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Mini-Review

Ofatumumab

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Ofatumumab is an anti-CD20 IgG1κ human monoclonal antibody that is being considered by the US Food and Drug Administration and the European Medicines Agency for marketing approval as a treatment for chronic lymphocytic leukemia. The mAb is also being studied as a treatment for lymphoma, rheumatoid arthritis and multiple sclerosis. The candidate targets the same antigen as rituximab, but ofatumumab binds a novel, membrane-proximal epitope, and dissociates from its target at a slower rate compared to rituximab. Ofatumumab might be approved in the US by August 2009.

Introduction

Leukemia, lymphoma and rheumatoid arthritis (RA) are serious and life-threatening diseases for which there is significant unmet medical need for new treatments. Leukemia and lymphoma are two of the most common cancers diagnosed globally. Among various types of leukemia and lymphomas, chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphomas (NHL) have an incidence of approximately 15,000 and 63,000 new cases per year, respectively, in the US. In 2005, the US Center for Disease Control and Prevention estimated that more than 1.5 million people in the US are suffering from RA, and the annual cost of RA therapy is over $51 billion. After decades of effort, research has shown that these diseases have a common characteristic: they are all highly associated with B-cell dysfunction.[1-3]

The concept of B-cell-targeting therapy was proposed as early as 1940.[4] However, the approach was not feasible until the invention of monoclonal antibody (mAb) technology in 1975.[5] Thereafter, numerous preclinical and clinical studies have demonstrated that depletion of B-cells can significantly alleviate symptoms of these diseases.[6,7] CD20 is a complex plasma membrane molecule that is highly expressed on the surface of human B-cells[8] and has proven to be a key B-cell target. This membrane protein is specifically expressed on cells from the pre-B-cell stage and throughout B-cell maturation until formation of plasmacytoid immunoblast cells. Although the function of CD20 is not yet fully understood, it appears to regulate B-cell growth and calcium flux.[9] Many studies have demonstrated that crosslinking of CD20 with mAbs can recruit immunological molecules that trigger strong cytotoxic effects, such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).[10] Moreover, CD20 has very high expression levels in patients with B-cell lymphoma, and there is almost no free CD20 in serum to compete with binding of mAbs.[11,12] These characteristics make CD20 an excellent target for B-cell related disease therapy.

Preclinical study results for a novel human anti-CD20 mAb, ofatumumab, indicated a potential role in the treatment of lymphoma.[13-15] Clinical studies of ofatumumab in B-cell related indications were initiated by Genmab (Copenhagen, Denmark). In December 2006, Genmab licensed worldwide rights for ofatumumab to GlaxoSmithKline (GSK) in a deal potentially worth $2.1 billion. Ofatumumab was granted Fast Track Status for CLL by the US Food and Drug Administration (FDA) in December 2004, and was designated an orphan drug for CLL by the European Medicines Agency (EMEA) in November 2008. The candidate is undergoing regulatory review in both the US and Europe as a treatment for CLL. Phase 3 clinical studies in RA and NHL are ongoing; a Phase 2 clinical trial of MS was also initiated in April 2008.

Origin and Preclinical Analysis

Ofatumumab was generated in transgenic mice using the following protocol: Transgenic mice were immunized with human CD20 transfected cells using a prime-boost strategy. Hybridoma that secreted human IgG1 anti-CD20 antibodies were extracted from successfully immunized mice.[13,14] Using genetic engineering techniques, heavy and light chain genes from one human anti-CD20 cell line, 2F2, were transfected into a murine myeloma cell line (NS/O) for production of ofatumumab.

The mechanism of action of ofatumumab was studied in-depth, and compared to that of the marketed chimeric anti-CD20 mAb, rituximab. In binding studies, ofatumumab showed specific CD20 affinity; binding was only detected from NS/0 cells transfected with CD20, but not non-transfected cell lines.[13] At approximately 0.5 μg/mL and 1 μg/mL, ofatumumab killed up to 90% of

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Table 1 **Clinical studies in chronic lymphocytic leukemia**

