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Ataticept

Recombinant Fusion Protein
Oncolytic

Rec INN; USAN

TACI-Fc5
TACI-Ig
sTACI

[86-Serine, 101-glutamic acid, 196-serine, 197-serine, 222-aspartic acid, 224-leucine][human tumor necrosis factor receptor superfamily member 13B-(30-110)-peptide (TACI fragment containing TNFR-Cys 1 and TNFR-Cys 2) fusion protein with human immunogobulin G_1-(232 *C*-terminal residues)-peptide (γ1-chain Fc fragment), (92-92':95-95')-bisdisulfide dimer

Human transmembrane activator and CAML interactor (TACI) - Immunoglobulin G_1 Fc domain fusion protein (Fc5)

1-81-TACI (human) fusion protein with 82-313-modified immunoglobulin G_1 (human γ1-chain Fc fragment), dimer. Monomers are covalently linked by disulfide bridges at cysteines 92 and 95 of each monomer

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Abstract

Atacicept (TACI-Ig, TACE-Fc5) is a soluble recombinant fusion protein containing the extracellular BAFF/APRIL-binding domain of the TACI receptor and the Fc region of human IgG that blocks both BAFF and APRIL, two members of the tumor necrosis factor (TNF) superfamily known to play key roles in B-cell activation. BAFF and APRIL are upregulated in B-cell malignancies and autoimmune diseases, and blocking their activity via atacicept may prove to be a potential therapeutic approach. Preclinical studies have demonstrated the ability of atacicept to suppress the production of autoreactive antibodies and inhibit the development of mature spleen B cells by arresting the transition of immature B cells from the T1 to the T2 stage. Atacicept was also shown to inhibit disease progression in mouse models of rheumatoid arthritis and systemic lupus erythematosus (SLE). Preliminary data from clinical studies support the biological activity, tolerability and safety of s.c. atacicept administration. Atacicept is currently undergoing phase II/III clinical trials for the treatment of autoimmune conditions such as rheumatoid arthritis, multiple sclerosis, SLE amd optic neuritis, as well as phase I trials for multiple myeloma, chronic lymphocytic leukemia and non-Hodgkin's lymphoma.

Background

In a healthy immune system B cells play a major role in the regulation of the immune response by maintaining cellular and humoral memory and coordinating inflammatory pathways. B cells produce proinflammatory cytokines, influence T-cell activation and expansion, and may also act as antigen-presenting cells (1).

The precise regulation of B-cell survival, development and activation is paramount for the generation of a fully competent B-cell response to a diverse range of foreign antigens, while ensuring tolerance to self-antigens. Dysregulation of B-cell proliferation leads to malignancies, whereas the inability to tolerate self-antigens coupled with the costimulation of autoreactive T cells is the cause of autoimmunity.

B-cell maturation, differentiation and survival are modulated by the coordinated function of BAFF (B-cell activating factor; also known as TN13B, TALL-1 and BLyS) and APRIL (A proliferation inducing ligand; also known as TNF13, TALL-2 and TRDL-1), two members of the tumor necrosis factor (TNF) superfamily (2, 3). BAFF and APRIL are involved in B-cell homeostasis and immunoglobulin expression (4). Both factors are able to promote the survival of normal and malignant B cells and APRIL also acts as a costimulator of T cells (5).

BAFF and APRIL function by binding to members of the TNF receptor family: transmembrane activator and CAML interactor (TACI, or TR13B) and B-cell maturation protein (BCMA, or TNR17). BAFF, but not APRIL, also binds specifically to the BAFF receptor (BAFF-R) (6, 7). As a result of their effects on B- and T-cell function, BAFF and APRIL are considered instrumental in the development of autoimmune diseases, and blocking their activity may be a potential therapeutic approach to target B-cell-associated malignancies and autoimmune conditions.

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In an effort to inhibit the stimulatory effect of BAFF and APRIL on B-cell proliferation, atacicept (TACI-Ig, TACI-Fc5), a soluble recombinant fusion protein comprising the extracellular ligand-binding domain of the TACI receptor and the Fc region of human immunoglobulin G (IgG), was generated (6, 8).

The potential use of atacicept as a therapeutic agent in human B-cell malignancies and autoimmune diseases is currently being investigated by Merck Serono under license from ZymoGenetics. Atacicept is undergoing phase II/III clinical trials in order to establish its efficacy in the treatment of rheumatoid arthritis, SLE, multiple sclerosis and optic neuritis, and phase I trials for chronic lymphocytic leukemia, multiple myeloma and non-Hodgkin's lymphoma.

