

Technology evaluation: Lumiliximab, Biogen Idec

Janice M Reichert

Address

Tufts Center for the Study of Drug Development
192 South Street
Suite 550
Boston
MA 02111
USA
Email: janice.reichert@tufts.edu

Current Opinion in Molecular Therapeutics 2004 6(6):675-683
© The Thomson Corporation ISSN 1464-8431

Biogen Idec (formerly IDEC Pharmaceuticals) is developing lumiliximab, a primatized anti-CD23 macaque/human chimeric antibody that inhibits the production of the IgE antibody, for the potential treatment of allergic conditions.

Introduction

The symptoms suffered by patients with allergic asthma and seasonal allergic rhinitis result from a cascade of events that are initiated by the binding of allergen to immunoglobulin (Ig)E [564119]. IgE forms a complex by binding to a specific target on the allergen. The IgE-allergen complex binds to CD23 (also known as FcεRII), a 45-kDa membrane glycoprotein receptor expressed on antigen-presenting cells, basophils, lymphocytes (eg, B-cells, eosinophils, monocytes and platelets) and airway smooth muscle cells, which acts as a low-affinity cell-surface receptor for the Fc portion of IgE [564130]. Subsequently, the activities of CD23+ cells, including IgE production and secretion of inflammatory mediators such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)α, are upregulated. The symptoms of allergy, such as intermittent shortness of breath in allergic asthma patients and sneezing, rhinorrhea or nasal congestion in allergic rhinitis patients, are the end result of the actions of the secreted mediators. Thus, antagonizing CD23 has potential as a therapeutic intervention that decreases the response to allergens by selectively downregulating IgE production [564835].

Chronic lymphocytic leukemia (CLL) is a heterogeneous group of diseases characterized by the clonal neoplastic proliferation of mature B-cells and their accumulation in blood, bone marrow and lymphatic tissues [564120]. The disease primarily affects middle-aged and elderly adults. Clinical heterogeneity is observed; some patients live with indolent disease, while others suffer more aggressive forms. There is evidence suggesting that the absence of mutations of the leukemic cell Ig heavy chain variable region (V_H) genes indicates that a more aggressive form of the disease is present [527747]. CD23 is a B-cell differentiation antigen that is believed to be associated with B-cell stimulation, and is overexpressed in certain B-cell malignancies, such as CLL. It is sometimes secreted from the B-cell, and can be detected as a soluble molecule in the blood. A high concentration of this soluble CD23 is an indication of disease progression [564120].

Biogen Idec Inc is developing lumiliximab, a primatized, IgG1κ monoclonal antibody (mAb) against CD23, as a

Originator Biogen Idec Inc

Status Phase II Clinical

Actions Anticancer, Apoptosis stimulator, CD23 antagonist, Immunoglobulin E antagonist, Immunomodulator

Indications Allergic rhinitis, Allergy, Asthma, Chronic lymphocytic leukemia

Biotechnology Chimeric monoclonal antibody

Synonyms gomiliximab, IDEC-152, SI-3401, ST-152 primatized anti-CD23 antibody

CAS Immunoglobulin G1, anti-(human immunoglobulin E receptor type II) (human-Macaca irus monoclonal IDEC-152 γ1-chain), disulfide with human-Macaca irus monoclonal IDEC-152 κ-chain, dimer
Registry No: 357613-86-6

potential treatment for diseases caused by cells that express or overexpress CD23, including allergic asthma, allergic rhinitis and CLL. Primatized mAbs such as lumiliximab are genetically engineered from cynomolgus macaque antibody variable regions and human constant regions [471021]. This technology is proprietary to Biogen Idec. In theory, the products are less likely to cause a human anti-murine immune antibody (HAMA) response compared with mAbs containing murine sequences, and, therefore, might be suitable for long-term, chronic use. The potential efficacy of immunotherapy is often reduced by the presence of HAMA, because of neutralization and accelerated clearance of the therapeutic mAb by the patient's immune system. Several other technologies have been developed to produce more efficacious mAbs by reducing immunogenicity. For example, chimeric mAbs are constructed from variable regions derived from a murine source and constant regions derived from a human source, and humanized mAbs are constructed with only the antigen-binding regions derived from a murine source, with the remainder of the variable regions and constant regions derived from a human source. In addition, fully human mAbs are in clinical study; the first of which, adalimumab, was approved in the US in December 2002 [564122], [564125]. To date, a total of four primatized mAbs have entered clinical study for treatment of autoimmune diseases and cancer; these are mAbs against CD4 (keliximab and clenoliximab; Biogen Idec Inc) [317457], [338079], CD80 (galiximab; Biogen Idec Inc) [516978] and CD23 (lumiliximab) [412124].

