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Zanolimumab

Rec INN; USAN

Anti-CD4 Monoclonal Antibody
Treatment of T-Cell Lymphoma

HM6G
HuMax-CD4®
MDX-016
MDX-CD4

Immunoglobulin G_1, anti-(human CD4 [antigen]) (human monoclonal 6G5 heavy chain), disulfide with human monoclonal 6G5 light chain, dimer

CAS: 652153-01-0

EN: 271789

Abstract

Zanolimumab (HuMax-CD4®) is a human monoclonal antibody that acts as a CD4 antagonist. Zanolimumab locks on to an epitope expressed by a subset of T-cells and on human monocytes on membrane-bound CD4. Zanolimumab concentration-dependently inhibits T-cell activation and proliferation, thereby affecting and downregulating circulating and skin-residing $CD4^+$ cells. Zanolimumab has not proven effective in the treatment of psoriasis or rheumatoid arthritis. It appears, however, to have promise in treating cutaneous T-cell lymphoma (CTCL) and in particular its variant, mycosis fungoides (MF). Zanolimumab appears to be less effective against Sézary syndrome. It is also being investigated for noncutaneous T-cell lymphoma (NCTCL).

Introduction

Zanolimumab is a human monoclonal antibody that acts as a CD4 antagonist. A high-affinity, human monoclonal $IgG_{1\kappa}$ antibody, zanolimumab targets the CD4 molecule on T-cells. Zanolimumab is available in an intravenous formulation. Zanolimumab was originally studied for the treatment of both rheumatoid arthritis and psoriasis, although trials for both were discontinued due to lack of efficacy. Phase II studies for use in the treatment of cutaneous T-cell lymphoma (CTCL) in both early and advanced stages have shown initial promise, especially in the treatment of the mycosis fungoides (MF) variant, and a phase III trial is under way.

Preclinical Pharmacology

Zanolimumab locks on to an epitope expressed by a subset of T-cells and on human monocytes on membrane-bound CD4. The binding avidity (K_a) of zanolimumab to T-cells isolated from humans was 20 x 10^9 M^{-1}. Zanolimumab concentration-dependently inhibits T-cell activation and proliferation. The mechanism remains to be fully defined, but may involve antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by natural killer (NK) cells, resulting in CD4 cell downmodulation, inhibiting signal transduction and physically blocking the interaction of CD4 with major histocompatibility class (MHC) II molecules (1, 2).

Zanolimumab affects circulating and skin-residing $CD4^+$ cells. Researchers analyzed the depleting effect of zanolimumab on $CD4^+$ T-cells in human inflammatory skin in a murine human psoriasis skin xenograft model by injecting zanolimumab intraperitoneal. at 20 mg/kg on day 1 and at 10 mg/kg on days 8 and 15. They noted a significant reduction in the number of $CD4^+$ T-cells after zanolimumab treatment (3.0 cells/mm section) compared with a phosphate-buffered saline (PBS) control (18.2 cells/mm section). Researchers further investigated the mechanism of T-cell depletion caused by zanolimumab in PBS cell-derived PKH26-labeled $CD4^+$ T-cells incubated with zanolimumab (0-1 μg/ml). Zanolimumab did not induce complement-dependent cytotoxicity or apoptosis but did trigger ADCC that was mediated by NK cells. The percentage of cell lysis increased concentration-dependently, ranging from 14% to 90% (1).

