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Visilizumab

Prop INN, USAN

Treatment of Transplant Rejection
Treatment of IBD
Antipsoriatic

1DT3-D
HuM291
SMART anti-CD3
Nuvion™

Immunoglobulin G_2, anti-(human antigen CD3) (human-mouse monoclonal HuM291 γ_2-chain), disulfide with human-mouse monoclonal HuM291 κ-chain, dimer

CAS: 219716-33-3
EN: 241764

Abstract

Despite the availablity of several immunosuppressive regimens, acute graft-*versus*-host disease (GvHD) continues to be a major problem for recipients of kidney, heart, liver and hematopoietic cell transplantation and particularly in those patients with glucocorticoid-refractory GvHD. The murine antibody OKT3 which induces T-cell activation through Fc γ receptor (FcR) binding and recruitment of antigen-presenting cells has shown clinical efficacy against GvHD. However, it is associated with severe cytokine release syndrome and stimulation of a human anti-mouse antibody response, thus limiting its clinical application. A possible solution to reduce toxicity in this clinical scenario would be to avoid T-cell activation. Thus, non-FcR-binding anti-CD3 monoclonal antibodies (MAbs) have been developed which do not activate resting T cells and have been shown to be associated with less cytokine-induced toxicity *in vivo*. Visilizumab is a novel non-FcR-binding anti-CD3 Mab that has been chosen for further development as a treatment for acute GvHD.

Introduction

Although several effective immunosuppressive therapies are available for prophylaxis after transplantation, acute graft-*versus*-host disease (GvHD) continues to be a major obstacle for success following kidney, heart, liver and hematopoietic cell transplantation. Systemic glucocorticoids are commonly used to treat established acute GvHD although more than 60% of the patients treated continue to suffer from the disease. There is presently no dependable therapy for these particular patients with glucocorticoid-refractory GvHD who continue to show poor survival (1-5).

Acute GvHD is mediated by donor T cells. Thus, induction of central and peripheral T-cell tolerance by using specific antigens is an attractive treatment option to eliminate the disease. Research efforts have focused on developing specific antigens which cause activation-induced apoptosis of peripheral T cells via interactions with the T-cell receptor (TCR) and ultimately result in peripheral transplant tolerance. Studies using a murine model of acute GvHD have shown that triggering TCR anti-CD3 antibodies resulted in selective apoptosis of recipient alloantigen-activated donor T cells and prevention of GvHD (6, 7). In fact, the murine anti-CD3 antibody OKT3 (Orthoclone OKT3; Ortho Pharmaceutical Corp.), which can transiently deplete circulating $CD2^+CD3^+$ T cells thus suppressing cell-mediated immune responses, has been shown to be an effective immunosuppressive agent for the prevention or treatment of acute rejection following kidney, heart or liver transplantation. OKT3 has been specifically indicated for steroid-refractory allograft rejection (5, 8-13). However, the clinical use of OKT3 is limited since treatment with this murine antibody is associated with severe cytokine release syndrome (CRS) and stimulation of a human anti-mouse antibody (HAMA) response (14-18). OKT3 induces T-cell activation through Fc γ receptor (FcR) binding and recruitment of antigen-presenting cells. Activation of resting T cells leads to cytokine release and thus possible increased toxicity. Thus, one possible solution to ensure less toxicity would be to avoid T-cell activation. Non-FcR-binding anti-CD3 monoclonal antibodies (MAbs) have been developed which do not activate resting T cells and have been shown to be associated with less toxicity due to cytokine release *in vivo* (19, 20).

