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Siplizumab

USAN

Antipsoriatic
Treatment of Transplant Rejection

MEDI-507

Immunoglobulin G_1, anti-(human CD2 [antigen]) (human-rat monoclonal MEDI-507 γ_1-chain), disulfide with human-rat monoclonal MEDI-507 light chain, dimer

CAS: 288392-69-8

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Abstract

Psoriasis is a chronic autoimmune inflammatory skin disease for which there is no known cure. The disorder is known to be T-cell-dependent and thus immunosuppressive treatment may be effective in its management. Research efforts in the search for an effective treatment for psoriasis are presently focusing on the discovery of monoclonal antibodies (MAb) or fusion proteins specific for adhesion/signaling molecules involved in T-cell activation. CD2, for example, is an attractive target. It is a glycoprotein present on T cells and natural killer (NK) cells that, via interactions with LFA-3 (CD58) on antigen-presenting cells, plays a crucial role in T-cell activation. Siplizumab (MEDI-507) is a novel MAb with a human IgG_1, κ directed to CD2. The agent has shown potent immunomodulatory effects, selectively suppressing the function of T and NK cells, and has also demonstrated clinical efficacy as a treatment for psoriasis and in the prevention of graft-*versus*-host disease.

Introduction

Psoriasis is an inherited chronic autoimmune inflammatory skin disease afflicting 2% of the U.S. and European populations with approximately 150,000-260,000 new cases reported annually in the U.S. The disorder involves genetic, immunological and infectious factors and about 15% of all individuals suffering from psoriasis develop inflammatory arthritis (1-3). The most common type of psoriasis is vulgaris or plaque psoriasis. Other existing forms include guttate, inverse, pustular and erythrodermic. Psoriasis is characterized by epidermal cell hyperproliferation, infiltration of inflammatory cells and angiogenesis resulting in erythematous plaques. A 40-fold increase in the number of epidermal mitotic cells is observed in addition to a decrease in the transit time of these cells through the living layer from approximately 12 to 2 days (4). Moreover, there are extensive changes in epidermal histology and gene expression comparable to that seen during wound healing. The nonliving cornified skin layer becomes thicker and disorganized and keratinocytes begin to express new structural proteins such as intermediate filament subunits keratins 6 and 16 and precursor proteins for the epidermal cornified envelope (1, 5-8).

Psoriasis is a T-cell-dependent autoimmune disease, although genetic and environmental factors all play a role in its pathology. Because psoriasis involves an interaction between inflammatory cells, particularly T cells and keratinocytes, immunosuppressive treatment can be an effective therapy. T cells infiltrating psoriatic lesions include those with a memory-effector phenotype (CD45RO+) that express CD4 or CD8 markers. These cells preferentially secrete interferon-γ and low levels of IL-4 which is indicative of Th1 cells. The factor(s) which stimulate T-cell activation in psoriasis remain unclear. It is known that streptococcal A-induced throat infections can lead to guttate psoriasis and a structural relationship has been found between streptococcal protein M and keratin type I whereby T cells activated by streptococcal infection recognize the keratin in keratinocytes. The result is a cross-reactivity against keratinocytes (1, 9-11). Other evidence, including results from a study in which HPV5 DNA was identified in skin of 90% of psoriatic patients, suggests that the human papillomavirus type 5 (HPV5) may also be involved in the pathogenesis of psoriasis (12).

Several therapies are currently available for the management of psoriasis, including treatment with methotrexate, retinoids and ciclosporin. However, safety concerns

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have restricted the clinical use of these agents. Topical therapies with varying mechanisms of actions are also available and include ultraviolet light, glucocorticoids, 1,25-dihydroxyvitamin D_3 analogs and the retinoid, tazarotene. Other possibly more effective therapeutics under development are the immunosuppressive biological macromolecules such as hu1124 (efalizumab), the humanized version of the murine anti-human CD11a monoclonal antibody (MAb) MHM24 and alefacept (Amevive™), a soluble LFA-3 construct in the form of a human Ig fusion protein that can block or suppress receptors required for T-cell activation (13, 14). Research efforts are continuing to focus on the discovery of other MAbs or fusion proteins specific for adhesion/signaling molecules to be used as immunotherapies. These new therapies are more selective and less toxic. Disruption of the different accessory molecule pathways (*e.g.*, CD2/lymphocyte function antigen-3 [LFA-3, CD58], ICAM-1/LFA-1, CD28/B7, VLA4/VCAM) that are involved at different points during T-cell activation enabling optimal T cell responses results in inhibition of T-cell responses.

A particularly interesting target is CD2, a 50-55 kDa glycoprotein present on T cells and natural killer (NK) cells that functions as an adhesion and signaling molecule playing a crucial role in T-cell activation through its interaction with its primary ligand LFA-3 (CD58) on antigen-presenting cells. The intracellular domain of CD2 can also induce or enhance signaling associated with protein tyrosine kinases lck and fyn that are involved in the phosphorylation of the CD3ζ chain (1, 15). One novel agent that is a MAb to CD2 is a humanized version of the rat MAb BTI-322 (LO-CD2a) (16, 17). Siplizumab (MEDI-507) is a human IgG_1 MAb with the κ-chain directed to an epitope distinct from the N-terminal ligand binding domains T11-2 or T11-2 and it has been shown to selectively suppress the function of T and NK cells. Due to its potent, selective immunomodulatory efficacy, siplizumab was chosen for further development as a treatment for chronic inflammatory conditions such as psoriasis and for autoimmune disorders such as in acute organ rejection and graft-*versus*-host disease (GvHD).

