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Atlizumab

JAN

Treatment of Rheumatoid Arthritis
Treatment of Lymphoma
Treatment of IBD
Treatment of Multiple Myeloma

MRA
R-1569

Immunoglobulin G_1, anti-(human interleukin 6 receptor) (human-mouse monoclonal MRA heavy chain), disulfide with human-mouse monoclonal MRA κ-chain, dimer

CAS: 375823-41-9
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Abstract

Interleukin 6 (IL-6) is a pleiotropic cytokine that regulates immunological responses in host defense, inflammation, hematopoiesis and oncogenesis. Overproduction of IL-6 is observed in several human inflammatory diseases such as rheumatoid arthritis and Castleman's disease and *in vivo* studies using IL-6 transgenic mice have demonstrated that incorporation of the human IL-6 gene results in abnormalaties characteristic of patients suffering from rheumatoid arthritis and Castleman's disease. Thus, an important role for IL-6 in the pathology of these diseases and the potential efficacy of IL-6 blocking agents as a treatment are evident. A new therapeutic strategy involving a humanized antibody to human IL-6 receptor has been reported. Atlizumab is a humanized monoclonal antibody to the human IL-6 receptor that was constructed by grafting the complementarity determining regions (CDR) from mouse PM-1 (a specific monoclonal antibody against human the IL-6 receptor) into human IgG. Atlizumab showed preclinical efficacy in inhibiting IL-6 signal transduction and was selected for further development.

Introduction

Interleukin 6 (IL-6) is a pleiotropic cytokine produced by T-cells, B-cells, monocytes, fibroblasts, keratinocytes, endothelial cells, mesangial cells and some tumor cells. The cytokine exhibits numerous biological activities including regulation of immunological responses in host defense, inflammation, hematopoiesis and oncogenesis. The widespread regulatory activities of IL-6 include induction of T-cell growth and cytotoxic T-cell differentiation via enhancement of IL-2 production and receptor expression. IL-6 acts synergistically with IL-3 on hematopoiesis to form multilineage blast cell colonies and induces terminal macrophage and osteoclast differentiation. The cytokine can act as a megakaryocytic differentiation factor to induce platelet production and as a growth factor, inducing proliferation of mesangial cells, epidermal keratinocytes and plasmacytoma cells, multiple myeloma cells and renal carcinoma cells. It has also been shown to be involved in the acute phase reaction, suppressing albumin production and stimulating production of C-reactive protein (CRP), fibrinogen, α_1-antitrypsin and serum amyloid A production in hepatocytes (1-13).

Overproduction of IL-6 is observed in several human inflammatory diseases such as rheumatoid arthritis and Castleman's disease and interesting observations have been made in *in vivo* experiments using IL-6 transgenic mice. Incorporation of the human IL-6 gene in C57/BL/6 mice resulted in polyclonal hypergammaglobulinemia, splenomegaly, lymphadenopathy, thrombocytosis, inflammatory cell tissue infiltration, mesangial cell proliferation in the kidney, increased fibrinogen levels, decreased serum albumin levels, increased megakaryocytes in bone marrow and death within 4-5 months. Some of these abnormal effects induced by IL-6 overproduction are characteristic of patients suffering from rheumatoid arthritis and Castlman's disease, suggesting a crucial role for IL-6 in the pathology of these diseases and the potential efficacy of IL-6 blocking agents as a treatment (14-16).

Rheumatoid arthritis is a chronic typical immune-inflammatory disease that is characterized by persistent autoimmune activity, pain and inflammation of symmetrical joints, local destruction of bone and cartilage and pannus formation. Patients display increased platelet counts, gamma globulin, CRP, erythrocyte sedimentation rates and serum amyloid A protein and serum/synovial fluid

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IL-6 levels. It has been suggested that IL-6 overproduction is responsible for these effects in addition to osteoporosis and bone cartilage destruction seen in the disease (17-19). On the other hand, Castleman's disease is an atypical lymphoproliferative disorder that is classified into hyaline-vascular or plasma-cell type according to the histological features of affected lymph nodes. The plasma-cell type is characterized by chronic inflammatory symptoms such as fever, fatigue, anemia, an increased erythrocyte sedimentation rate and increased CRP and fibrinogen levels. In addition, patients suffer from hypergammaglobulinemia and autoantibodies are present. Patients may develop lymphocytic interstitial pneumonia and mesangial proliferative glomerulonephritis. All of these abnormalities are consistent with IL-6 overproduction (20-22).