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There are currently several MAbs under development for treatment of various autoimmune diseases such as GvHD as well as psoriasis, multiple sclerosis, uveitis and rheumatoid arthritis. One such agent is the novel non-FcR-binding anti-CD3 MAb visilizumab (HuM291, Nuvion™). Visilizumab is a bispecfic humanized immunoglobulin G_2 (IgG_2) MAb formed by the fusion of the mouse 1D10 antibody specific to 28/32 kDa heterodimeric antigen present on the surface of malignant B cells and the OKT3 antibody specific to the invariant CD3episilon chain of TCR on the surface of T cells. Moreover, visilizumab bears specific mutations in the Fc domain that decreases its affinity for the FcR and thus is less mitogenic to human T cells. Visilizumab also dissociates rapidly from TCR, resulting in minimal internalization of TCR and thus longer expression of the receptor. This allows for sustained signaling by visilizumab leading to apoptosis (19, 21). Visilizumab has been chosen for further development as a prophylaxis and treatment for acute GvHD as well as other autoimmune diseases including psoriasis, ulcerative colitis, myelodysplastic syndrome and systemic lupus erythematosus.

Pharmacological Actions

The efficacy of visilizumab was compared to OKT3 *in vitro* and *in vivo* in a study using preactivated human T cells and immunodeficient SCID mice transplanted with human PBMCs. Visilizumab induced significantly more apoptosis at 24 h compared to the murine OKT3 and dissociated more rapidly from the T-cell surface and caused less T-cell internalization as compared to murine OKT3. Crosslinking surface bound visilizumab to antiglobulin resulting in a reduction of apoptosis to levels seen with OKT3, indicating that crosslinking by Fc/FcR interactions inhibits apoptosis. It was concluded that because visilizumab dissociates rapidly from TCR, it enables prolonged expression of TCR and thus sustained signaling resulting in increased activation-induced T-cell apoptosis. The immunosuppressive activity of visilizumab *in vivo* correlated with the *in vitro* results. Visilizumab-treated mice were protected longer from lethal GvHD than OKT3- or vehicle-treated animals. It was concluded that visilizumab may induce transplantation tolerance via selective depletion of activated pathogenic T cells (22).

An *in vitro* study using human peripheral blood mononuclear cells (PBMCs) isolated from healthy volunteers further examined the signaling effects of visilizumab on T lymphocytes. Results revealed that the MAb caused incomplete phosphorylation of TCRζ indicating partial agonist signaling. Visilizumab activated ERK1/2 and upregulated CD69 (29% at 24 h and 43% at 48 h) and CD25 (8% at 24 h and 15% at 48 h) surface expression in both $CD45RO^-$ and $CD45RO^+$ T cells; visilizumab did not activate ZAP-70 or phosphorylate the transmembrane linker molecule LAT. Moreover, a dose-dependent (0.1-10 μg/ml) induction of anergy via a mechanism independent of TCR modulation was observed in human primary resting T cells treated with the MAb. Addition of IL-2 prevented the induction of T-cell unresponsiveness due to visilizumab treatment, with cells proliferating normally to rechallenge with OKT3 (0.1 μg/ml) and anti-CD28 antibodies (5 μg/ml) (23).

The efficacy and safety of visilizumab was further characterized *in vitro* and *in vivo* in a study using chimpanzees. Treatment of chimpanzee PBMCs *in vitro* with visilizumab resulted in downregulation of CD3 and marked reductions in cytokine production and cell proliferation as compared to OKT3. The safety of the agent was demonstrated *in vivo* in chimpanzees administered multiple doses (3-6 doses of 0.1, 1 and 10 mg/animal over 1-2 weeks). No adverse events, toxicities or CRS were observed with multiple dosing. The elimination $t_{1/2}$ value of the agent was 81.5 h and serum levels after 3 doses of 10 mg were greater than 1000 ng/ml; these levels were sustained for 1 week. Multiple doses of 10 mg resulted in complete depletion of circulating $CD2^+CD3^+$ T cells for up to 10 days after the last dose. By day 28, T cells recovered and were responsive to stimulation by alloantigens and PHA. Anti-visilizumab antibodies were detected in 4 of 12 treated animals; however, they were transient in 2 of these 4 animals (24).