Lumiliximab binds to CD23 expressed on the surface of target cells and induces cell lysis through antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis [471021], [472393]. ADCC and CDC are host defense mechanisms activated by sites in the Fc constant domain of the mAb. The exact nature and level of activation varies with the antibody isotype. For example, IgG1 and IgG4 vary in their ability to

initiate CDC and bind Fc receptors [471021], [564126]. In CDC, the serum complement protein C1q binds to the antigen-antibody complex, leading either directly to cell death or to phagocytosis caused by deposition of another component of complement, C3, and recognition of C3 by receptors on phagocytic cells [471021]. The induction of apoptosis is thought to occur through binding of the constant domain to Fc receptors on host effector cells. Cross-linking of the mAb induces apoptosis through mechanisms that are not fully elucidated, but may include activation/upregulation of pro-apoptotic proteins and inactivation/downregulation of anti-apoptotic proteins [473757].

The US FDA awarded Orphan Drug status to lumiliximab, as a treatment for CLL, with a designation date of February 2003 [564118].

Synthesis and SAR

Lumiliximab is a primatized chimeric monoclonal antibody constructed using genetic engineering techniques to fuse an Old World monkey antigen-binding portion to a human constant region that binds to human Fc receptors and inhibits the expression of IgE [527764]. The production of lumiliximab and other antibodies against CD23 are described in detail in the patent application by IDEC that first claimed lumiliximab [WO-09837099], and the original document disclosing the primatization procedure [WO-09302108]. Specifically, cynomolgus macaques were immunized with soluble human CD23. When an appropriate titer of anti-CD23 antibodies was detected in the monkey serum, the animal was sacrificed and the spleen and lymph nodes removed. The tissues were separately homogenized into single-cell suspensions, and the cells were fused to a mouse-human heterohybridoma cell line. Cells were grown in a 96-well plate in a growth medium containing hypoxanthine, thymidine and azaserine, which keeps the fused cells alive. Wells were then screened for the presence of anti-human CD23 antibody using a cell enzyme-linked immunosorbent assay (ELISA) to identify stable hybridomas [WO-09837099].

Five hybridomas that produce CD23-binding primate mAbs (5E8, 6G5, 2C8, B3B11 and 3G12) were selected [527764]. 5E8 and 6G5 were primatized by cloning of the primate Ig variable domains via isolation of the mRNA and synthesis of cDNA, and isolation of the light and heavy chain variable regions by PCR from the cDNA. The variable regions were then cloned into a mammalian expression vector containing human γ chain and λ light chain constant regions and the resulting DNA was expressed in suitable cells, in this case CHO cells. Antibody isolation was carried out by centrifugation, followed by protein A column purification [527764], [WO-09837099]. Two versions each of two isotypes of primatized 5E8 (p5E8G1, p5E8G1N-, p5E8G4P and p5E8G4PN-) were produced in this manner. The isotype versions differed by the presence or absence of mutations in the constant region and/or heavy chain variable region. All four versions had apparent K_d values (0.3 to 1.0 nM, respectively) that were similar to those of the primate mAb 5E8 (apparent K_d = 0.5 to 4.4 nM). However, only the p5E8G1 versions were as effective as the primate mAb parent in an *in vitro* assay of IgE suppression; compared

with p5E8G1N-, p5E8G1 showed slightly greater suppression at the lowest concentration tested (0.03 μ g/ml). p5E8G1 was selected for further development as lumiliximab [WO-09837099]. Several therapeutic formulations are disclosed in WO-09837099, including those suitable for administering mAbs or fragments by parenteral, oral and topical routes.

Preclinical Development

Lumiliximab binds CD23 with a K_d value of 0.12 nM [504688]. *In vitro*, lumiliximab inhibited IgE production by IL-4-induced human peripheral blood mononuclear cells (PBMCs) [527764]. The F(ab')₂ portion did not inhibit IgE production, but interfered with IgE inhibition by the intact antibody in a dose-dependent manner. These results suggest that inhibition of IgE production is not accomplished by cross-linking of CD23 alone, or by inhibition of the binding of CD23 to its natural ligand, and implies a mechanism whereby cross-linking of CD23 to an IgG receptor is required for inhibition of IgE production [412387], [527764].

