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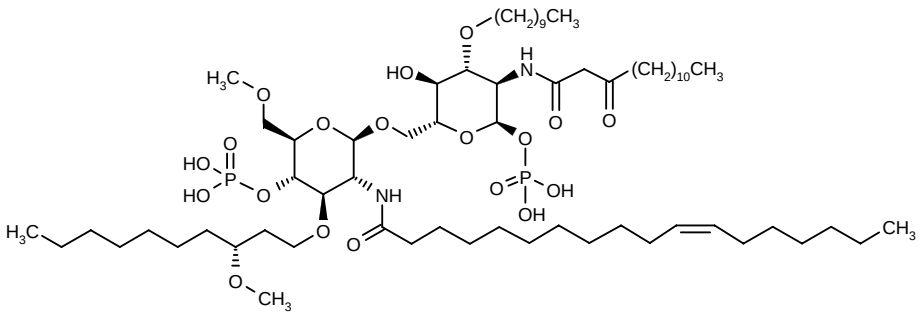
E-5564

Treatment of Septic Shock
TLR4 (LPS) Receptor Antagonist

3-*O*-Decyl-2-deoxy-6-*O*-[2-deoxy-6-*O*-methyl-3-*O*-[3(*R*)-methoxydecyl]-2-[11(*Z*)-octadecenamido]-4-*O*-phosphono-β-D-glucopyranosyl]-2-(3-oxotetradecanamido)-1-*O*-phosphono-α-D-glucopyranose



$C_{66}H_{126}N_2O_{19}P_2$

Mol wt: 1313.664

CAS: 185955-34-4

EN: 278145

Abstract

Sepsis, a significant cause of morbidity and mortality in all hospitalized patients, is the result of an overexaggerated host immune response to the presence of infection, rather than to the pathogen itself. Despite years of research into the pathophysiology of sepsis, there is still no effective therapy to combat its deleterious effects. Lipopolysaccharide (LPS) is a molecule on the surface of the bacterial cell that the innate immune system uses to initiate its response. It is part of the lipid A molecule present on all Gram-negative organisms, the presence of which mediates proinflammatory cytokine release. E-5564 is a synthetic lipid A antagonist that works at the LPS receptor to competitively antagonize the effects of naturally occurring LPS. In doing so, E-5564 is hypothesized to have the ability to halt the sepsis cascade, without causing any other agonistic effects through its binding at this receptor site. Early preclinical and phase I studies have shown that E-5564 administration inhibits LPS-mediated increases in proinflammatory cytokine levels and dose-dependently reduces the severity of endotoxin-induced sepsis syndrome in human models of sepsis. E-5564 is currently in phase II trials for its potential use in the treatment of sepsis and septic shock.

Introduction

Sepsis is literally translated to mean infection. More specifically, it describes the body's inability to regulate the normal inflammatory response to infection. In clinical terms, sepsis describes the state resulting from an exaggeration of the body's systemic inflammatory response. This response can be described in a number of ways, either in terms of the observed features of the condition or as a biochemical entity. The clinical signs indicative of sepsis include fever, tachycardia and increased respiratory rate. The physiological stress characteristic of sepsis is determined by measuring the immune response to infection (via white blood cell count). Perhaps more important in the context of sepsis treatment is the characterization of sepsis as an alteration in the normal blood biochemistry, a change that is associated with an increase in the presence of proinflammatory cytokines in the systemic circulation (1).

Sepsis can progress to septic shock. Septic shock depicts the presence of sepsis complicated by hypotension and describes a state of potentially fatal organ hypoperfusion. Septic shock gives rise to a wide range of physiological complications affecting normal renal, hepatic, cardiovascular and endocrine function, a process which often has lethal results.