Pharmacological Actions

The *in vitro* activity of MEDI-507 was examined in order to characterize its mode of action. Binding studies using human peripheral blood mononuclear cells (PBMCs) isolated from healthy adult volunteers and [^{125}I]-labeled MEDI-507 showed that both BTI-322 and MEDI-507 equally compete for the same epitope (IC_{50} = 1 nM for both MAbs) which is distinct from T11-1 and T11-2. The effect of the MAbs were compared in a primary mixed lymphocyte reaction (MLR) with results showing similar activity for the 2 MAbs. In contrast to an isotype-matched human IgG molecule and MEDI-507 $F(ab')_2$ fragments which had no inhibitory effects, maximum inhibition of proliferation (about 98%) was observed at the onset of the reaction with significant subsequent inhibition seen through day 5. Analysis of the MEDI-507-treated cells from the MLR revealed marked deletion of T and NK cells. Moreover, when the NK cell population was removed from the MLR, MEDI-507 did not inhibit proliferation or delete T cells. However, reconstitution with autologous NK cells (95% or more CD16+CD56+) restored MEDI-507 activity. Examination of DNA fragmentation of MEDI-507-treated activated PBMCs showed that after 4 days of activation, no degradation of chromosomal DNA was observed, indicating a lack of apoptosis. From these results, it was concluded that NK cells preferentially target activated T cells with MEDI-507 bound to CD2 via a nonapoptotic cytotoxic mechanism (18).

Clinical Studies

Results are available from 3 initial trials with siplizumab involving patients with moderate to severe psoriasis with at least 10% of their body surface area affected. The first trial was an open-label phase I trial examining the safety of single i.v. infusion doses (0.4-40 μg/kg) of the agent in a total of 14 patients, while the second trial was an open-label, dose-escalation phase I/II study involving 26 patients who received up to 8 weekly i.v. infusions of the agent (0.0012-0.04 mg/kg). The third trial was also an open-label, dose-escalation trial involving 39 patients who received up to 12 weekly s.c. injections of siplizumab (0.1-7.0 mg). Overall, siplizumab was concluded to be well tolerated with generally mild and transient (*i.e.*, a decrease observed with continued dosing) adverse effects associated with treatment. The most common adverse events reported were chills, headache, reduced heart rate and injection site reaction (following s.c. administration only). Although dose-dependent reductions in mean absolute lymphocyte counts that correlated with clinical outcome were seen after both i.v. and s.c. administration, the reductions following s.c. administration were less marked. In the multiple i.v. dose study, improvements in the Psoriasis Area and Severity Index (PASI) scores were seen with all doses, although the clinically greatest benefits were seen in patients treated with doses of 1.2 μg/kg or higher. A dose of 40 μg/kg i.v. resulted in the highest peak serum levels of the agent and maximum activity. The greatest activity against the disease following s.c. dosing with siplizumab was seen with the higher doses of 5 and 7 mg/kg s.c. Results from all trials showed that at the highest siplizumab doses (0.04 mg/kg i.v. and 5 or 7 mg/kg s.c.) more than 55 and 33% of the patients experienced at least a 50 and 75% improvement, respectively, in PASI scores; overall, 70% of the patients experienced an improvement in PASI of 25% or greater. Follow-up analysis confirmed the safety and efficacy results seen during treatment and indicated the durability of response after treatment (19-23) (Table I).

Three multicenter, randomized, double-blind, placebo-controlled phase II trials are currently underway to determine the efficacy and safety of siplizumab as a treatment for psoriasis. They include an s.c. administra-