A related anti-CD23 mAb p6G5G1 (the G1 type of a primatized antibody produced alongside lumiliximab) inhibited IgE production by PBMCs stimulated with IL-4 and an anti-CD40 antibody. Germline C ϵ RNA synthesis was inhibited, but CD23a and CD23b mRNA levels were not reduced. These data suggest that the mAb blocks Ig class switching to IgE through the inhibition of germline ϵ chain RNA synthesis [404493].

The chemically crosslinked heterodimer of rituximab/5E8 (Biogen Idec and Genentech's mouse/human chimeric anti-CD20 monoclonal antibody rituximab, and the primate precursor version of lumiliximab) demonstrated enhanced apoptotic activity compared with the unmodified mAb components. This suggests an alternative method of inducing apoptosis without effector cell cross-linking. A rituximab/5E8 heterodimer, a rituximab homodimer, an unmodified 5E8 and rituximab mAbs were tested for apoptotic activity at four concentrations (0, 0.625, 2.5 and 10 μ g/ml) on two lymphoma cell lines. Compared with the controls, the 10 μ g/ml heterodimer and the 10 μ g/ml rituximab homodimer induced increased apoptotic activity in SKW cells (human B-lymphoma cells that express CD20, CD80 and CD23). Increased apoptotic activity was also observed in DHL-4 cells treated with 2.5 and 10 μ g/ml of either the heterodimer or the rituximab homodimer [471021].

A number of studies have assessed the efficacy of lumiliximab against B-cell lymphoma [432438], [432863], [447539], [504688]. Lumiliximab induced dose-dependent apoptosis in CD23+ human B-cell lymphoma cell lines *in vitro*, as assessed by fluorescence-activated cell sorting-based detection of activated caspase-3. Apoptosis was dependent on lumiliximab cross-linking with goat anti-human IgG F(ab)₂ fragments. Incubation with 10 μ g/ml of lumiliximab induced apoptosis in more than 60% of cells, and reduction of the dose to as low as 0.1 μ g/ml resulted in approximately 10% apoptosis. Lumiliximab enhanced apoptosis induced by rituximab in SKW cells from 30% with 10 μ g/ml of rituximab alone, to 50% after addition of 0.5 μ g/ml of lumiliximab. Apoptosis of SKW cells was also increased

from 20 to 70% by the addition of 1 mg/ml of lumiliximab to 10 mM of fludarabine. Similar treatment of CLL cells increased the rate of apoptosis from 30 to 60%.

Overlapping studies have elucidated the mechanism of induction of apoptosis by lumiliximab in CLL cells [473757], [484178], [515913]. Apoptosis was mediated by activation of caspase-9 and caspase-3, and was accompanied by cleavage of poly(ADP-ribose) polymerase (PARP). Lumiliximab induced marked downregulation of X-linked inhibitor of apoptosis protein (XIAP), Bcl-x_L and Mcl-1, but expression of cIAP-1, cIAP-2, survivin and Bcl-2 remained unchanged. These results suggest a mechanism for lumiliximab-mediated apoptosis that involves activation of caspase-3 and -9, and a decrease in the expression of several important anti-apoptotic proteins, including Mcl-1, Bcl-x_L and XIAP in CLL cells. The mitochondrial translocation of Bax and release of cytochrome C were also detected. These observations suggest the involvement of the intrinsic pathway of apoptosis. Assays involving B-lymphoma cells have demonstrated that lumiliximab is capable of killing tumor cells via apoptosis, ADCC and CDC [473757], [484178], [515913].

Apoptosis induction was assessed in cells from CLL patients with various treatment histories, and in samples from patients treated with lumiliximab [515913], [529904]. The apoptotic activity induced by lumiliximab treatment of CLL cells was associated with the cleavage of caspase-3 and -9, PARP, activation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinases, and decreased activation of AKR. Cell samples from three CLL patients who received lumiliximab (250, 375 or 500 mg/m²/week) in a dose-escalating phase I study were assessed to measure *in vivo* induction of apoptosis, following infusion on days 1 and 2 of treatment. Samples were taken prior to infusion, and then 30 min and 2 h after treatment. The observed induction of apoptosis was not dose dependent and ranged from 5.34 to 7.93% on day 1, and 15.87 to 71.74% on day 2; the lowest induction of apoptosis on day 2 was in the patient from the highest-dose group, and the greatest apoptosis was in the 375-mg/m² group. Activation of caspase-3 was not evident within 2 h of infusion, but was consistently observed prior to administration of the second infusion. *In vivo* decreases in Bcl-2 and Mcl-1 expression, activation of JNK and p38, and decreased activation of AKR and downmodulation of Mcl-1 and XIAP were also observed [515913], [529904]. These results suggest that similar signaling pathways are affected by *in vitro* and *in vivo* treatment with lumiliximab.