Researchers have therefore devised a new therapeutic strategy involving a humanized antibody to the human IL-6 receptor. Atlizumab (rhPM-1, MRA) is a humanized monoclonal antibody to the human IL-6 receptor that was constructed by grafting the complementarity determining regions (CDR) from mouse PM-1 (a specific monoclonal antibody against the human the IL-6 receptor) into human immunoglobulin G (IgG) (23). Atlizumab showed preclinical efficacy in inhibiting IL-6 signal transduction and was selected for further development as a treatment for IL-6 related diseases such as rheumatoid arthritis and Castleman's disease, as well as juvenile idiopathic arthritis, Crohn's disease, systemic lupus erythematosus, lymphoma and multiple myeloma.

Pharmacological Actions

The blocking effects of atlizumab (5 mg/kg i.v. on day 0) on IL-6 function were demonstrated *in vivo* in cynomolgus monkeys injected s.c. with human IL-6 (5 μg/kg once daily on days 0-6). The single dose of atlizumab completely inhibited the 2-fold increase in blood platelet counts and increases in serum CRP induced by IL-6 treatment. These suppressive effects of the agent were sustained up to 1 week after dosing (24).

Treatment with atlizumab (1 and 10 mg/kg i.v. once weekly for 13 weeks starting on day 1 of collagen immunization) was markedly effective in inhibiting development of collagen-induced arthritis in cynomolgus monkeys *in vivo*. Significant suppression of the clinical symptoms of arthritis including increases in inflammatory parameters such as serum CRP, fibrinogen and erythrocyte sedimentation rate and inhibition of joint destruction were observed in animals treated with the 10 mg/kg dose. Anti-atlizumab antibodies were detected in 5/5 animals treated with the 1 mg/kg dose but only in 1 animal treated with 10 mg/kg (25).

Atlizumab was also shown to be effective *in vitro* in inhibiting proliferation of cloned (KPMM2) and isolated myeloma cells from 20 patients with advanced stage multiple myeloma. The agent significantly and dose-dependently (0.01-50 μg/ml) inhibited growth of the myeloma cell line cultured in the presence of 20 ng/ml IL-6. Moreover, the agent inhibited proliferation (more than 30% in the presence of 10 ng/ml human IL-6) of freshly isolated myeloma cells in 10 of 19 cases; significant inhibition of proliferation was observed in 7 of the 19 cases (28.6 ± 20.2%). Further analysis of the action of the antibody revealed that the agent induced apoptosis of cells. It was suggested that atlizumab was effective in those patients whose multiple myeloma was dependent on IL-6 for growth (26).

Atlizumab was found to sensitize cisplatin-resistant human renal carcinoma cells (Caki-1/DDP and freshly derived cell lines which secrete IL-6 and express IL-6 receptors) to cisplatin *in vitro*. Treatment with atlizumab reversed cisplatin resistance without affecting intracellular cisplatin accumulation. Glutathione *S*-transferase (GST)-π was downregulated in atlizumab-treated Caki-1 cells, indicating a possible mechanism of action for the sensitizing effect of the agent. These results suggest that atlizumab may be effective in combination with cisplatin as a treatment for cisplatin-resistant renal cell carcinoma (27).

A study using a murine model of Crohn's disease demonstrated that treatment with atlizumab abrogated colitis. Colitis was induced by transfer of CD45RBhigh $CD4^+$ T-cells from Balb/c mice to C.B-17-scid mice. Atlizumab-treated mice (2 mg i.p. after T-cell transfer followed by 1 mg weekly) exhibited normal growth as compared to controls (treated with rat IgG) who had weight loss by 3 weeks after transfer of T-cells. Treatment with the agent improved colitis so that a reduction in infiltration of LFA-1^+ monocytes/macrophages and VLAA-4^+ T-cells was observed. In addition, a marked suppression of ICAM-1 and VCAM-1 expression was observed in the colonic vascular endothelium of treated animals. Expression of IFN-γ, TNF-α and IL-1β expression was also decreased with treatment; no significant changes were observed on MAdCAM-1, IL-4, IL-10 or TGF-β expression. Treated mice also exhibited downregulated mucosal inducible nitric oxide synthase (iNOS) as compared to controls in which activity of the enzyme was upregulated. Apoptosis was observed in treated mice, with a reduction in $CD4^+$ T-cell numbers in the colon and spleen. Results suggest that atlizumab may be effective as a treatment for Crohn's disease (28).