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

Indication	Design	Treatments	n	Conclusions	Ref.
Psoriasis	Open, pooled/ meta-analysis	Study I: Siplizumab iv Study II: Siplizumab, 0.4-40 g/kg iv 1x/1wk x 8 wk	40	Multiple doses of siplizumab were well tolerated and effective in psoriasis. Clinically significant disease response was observed at doses of 1.2 μg/kg or higher	19
Psoriasis	Open	Siplizumab, 0.1-7 mg sc 1x/wk x 12 wk Siplizumab iv (control)	39	Siplizumab was well tolerated and decreased disease activity in psoriasis	20
Psoriasis	Open, pooled/ meta-analysis	Study I: Siplizumab iv Study II: Siplizumab, 0.4-40 mg/kg iv 1x/wk x 8 wk Siplizumab, 0.012 mg/kg iv 1x/wk x 8 wk Siplizumab, 0.04 mg/kg iv 1x/wk x 8 wk Study III: Siplizumab, 0.1-7.0 mg/kg sc 1x/wk x 12 wk Siplizumab, 3.0 mg/kg sc 1x/wk x 12 wk Siplizumab, 5.0 mg/kg sc 1x/wk x 12 wk Siplizumab, 7.0 mg/kg sc 1x/wk x 12 wk	79	Multiple doses of siplizumab were well tolerated and effective in psoriasis, having significant biological activity even at doses <0.1 mg/kg	21
Malignant neoplasm		Siplizumab, 0.1 mg/kg x 1 d (d -2) → Siplizumab, 0.6 mg/kg x 3 d (d –1, 0, 1) + Cyclophosphamide, 50 mg/kg/d x 3 d (d –5 to –3) + Ciclosporin Siplizumab, 0.1 mg/kg x 1 d (d –7) → Siplizumab, 0.6 mg/kg x 2 d (d –6, –5) + Cyclphosphamide, 50 mg/kg/d x 3 d (d –5 to –3) + Ciclosporin	7	The host or donor T-cell avoiding depletion with siplizumab might play an important role in graft loss and in the development of graft-*vs*.-host disease in recipients of extensively HLA-mismatched bone marrow transplants	25
Bone marrow transplant, leukemia, lymphoma	Open	Cyclophosphamide, 50 mg/kg x 3-4 d (d –6 to –3) + Anti-thymocyte globulin (equine), 15-30 mg/kg from d -2 to +5 + Thymic irradiation (in 8 patients without previous mediastinal irradiation) + Ciclosporin, from d –1 Cyclophosphamide, 50 mg/kg x 3-4 d (d –6 to –3) + Thymic irradiation (in 8 patients without previous mediastinal irradiation) + Ciclosporin, from d –1 + Siplizumab, 0.1 mg/kg (d –2) [increased to 0.6 mg/kg x 3 d (d –1 to +1)] or Siplizumab, 0.1 mg/kg (d –7) [increased to 0.6 mg/kg x 2 d (d –6 to –5)]	21	Siplizumab was more effective than anti-thymocyte globulin (equine) in preventing graft-*vs*.-host disease after haploidentical disease bone marrow transplantation	26
Graft-*versus*-host disease, lymphoma		Siplizumab + [if no previous mediastinal therapy] Thymic irradiation, 700 cGy on d –1 + Cyclophosphamide, 150-200 mg/kg/d (peritransplant) + Ciclosporin (beginning d –1 with rapid taper to discontinuation by d 35) → Prophylactic donor leukocyte infusions Anti-thymocyte globulin (equine), 15-30 mg/kg x 3-4 d (d –2 to 5) + [if no previous mediastinal therapy] Thymic irradiation, 700 cGy on d –1 + Cyclophosphamide, 150-200 mg/kg/d (peritransplant) + Ciclosporin (beginnign d –1 with rapid taper to discontinuation by d 35) → Prophylactic donor leukocyte infusions	20	Siplizumab might be effective in patients with chemorefractory diffuse large B-cell lymphoma receiving non-myeloablative bone marrow transplantation	27

tion trial involving 420 patients at 44 sites in North America, an i.v. administration trial with 124 patients at about 25 sites in North America and a s.c. trial with 121 patients at about 20 European sites (23).

Siplizumab has also completed early clinical evaluation in GvHD. Results from phase I/II trials in patients with steroid-naive, severe GvHD demonstrated that siplizumab when combined with conventional steroid therapy was well tolerated. One study involved 7 patients with advanced hematologic malignancies receiving non-myeloablative conditioning which included siplizuman (group A: 0.1 mg/kg on day -2 followed by 0.6 mg/kg on

days –1, 0 and 1; or group B: 0.1 mg/kg on day –7 followed by 0.6 mg/kg on days –6 and –5), cyclophosphamide (50 mg/kg/day on days –5, –4 and –3) and ciclosporin (starting on day –1) administered before HLA-mismatched bone marrow transplants; 5 of the 7 patients also received thymic irradiation (700 cGy) on day –1. Mean T-cell counts on days 28 were lower than cell counts from patients in group B (4 ± 2.6 *vs.* 138 ± 160 T cells/mm^3; $p = 0.06$). Similar mean B (0 and 3 cells/mm^3) and NK (46 and 81 cells/mm^3) cell counts were observed for both treatment groups. On day 28, most of the T cells present (62-99%) in the 4 patients in group A were host-derived, in contrast to group B in which most of the T cells (60 and 97%) of 2 of the 3 patients were donor-derived. Mixed chimerism was seen in all white blood cell lineages in all patients. However, while chimerism was sustained through day 100 in 2 of the 3 patients in group B, chimerism in the 4 patients in group A was undetectable by days 21, 47, 70 and 100, respectively. None of the patients in group A developed GvHD as compared to 2 patients with sustained chimerism in group B who developed acute grade II and IV GvHD, respectively. It was concluded that host or donor T cells which escape siplizumab-induced depletion may be involved in graft loss and development of GvHD, respectively (24-27) (Table I).

Siplizumab continues to undergo phase II testing for the treatment of psoriasis and the prevention of GvHD (24, 28).

Source

MedImmune Inc. (US) codeveloped with BioTransplant, Inc. (US).

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