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AMG-162

Treatment of Osteoporosis
Bone Cancer Therapy
Treatment of Rheumatoid Arthritis
Human Anti-RANKL Monoclonal Antibody

Fully human monoclonal antibody to receptor activator of NF-κB ligand (RANKL)

EN: 341320

Abstract

Receptor activator of NF-κB ligand (RANKL) is a critical factor in the differentiation and activation of osteoclasts. As a fully human monoclonal antibody to RANKL, AMG-162 binds to RANKL with high affinity and has potential application as a bone antiresorptive agent for the treatment of bone disorders, including osteoporosis and bone metastasis. In cynomolgus monkeys, subcutaneous administration of AMG-162 resulted in highly significant and dose-dependent reductions in serum and urine markers of bone resorption and formation compared with control groups. A significant and dose-dependent increase in bone mineral density was also observed. In postmenopausal women, rapid, dose-dependent and sustained decreases in urinary and serum markers of bone resorption were observed, and in women with low bone mineral density, increases of 4-7% were evident 12 months after initiation of treatment. AMG-162 is in phase III development for the treatment of osteoporosis in postmenopausal women, as well as phase II testing for its potential in metastatic bone disease and rheumatoid arthritis.

Introduction

Receptor activator of NF-κB ligand, or RANKL, is a member of the tumor necrosis factor (TNF) family of cytokines. Naturally occurring proinflammatory cytokines potentiate the inflammatory response by activating chemokines and other inflammatory mediators, and are implicated in the pathogenesis of a number of diseases. RANKL is a crucial modulator of bone remodeling that is required for the development and activation of osteoclasis, or bone erosion. It is therefore a novel and effective target for the treatment of osteolytic bone disorders, including osteoporosis. In osteoporosis, bone fragility is increased because the process of bone resorption overtakes that of new bone formation (1, 2).

AMG-162 is a fully human monoclonal antibody that binds with high affinity and specificity to RANKL. It is being developed as an antiresorptive therapy for the treatment of osteoporosis, and also for cancer-related bone diseases, where aberrant expression of RANKL has been observed in malignant cells. As an inhibitor of the inflammatory process in rheumatoid arthritis, AMG-162 is also being investigated as a new treatment for this disorder (3).

Pharmacological Actions

The effect of monthly dosing with AMG-162 on markers of bone turnover and bone mineral density was evaluated in cynomolgus monkeys administered placebo or AMG-162 at doses of 1, 10 or 50 mg/kg s.c. over 6 months. Doses of 10 and 50 mg/kg resulted in highly significant, dose-dependent reductions in serum and urine markers of bone turnover. Percent reductions in markers compared to those of controls were greater at 3 months than at 6 months after initiation of treatment. Serum osteocalcin at 3 months was 59% less than that of controls in the group receiving 10 mg/kg and 80.7% less than controls in the group administered 50 mg/kg. Corresponding values for urinary *N*-telopeptide (uNTx) were 66.3% and 91.3%, respectively, less than those observed in the control group. Bone mineral density was also significantly increased at 3 and 6 months in a dose-dependent manner, with increases of 11.2% and 14.6% for the proximal tibia and distal radius, respectively, at 6 months in the highest dose group (4).

The pharmacodynamics and pharmacokinetics of AMG-162 were studied in other experiments in

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cynomolgus monkeys. Rapid and profound suppression of bone resorption, as defined by levels of NTx in urine and serum, was obtained. In a single-dose study, AMG-162 was administered at doses of 0.005-3.0 mg/kg i.v. and s.c. In this study, serum NTx (sNTx) was used as the pharmacodynamic marker of bone resorption. Maximum suppression occurred between 1 and 10 days postdose and increased dose-proportionally to a maximum of 71% and 75%, respectively, in the i.v. and s.c. dosing groups. The duration of sNTx suppression was also dose-dependent, reaching 56 days in the 3 mg/kg s.c. group. Peak concentrations of AMG-162 were reached 10.7-96 h postdose. The extent and duration of effect were similar following i.v. and s.c. administration. AMG-162 demonstrated nonlinear pharmacokinetics and serum profiles following i.v. administration were generally triphasic (5).

In another single-dose study, AMG-162 was administered at doses of 0.1-10 mg/kg i.v., or at a dose of 1.0 mg/kg s.c. The average maximum suppression of uNTx following i.v. and s.c. administration was 81-94% and 93%, respectively. Maximal suppression was reached between 1 and 19 days postdose. Duration of suppression increased with i.v. dose to a maximum of 91 days in the 10 mg/kg group. Following this dose, AMG-162 was detectable after 18 weeks. In both single-dose studies, as serum levels of AMG-162 decreased to 2000 ng/ml and below, placebo-normalized serum and urine NTx levels started to return towards baseline values (6).

Clinical Studies

The safety and efficacy of a single s.c. dose of AMG-162 were evaluated in a randomized, double-blind, placebo-controlled study in 49 healthy postmenopausal women. Doses of AMG-162 of 0.01, 0.03, 0.1, 0.3, 1.0 and 3.0 or placebo were administered and subjects were followed up for 6 or 9 months. There was a rapid, dose-dependent decrease in uNTx. Maximal suppression of 84% was observed in the highest dose group at 3 months. In this group, suppression remained above 70% from 12 h postdose until the 6-month time point, and was sustained at 51% at 9 months. The pharmacodynamic response to AMG-162 was consistently observed across all subjects in the higher dose groups. At 3 months, the mean percent decreases from baseline in uNTx were 65%, 78% and 84%, respectively, in the 0.3, 1.0 and 3.0 mg/kg groups; the corresponding values at 6 months were 22%, 59% and 81%. In the placebo group, the mean percent change from baseline was within 10%, with the exception of the first measurement at 12 h. The sNTx values confirmed the findings of the urinary values, although the magnitude of the decrease was not as large. AMG-162 was well tolerated, with no serious adverse events and no clinically significant changes in routine laboratory variables observed. The pharmacokinetics of AMG-162 were nonlinear and serum concentrations > 2000 ng/ml were maintained for a prolonged period (up to 6 months at the highest dose). The changes in NTx values observed in this first clinical study indicated the ability of AMG-162 to specifically inhibit osteoclastic bone resorption, as well as the possibility of infrequent dosing (7, 8).

A total of 411 postmenopausal women with low bone mineral density were enrolled in a randomized, double-blind, placebo-controlled study to evaluate the efficacy of AMG-162. Doses of 6, 14 or 30 mg AMG-162 were administered every 3 months, or 14, 60, 100 or 210 mg every 6 months. Another group also received oral alendronate once weekly. Both dosing regimens resulted in a sustained antiresorptive response. Decreases in serum C-telopeptide were significantly greater in all AMG-162 treatment groups compared to alendronate up to month 2, and in the 3 highest dose groups up to month 4. Dose-dependent increases in bone mineral density were observed, with an increase of 4-7% in lumbar spine bone mineral density in all AMG-162 groups at month 12. AMG-162 was well tolerated, dyspepsia being the most frequently reported adverse event (9, 10).

AMG-162 is currently in phase II clinical development for the treatment of metastatic bone disease and rheumatoid arthritis, and a pivotal phase III study is under way in postmenopausal women with osteoporosis (3).

Source

Amgen, Inc. (US).

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