the double product. However, analysis of DNA ladders and DNA labeling in a TUNEL assay revealed that ischemia/reperfusion-induced apoptosis was markedly decreased in pexelizumab-treated animals as compared to animals treated with a nonblocking MAb. It was concluded that treatment with pexelizumab inhibited terminal complement components C5a and C5b-9, resulting in marked reductions in ischemia/reperfusion-induced cell apoptosis, necrosis and PMN infiltration (9).

Pharmacokinetics

The pharrmacokinetics of single-dose pexelizumab (0.2, 0.5, 1 and 2 mg/kg i.v.) were examined in 2 phase I trials: a single-blind, placebo-controlled, ascending-dose trial in healthy male volunteers and an open-label, single-blind, placebo-controlled, ascending-dose study in primary coronary artery bypass grafting (CABG) patients. The serum $t_{1/2}$ of pexelizumab was greater than 10 h and dose-dependent systemic inhibition of the complement cascade was observed. The highest dose completely inhibited complement-dependent hemolytic activity for 4 h and significant inhibition was sustained for more than 12 h. The pharmacokinetic parameters obtained in patients suggested that the duration of complement inhibition correlates with the duration of cardiopulmonary bypass. Pexelizumab was safe and well tolerated, with no significant adverse events or immune responses reported. From these results, it was speculated that treatment with pexelizumab could markedly reduce complement-mediated injuries during CPB (10). The results of this study and some that follow are summarized in Table I.

Clinical Studies

The safety, tolerability and efficacy of pexelizumab (0.2, 0.5, 1 or 2 mg/kg i.v. over 10 min followed by CPB) were demonstrated in a prospective, open-label, randomized, placebo-controlled, dose-escalation study involving 35 patients undergoing primary, nonemergent CABG with CPB. The agent had a sustained half-life ranging from 7 to 14.5 h, with significant dose-dependent inhibition of complement hemolytic activity observed for up to 14 h with the 2 mg/kg dose. Significant and dose-dependent inhibition of the proinflammatory complement byproducts sC5b-9 (50, 90, > 99 and > 99% for the respective dose groups) and a significant decrease in surface CD11b expression (*i.e.*, an indication of leukocyte activation) were also seen in patients treated with 1 or 2 mg/kg pexelizumab. Moreover, a significant 40% reduction in myocardial injury, as indicated by reductions in serum creatine kinase (CK)-MB isozyme release, was reported in the 2 mg/kg group as compared to placebo. According to scores from the Sequential Mini-Mental State Examination (MMSE), patients receiving 2 mg/kg had an 80% decrease in new cognitive deficits on postoperative days 5-7 as compared to placebo. Patients given the 1 and 2 mg/kg doses also had a 1-U reduction in postoperative blood loss. No differences were observed in the incidence of adverse events between placebo and pexelizumab groups (11).

The safety and efficacy of pexelizumab (2 mg/kg bolus alone or followed by 0.05 mg/kg/h 24-h infusion prior to CPB) in suppressing C5 complement, reducing myocardial infarction and reducing death were shown in a multicenter, randomized, double-blind, placebo-controlled phase II trial in 914 CABG (with or without valve surgery) patients undergoing CPB. The primary endpoint of the study was composite death, myocardial infarction (Q-wave or peak CK-MB greater than 60 ng/ml), severe left ventricular dysfunction or new central neurological deficit on postoperative days 4 and 30. Complement suppression was observed in patients receiving pexelizumab as a bolus alone (at 4 h) or together with an infusion (at 24 h). No significant differences in the primary composite endpoint were observed between the 2 dosing regimens. However, in CABG patients (without valve replacement and peak CK-MB > 60 mg/ml) receiving both the pexelizumab bolus and infusion, the rate of death tended to decrease (79%; p=0.24) and peak CK-MB tended to be reduced (24%; p=0.09) as compared to placebo at day 30. CK-MB reductions were significant in those patients with a CK-MB level greater than 70 ng/ml (*e.g.*, 67% reduction in patients with CK-MB > 100 ng/ml at day 30). No significant differences in CK-MB distribution were noted between placebo and the 267 patients who received the pexelizumab bolus alone. Treatment with the bolus and infusion did significantly reduce the incidence

