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Metelimumab

Prop INN

Agent for Scleroderma
Human Anti-TGF-β1 Monoclonal Antibody

CAT-192
SL15

Immunoglobulin G_4, anti-(human transforming growth factor β_1) (human monoclonal CAT-192 γ_4-chain), disulfide with human monoclonal CAT-192 κ-chain dimer

CAS: 272780-74-2

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Abstract

Systemic sclerosis, or scleroderma, is a chronic, clinically heterogeneous disorder affecting connective tissue of the skin, internal organs and the walls of blood vessels. Treatment includes the use of diverse agents to treat specific symptoms of organ systems, with varying success, but there are no treatments available that are capable of significantly altering the course of disease. Because cytokines and chemokines such as IL-6, IL-10, IL-18, MCP-1 (monocyte chemoattractant protein-1), MDC (macrophage-derived chemokine) and TGF-β_1 have been implicated in the fibrotic processes underlying systemic sclerosis, immunomodulation including neutralization of these factors represents an attractive strategy for treating the disease. Metelimumab (CAT-192) is a human IgG_4 monoclonal antibody that neutralizes TGF-β_1 which has been chosen for further development for the treatment of diffuse cutaneous systemic sclerosis. In clinical studies, metelimumab was shown to be generally safe and well tolerated, with a long half-life, and has reached phase I/II development.

Introduction

Systemic sclerosis is a chronic, clinically heterogeneous disorder affecting connective tissue of the skin, internal organs and the walls of blood vessels. Also known as scleroderma, diffuse scleroderma, diffuse sclerosis, diffuse cutaneous scleroderma and progressive systemic sclerosis, the disorder has an incidence of 2.6-28 per million individuals per year, with women aged 30-50 the most frequently diagnosed; its occurs 4 times less frequently in men and is relatively rare in children (1-3).

Systemic sclerosis is characterized by alterations in microvasculature, disturbances in the immune system and excessive deposition of collagen and other matrix factors in the skin, blood vessels, skeletal muscles and internal organs (especially the esophagus, gastrointestinal tract, heart, lungs and kidneys). Symptoms are diverse and may be local or systemic (*i.e.*, diffuse) in nature, and their severity varies widely from patient to patient. The symptoms of systemic sclerosis may include: Raynaud's phenomenon, thick and shiny skin on the hands and forearms, hardening of the skin, tight, mask-like facial skin, ulcerations on the fingers and toes, esophageal reflux or heartburn, difficulty swallowing, bloated feeling after eating, weight loss, diarrhea, constipation and shortness of breath (1).

There are several subclasses of systemic sclerosis, which are differentiated by the areas of the body affected and the symptoms. Localized forms of scleroderma are characterized by discrete patches or linear sclerosis of the skin and associated organs (nails, hair and glands) and of the immediately subjacent tissues, without systemic involvement. Systemic forms of scleroderma may be further classified as limited, diffuse or CREST. The CREST syndrome is characterized by calcinosis, usually in the fingers, Raynaud's phenomenon, loss of muscle control of the esophagus causing difficulty swallowing, sclerodactyly and telangiectasia. In patients with mixed connective tissue disease (MCTD), features of scleroderma coexist with other connective tissue disorders such as rheumatoid arthritis, systemic lupus erythematosus or polymyositis (1, 4, 5).

In the majority of those affected with systemic sclerosis, the disease is progressive. In some, remission occurs with a slow progression. People who only have skin

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involvement have a better prognosis. Death may occur from gastrointestinal, cardiac, kidney or pulmonary involvement. The survival rate in general is between 34% and 73% (1, 6).

Several cytokines and chemokines have been implicated in the fibrotic processes underlying systemic sclerosis. IL-10, MCP-1 (monocyte chemoattractant protein-1) and serum IL-6 are linked to pulmonary fibrosis, while MCP-1 and IL-18 have been implicated in the development of kidney disease. Macrophage-derived chemokine (MDC) and IL-10 have been suggested to be involved in esophageal symptoms of systemic sclerosis. In addition, TGF-β_1, which is produced in response to injury in most parts of the body, is believed to be responsible for the formation of excessive scar tissue, *i.e.*, fibrosis. TGF-β_1 both stimulates matrix production and blocks matrix degradation. Immunomodulation including neutralization of cytokines and chemokines therefore represents the most attractive strategy for treating the disease (7, 8).