Despite advances in supportive care, sepsis remains a common cause of death in all hospitalized patients. U.S. figures have determined septic shock to be the leading cause of death among critically ill patients in the ICU,

K. Chilman-Blair, P.A. Leeson, M. Bayés. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

where 30-70% of all patients with sepsis have been reported to have a fatal outcome. Moreover, it is estimated that septic shock results in 500,000 fatalities each year worldwide. This unacceptably high frequency of lethal outcomes imposes a huge economic burden on the health system, with costs of over USD 16 billion per year being cited in America alone. Sepsis, therefore, represents a serious unmet need in terms of both mortality and cost of intensive care (2, 3).

Sepsis results from a generalized inflammatory – and procoagulant – response to foreign infection. Sepsis begins with host invasion of an infectious organism. The sepsis cascade can be triggered by a number of exogenous bacteria, including Gram-positive streptococci and staphylococci strains. However, the most commonly defined organisms responsible for sepsis are Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli* and other *Enterobacter* species.

During the onset of sepsis, the inflammatory response to infection becomes hyperactive. This innate immune response is most often protective for the host and leads to resolution of infection. The problem arises in sepsis whereby there is an overproduction of inflammatory mediators. This exaggerated immune response leads to the signs and symptoms of septic shock and, eventually, to death of the host. In this way, the pathogenesis of sepsis is determined not by the bacteria per se but rather by the body's overcompensatory response to infection (4).

Lipopolysaccharide (LPS, or endotoxin) has been implicated as the primary mediator in the sepsis cascade. LPS constitutes the lipid portion of the outer leaflet of the cell wall of Gram-negative bacteria and is essential for their growth and development. The bacterial endotoxin is released into the bloodstream when bacteria are broken down in the body following bacterial lysis and death. In this way, LPS works as a flag to alert the immune system of the presence of foreign bacteria (5).

LPS is a potent microbial mediator. The presence of LPS induces an intense inflammatory/procoagulant response by elements of the innate immune system. Endogenous mediators of the immune system (released following activation of the inflammatory/procoagulant cascade) subsequently act at target cells in the body. It is these target cells that go on to produce the sequelae of symptoms associated with shock.

LPS produces these effects by associating with cell surface receptors. Mammals are equipped with LPS-sensing apparatus consisting of LPS-binding protein (LBP), CD14 and Toll-like receptor 4 (TLR4). LPS interacts with LBP and CD14, which presents LPS to TLR4, thereby activating gene expression for the production of proinflammatory cytokines. Stimulation of these receptors normally facilitates the elimination of invading microorganisms. Potent stimulation, however, produces severe reactions in the host (6).

Activation of these receptor sites stimulates macrophages, neutrophils and lymphocytes into producing powerful proinflammatory cytokines IL-1, IL-6, IL-8 and TNF-α. All of these endogenous inflammatory mediators exacerbate the host immune response. Accumulating LPS levels, therefore, indirectly lead to the development of fever, chills and leukopenia via activation of the body's own response to infection. A repeated overexaggerated immune response will lead to multiorgan failure and death.

Rates of sepsis are on the increase worldwide, even in the face of a growing number of available antibiotic therapies. While antibiotics help to control the infection, they do not prevent the end-organ damage associated with the sepsis cascade. Antibiotic monotherapy, therefore, is not indicated in the treatment of sepsis (7).

There is currently no one specific or effective therapy for the treatment of sepsis. Strategies focused on adjuvant drug targets have subsequently become increasingly important in the management of this condition. Advances in molecular biology have improved our understanding of this disease process and have opened up new avenues of potential therapeutic approaches (8).

The correlation between LPS levels and sepsis has meant that endotoxin has become an important therapeutic target in the management of septic shock. It is hoped that the administration of drugs designed to block the action of LPS activity may be used to halt the sepsis cascade at a molecular level. Thus, research efforts have been directed toward determining the structural properties of LPS with the aim of designing pharmacological agents that can inhibit the action of this complex macromolecule (9).