Indications	Phases	Trials design	Status and results	Reference
Refractory CLL	Phase 1/2	33 relapsed or refractory CLL patients, either 100 (Group A), 300 (Group B) or 500 (Group C) mg doses were administered in first of 4 treatment weeks. Concentrations were increased to 500 (A), 1,000 (B), and 2,000 (C) mg in following three weeks.	Study completed. Remission rate was 50% in high dosage group. All patients experienced B-cell depletion, and most patients in Group C had lymph node reduction.	18; NCT00093314
Previously untreated CLL	Phase 2	Recruiting 56 patients in a two-dose, parallel group trial. A total of six monthly infusions with ofatumumab in combination with fludarabine and cyclophosphamide will be administered. The first infusion will be 300 mg, followed by five infusions of 1,000 mg	Ongoing.	NCT00410163
Relapsed CLL	Phase 2	Enrolling 25 patients who progressed following response or stable disease after ofatumumab treatment in a previous study. Doses of eight once weekly infusions (1 x 300 mg + 7 x 2,000 mg), then 2,000 mg once monthly will be given for two years.	Ongoing.	NCT00802737
Refractory CLL	Phase 3	Recruiting 225 CLL patients refractory to fludarabine and alemtuzumab treatment. A 300 mg dose was administered initially, the dose was increased to 2,000 mg for seven consecutive weeks, and then four monthly doses of 2,000 mg dose were given.	On-going. Interim analysis of results for 138 patients: response rates were 58% for 59 double refractory patients and 47% for 79 patients refractory to fludarabine treatment.	19; NCT00349349
Relapsed CLL	Phase 3	Recruiting 352 relapsed CLL patients. Study will examine ofatumumab added to fludarabine-cyclophosphamide vs the fludarabine-cyclophosphamide combination.	Ongoing.	NCT00824265
CLL	Phase 3	Recruiting estimated 444 previously untreated CLL patients. Ofatumumab in combination with chlorambucil and be compared to chlorambucil monotherapy. Ofatumumab dosed at 300 mg on day 1, 1,000 mg on day 8, with subsequent cycles of 1,000 mg at day 1 every 28 days.	Ongoing.	NCT00748189

CLL, chronic lymphocytic leukemia. Note: Additional information for each trial can be found at www.clinicaltrials.gov by searching for the appropriate NCT reference number.

SU-DHL4 and Daudi cells, respectively, by CDC induction. The percentage of cells killed was notably higher than that due to rituximab at the same concentration. In addition, ofatumumab lysed approximately 75% of complement-resistant Raji cells at 10 μg/mL, whereas less than 20% were lysed when Raji cells were treated with the same concentration of rutuximab.

Further studies demonstrated that although ofatumumab and rituximab bind the same antigen, ofatumumab dissociates from its target at a slower rate compared to the marketed product,[13] and binds a novel, membrane-proximal epitope.[16] In experiments using radiolabeled antibodies, more than 70% of ofatumumab, but only 30% of rituximab, remained bound to DOHH cells after three hours. Epitope mapping has indicated that ofatumumab binds an epitope located closer to the N-terminus of CD20 compared to the location targeted by rituximab and includes an extracellular loop of the antigen. The CDC potency of ofatumumab may be due to both the slow off-rate and the precise location of binding on CD20.

A mouse model was used to assess tumor inhibition by ofatumumab.[17] Severe combined immunodeficiency (SCID) mice were first injected with Daudi B-cells transfected with luciferase, and then treated with either 0.5 mg/kg of ofatumumab or anti-KLH mAb as a control. Peak plasma concentration of ofatumumab was approximately 5 μg/mL. Tumor growth was assessed by bioluminescence. Compared with the control group, the ofatumumab cohort showed delayed tumor induction (3–4 weeks) and lower tumor growth rate. In cynomolgus monkeys, a 1.25 mg/kg intravenous (IV) dose administered daily for four days effectively depleted B-cells; initial plasma concentrations were approximately 50 μg/mL.[17] The cell count did not return to a normal level until 96 days later, but the animals developed primate antihuman antibodies (PAHA). Taken together, the results from the mouse and monkey experiments suggested that high initial dosing would be necessary to saturate CD20, but maintenance at 5–10 μg/mL would likely be sufficient for prolonged activity. Further in-vitro experiments indicated ofatumumab is effective in killing B-cells extracted from CLL patients.[14]

Clinical Studies in Chronic Lymphocytic Leukemia

As of April 2009, at least seven studies of ofatumumab as a treatment for CLL had been initiated. Six were either Phase 1/2, 2 or 3 studies (Table 1), while one was an open-label Phase I study (NCT00742144) of ofatumumab in Japanese follicular lymphoma or CLL patients.