Table I: Clinical studies of pexelizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Coronary angioplasty	Randomized, double-blind, pooled/meta-analysis	Pexelizumab, 0.2 mg/kg iv Pexelizumab, 0.5 mg/kg iv Pexelizumab, 1.0 mg/kg iv Pexelizumab, 2.0 mg/kg iv Placebo		Pexelizumab at doses up to 2.0 mg/kg was well tolerated and showed evidence of inhibiting complement-dependent hemolytic activity for 4 h in healthy volunteers and patients needing a coronary artery bypass graft	10
Coronary angioplasty	Randomized, open	Pexelizumab, 0.2 mg/kg iv (n=4) Pexelizumab, 0.5 mg/kg iv (n=4) Pexelizumab, 1.0 mg/kg iv (n=10) Pexelizumab, 2.0 mg/kg iv (n=10) Placebo (n=6)	35	Pexelizumab was well tolerated and dose-dependently inhibited the production of the proinflammatory complement byproducts sC5b-9 in patients undergoing cardiopulmonary bypass. The highest doses were associated with reductions in leukocyte activation, myocardial injury, incidence of new cognitive deficits and postoperative blood loss	11
Coronary angioplasty	Randomized, double-blind, multicenter	Pexelizumab, 2.0 mg/kg iv bolus (n=267) Pexelizumab, 2.0 mg/kg iv bolus → 0.05 mg/kg/h over 24 h (n=263) Placebo (n=270)	914	The administration of pexelizumab as an i.v. bolus of 2.0 mg/kg followed by an i.v. infusion of 0.05 mg/kg/h over 24 h was more effective than placebo or bolus pexelizumab alone in reducing the incidence of postsurgical myocardial infarction in patients undergoing coronary artery bypass graft without valve surgery. Pexelizumab had no effects on patients undergoing coronary artery bypass graft with valve surgery	12, 13
Systemic lupus erythematosus	Randomized, double-blind	Pexelizumab, 0.1 mg/kg iv Pexelizumab, 0.3 mg/kg iv Pexelizumab, 0.75 mg/kg iv Pexelizumab, 2.0 mg/kg iv Pexelizumab, 4.0 mg/kg iv Pexelizumab, 8.0 mg/kg iv Placebo	24	Pexelizumab was well tolerated in patients with systemic lupus erythematosus. A single i.v. dose of 8.0 mg/kg of pexelizumab was effective in inhibiting serum complement activity for 10 days, and some clinical parameters of the disease tended to improve after follow-up for 56 days	14

of composite death or myocardial infarction (CK-MB > 100 ng/ml) by 66% and 67% at days 4 and 30, respectively. Pexelizumab had no significant effects in the 114 patients who underwent CABG with valve surgery. It was concluded that pexelizumab-induced C5 suppression was more marked in CABG patients with large myocardial infarction and cardiac enzyme leakage (12, 13).

Pexelizumab has also been shown to be effective in inhibiting cleavage of C5 to C5a and C5b-9 in patients with systemic lupus erythematous (SLE). A randomized, placebo-controlled, double-blind phase I study involving 24 SLE patients examined the safety and efficacy of single-dose pexelizumab (0.1, 0.3, 0.75, 2, 4 or 8 mg/kg i.v.) and concluded that the agent was safe and well tolerated. The incidence of adverse events tended to be dose-dependent. A greater than 80% inhibition of C5 was observed in patients receiving the 2, 4 and 8 mg/kg doses, which was sustained for 1, 5 and 10 days, respectively, after which levels returned to baseline (by 2, 14 and 14 days, respectively). No differences were observed in SLEDAI or physician global assessment, although patient disease assessment in the 8 mg/kg pexelizumab group tended to improve at days 28 and 56. From these results, it was concluded that phase II trials are warranted in SLE patients (14).

Favorable results were announced for pexelizumab after completing 2 phase II trials (COMPLY and COMMA) in which the agent was included as a treatment for acute myocardial infarction. Pexelizumab will start phase III development in patients undergoing CABG with CPB. Enrollment had been completed for a multicenter, placebo-controlled phase III PRIMO-CABG (Pexelizumab for Reduction in Infarction and MOrtality in CABG surgery). Approximately 3,000 patients undergoing CABG with CPB will participate and the safety and efficacy of pexelizumab (bolus followed by 24-h continuous infusion) in reducing composite death or myocardial infarction will be assessed (15, 16).

Source

Alexion Pharmaceuticals Inc. (US); codeveloped with The Procter & Gamble Co. (US).

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