The LPS molecule is made up of an inner core oligosaccharide and lipid A portion. Lipid A is biologically active and is said to be the toxemic portion of LPS. Compounds that bind lipid A are hypothesized to limit its detrimental effects. With this in mind, Eisai has developed a range of compounds that bind preferentially to the lipid A binding site, therefore renderingg the naturally occurring lipid A molecule inactive. Of these newly developed agents, E-5564 was shown to be a potent antagonist at this receptor site and was selected as a clinical candidate for the treatment of sepsis.

Pharmacological Actions

E-5564 is a synthetic lipid A antagonist (10). It is structurally synonymous to the lipid A portion of the endotoxin molecule (based on synthetic replication from the lipid A part of the nontoxic *Rhodobacter sphaeroides* species). E-5564 is distinct from lipid A in that it does not possess an ionization site for positive ion. E-5564 blocks the action of LPS by preferentially binding at its cell surface receptor. E-5564 does not exhibit intrinsic agonistic activity through its affiliation with the endotoxin receptor site. Therefore, while E-5564 is structurally similar to LPS, it works to block host responsiveness to endotoxin and is therefore classified as a lipid A antagonist (11, 12).

It is not entirely understood how E-5564 works to inhibit the septic shock cascade. As expected from its structural homology to lipid A, E-5564 blocks LPS-

mediated sepsis by interacting at the lipid A binding site. The signaling unit of the LPS receptor is a member of the toll-like receptor (TLR) family. The TLR family has been implicated in the elicitation of the innate immune response, as interaction with these receptors is associated with an increased production of proinflammatory cytokines. Furthermore, animal studies have shown that mutation or deletion of TLRs results in an attenuated response to LPS (13).

E-5564 also interacts, however, with LBP and CD14. These aspects do not seem to be critical to the antagonistic activity of E-5564, as it can behave as an antagonist in their absence (*i.e.*, under serum-free conditions). Therefore, while E-5564 is known to be an antagonist at TLR4, the exact mechanism of action is still being determined (14).

The *Rhodobacter sphaeroides* species, from which E-5564 is derived, has been deemed a naturally occurring antagonist at the TLR4 receptor site. Its action is not always antagonistic, however, as previous studies have shown *Rhodobacter sphaeroides* to exhibit agonistic properties in the presence of chlorpromazine and other amphipathic drugs. Therefore, the enduring antagonistic qualities of E-5564 were tested in the presence of these agents in order to determine whether E-5564 had comparable results. Results from these in vitro analyses in both serum-free medium and human blood showed that E-5564 maintained its antagonistic properties in the presence of chlorpromazine, fluphenazine, trifluoperazine and lidocaine. E-5564 inhibited LPS-mediated increases in IL-6 at a range of concentrations tested. The authors concluded that while E-5564 is a lipid A analogue, it was devoid of any agonistic properties in these studies (15).

Preclinical Studies

LPS is used in both human and animal models of sepsis. The administration of endotoxin in primate models has been shown to invoke a clinical syndrome comparable to that observed in septic shock in humans. Furthermore, human studies have shown that endotoxin infusions in healthy volunteers produce the clinical symptoms indicative of a mild sepsis syndrome, including varying degrees of nausea, headache, chills and joint pain. This can be done by either infusing the whole bacteria into the host or by intravenously injecting a mild form of the LPS molecule itself. These models have been very important not only in the determination of the pathophysiology of sepsis but also for the elucidation of antiendotoxin efficacy (16, 17)

E-5564 has displayed antiendotoxin activity in both *in vivo* and *in vitro* studies through the employment of different LPS models of sepsis. E-5564 has been shown to work as a competitive inhibitor of LPS, and therefore displays its antagonistic properties in a dose-dependent manner in response to LPS concentration (4, 18).

In vitro

Preclinical studies have shown that E-5564 antagonizes cytokine induction following microbial invasion. While the presence of LPS normally increases the production of proinflammatory mediator TNF-α, this induction was inhibited with concomitant administration of E-5564 in a recently conducted *in vitro* study. LPS 10 ng/ml was delivered to heparinized human blood, generating a rise in TNF-α, with maximum response observed at 3 h postinoculation. This induction was inhibited by 100% following administration of E-5564 10 nM, with IC_{50} values ranging between 1 and 13 nM (mean 1.6 nM). Subsequent results also showed that E-5564 inhibits production of IL-1, IL-6, IL-8, and IL-10 in a dose-dependent manner (14).