Researchers also investigated the effects of bolus injections *versus* slow infusion on circulating $CD4^+$ cells in chimpanzees and cynomolgus monkeys. Eight chimpanzees received 0.1, 0.6 or 2.0 mg/kg of the antibody over a 1-min period, and 11 monkeys received 0.2, 0.6 or 2.0 mg/kg of the antibody or PBS over 30 s. In monkeys, circulating $CD4^+$ cells were depleted for up to 6 months with 2 mg/kg of zanolimumab, while only a transient

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decrease (on day 1) was observed in chimpanzees at the same dose. In both species, lower doses induced a transient reduction in the quantity of $CD4^+$ and $CD8^{+/-}$ cells. Investigators then administered slow infusions of 0.02, 0.05, 0.2 or 0.5 mg/kg of zanolimumab over 30 min and 2 mg/kg over 30 min or 2 h to 17 additional monkeys. Increasing infusion time from 30 s to 30 min for doses of 0.5 mg/kg or below did not alter circulating $CD4^+$ cell numbers. However, the slower infusion reduced the $CD4^+$ cell depletion produced by 2 mg/kg of zanolimumab: on day 1 after infusion, $CD4^+CD8^-$ cells decreased on average by 49% from baseline compared with 68% for the bolus infusion. Conversely, a slower infusion rate was also associated with a faster recovery time; after 1 month, an average of 30% of $CD4^+CD8^-$ cells were depleted in monkeys which received the slower infusion compared with 64% in those which received the bolus infusion (1, 3).

The duration of zanolimumab binding to circulating $CD4^+$ cells was dose-dependent in both chimpanzees and monkeys. In chimpanzees, the half-life of $CD4^+$-bound zanolimumab was approximately 0.1, 1.4 and 2.5 days for the 0.1, 0.6 and 2.0 mg/kg doses, respectively, while in monkeys the half-life was 5, 7 and 8 days for doses of 0.2, 0.5 and 2.0 mg/kg, respectively (1, 3).

Pharmacokinetics and Metabolism

For chimpanzees which received the zanolimumab bolus infusion (0.1-2.0 mg/kg), C_{max} and area under the curve (AUC) values increased in a dose-dependent fashion, from 0.08 to 26 μg/ml and from 0.19 to 295 μg.h/ml, respectively. The mean residence time was 2.5 h at the lowest dose and 12 h at the highest dose, while the clearance rate decreased from 520 ml/kg/h at the lowest dose to 6.9 ml/kg/h at the highest dose. In monkeys receiving bolus infusions, researchers found the mean residence time (~ 2 days) and the clearance rate (~ 37 ml/kg/day) to be similar regardless of dose, although the AUC increased dose-dependently (from 5.8 to ~ 68 μg.day/ml). This difference in zanolimumab pharmacokinetics might be due to greater CD4 expression on chimpanzee monocytes than on monkey monocytes. In the cynomolgus monkeys that received slow infusions of zanolimumab, C_{max} and AUC values increased dose-dependently, from 0.26 to 45 μg/ml and from 7.2 to 2100 μg.h/ml, respectively. In contrast to the bolus infusions, the slowest clearance (0.96 ml/kg/h) was seen in the highest dose group (compared with 2.9 ml/kg/h at the lowest dose), and there was a trend for longer mean residence time values (from 2 to 3 or 4 days) with decreasing zanolimumab doses (1, 3).

Clinical Studies

Zanolimumab proved ineffective for the treatment of rheumatoid arthritis (RA) and research in this area has been discontinued. Genmab reported this finding in September 2002 based on results from the initial stage of a phase II trial comparing the use of methotrexate plus zanolimumab with methotrexate alone. At the primary endpoint of the study at week 7, while the medication was well tolerated with few side effects, no significant difference was seen in the American College of Rheumatology (ACR) scores from patients receiving methotrexate compared to patients treated with zanolimumab in combination with methotrexate. In the placebo group, 24% of patients achieved an ACR20 response compared to 11-29% in the four active dose (20, 80, 160 and 280 mg) groups. Of the 155 patients involved in the phase II trial, 7 serious adverse events were reported, 1 of which was due to pneumonia infection (1, 4, 5).

Initially, zanolimumab had seemed to be a promising RA treatment based on an open-label study in 10 patients with active RA who received a single dose of zanolimumab in combination with low-dose methotrexate. These patients reported median decreases in the number of swollen (57%) and painful joints (46%), while the median physician's global assessment of disease activity dropped by 54%. Two of the 10 patients achieved an ACR20 response (1, 6).