To date, there are no agents available that are capable of significantly altering the course of disease in patients with systemic sclerosis. However, several drugs have been used to treat specific symptoms or organ systems with varying degrees of success. These include corticosteroids, penicillamine or immunosuppressants for systemic disease; nifedipine for Raynaud's phenomenon; antacids, proton pump inhibitors or H_2 blockers for reflux esophagitis; and angiotensin-converting enzyme (ACE) inhibitors for renal disease. Endothelin antagonists are being used increasingly to treat pulmonary hypertension, a leading cause of death in patients with scleroderma. One novel drug, metelimumab (CAT-192), appears to be a particularly exciting potential treatment for the diffuse cutaneous form of the disease. Metelimumab is a human IgG_4 monoclonal antibody (MAb) that neutralizes TGF-β_1 and has been chosen for further development for the treatment of diffuse cutaneous systemic sclerosis (1).

Pharmacological Actions

Metelimumab was shown in *in vitro* binding assays to be selective for TGF-β_1 over TGF-β_2 and TGF-β_3. The MAb inhibited [^{125}I]-TGF-β_1 binding to A549 cells which bear TGF-β type II receptors with a pIC_{50} of 8.43. The antifibrotic effects of metelimumb were demonstrated *in vivo*. Experiments using double transgenic mice (harboring a collagen type I α_2 chain promoter driving the β-galactosidase and luciferase reporter genes) instilled with bleomycin to induce pulmonary fibrosis showed that treatment with metelimumab (0.5 mg/kg i.v. on days 0, 4 and 9) significantly reduced bleomycin-induced pulmonary collagen type I promoter activity (28.9 ± 5.62% *vs.* 100 ± 17.19% in bleomycin-treated controls). The results suggested that the MAb may be effective in treating fibrotic diseases (9).

Pharmacokinetics

The pharmacokinetics of metelimumab were examined in an ascending-dose (0.1, 0.5, 1, 5 and 10 mg/kg infused over 30 min), placebo-controlled study in 25 healthy volunteers. Metelimumab was generally well tolerated and no serious adverse events were observed. Of a total of 52 adverse events reported (4, 10, 9, 7, 14 and 8 in placebo, 0.1, 0.5, 1, 5 and 10 mg/kg groups, respectively), only 5 were considered to be related to metelimumab treatment. C_{max} values for 1, 5 and 10 mg/kg doses of metelimumab were 21 ± 6.7, 145 ± 8.9 and 265 ± 304 μg/ml, respectively. Clearance values were low (0.58 ± 0.04 and 0.66 ± 0.04 ml/kg/day for 5 and 10 mg/kg, respectively) and the apparent volume of distribution approximated the plasma volume (V_z = 3.1 ± 0.46 and 2.3 ± 0.27 l/70 kg, respectively). The terminal elimination half-life values for the 5 and 10 mg/kg doses were 53 ± 3.2 and 34 ± 3.1 days, respectively. The long $t_{1/2}$ values obtained in this study may reflect the fact that TGF-β_1 is generally absent from healthy individuals. Thus, these values they may not be the same for patients with active TGF-β_1 (10).

Clinical Studies

A multicenter, randomized, placebo-controlled phase I/II trial in 45 patients with diffuse cutaneous systemic sclerosis (within 18 months of disease onset) examined the safety of metelimumab (0.5, 5 or 10 mg/kg i.v. once every 6 weeks for 18 weeks). Metelimumab was generally safe and well tolerated at the dose levels tested. Four deaths occurred, although none was related to treatment. Serious adverse events were seen in 13 patients (including 2 on placebo). Serum levels of metelimumab were at levels that are biologically active (> 10 μg/ml) and the half-life was determined to be 24 ± 2.1 days. There was no significant change in secondary outcomes, which included modified Rodnan skin score (mRSS), durometer measures of skin hardness, a systemic sclerosis health assessment questionnaire, assessment of organ-based disease and biomarkers. However, improvement in mRSS significantly correlated with disease duration. This study was not designed to determine the efficacy of the MAb (11).

Metelimumab is now undergoing phase I/II testing for the treatment of systemic sclerosis (12).

Sources

Cambridge Antibody Technology Ltd. (GB); Genzyme Corp. (US).

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