The effects of E-5564 on TNF-α production were also assessed following inoculation with LPS from differing strains of bacteria, as well as with whole bacterial organisms. The lipid A portion from *E. coli* was also tested in this way. These various inflammatory initiators were first administered to the blood samples to confirm a consequent rise in TNF-α. As observed in the purified LPS analysis, E-5564 was then shown to inhibit these LPS-induced changes, with IC_{50} values ranging between 0.65 and 12.4 nM for all samples tested (14).

E-5564 inhibited the production of TNF-α in the presence of Gram-negative, but not Gram-positive, bacteria. The antagonistic properties of E-5564 are therefore only relevant to infection related to Gram-negative sepsis. This difference in effect was suggested to be due to the distinct receptor subtypes being activated in Gram-negative and Gram-positive bacteria (TLR4 *vs.* TLR2, respectively) (14).

Investigators subsequently examined the potential agonistic effects of E-5564 by administering 10 nM alone to samples of heparinized blood. Blood samples were then incubated for up to 9 h before being tested for induction of IL-1, IL-6, IL-8, IL-10 and TNF-α. Results showed that levels of all proinflammatory cytokines tested were at baseline levels after incubation, thereby underlining the use of E-5564 as an antagonist only at this receptor site (14).

The antagonistic activity of E-5564 was further studied in a number of tests involving the macrophage-mediated immune response. Macrophages from rats and guinea pigs were isolated and incubated with *E. coli* LPS in order to stimulate IL-6 and TNF-α. Once again, E-5564 was shown to inhibit macrophage release of IL-6 and TNF-α in both murine and guinea pig models (14).

Ex vivo

The ability of E-5564 to inhibit LPS-induction of TNF-α was determined via *ex vivo* analysis. Eleven healthy volunteers (7 males, 4 females) took part in this double-blind, placebo-controlled, dose-finding study. Blood samples were collected following E-5564 infusions

and were incubated for 3 h with LPS 0.05, 1.0 and 10 ng/ml before being tested for the presence of TNF-α. TNF-α response was dependent on both the dose of E-5564 and on the subsequent dose of LPS. All E-5564 doses abolished the effects of LPS 0.05 ng/ml on TNF-α production; however, higher LPS doses required higher E-5564 doses to antagonize these effects (19).

In vivo

E-5564 has been shown to be a potent antiendotoxin in a number of *in vivo* studies. The prophylactic efficacy of low, medium and high doses of E5564 was tested in a rat model of *E. coli* sepsis. Rats were randomized to receive active treatment (i.v. bolus of E-5564 0.3, 1.0 or 2 mg/kg, followed by a 24-h infusion of E-5564 0.03, 0.1 or 0.2 mg/kg/h) or placebo. Rats were administered *E. coli* 1.6 x 10^9 colony forming units 1 h after E-5564 prophylaxis. All rats were treated with the antibiotic ceftriaxone at 6, 24 and 48 h. Rats were considered to be survivors if they were still alive 168 h after LPS administration. Of rats receiving placebo, 73% were nonsurvivors at 168 h. Low, medium, and high doses of E-5564 increased odds of survival by 2.7, 1.3 and 3.8, respectively. Prophylaxis with E-5564 was therefore shown to reduce Gram-negative related death in rats (20).