Clinical Studies

Visilizumab was shown to effectively induce peripheral T-cell apoptosis in a study involving 11 patients with acute GvHD following allogeneic hematopoietic cell transplantation prior to steroid therapy. T-cell apoptosis was measured from cultured freshly isolated PBMCs treated for 24 h with visilizumab or the murine IgG_{2b} anti-CD3 antibody BC3 (50 ng/ml). While visilizumab significantly increased lymphocyte apoptosis to 49.5 ± 13.6 from basal spontaneous levels of 26 ± 9.3, no significant increase was observed with BC3 (28.4 ± 9.5). Visilizumab was ineffective in significantly increasing T-cell apoptosis in 6 patients without acute GvHD (22.3 ± 15.3 to 24.7 ± 2.1). Initially, visilizumab-induced apoptosis was more rapid in $CD4^+$ T cells but by 48 h, progression of apoptosis was equal for both $CD4^+$ and $CD8^+$ cells. From these results, it was concluded that visilizumab may be clinically more immunosuppressive than BC3 and more selective in inducing deletion of host-reactive T cells responsible for GvHD (25).

The efficacy of visilizumab (0.0015, 0.0045, 0.015, 0.03 or 0.045 mg/kg every other day for a total of 3 doses) was examined in an open-label, multiple-dose phase I trial involving 16 renal transplant recipients concomitantly undergoing steroid treatment (250 mg/day Solumedrol for 3 consecutive days) for acute rejection. Significant $CD3^+$ cell depletion was observed following treatment with 3 doses of 0.045 mg/kg (24, 5, 40, 107 and 69 cells on days 1, 3, 5, 7 and 14, respectively, *vs.* 481 cells at baseline). The median time to recovery of $CD3^+$ cells (>100 cells) was 24 days for 4 of the 5 patients treated with the highest dose. All but 1 patient had levels of TNF-α,

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

Indication	Design	Treatments	n	Conclusions	Ref.
Renal transplant	Open	Visilizumab, 0.0015 mg/kg 1/2 d x 3 doses + Methylprednisolone sodium succinate, 250 mg/d x 3 d Visilizumab, 0.0045 mg/kg 1/2 x 3 doses + Methylprednisolone sodium succinate, 250 mg/d x 3 d Visilizumab, 0.015 mg/kg 1/2 d x 3 doses + Methylprednisolone sodium succinate, 250 mg/d x 3 d Visilizumab, 0.03 mg/kg 1/2 d x 3 doses + Methylprednisolone sodium succinate, 250 mg/d x 3 d Visilizumab. 0.045 mg/kg 1/2 d x 3 doses + Methylprednisolone sodium succinate, 250 mg/d x 3 d	16	Significant depletion of CD3 cells with littñe evidence of cytokine release was observed in patients receiving doses of 0.03 mg/kg or higher	26
Renal transplant	Open	Visilizumab, 0.015 μg/kg iv sd (before transplantation) Visilizumab, 0.15 μg/kg iv sd (before transplantation) Visilizumab, 0.0015 mg/kg iv sd (before transplantation) Visilizumab 0.0045 mg/kg iv sd (before transplantation) Visilizumab, 0.015 mg/kg iv sd (before transplantation)	15	The three highest doses of vislizumab dose-dependently depleted T cells within hours of administration with a good tolerability and mild to moderate symptoms of cytokine release	27
Graft *versus* host diseases	Open	Visilizumab, 0.25 mg/m^2 1/2d x 7 doses (n=3) Visilizumab, 1 mg/m^2 1/2d x 7 doses (n=3) Visilizumab, 3 mg/m^2 x 1 dose (n=11)	17	Visilizumab demonstrated good tolerability and efficacy in advanced graft-*versus*-host disease	28

interferon-γ and IL-6 below the detection limit and only minimal symptoms of cytokine release were observed. According to physician assessment, acute rejection was reversed in 7 of 8 patients in the groups receiving 0.03 or 0.045 mg/kg doses (26) (Table I).

