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Ofatumumab

Rec INN

Human Anti-CD20 Monoclonal Antibody
Treatment of Lymphoma/Leukemia
Treatment of Rheumatoid Arthritis

2F2
HuMax-CD20™

Immunoglobulin G_1, anti-(human CD20 [antigen])(human monoclonal HuMax-CD20 heavy chain), disulfide with human monoclonal HuMax-CD20 κ-chain, dimer

CAS: 679818-59-8
EN: 333936

Abstract

Ofatumumab (HuMax-CD20™), a fully human antibody targeting the B-cell-associated CD20 antigen, is in clinical development for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and rheumatoid arthritis. Preclinical studies showed that ofatumumab inhibited the growth of B-cell tumors in SCID mice more efficiently than rituximab, and ofatumumab infusion in cynomolgus monkeys led to profound, long-lasting and dose-dependent B-cell depletion. Pharmacokinetic analysis demonstrated that in patients with NHL ofatumumab had a longer half-life than rituximab. Ofatumumab was generally well tolerated in clinical studies, and the majority of adverse events appeared to be infusion-related. Phase I/II trials demonstrated efficacy in the treatment of NHL, CLL and rheumatoid arthritis, and phase II and III studies of ofatumumab are ongoing.

Background

Rituximab, a chimeric human-mouse anti-CD20 monoclonal antibody (MAb), has been rapidly integrated into the management of non-Hodgkin's lymphoma (NHL) and other B-cell malignancies. The agent is very effective when used in combination with conventional chemotherapy, including cyclophosphamide, doxorubicin, vincristine and prednisone. However, the efficacy of rituximab remains variable and often modest when used alone. New anti-CD20 antibodies with improved efficacy are therefore needed. Using human immunoglobulin transgenic mice, a panel of fully human anti-CD20 MAbs were generated. *In vitro* and *in vivo* studies indicated that ofatumumab (HuMax-CD20™) holds considerable promise for improved clinical activity. Early studies showed that ofatumumab had a better binding profile, stronger complement-dependent cytotoxicity (CDC) and similar antibody-dependent cell-mediated cytotoxicity (ADCC) compared to rituximab (1-5).

Ofatumumab is currently in clinical development for the treatment of NHL, CLL and rheumatoid arthritis. At the end of 2004, the MAb received fast track designation from the U.S. Food and Drug Administration (FDA) to treat patients with CLL who have failed fludarabine therapy. In 2006, Genmab granted a worldwide co-development and marketing license to GlaxoSmithKline (6-9).

Preclinical Pharmacology

The biological properties of ofatumumab were studied *in vitro* and *in vivo*. *In vitro*, ofatumumab demonstrated strong binding to $CD20^+$ cells, a very slow off rate and rapid translocation of CD20 into lipid rafts. Ofatumumab was shown to mediate tumor cell lysis via activation of the classical pathway of complement. The agent was very active in inducing CDC in the presence of human plasma or whole blood and was able to lyse rituximab-resistant target cells. Epitope mapping showed a novel binding site for ofatumumab. Although the slow off rate of ofatumumab accounted for the CDC potency, the study indicated that the novel binding sites of ofatumumab, including the binding site for rituximab and the extracellular loop of CD20, were more critical to the CDC potency. Ofatumumab displayed significant ADCC activity comparable to rituximab (1-5). *In vivo*, ofatumumab increased survival in an SCID mouse Daudi lymphoma xenograft model, being more potent than rituximab, and long-lasting B-cell depletion in blood and lymph nodes was observed in cynomolgus monkeys infused with the antibody (2-5).

Pharmacokinetics and Metabolism

The pharmacokinetics of ofatumumab were evaluated in an open-label, dose-escalation, multicenter phase I/II trial in 40 patients with relapsed or refractory $CD20^+$ follicular NHL. Ofatumumab showed a long half-life

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($t_{1/2}$ = 447, 245, 322 and 621 h, respectively, following doses of 300, 500, 700 and 1000 mg as 4 weekly i.v. infusions), increasing from a median of 89 h after the first infusion to 342 h after the fourth infusion. Median C_{max}, clearance and AUC values for doses of 300, 500, 700 and 1000 mg were 129, 185, 380 and 610 μg/ml, respectively, 9, 19, 10 and 7 ml/h/kg, respectively, and 75,000, 51,000, 185,000 and 326,000 μg.h/ml, respectively. Although early pharmacokinetic analysis showed that clinical responders had higher AUC values and a longer half-life than nonresponders, no correlation between pharmacokinetics and response was found (10-12).

Safety

Ofatumumab was well tolerated in the above-mentioned phase I/II study in 40 patients with relapsed or refractory follicular NHL. No dose-limiting toxicities (DLTs) were reported during the study and the maximum tolerated dose (MTD) was not reached. The majority of the adverse events appeared to be related to cytokine release and included rigors, fatigue, pruritus, fever, dyspnea, nausea, hypotension and rash. Little hematological toxicity was seen and was confined to 6 events of grade 1 neutropenia (10-13). The results from this and several of the following studies are shown in Table I.

Ofatumumab also proved safe in the treatment of patients with CLL. In this phase I/II trial, 3 cohorts of 3, 3 and 27 patients received an initial i.v. infusion of 100, 300 and 500 mg, respectively, followed by 3 further infusions of 500, 1000 and 2000 mg, respectively, and were followed for 12 months. Again, the MTD was not reached and no anti-human antibodies were detected. Early results showed that adverse events were mainly observed on days of infusion and were mostly related to cytokine release. Approximately half of the patients developed infections which did not appear to be related to ofatumumab (14, 15).