E-5564 has been shown to reduce endotoxin-induced death in a number of animal models. The ability of E-5564 to prevent death in BCG-primed mice and guinea pigs administered a lethal dose of LPS was evaluated in a recent *in vivo* study. The animals were given E-5564 or placebo with a lethal dose of LPS 100 μg/kg in mice and 1000 μg/kg in guinea pigs. TNF-α levels were measured in the blood 1 h postadministration. The overall ED_{50} of E-5564 was calculated to be 37 μg/kg in these studies. E-5564 30, 100, 300 and 1000 μg/kg inhibited plasma TNF-α concentrations by 24%, 38%, 81% and 93%, respectively, in the murine model, while administration of E-5564 30, 100 and 300 μg/kg inhibited plasma TNF-α concentrations by 29%, 57% and 94% in guinea pigs. E-5564 was further shown to dose-dependently inhibit LPS-induced death in mice (14).

The effect of E-5564 on septic shock in mice was also studied following *E. coli* administration. E-5564 5 mg/kg and latamoxef 30 mg/kg (a β-lactam antibiotic) were administered either alone or in combination following *E. coli* injection. Survival at 72 h was compared with a control group of mice that received no treatment. Results showed that only 10% of controls were survivors at 72 h, while the combination of E-5564 and latamoxef resulted in a survival rate of 80% at 72 h (14).

E-5564 caused an adverse outcome in a rat model of extravascular sepsis. Rats were randomized to receive E-5564 or placebo 1 h following challenge with LPS-containing *E. coli*. LPS was administered via intravenous or extravascular (*i.e.*, intrabronchial and intraperitoneal) routes. Rats were considered to be survivors if they were still alive 168 h after LPS administration. E-5564 decreased the relative risk of death in rats receiving i.v. LPS (RR = –0.52), whereas the risk of death was increased in rats receiving intrabronchial or intraperitoneal LPS (combined RR = 0.18). Thus, E-5564 was associated with a lack of benefit and even potential harm in rodents infected extravascularly compared with intravascularly (21).

In vivo analysis was used to determine the minimum effective dose (MED) of E-5564 in dose-finding studies. MED was defined as the lowest dose that completely blocked all signs and symptoms of endotoxemia in healthy volunteers given a similar dose of endotoxin. E-5564 50, 100 and 250 μg infusions were given in conjunction with a dose of endotoxin (LPS 4 ng/kg). Following administration of E-5564 100 and 200 μg, the serum levels of IL-6 and TNF-α decreased by up to 99%. These changes were mirrored clinically by a reduction in the incidence of headache and chills. Fevers were absent in all subjects tested. White blood cell count remained low, and CRP release was inhibited by over 91%. E-5564 100 μg was therefore deemed the MED, revealing a slightly higher potency compared with its predecessor E-5561 (18).

Pharmacokinetics

E-5564 is a second-generation lipid A antagonist that has similarities to the first-generation antagonist, E-5531. E-5531 was successful in inhibiting the actions of LPS at the TLR4 receptor site; however, its antagonistic activity was observed to decrease with time. E-5564 has improved synthesis, purification, stability and formulation when compared with its predecessor. Even though E-5564 is structurally and synthetically less complex than E-5531, it is at least 7 times more potent than E-5531 and is therefore considered to be a superior candidate for pharmaceutical use (14, 18, 22).

The pharmacokinetic profile of E-5564 was determined in a series of experiments in rats. Single-dose administration of E-5564 (0.1, 0.3 or 1.0 mg/kg i.v.) showed linear pharmacokinetics (AUC and total plasma clearance were independent of dose). The $t_{1/2}$ of E-5564 0.1 mg/kg was 5.5 h, and the volume of distribution was 73.0 ml/kg, indicating a restricted distribution volume. Identification of E-5564 in hepatic, splenic, adrenal and bone marrow tissue following i.v. administration clarified this finding (a distribution profile comparable with LPS). The main metabolic route for E-5564 was through dephosphorylation, with monophosphorylated metabolites being observed in the feces (23).

Protein and lipoprotein distributions of E-5564 were determined following continuous i.v. infusion in 10 human volunteers. Infusions of E-5564 0.5 and 3.5 mg/h were delivered over a 72-h period, after which time blood samples were taken to observe lipoprotein distribution patterns via *ex vivo* analysis. E-5564 was shown to associate predominantly with the HDL portion (55%) in plasma,

with up to 10% and 12% being associated with LDL and VLDL portions, respectively (24).