Phase II trials have also shown zanolimumab to be ineffective in the treatment of psoriasis. Initial data from the phase II dose-finding study which involved dosing zanolimumab (20, 80, 160 or 280 mg) or placebo once weekly for 7 weeks with follow-up to last until week 16 showed that zanolimumab produced a significant dose-response at doses up to 160 mg. At week 7, the mean Psoriasis Area and Severity Index (PASI) score for 79 of 85 patients was reduced in all treatment groups, with a 30% difference between the placebo and 160-mg dose groups. Final data from the trial, reported in April 2002, showed that 38% of patients at the highest dose achieved a 25% or greater reduction in PASI score, and the treatment was safe and well tolerated. Further results showed that zanolimumab caused a dose-dependent decrease in $CD4^+$ T-cells and that memory T-cells were affected more than naïve T-cells. In an international phase IIb trial in 300 patients with moderate to severe psoriasis vulgaris, however, researchers reported that while zanolimumab was safe and well tolerated and produced a dose-dependent depletion of $CD4^+$ T-cells, it was ineffective for the treatment of psoriasis. Research for this indication has ceased (1, 7, 8).

Although there are five medications (bexarotene, denileukin diftitox, forodesine, vorinostat and gemcitabine) and two combination regimens (CHOP, for cyclophosphamide, doxorubicin, vincristine and prednisone, and alemtuzumab, fludarabine, cyclophosphamide and doxorubicin) used for the treatment of CTCL, zanolimumab shows promise as another medication to add to this armamentarium due to its ability to target $CD4^+$ cells (9). The FDA has designated zanolimumab a fast track product for patients with CTCL who have failed currently available therapy. Zanolimumab has also been granted orphan drug status in the U.S. and Europe for the treatment of mycosis fungoides (MF). Genmab and the FDA have reached an agreement on the design of a pivotal study protocol for zanolimumab to treat CTCL. The phase III pivotal study being undertaken to support the approval of zanolimumab will include patients with the

most common form of CTCL, mycosis fungoides, who are refractory to or intolerant of bexarotene and one other standard therapy, and will consist of two stages. Because Genmab changed the manufacturer of zanolimumab in order to prepare for potential commercial launch, Genmab agreed with the FDA to treat 18 patients at three different doses prior to treating the remaining 70 patients in a randomized manner at the two higher doses. The first stage of the trial was open-label and was designed to characterize the new antibody material compared to that used in previous studies. Six patients at each dose level received 4, 8 or 14 mg/kg of zanolimumab, which translates for an average person weighing 70 kg to doses of 280, 560 and 980 mg, respectively. The second stage of the trial is blinded and will include 70 patients randomized to either 8 or 14 mg/kg of zanolimumab once weekly for 12 weeks. The primary endpoint will be the complete and partial response rate during treatment and an 8-week follow-up period. Responses must have lasted at least 4 weeks and will be assessed by the Physician's Global Assessment (PGA), which takes all disease manifestations into account. With this assessment, partial responses are defined as improvement of at least 50%, while complete responses represent 100% improvement. Preliminary results from the first stage of the pivotal study were reported in December 2006. Five of 12 patients (42%) in the two highest dose groups experienced a clinical response: 1 of 6 patients (16%) in the 8 mg/kg dose group and 4 of 6 patients (67%) in the 14 mg/kg dose group achieved partial responses. Patients treated at the 4 mg/kg dose level had no response to zanolimumab. This dose level is not being used in the second part of the study (1, 10, 11).