Phase 1/2

During September 2004 to April 2006, a Phase 1/2 dose-escalating study of ofatumumab as a treatment for relapsed or refractory CLL was conducted at 12 sites in the US and Europe.[18] A total of 33 patients were included. The majority (27/33) of patients received a total of four doses administered once weekly; an initial dose of 500 mg was followed by three 2,000 mg doses. The response rate for this group was 50%, with partial remission observed in 12 patients. Serious adverse events included herpes zoster infection (1 patient), cytolytic hepatitis (1 patient), neutropenia (2 patients) and one death from interstitial pneumonia.

Phase 2

A Phase 2 study of ofatumumab in combination with fludarabine and cyclophosphamide is currently on-going, with enrollment of 56 previously untreated CLL patients anticipated. The study is an open-labeled, randomized, two-dose, parallel group trial that is expected to be complete by 2013. Each patient will receive six infusions of ofatumumab in combination with fludarabine and cyclophosphamide. The first infusion will be 300 mg, followed by five infusions of 500 mg; infusions will be given every four weeks until a total of six infusions have been administered.

Another on-going Phase 2 study is investigating the effects of ofatumumab retreatment and maintenance in CLL patients who were administered the mAb in a previous study (Hx-CD20-406). In this single arm study, patients will receive eight once weekly infusions (300 mg, then 7 x 2,000 mg doses), followed by 2,000 mg doses once monthly for two years. Enrollment is estimated at 25 patients. [NCT00802737].

Phase 3

A single-arm, international, multi-center Phase 3 study of ofatumumab in refractory CLL patients was initiated in June 2006. Patients were treated with 300 mg ofatumumab initially, then 2,000 mg weekly for seven consecutive weeks, and finally four monthly infusions of 2,000 mg. Preliminary results indicate a response rate was 58% in 59 patients who were refractory to both fludarabine and alemtuzumab and 47% for patients who were refractory to fludarabine and had not received alemtuzumab due to the presence of bulky tumor masses in their lymph nodes.[19] The median overall survival time was 13.7 and 15.4 months, respectively, for the two groups of patients.

In an ongoing open label, randomized Phase 3 study, ofatumumab added to fludarabine-cyclophosphamide is being compared to treatment with the fludarabine-cyclophosphamide combination in patients with relapsed CLL. The highest single dose of ofatumumab administered will be 1,000 mg, rather than the 2,000 mg highest dose administered in the first Phase 3 study. The study is expected to enroll 352 patients, and to be completed by 2015.

A Phase 3, open-label, randomized, study of ofatumumab in combination with chlorambucil as a treatment for CLL is also currently ongoing. The combination of therapeutics will be compared to treatment with chlorambucil only. Ofatumumab will be dosed as follows: 300 and 1,000 mg infused on days one and eight, respectively, the subsequent cycles of 1,000 mg at day 1 for every 28 days will be administered. The study will include a minimum of three cycles and a maximum of 12 cycles, and will evaluate progression-free survival, overall response and overall survival.

Clinical Studies in Additional Indications

Although ofatumumab is undergoing regulatory review as a treatment for CLL, the candidate is also being studied as a treatment for lymphoma, rheumatoid arthritis and multiple sclerosis.

Lymphoma

Ofatumumab has, or is, being studied as a treatment for lymphoma in at least five Phase 1/2, 2 or 3 studies (Table 2).

Phase 1/2

In a dose-escalating Phase 1/ 2 study, 40 patients with relapsed or refractory follicular non-Hodgkin lymphoma were administered either 300, 500, 700 or 1,000 mg ofatumumab for four weeks. Immediate, profound and long-lasting B-cell depletion was observed; 65% of patients reverted to negative BCL2 status.[20] The clinical response rate was not dose-dependent, and ranged from 20–63%. Median time to progression was 8.8 months for all patients, but 32.6 months for responders. The number and severity of adverse events did not appear to have a relationship to dose; the maximum tolerated dose was not identified for any patient.