The plasma lipoprotein distribution of E-5564 was further determined in human plasma samples exhibiting a variation of lipoprotein profiles. Samples taken from hypolipidemic, normolipidemic and hyperlipidemic patients were incubated with radioactive E-5564 for 5-360 min. E-5564 was found to associate with the HDL fraction in hypolipidemic and normolipidemic samples; however, E-5564 was recovered from the triglycerides fraction in more hyperlipidemic samples. These results suggest that the distribution of E-5564 may be altered in hyperlipidemic patients (25).

The pharmacokinetics of E-5564 were tested in a group of LPS-binding protein (LBP) knockout mice compared to control mice. As LBP is important for the activity and clearance of LPS, this study was carried out to determine its interaction with the LPS analogue. E-5564 0.5 mg/kg i.v. was administered to both groups of mice, with plasma concentrations of E-5564 being measured 2 h postadministration. Results from surface plasmon resonance imaging showed that E-5564 interacts with LBP in much the same way as LPS. AUC values were found to be 851 and 818 μg/ml/min in the knockout amd control mice, respectively. The $t_{1/2}$, however, was not significantly different between groups. Therefore, while E-5564 interacts with LBP, the *in vivo* pharmacokinetics were comparable between groups in this study (26).

E-5564 exhibits biphasic elimination in both canine and rodent models, with a comparable volume of distribution being observed in both species. Elimination was significantly longer in dogs compared with rats (27).

E-5564 has a low plasma clearance and therefore exhibits a long plasma half-life ($t_{1/2}$ = 40-50 h). E-5564 becomes inactivated in the systemic circulation by binding to endogenous LPS molecules in the circulation. The antagonistic efficacy of E-5564 is therefore reduced even though it appears to remain chemically unmodified in the blood. There is a subsequent disparity between the pharmacokinetic half-life and the relatively short pharmacological action of the drug.

The lack of correlation between the pharmacokinetics and pharmacodynamics of E-5564 was highlighted using a canine LPS-challenge model. Beagle dogs received E-5564 or placebo infusions prior to inoculation with *E. coli*-containing LPS. While E-5564 was shown to inhibit LPS-mediated changes in temperature, blood pressure, heart rate and white blood cell count, the changes were limited to the time period over which the drug was being infused. An immediate decline in antagonistic activity was noted at treatment cessation (28).

Clinical Studies

The efficacy of single-dose E-5564 was assessed in a randomized controlled trial in 24 healthy male volunteers aged 18-45 years, with a mean weight of 77 kg. All subjects had normal findings following clinical examination and laboratory testing at baseline. In this model of experimentally induced endotoxemia, 30-min infusions of E-5564 50, 100 and 250 μg were compared with placebo. All infusions were given to subjects prior to LPS inoculation (delivered as i.v. CCRE 4 ng/kg). Blood samples were taken at 24 h, at which time clinical observations were also made.As expected, the bolus injections of LPS induced a mild septic syndrome in the healthy subjects. Single-dose E-5564 was effective in reducing these effects at all doses studied. LPS-induced leukocytosis was inhibited following administration of E-5564 100 and 250 μg. Furthermore, the LPS-mediated increases in TNF-α and IL-6 were blocked by E-5564 100 and 250 μg compared with placebo. These effects were dose-dependent and were completely abolished with doses of E-5564 100 μg and higher. The E-5564 50 μg dose also blocked TNF-α production, but only inhibited the IL-6 response. Clinical signs of endotoxemia were also reduced following E-5564 administration. The incidence of fever, chills, headache, myalgia and tachycardia were significantly decreased following E-5564 administration (11, 29). The results of these studies and some that follow are summarized in Table I.