In June 2007, Kim *et al*. reported the results of two essentially identical prospective, multicenter, open-label, uncontrolled phase II studies (Hx-CD4-007 and Hx-CD4-008) of zanolimumab, which followed up on abstract data published in 2003 (12-14). One study included 25 patients with treatment-refractory and persistent early-stage CTCL (mycosis fungoides [MF] stage IB-IIA) given doses of 280 or 560 mg weekly, while the other included 22 patients with treatment-refractory and persistent advanced-stage CTCL (MF stage IIB-IVB and Sézary syndrome) given doses of 280 or 980 mg. Of the 47 patients enrolled, 38 had MF and 9 had Sézary syndrome. Most patients (36) were male and all but 1 were Caucasian. Patients with evidence of large-cell transformation, poorly differentiated tumors or prior treatment with anti-CD4 monoclonal antibodies were excluded from the study. All of the patients had failed at least two prior treatments, while half of the early-stage patients (11 of 25) and more than two-thirds of the advanced-stage patients (15 of 22) had failed four or more. Patients received 17 weekly infusions of zanolimumab over 16 weeks, with a follow-up visit 4 weeks later and further follow-up visits every 4 weeks for responders. The primary endpoint was objective response as assessed by composite assessment (CA) of index lesion disease activity score. A maximum of 5 lesions were evaluated on a scale of 0-8 based on degree of erythema, scaling, plaque elevation and hypo/hyperpigmentation, while surface area was graded from 0-18, with the CA index being the sum of these grades. Secondary endpoints included PGA, time to response, response duration and time to progression. Thirteen of 38 MF patients achieved an objective response, defined as a 50% or greater decrease in CA index from baseline, as did 2 of 9 Sézary syndrome patients. The response rate for MF patients was 56% in the high-dose zanolimumab groups (10 of 18) *versus* 15% in the low-dose groups (3 of 20), with a median response duration of 81 weeks. Using the PGA scoring system, the response rate (defined as at least 50% improvement in disease) rose to 15 of 38 MF patients and 3 of 9 Sézary syndrome patients. Response appeared to be closely correlated with a maximal zanolimumab trough value of > 10 μg/ml, with 50% (14 of 28) achieving that level having a response as measured by the CA index compared with 5% (1 of 19) who fell below that level. Kim *et al*. further noted a predicted decline in $CD4^+$ T-cells during treatment that correlated with dose level. In low-dose patients with early- and late-stage MF, the median $CD4^+$ T-cell count at 1 week after the final infusion was 264 (range: 53-670) and 195 (range: 16-935). In high-dose early- and late-stage MF patients, respective values were 81 (range: 13-327) and 42 (range: 15-51). The weekly $CD4^+$ T-cell decline during the study ranged from 12-14% in the low-dose MF groups to 22-24% in the high-dose MF groups, although the recovery rate of T-cells was similar for all groups. These differences in $CD4^+$ T-cell numbers did not correspond to the number of infections observed. The investigators concluded that zanolimumab demonstrated significant clinical efficacy for ameliorating refractory MF, with: 1) an early onset of response; 2) a high response rate; and 3) durable responses. Pruritus improved in 82% and 69% of patients with early- and advanced-stage CTCL, respectively. At 280 mg, the median $CD4^+$ T-cell count was 878/ml at baseline, which was reduced to 557/ml after four infusions of zanolimumab. In MF patients, a 55% response rate was achieved in patients reaching serum levels of at least 10 μg/ml zanolimumab, compared with 6% in patients not reaching this serum level. In the 280-, 560- and 980-mg zanolimumab dose groups, 25%, 93% and 100% of patients, respectively, had trough values above 10 μg/ml. Response rates were 15%, 50% and 75% in the 280-, 560- and 980-mg groups, respectively. A median response duration of > 45 weeks was observed and 85% of the responding patients achieved a clinical response within 8 weeks. Of 9 Sézary syndrome patients, 4 (44%) obtained a 50% reduction in CA score, with 1 achieving a partial response. However, this response was generally short-lived and depletion of $CD4^+$ T-cells was limited. Patients reported 276 adverse events over the course of the study, of which 15 were considered serious. Of these adverse events, 3 serious and 6 nonserious events were considered to be related to zanolimumab. Related nonserious adverse events included dermatitis, aggravated pruritus, eczema, muscle fiber rupture and flu-like symptoms.