Phase 2

A Phase 2 open-label single arm study of ofatumumab in patients with relapsed/progressive diffuse large B-cell lymphoma who are ineligible for transplant or who have experienced relapse/progression after autologous transplant was initiated in December 2007. An estimated 75 patients are enrolled and were administered eight weekly infusions (300 mg, followed by seven infusions of 1,000 mg). The study is expected to be complete in July 2014.

Ofatumumab is being studied in an open-label, randomized, two-dose, parallel group, Phase 2 study of patients with previously untreated follicular lymphoma. Patients were administered a total of six infusions of ofatumumab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) every three weeks. Ofatumumab doses were 300 mg, followed by five infusions of either 500 or 1,000 mg. Patients recruitment has been completed, and preliminary results are expected in 2013.

A Phase 2 study of ofatumumab as a treatment for Waldenström macroglobulinemia, which is a rare form of non-Hodgkin lymphoma, is also on-going. Symptoms of the disease are caused by high levels of IgM produced by proliferating lymphoplasmacytic cells. The study started in March 2009. Enrollment of 36 patients is anticipated and completion is expected in March 2013.

Phase 3

A single-arm Phase 3 trial of NHL patients who are refractory to rituximab as monotherapy or in combination with chemotherapy began in 2006. Patients in two dose groups received eight weekly

infusions of ofatumumab (initial infusion of 300 mg, followed by seven weekly infusions of either 500 or 1,000 mg). Disease status was assessed every three months for two years. The results of this study had not yet been published as of April 2009.

Rheumatoid Arthritis

At least four Phase 1/2, 2 or Phase 3 clinical studies of ofatumumab as a treatment for rheumatoid arthritis have been initiated [Table 2]. A Phase 1/2A study (NCT00686868) to investigate a subcutaneous route of administration has also been initiated.

A double-blind, randomized, placebo-controlled, dose escalation Phase 1/2 study of patients with active RA was started in February 2005. Ofatumumab was administered to 225 patients who had failed other anti-rheumatic drugs at doses of 300, 700 or 1,000 mg. Patients were then assessed based on American College of Rheumatology (ACR) scores, which require a defined percentage reduction in number of symptoms and measures of disease, after 24 weeks. Study data indicated that patients administered doses of 300, 700 or 1,000 mg ofatumumab had ACR20 scores of 41, 49 and 46%, respectively, while the ACR20 score of patients receiving placebo was 15%.[21] No increased frequency of infections was observed, and all patients tested negative for the presence of human anti-human antibodies.

Two Phase 3 double-blind, randomized, placebo-controlled studies of approximately 250 patients each are being conducted to further measure the efficacy and safety of ofatumumab in RA patients who have had inadequate response to either methotrexate or TNFα antagonist therapy. These studies are on-going, and are expected to be completed in 2011.

Multiple Sclerosis

To date, ofatumumab has entered one study as a treatment for multiple sclerosis. An estimated 324 patients with relapse remitting disease will be administered one of three doses, and two treatment courses (2 x 2 IV infusions) with a six month interval. Lesions in the brain will be assessed by MRI scans; measurements of lesions will be used to determine dose response. This trial is expected to be completed in 2012.

Future Prospects

A number of anti-CD20 mAbs are under development or are already on the market. Compared to the marketed product anti-CD20 product rituximab, ofatumumab has demonstrated greater cytotoxic potential in killing B-cells though CDC pathways. Thus, ofatumumab may offer alternative therapy for patients who are resistant to rituximab. Other anti-CD20 mAbs are in clinical development, including afutuzumab (Hoffmann-LaRoche/Biogen Idec), veltuzumab (Immuomedics) and ocrelizumab (Genentech/Biogen Idec). These candidates have also shown positive results in clinical trials, and are expected to enrich the pipeline of mAb therapy for B-cells related disease.

Ofatumumab has been, or is being, evaluated for safety and efficacy as a treatment for CLL, lymphoma, RA and MS. Pharmacokinetic research indicates that the activity of ofatumumab may be due to its slower off-rate and increased ability to activate complement pathways. Efficacy data from studies of ofatumumab in CLL and RA patients have so far been encouraging. Taken together, these results suggest that ofatumumab has promising market potential.