Preclinical Pharmacology

Atacicept treatment of normal mice (100 μg i.p. 3 times a week for 2 weeks) blocked the transition of immature T1 B cells to the T2 precursors of mature splenic B cells and reduced the levels of circulating Ig (2). Atacicept was found to block the development of specific B-cell populations in the periphery by neutralizing BAFF and APRIL and to inhibit disease progression in mouse models of rheumatoid arthritis and systemic lupus erythematosus (SLE) (2, 6).

Atacicept treatment (i.p. injection 3 times a week for 3 weeks) of DBA/1 mice with collagen-induced arthritis (CIA) reduced serum antibody titers. Histological assessment of treated animals showed undamaged articular cartilage, reduced inflammation and decreased hypertrophy of the synovium, accompanied by a decrease of inflammatory cells in the soft tissues around the joints (2).

In vivo, the effects of atacicept on the progression of SLE were assessed in the NZBWF1 (also referred to as NZB/NZW F1) mouse strain, which develops chronic spontaneous autoimmune disease and is used as a model of SLE (6). Symptoms characteristic of SLE include high titers of anti-dsDNA antibodies, proteinuria and glomerulonephritis. Administration of atacicept to 15- to 21-week-old female NZBWF1 mice (100 μg 3 times a week for 5 weeks) significantly reduced the proportion of animals with proteinuria ≥ 100 mg/dl for up to 10 weeks following the last treatment compared to animals treated with Fc control protein or phosphate-buffered saline (PBS; vehicle control). A survival rate of 100% at 38 weeks of age was observed in the atacicept-treated animals compared to 47% survival for the Fc-treated group at 12 weeks following the last treatment. No significant differences were observed in anti-dsDNA autoantibody production in the different treatment groups. However, a significant 53% reduction in the percentage of peripheral blood B cells at 28 weeks of age was observed in atacicept-treated compared to Fc-treated mice. This decrease in B cells persisted until 31 weeks of age (5 weeks following the last treatment) and returned to control levels by 37 weeks of age (6).

In a mouse model of chemically induced autoimmunity, atacicept treatment (100 μg 3 times a week for 2 weeks) reduced autoantibody production in $HgCl_2$-induced autoimmunity in the mercury-susceptible mouse strain A.SW (9). Treatment with atacicept during the induction phase of mercury-induced autoimmunity significantly reduced anti-nucleolar autoantibody (ANoA) IgG_1 levels, whereas pretreatment with atacicept prevented total serum IgE induction. A dramatic reduction in B-cell numbers undergoing T1–T2 transition during splenic B-cell development was also observed.

The effects of atacicept exposure on the ability of mice to clear influenza virus were also evaluated (10, 11). C57Bl/6 mice were treated with either vehicle control, dexamethasone (positive control) or atacicept (0.05, 0.50 and 5.0 mg/kg) s.c. 3 times a week from within 1 week prior to infection with mouse-adapted human influenza A/Port Chalmer/1/73 (H3N2) virus through 21 days postinfection. Atacicept-treated mice displayed a dose-dependent reduction in spleen weight and influenza-specific IgM and IgG production in the lung and serum compared to vehicle control animals. Animals exposed to atacicept displayed a decrease in the number of B but not T cells in the peripheral blood. However, unlike treatment with dexamethasone, atacicept had no effect on viral clearance and animal survival.

Myelomatous SCID-hu mice (an animal model of multiple myeloma) were generated with either high or low *TACI* gene expression (TACI-high and TACI-low). Following the establishment of myeloma growth, the mice were treated i.p. with atacicept (5 or 10 mg/kg 3 times a week). Atacicept reduced tumor burden in animals bearing TACI-high multiple myeloma cells and delayed growth or showed no effect in mice with TACI-low multiple myeloma cells (12, 13). Ex vivo, myeloma plasma cells from patients with active myeloma were co-cultured with osteoclasts for 5-7 days in the absence or presence of atacicept (1-10 μg/ml) and atacicept inhibited osteoclast-induced survival of myeloma cells by > 35% (13).

Pharmacokinetics and Metabolism

The preclinical safety, pharmacokinetics (PK) and pharmacodynamics (PD) of atacicept were evaluated in a recent study carried out in mice and cynomolgus monkeys (14). Atacicept administered s.c. to mice (single dose or repeated dosing 3 times a week for 2, 4 and 26 weeks) and monkeys (single dose or repeated dosing twice a week for 4, 13 and 39 weeks) was generally deemed safe and well tolerated. Single doses of 1 mg/kg atacicept resulted in 76% and 92% bioavailability, respectively, in mice and monkeys. Bioavailability levels remained high at doses ranging from 1 to 15 mg/kg. The time to maximum serum concentrations (t_{max}) was 4-16 h and 6-8 h, respectively, and the mean serum half-life ($t_{1/2}$) was 40-50 h and 140-190 h, respectively, in mice and monkeys. Repeated atacicept administration was associated with decreased serum concentrations of IgG (up to 50% reduction) and IgM (> 99% reduction). The concen-

trations of circulating mature B cells were also reduced by up to 60%. These effects of atacicept were dose-related and reversible over a follow-up period of 25 weeks.