Of the serious adverse events, 2 involved cytokine release syndrome in 2 patients with insulin-dependent diabetes mellitus, while a third related to a patient who suffered bacterial and viral infections that, while not uncommon in the CTCL patient population, could possibly have been caused by zanolimumab. All patients recovered. More common adverse events reported during the study included fatigue, flu-like symptoms, eczema, dermatitis, pruritus and skin infections. Interestingly, although 24% (9 of 38) of MF patients developed eczema and dermatitis, 78% of these (7 of 9) responded to zanolimumab. Kim *et al*. also reported 3 related serious adverse events that occurred during post-study follow-up; why 2 of them were considered treatment-related is not immediately clear (12).

About half of all cases of noncutaneous T-cell lymphoma (NCTCL) are $CD4^+$. This group includes peripheral T-cell lymphoma unspecified and angioimmunoblastic T-cell lymphomas, of which 75% are $CD4^+$, and anaplastic large-cell lymphomas, of which 20% are $CD4^+$. Most cases of NCTCL originate in lymph nodes (1).

Genmab has initiated a multicenter phase II study of zanolimumab in 20 patients with refractory or relapsed NCTCL. Patients will receive 980 mg of zanolimumab once weekly for 12 weeks and will be followed until disease progression. The primary endpoint of the study is objective tumor response from the start of treatment to week 18. Responses will be assessed by using standard response criteria for non-Hodgkin's lymphoma (NHL). Some of these results have been published (1, 10, 15, 16). Preliminary results of this study reported in December 2006 showed that 4 of 14 patients (28.5%) had objective responses, including 2 with complete remission and 2 with partial responses. According to preliminary results, 4 of the 14 NCTCL patients had treatment-related serious adverse events. One patient experienced hyperthermia and hypotension, 1 patient had a grade 2 serious infusion-related reaction and 2 patients had 2 grade 4 serious adverse events: febrile neutropenia and thrombocytopenia. The low thrombocyte count occurred on the day after the first infusion and returned to normal 8 h after the first measurement; the patient received 5 additional infusions of zanolimumab without recurrence (1, 10, 16).

Conclusions

Several treatments are currently approved for CTCL (17, 18). If the results of the phase II studies reported by Kim *et al*. are borne out in the ongoing phase III trial, zanolimumab appears to be a useful treatment to add to the armamentarium of CTCL medications. Zanolimumab's particular mechanism of action is intellectually appealing, as it involves blocking a receptor that is important for and commonly expressed on the T-cells involved in CTCL. Enthusiasm for zanolimumab for use in the treatment in CTCL should be tempered by the fact that its complete response rate in advanced disease is < 50%, its long-term utility is not known, and it ultimately failed to show efficacy in the treatment of psoriasis and RA despite similarly promising preliminary reports.

As the long-term remission rate with drugs for CTCL is not high, combination therapy which might boost remission rates is appealing. Once the data from the phase III trials are available, the use of zanolimumab in combination with other therapies can be explored. Whereas bexarotene, which is not immunosuppressive, is an ideal candidate for combination therapy, zanolimumab, which does affect the function of T-cells, might be less optimal. This is speculative, as zanolimumab has not yet been approved and it has not been used as a part of combination therapy for CTCL in published reports. On the one hand, as zanolimumab has failed clinical trials for psoriasis and other indications, optimism regarding it efficacy for CTCL must be tempered. On the other hand, its mechanism in the treatment of CTCL is appealing, arousing hopes for its success.

Sources

Genmab A/S (DK) (worldwide rights were until recently licensed to Merck Serono); developed under a license agreement with Medarex, Inc. (US).

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