Clinical Studies

The safety and efficacy of atlizumab (2, 4 or 8 mg/kg every 2 weeks for 6 months) were examined in an open-label, multiple-dose trial involving 15 patients with rheumatoid arthritis. Treatment was concluded to be well tolerated with no serious adverse events or discontinuations reported. An increase in serum total cholesterol did develop in 10 of the 15 (66%) treated patients. No antinuclear, anti-DNA or anti-atlizumab antibodies were detected. A normalization of serum CRP, erythrocyte sedimentation rate and serum amyloid A protein were

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

Indication	Design	Treatments	n	Conclusions	Ref.
Rheumatoid arthritis	Open, multicenter	Atlizumab, 2 mg/kg 1x/2 wk x 24 wk Atlizumab, 4 mg/kg 1x/2 wk x 24 wk Atlizumab, 8 mg/kg 1x/2 wk x 24 wk	15	Atlizumab was well tolerated and improved clinical and laboratory abnormalities at all doses studied in patients with active rheumatoid arthritis. With the exception of moderate total cholesterol elevation, no serious adverse events were observed and no anti-MRA antibodies were detected	29
Rheumatoid arthritis	Open	Atlizumab, 50 mg iv 2x/wk x 2 mo	8	Atlizumab decreased the levels of matrix metalloproteinase 3 and was effective in the treatment of patients with rheumatoid arthritis	30
Rheumatoid arthritis	Randomized, double-blind, multicenter	Atlizumab, 0.1 mg/kg iv over 1 h (n=9) Atlizumab, 1.0 mg/kg iv over 1 h (n=9) Atlizumab, 5.0 mg/kg iv over 1 h (n=9) Atlizumab, 10.0 mg/kg iv over 1 h (n=7) Placebo (n=11)	45	Atlizumab was well tolerated and improved the signs and symptoms of rheumatoid arthritis by inhibiting IL-6. The apparent therapeutic dose in this study was at least 5 mg/kg	31
Rheumatoid arthritis	Randomized, double-blind, multicenter	Atlizumab, 4 mg/kg iv q 4 wk x 3 mo Atlizumab, 8 mg/kg iv q 4 wk x 3 mo Placebo	164	Atlizumab was well tolerated and dose-dependently reduced disease activity in rheumatoid arthritis patients	32
Castleman's disease	Open	Atlizumab, 1-100 mg iv over 1 h bid → 50-100 mg iv over 1 h od x 5-42 wk Atlizumab, 1-100 mg iv over 1 h bid → 50-100 mg iv over 1 h bid x 5-42 wk	7	Atlizumab was well tolerated and effective in the treatment of patients with Castleman's disease. The drug improved thrombocytosis, lymphadenopathy and the levels of C-reactive protein, fibrinogen, serum amyloid A protein, hemoglobin, albumin and immunoglobulin in serum. These effects were also associated with improvements in renal function abnormalities in patients with amyloidosis	33

observed with treatment in 12 patients (80%); the remaining 3 patients were unable to maintain blood atlizumab levels. All patients had increases in serum albumin. Reductions in tender and swollen joint counts were observed with treatment. The American College of Rheumatology (ACR) 20% and ACR50% responses were 60% and 6.7%, respectively, at 6 weeks, and 80% and 40%, respectively, at 6 months (29) (Table I).

A study examined the serum metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) in 8 patients with rheumatoid arthritis participating in the above open trial involving atlizumab (50 mg/body i.v. infusion twice weekly) and in 5 patients with Castleman's disease also treated with the agent. MMP-3 levels in patients with rheumatoid arthritis were significantly higher than those observed in patients with Castleman's disease and in normal subjects. At 2 months of treatment, 7 and 4 of the 8 patients with rheumatoid arthritis achieved ACR20% and ACR50%, respectively, and displayed significantly reduced MMP-3 levels (30).