The safety, PK and PD of atacicept were also assessed in four phase I clinical trials performed in healthy volunteers (15), patients with rheumatoid arthritis (16) and patients with SLE (17).

In the first study, a single s.c. dose of atacicept (2.1, 70, 210 or 630 mg) or placebo was administered to healthy male volunteers and the participants were monitored for a period of 7 weeks. The main PK evaluations based on the 70-, 210- and 630-mg doses revealed consistent multiphasic free drug PK profiles at the three different dose levels. A fairly rapid absorption phase was followed by a 1-2-week distribution phase and a long terminal phase. The median t_{max} was 16 h for all three doses (12-36 h) and the AUC increased in an approximately dose-dependent manner. A dose-dependent effect on the levels of IgM was also observed following doses of 70, 210 and 630 mg, whereas placebo and 2.1 mg atacicept had no effect. The greatest reduction in IgM levels (23%; range: 12-25%) was observed in the 630-mg group at 35 days postdose. The concentration of serum IgM remained low even 47 days postadministration when serum atacicept levels were unquantifiable and recovered to approximately 10% of baseline values at 100-150 days postadministration. No treatment-related effects on IgG levels or lymphocyte subpopulations were observed (15).

In the second study, the PK and biological activity of atacicept were evaluated in patients with moderate to severe active rheumatoid arthritis (16). Atacicept was administered s.c. either as a single dose or repeated doses at 2-week intervals in six escalating-dose cohorts (single-dose cohorts 1, 3 and 5 receiving 70, 210 and 630 mg, respectively, and repeated-dose cohorts 2, 4 and 6 receiving 3 x 70 mg, 3 x 210 mg and 7 x 420 mg, respectively). PK profiles of atacicept in all cohorts were nonlinear. Following the first dose, the PK profiles of free drug displayed a multiphasic behavior with a rapid absorption phase followed by a distribution phase lasting 2 weeks and a prolonged terminal phase (median t_{max} = 24 h for all cohorts; median $t_{1/2}$ range = 104 h [cohort 6] to 1070 h [cohort 3]; median C_{max} range = 419 ng/ml [cohort 1] to 5530 ng/ml [cohort 5]; median AUC range = 34.8 mg.h/l [cohort 1] to 643 mg.h/l [cohort 5]). The biological activity of atacicept as estimated by the production of nonspecific Ig antibodies was deemed to be dose-related. The highest atacicept doses (cohorts 4, 5 and 6) caused a significant > 50% reduction in serum IgM levels, whereas statistically significant reductions in IgA (~40%) and IgG (~20%) were only observed in cohort 6.

Six cohorts of 8 patients each with SLE were treated with atacicept (single doses of 0.3, 1, 3 or 9 mg/kg s.c. in cohorts 1-4; 1 or 3 mg/kg s.c. weekly x 4 in cohorts 5 and 6) in one phase I study, and another evaluated single i.v. doses of 3, 9 or 18 mg/kg and two doses of 9 mg/kg 3 weeks apart. Pharmacokinetics were nonlinear but consistent and predictable across doses, routes and schemes of administration. Pharmacokinetic profiles for free and total drug were multiphasic, with a median terminal half-life of 30-83 days. Bioavailability following s.c. administration was 28-40% (17).

Clinical Studies

The maximum tolerated and the optimal biological doses of atacicept in patients with refractory or relapsed multiple myeloma or active, previously treated Waldenström's macroglobulinemia were evaluated in an open-label, dose-escalation phase I/II study (18-20). One cycle of 5 weekly s.c. injections of atacicept (2, 4, 7 or 10 mg/kg) was administered to eligible patients (12 multiple myeloma and 4 Waldenström's macroglobulinemia patients). Only subjects who demonstrated at least stable disease following the first cycle were allowed to continue to the extension phase of the trial. This phase comprised either two additional cycles separated by a 4-week washout period or 15 weekly injections of 10 mg/kg. Preliminary data from this study revealed no dose-limiting toxicity (DLT) or serious adverse events (SAE) associated with atacicept administration. After the first cycle, 5 multiple myeloma patients and 3 Waldenström's macroglobulinemia patients had stable disease, and of 8 patients entering the extension phase, 4 with multiple myeloma and 1 with Waldenström's macroglobulinemia had stable disease. The majority of patients exhibited a decrease in polyclonal immunoglobulins and plasmocytes.