The efficacy of visilizumab (0.015 or 0.15 μg/kg or 0.0015. 0.0045 or 0.015 mg/kg i.v. bolus 1-7 days before transplantation) was further characterized in a phase I single-dose study involving 15 patients with end-stage renal disease scheduled to receive renal allografts from living donors. Single-dose visilizumab was well tolerated. The most frequent adverse events were mild to moderate headache (73%), nausea (47%), chills (53%) and fever (47%) occurring within the first hours after visilizumab injection and resolving within 24-48 h; these adverse events were considered to be due to cytokine release. TNF-α, interferon-γ and IL-6 levels could only be detected (13-3122 pg/ml) 1-6 h postdosing in patients receiving the 3 highest doses but these levels were generally undetectable by 24 h postdosing. Four patients suffered serious adverse events possibly related to visilizumab which included clotting of a fistula in 2 patients with a history of fistula thrombosis given 0.0015 and 0.0045 mg/kg, respectively, chemical cellulitis in 1 patient treated with 0.0045 mg/kg and an increased serum creatinine and reduced hematocrit in 1 patient treated with 0.0045 mg/kg. Rapid and marked depletion of peripheral $CD2^+CD3^+$ T cells was seen within 2 h of injection of doses of 0.0015 mg/kg or greater. T cells were completely depleted for about 1 week with doses of 0.0045 and 0.015 mg/kg (27) (Table I).

The safety, efficacy and pharmacokinetics of visilizumab were examined in a phase I multiple-dose study involving 17 patients with glucocorticoid-refractory acute GvHD. Initially, 6 patients were administered doses of the agent (0.25 or 1 mg/m^2) on days 1, 3, 5, 7, 9, 11 and 13. However, because multiple dosing with 1 mg/m^2 resulted in delayed accumulation of visilizumab and prolonged lymphopenia, the remaining 11 patients were administered single doses of 3 mg/m^2 on day 1. Patients treated with 0.25 and 1 mg/m^2 had C_{max} values at 1 h after the first dose of 152 ± 23 and 791 ± 44 ng/ml, respectively, and terminal elimination half-life values of 103 and 177 h, respectively. Results from 3 patients treated with 1 mg/m^2 revealed that the number of doses administered significantly correlated with trough visilizumab levels indicating accumulation of the agent and delayed clearance. The C_{max}, terminal elimination half-life and mean systemic serum clearance values in patients treated with a single dose of 3 mg/m^2 were 2217 ± 148 ng/ml, 162 ± 18 h and 6.99 ± 1.23 l/m^2/h, respectively. Although high intersubject variability was noted, levels were not correlated to GvHD response rates. Improvement in GvHD was seen in all patients. A total of 15 patients were evaluable through day 42. Of the 6 patients receiving multiple visilizumab dosing, 1 complete response and 5 partial responses were seen. However, all 6 patients died at a median of 87 days after initiating therapy. Of the 11 patients receiving single-dose visilizumab, 6 had complete responses and 3 had partial responses and 7 had significantly increased survival (median 359 days). No allergic reactions were observed or development of human antibodies against visilizumab detected. Three

grade 1 acute infusional toxicities were reported. Two of the first 7 patients to start visilizumab treatment developed posttransplant lymphoproliferative disease (PLTD) and had plasma Epstein-Barr virus (EBV) DNA titers of > 1000 copies/ml. Thus, 5 of the next 10 patients who showed rising EBV DNA titers were given rituximab resulting in a lowering of EBV DNA to below detection limits and no development of PLTD (28) (Table I).

Visilizumab has entered a single-arm, multicenter phase II trial in 80 patients with steroid-resistant acute GvHD to evaluate survival at 180 days. The agent will be administered (3 mg/m^2) within 100 days following allogeneic hematopoietic cell transplantation and a second dose may be given if GvHD recurs within 14-42 days after an initial response. In addition, a phase I/II trial in primary GvHD is planned and visilizumab is expected to be evaluated in phase I trials in ulcerative colitis, myelodysplastic syndrome and systemic lupus erythematosus (29).

Manufacturer

Protein Design Labs, Inc. (US).

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