The safety and efficacy of atlizumab (0.1, 1, 5 or 10 mg/kg i.v.) were examined in a randomized, double-blind, placebo-controlled, single-dose, dose-escalation trial involving 45 patients with active rheumatoid arthritis. Treatment with the agent significantly improved the symptoms of arthritis and normalized acute phase reactants. Significant effects (ACR20%) were noted as early as 2 weeks in 5 patients (55.6%) receiving 5 mg/kg as compared to none in placebo. Significant improvements in the mean disease activity score were observed at week 2 in patients receiving 5 mg/kg (4.8) and 10 mg/kg (4.7), which were significantly lower than groups receiving 0.1 mg/kg (6.4) and 1 mg/kg (6.2) atlizumab or placebo (7.0). Significant reductions in serum CRP and erythrocyte sedimentation rate were also observed at 2 weeks in the groups receiving the 5 and 10 mg/kg doses. Corticosteroids or disease-modifying antirheumatic drugs (DMARDs) were required in 5, 4, 6 and 2 nonresponders in the 0.1, 1, 5 and 10 mg/kg treatment groups, respectively, as compared to none in placebo. The most common adverse event was diarrhea reported in 8% of the patients. Severe adverse events concluded not to be related to atlizumab were reported by 3, 1, 2 and 2 patients in the 0.1, 1 and 10 mg/kg atlizumab groups and placebo, respectively (31).

The efficacy and safety of atlizumab (4 or 8 mg/kg i.v. every 4 weeks for 3 months) was further demonstrated in a multicenter, randomized, double-blind, placebo-controlled study involving 164 patients with active rheumatoid arthritis who were resistant to DMARDs therapy. Patients

were allowed prednisolone (10 mg/kg or less) and/or NSAIDs but no DMARDs. Serious adverse events were reported in 1.9%, 3.6% and 3.7% of the patients in the 4 and 8 mg/kg atlizumab groups and placebo, respectively. The incidence of infections was 22.2%, 20.0% and 16.7%, respectively, and the overall incidence of adverse events was 81.5%, 89.1% and 72.2%, respectively. No anti-double-stranded DNA or anti-nuclear antibodies were detected. The mean percent reductions in tender and swollen joint numbers in the 8 mg/kg group at 12 weeks were 63.1% and 63.4%, respectively, as compared to 7.7% and 2.6%, respectively, in placebo. A pronounced reduction in serum CRP levels (1.3 ± 0.6 mg *vs.* 4.9 ± 0.4 mg/dl at baseline) and a significant decrease in serum MMP-3 levels were also observed in this group at 12 weeks. Moreover, serum osteocalcin and P1CP (markers of bone formation) were significantly increased. ACR20, ACR50 and ACR70 response rates were 57.4%, 25.9% and 20.4% for the 4 mg/kg group, respectively, and 78.2%, 10% and 16.4% for the 8 mg/kg groups, respectively. ACR responses in both treatment groups were significantly better than placebo. However, only the ACR20 response of the 8 mg/kg group was significantly better than that observed in the 4 mg/kg atlizumab group (32).

Atlizumab (50 and 100 mg i.v. once or twice weekly for 5-42 weeks) was effective in a study involving 7 patients with active multicentric plasma-cell or mixed-type Castleman's disease. Treatment was well tolerated with no severe adverse events observed. Transient, mild decreases in granulocyte counts were observed in 2 patients on the day following administration of atlizumab but counts spontaneously recovered within 2 days. Fever and fatigue disappeared immediately following administration of the agent. In addition, serum CRP, fibrinogen and albumin began to improve. Hypergammaglobulinemia, lymphadenopathy and renal function abnormalities in the 3 patients with secondary amyloidosis markedly improved after 3 months of treatment. In addition, histological examination of affected lymph nodes revealed that treatment decreased follicular hyperplasia and vascularity. No serum anti-atlizumab antibodies were detected in any of the patients (33).

Atlizumab has completed phase II development as a treatment for rheumatoid arthritis in Japan and Europe and will soon begin phase III trials for this indication. Atlizumab continues to undergo clinical development for Castleman's disease, juvenile idiopathic arthritis, Crohn's disease and multiple myeloma (34).

Source

Chugai Pharmaceutical Co., Ltd. (JP), licensed to F. Hoffmann-La Roche AG (CH) for codevelopment.

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