Similar to other mAb therapy, patients administered ofatumumab experiences cytokine-release syndrome. Release of cytokines into circulation causes various immunological reactions such as fever, nausea, rash and dyspnea. These side effects can be alleviated with corticosteroids treatment and are manageable in hospital. Of more concern are the two pneumonia cases that occurred during treatment. This suggests patients treated with ofatumumab may be more vulnerable to infections.

Four international patents have already been issued on anti-CD20 mAbs. Three, anti-CD20 mAb (WO-2004035607), use of anti-CD20 mAbs for the potential treatment and prevention of B-cell related disease (WO-2005103081) and chronic obstructive pulmonary disease to reduce dyspnea (WO-2008003319), are Genmab patents. The fourth, WO-2006076651, is a Genentech patent claiming use of anti-CD20 at a lower dose in autoimmune disease, such as RA and MS. The earliest expiration date of these patents is 2023.

In conclusion, data from a number of clinical studies suggests that ofatumumab has demonstrated safety and efficacy in at least CLL and RA. The candidate may bring hope to patients with B-cell related disease if and when it is approved for marketing.

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Table 2 **Clinical studies in lymphoma, rheumatoid arthritis and multiple sclerosis**

Indications	Clinical phase	Study design	Status and results	Reference
Lymphoma, relapsed or refractory, follicular	Phase 1/2	40 NHL patients administered four weekly infusions of 300, 500, 700 and 1,000 mg ofatumumab.	Study completed. Long-lasting B-cell depletion observed in all dose groups. Clinical response rate was not dose dependent and ranged from 20–63%. One patient (500 mg dose group) withdrew due to SAE attributed to treatment.	20; NCT00092274
Lymphoma, diffused large B-cell lymphoma	Phase 2	Recruiting 75 patients for open-label single arm study. Patients will receive eight weekly doses (1 x 300 mg, then 7 x 1,000 mg ofatumumab)	Ongoing.	NCT00622388
Lymphoma, follicular	Phase 2	Recruiting 56 patients for two dose, parallel group study of ofatumumab in combination with CHOP. Patients will receive six weekly doses (1 x 300 mg, then 5x either 500 mg or 1,000 mg ofatumumab every three weeks).	Ongoing.	NCT00494780
Lymphoma, Waldenstrom macroglobulinemia	Phase 2	Recruiting 36 patients for a non-randomized, open label, single group assignment study.	Ongoing.	NCT00811733
Lymphoma, follicular	Phase 3	Estimated enrollment of 112 patients refractory to rituximab. Patients will receive eight weekly doses (1 x 300 mg, then 7 x 1,000 mg ofatumumab)	Ongoing.	NCT00394836
RA	Phase 1/2	Enrolled 225 patients with active RA who previously failed DMARDs. Four treatment groups received placebo or 300, 700 or 1,000 mg ofatumumab.	Study completed. ACR20 achieved by 15%, or 41%, 49% and 46% of patients administered placebo or 300, 700 or 1,000 mg ofatumumab, respectively.	21; NCT00291928
RA	Phase 2	Recruiting 150 patients who previously participated in Trial Hx-CD20-403. 2 x 700 mg doses ofatumumab comprise one course; maximum of nine courses may be given.	Ongoing.	NCT00655824
RA refractory to methotrexate therapy	Phase 3	Estimated enrollment of 248 patients resistant to methotrexate therapy; 2 x 700 mg dose ofatumumab compared to placebo	Ongoing.	NCT00611455
RA refractory to TNFα antagonist therapy	Phase 3	Estimated enrollment of 236 patients resistant to TNFα antagonist therapy; 2 x 700 mg dose ofatumumab compared to placebo	Ongoing.	22; NCT00603525
Relapsing, remitting MS	Phase 1/2	Recruiting 324 patients with relapsing-remitting MS. Three doses will be compared to placebo. Two treatment courses (2 x 2 I.V. infusions) with a six month interval will be administered.	Ongoing	NCT00640328

ACR, American College of Rheumatology; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; DMARD, disease-modifying anti-rheumatic drugs; MS, multiple sclerosis; NHL, non-Hodgkin lymphoma; RA, rheumatoid arthritis; SAE, serious adverse event; TNF, tumor necrosis factor. Note: Additional information for each trial can be found at www.clinicaltrials.gov by searching for the appropriate NCT reference number.

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