Rossignol *et al.* reported the combined results from 6 phase I studies in over 120 healthy volunteers. Efficacy and tolerability data from both males and females were pooled for this meta-analysis. All subjects received either a 30-min infusion of E-5564 0.5-3.5mg, a continuous 72-h infusion of E-5564 0.5-3.5 mg or a twice-daily dosing regimen. While E-5564 was shown to be effective at all dose levels investigated, the drug's efficacy was not maintained over a long period of time. Within a 6-h time period, the cytokine response to E-5564 was blunted. These results led investigators to conduct an escalating dose study in order to determine whether E-5564 could completely block the effects of LPS by administering an increased E-5564 dose via a 72-h infusion. Continuous infusions of 252 mg (generating serum E-5564 levels of up to 40 μg/ml) were shown to provide a complete block of LPS-mediated sepsis and were well tolerated. Therefore, while lower doses of E-5564 show decreased efficacy over time, high-dose E-5564 can provide a complete block of signs and symptoms associated with sepsis for 12 h postdosing. Tolerability data showed that administration of E-5564 alone in healthy volunteers produced no alterations in vital signs. The only side effect observed with E-5564 administration was phlebitis at the site of injection, an effect that was shown to be both concentration- and time-dependent (*i.e.*, an increased incidence of phlebitis was reported in subjects receiving E-5564 at a dose of 0.5 mg/ml or higher over 8 h or more) (18).

Conclusions

E-5564 is a potent antagonist of bacterial endotoxin LPS and, therefore, has potential implications in the treatment of LPS-mediated sepsis. E-5564 at doses of

Table I: Clinical studies of E-5564 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind	E-5564, 50 μg iv over 30 min (n=6) E-5564, 100 μg iv over 30 min (n=6) E-5564, 250 μg iv over 30 min (n=6) Placebo (n=6)	24	An i.v. infusion of E-5564 inhibited the induction of leukocytosis and cytokine response by endotoxin; greater effects were found with the 100 and 250 μg doses. The drug was also well tolerated and dose-dependently attenuated the effects induced by endotoxin on body temperature, heart rate and cytokine levels in healthy volunteers	11, 29
Healthy volunteers	Pooled/meta-analysis	E-5564, 0.5-3.5 mg iv over 30 min E-5564, 0.5-3.5 mg/h iv over 72 h E-5564, dose titrated to 1 μg/ml bid E-5564, dose titrated to 2 μg/ml bid E-5564, dose titrated to 6 μg/ml bid E-5564, dose titrated to 10 μg/ml bid	120	The only significant adverse event associated with i.v. doses of E-5564 was phlebitis, which was common with single doses equal to or higher than 0.5 mg/ml for at least 8 or with multiple doses	18
Healthy volunteers	Randomized, double-blind	E-5564, 0.05 ng/ml iv bid over 84 h E-5564, 1 ng/ml iv bid over 84 h E-5564, 10 ng/ml iv bid over 84 h Placebo	11	E-5564 inhibited TNF-α production throughout the treatment period. The return of lipid A portion of bacterial endotoxin sensitivity depended on the dose of E-5564 infused	19
Healthy volunteers	Open	E-5564, 0.5 mg/h iv over 72 h (n=5) E-5564, 3.5 mg/h iv over 72 h (n=5)	10	E-5564 was safe and well tolerated, with the exception of phlebitis. E-5564 partitioned predominantly into plasma HDL and other plasma lipoproteins during and after long-term infusion	24

100-250 μg have been shown to competitively inhibit the effects of LPS in both animal and human models of sepsis, without showing any signs of additional agonistic activity. E-5564 produces its effects by decreasing the production of proinflammatory cytokines normally associated with the presence of LPS. Phase I studies report that a decrease in cytokine response ameliorates the clinical signs of sepsis (characterized by a resolve of heart rate, temperature, headache and muscle pain symptomatology). The antagonistic activity of E-5564 is dose-dependent and has been shown to be dependent on both E-5564 and LPS concentrations. As there is currently no other effective treatment for patients with sepsis or septic shock, the results from phase II studies are eagerly awaited.

Source

Eisai Co., Ltd. (JP).

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