Similar to the phase I/II studies in NHL and CLL, in a double-blind, randomized, multicenter, placebo-controlled phase I/II study in 39 patients with rheumatoid arthritis previously failing at least one disease-modifying antirheumatic drug (DMARD) and treated with 2 i.v. infusions of ofatumumab of 300, 700 or 1000 mg, the MTD was not reached. In the lowest dose cohort, 2 serious infusion-related adverse events (anaphylactoid reaction and urticaria) and 1 case of CTC grade 3 bronchospasm were observed, and higher dose cohorts were therefore premedicated with corticosteroids. Three patients reported CTC grade 3 events (fatigue and bronchospasm) in the 700- and 1000-mg cohorts. Most nonserious adverse events, which included rash, nausea, pyrexia and hypotension, were seen with the first infusion and diminished with the second infusion. No patient developed anti-human antibodies (16, 17).

Clinical Studies

The efficacy of ofatumumab for the treatment of NHL was also examined in the phase I/II dose-escalation trial in 40 patients with relapsed or refractory follicular NHL (see above). Rapid, efficient and sustained peripheral B-cell depletion was observed in all dose groups. Objective

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

Indication	Design	Treatments	n	Conclusions/Objetives	Ref.
Lymphoma, non-Hodgkin's	Open Multicenter	Ofatumumab, 300 mg i.v. infusion 1x/wk x 4 wks (n=10) Ofatumumab, 500 mg i.v. infusion 1x/wk x 4 wks (n=10) Ofatumumab, 700 mg i.v. infusion 1x/wk x 4 wks (n=10) Ofatumumab, 1000 mg i.v. infusion 1x/wk x 4 wks (n=10)	40	Weekly doses of ofatumumab were well tolerated and reduced median B-cell count in patients with follicular non-Hodgkin's lymphoma. Ofatumumab induced objective responses at all doses and in patients previously treated with rituximab	11, 13
Leukemia, chronic lymphocytic	Open Multicenter	Ofatumumab, 100 mg i.v. → 500 mg/wk i.v. x 3 (n=3) Ofatumumab, 300 mg i.v. → 1000 mg/wk i.v. x 3 (n=3) Ofatumumab, 500 mg i.v. → 2000 mg/wk i.v. x 3 (n=27)	33	Ofatumumab significantly depleted $CD19^+CD5^+$ cells, demonstrated acceptable toxicity and was active in chronic lymphocytic leukemia patients	15
Arthritis, rheumatoid	Randomized Double-blind Multicenter	Ofatumumab, 300 mg i.v. infusion 1x/2 wks x 2 cycles (n=12) Ofatumumab, 700 mg i.v. infusion 1x/2 wks x 2 cycles (n=10) Ofatumumab, 1000 mg i.v. infusion 1x/2 wks x 2 cycles (n=10) Placebo (n=7)	39	Ofatumumab was effective in inducing clinical responses in patients with rheumatoid arthritis. Rapid and sustained peripheral $CD19^+$ B-cell depletion was observed at all doses	16
Leukemia, chronic lymphocytic	Randomized Open	Ofatumumab + Fludarabine + Cyclophosphamide	56	A phase II study was initiated to examine the safety and efficacy of two dose regimens of ofatumumab in combination with fludarabine and cyclophosphamide in patients with previously untreated B-cell chronic lymphocytic leukemia	18

responses were obtained at each dose level as follows: 4 complete responses (CRs) and 1 unconfirmed CR (CRu) on 300 mg, 1 CR and 2 partial responses (PRs) on 500 mg, 2 PRs on 700 mg and 1 CRu and 4 PRs on 1000 mg; 18 further patients had stable disease. The objective response rate in patients previously treated with rituximab was 64% (9 of 14 patients), with 3 CRs, 1 CRu and 5 PRs (10-13).

In the phase I/II trial in CLL patients, reduced $CD19^{+}CD5^{+}$ cell counts were seen in all patients. Of the 26 evaluable patients, 1 had an unconfirmed PR and 11 had PRs, with a median time to disease progression of 161 days compared to 133 days in nonresponders. Time to progression and time to next therapy were positively correlated with AUC and inversely correlated with clearance (14, 15).

In the trial in patients with rheumatoid arthritis, ACR20, ACR50 and ACR70 responses were obtained at 24 weeks in 50%, 25% and 17%, respectively, of those receiving 300 mg, 70%, 40% and 20%, respectively, of those receiving 700 mg and 70%, 40% and 10%, respectively, of those receiving 1000 mg, compared to none on placebo. Good or moderate EULAR responses were also obtained in 70-80% of those on ofatumumab compared to 29% of those on placebo (16, 17).

A phase II trial in B-cell CLL evaluating ofatumumab in combination with fludarabine and cyclophosphamide is in progress (18), as are two phase III trials, one in B-cell CLL patients failing fludarabine and alemtuzumab (7, 9, 19) and another in patients with follicular lymphoma refractory to rituximab (7, 8, 20). A phase III trial of ofatumumab in the treatment of rheumatoid arthritis is expected to begin this year (7).

Sources

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