A phase I open-label, dose-escalation clinical study of atacicept was carried out between October 2005 and July 2006 in patients with relapsed and refractory non-Hodgkin's lymphoma (NHL) to address overall safety and maximum tolerated dose (MTD) (4, 21). Atacicept was administered s.c. weekly for 5 weeks to 4 patient cohorts receiving doses of 2, 4 or 7 mg/kg (n = 4 patients per dose cohort) and 10 mg/kg (n = 3 patients). Atacicept was well tolerated up to 10 mg/kg and showed biological activity; IgA, IgG and IgM concentrations displayed a mean dose-related reduction of 15-40% from baseline levels after 4 weeks of atacicept. The most common AEs associated with atacicept (occurring in $\geq$ 20% of patients) were fatigue (47%) and injection-site bruising (20%). None of the participants achieved a complete or partial response; 26.7% had stable disease at day 56 following 2 mg/kg atacicept treatment and 73.3% had progressive disease.

Preliminary results were reported from an open-label, dose-escalation phase I trial in patients with refractory or relapsed B-cell chronic lymphocytic leukemia (B-CLL) administered atacicept i.v. once weekly for 5 weeks at doses of 1, 4, 10, 15, 20 or 27 mg/kg. No dose-limiting toxicity and no treatment-related SAEs were observed. Stable disease was attained by 3 of 6 patients treated at 10 and 15 mg/kg, 1 of whom was refractory to fludarabine and remained stable for over 6 months (22).

The safety and tolerability of atacicept were also addressed in a phase Ib trial in patients with mild to moderate SLE (23). Atacicept or placebo was administered to

six cohorts of patients. Single-dose cohorts (cohorts 1-4) received one s.c. injection of 0.3, 1, 3 and 9 mg/kg of atacicept. In the repeated-dose cohorts (cohorts 5 and 6) weekly doses of 1 and 3 mg/kg of atacicept, respectively, were administered for a period of 4 weeks. The patients were followed for up to 6 weeks (single-dose cohorts) or 9 weeks (repeated-dose cohorts). Preliminary results from this study demonstrated biological activity for atacicept, with dose-dependent reductions of Ig levels and total B-cell numbers, which were more prominent in the repeated-dose cohorts (IgM, IgA and IgG reduction of ~ 50%, ~33% and ~16%, respectively, in cohort 6; total B-cell reductions of ~40-50% in cohorts 5 and 6). No effect on the numbers of T cells, natural killer (NK) cells or monocytes was observed. Treatment with atacicept was well tolerated with fairly rapid absorption (t_{max} ~24 h; initial distribution phase = 7-14 days). Atacicept was accompanied by mild injection-site reactions but no SAEs.

A multicenter, placebo-controlled, dose-escalating phase Ib study was recently carried out in patients with rheumatoid arthritis (24). Participants (N = 73) were divided into six escalating-dose cohorts receiving s.c. injections of atacicept or placebo as either single (70, 210 or 630 mg) or repeated doses (3 x 70 mg, 3 x 210 mg, 7 x 420 mg) administered at 2-week intervals. The study comprised 10 weeks of trial assessment followed by a single assessment at 3 months after the final dose. Overall, atacicept was well tolerated, with 44% of all patients exhibiting AEs, 56% of which were classified as mild or unrelated to the study medication. Local injection-site symptoms were reported in 24 of 73 patients, the most frequent of which was mild to moderate erythema. The results of hematology, biochemistry, urine, coagulation, vital sign and electrocardiogram (EKG) assessments did not suggest any potential safety concerns. Atacicept-related decreases in Ig (especially IgM) and rheumatoid factor (RF) levels were observed, which were more evident in the cohort treated with 7 doses of 420 mg (IgM decreased by 45%; RF decreased by 41-44%). Pilot information on clinical outcomes was also collected in this study, including DAS28 (Disease Activity Score 28-joint assessment) scores and ACR20 (American College of Rheumatology 20% improvement criteria) responses. DAS28 scores indicated an improvement in rheumatoid arthritis signs and symptoms, especially in the highest repeated dose cohort (mean DAS28 = 6.4 ± 1.3 and 5.1 ± 1.4 at baseline and on day 85 in atacicept-treated patients). During the 3-month atacicept treatment period, 32% of patients attained an ACR20 response or better based on self-assessment of pain and overall disease activity.

The efficacy of atacicept in the treatment of B-cell malignancies and autoimmune conditions is currently being assessed in several ongoing phase II/III clinical trials (25-30).

Sources

Merck Serono; licensed from ZymoGenetics, Inc.

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