Samples from CLL patients were evaluated for apoptosis after *in vitro* treatment with lumiliximab, rituximab and fludarabine using a flow cytometric-based detection system of activated caspase-3 [472393]. Overall, 65% of samples (11/17) showed more than 40% apoptosis when treated with lumiliximab alone. Rituximab induced a similar result in 62.5% of the samples (5/8), while fludarabine treatment resulted in more than 40% apoptosis in only 22% of the samples (2/9). A synergistic effect was observed when samples were treated *in vitro* with both lumiliximab and either rituximab or fludarabine.

The level of CD23 expression after *in vivo* lumiliximab treatment was investigated by measuring the antibody-binding capacity (ABC) for cells taken from CLL patients [527774]. The ABC for CD23 was relatively low in cells from the 68 CLL patients tested (median = 5749; range = 453 to 26920) compared with the binding of antibodies against CD20 and CD52, and there was significant variability between patients (SD = 4610). No significant difference in CD23 ABC was observed between peripheral blood and bone marrow CLL samples in the 23 patients for whom samples were compared. Five of these patients had been treated with lumiliximab and multiple samples were collected from these patients at various times during therapy. All treated patients showed a significant reduction in the percentage of CD23+ cells, and one patient became completely negative for CD23, despite the finding that there was no significant change in the number of leukemic cells or the ABC of CD20. The ABC in samples from lumiliximab-treated patients ranged from 0 to 3296 (median = 446) [527774]. The finding that CD23 is expressed at a relatively low level in CLL patients, with considerable variation between patients, may have implications for the monitoring of lumiliximab therapy.

Lumiliximab induced apoptosis in drug-resistant lymphoma cells [531819]. SKW cells were cultured with increasing concentrations of adriamycin. The resulting cells were resistant to fludarabine, expressed multidrug resistance protein-2, and exhibited loss of surface CD20, but retained parenteral levels of CD23 expression. Treatment with rituximab produced no response, whereas lumiliximab treatment induced apoptosis. Treatment of parent cells, but not drug-resistant SKW cells, with fludarabine resulted in apoptosis mediated by the activation of JNK, caspase-3, -8 and -9, cleavage of PARP, and reduced expression of Bcl-2. Treatment of SKW parent cells and CLL cells with lumiliximab resulted in decreased expression of Mcl-1 and XIAP. These results may explain why enhanced apoptosis was observed when the combination of fludarabine and lumiliximab was tested, and suggest the use of fludarabine and lumiliximab as combination therapy for both fludarabine-refractory and -responsive patients [531819].

The antitumor response was also evaluated *in vivo* in severe combined immunodeficient (SCID) mice (n = 10) injected with SKW cells [471021]. Inoculated mice were treated intraperitoneally on days 1, 3, 5, 7, 9 and 11 with either lumiliximab (400 µg), a combination of lumiliximab (200 µg) plus rituximab (200 µg), or placebo. All placebo-treated mice had died by day 30. On day 60, 40% of mice treated with lumiliximab and 70% treated with the combination of lumiliximab and rituximab had survived. In a separate experiment in SCID mice injected with SKW cells [504688] on day 45, 100% of control mice were dead, while 50 and 90% of mice treated with lumiliximab alone and in combination with rituximab, respectively, were alive.

Inhibition of IgE levels was observed in two chimpanzees administered an initial 3 mg/kg subcutaneous dose of lumiliximab followed approximately 7 weeks later by three biweekly doses [517270]. After the initial dose, a reduction of

50 to 70% of the serum total IgE relative to baseline (mean value of 14 to 17 $\mu\text{g/ml}$) was observed. Serum total IgE was further reduced by 65 to 90% with subsequent biweekly doses. The inhibitory effect on IgE levels persisted for at least 8 months after the last dose.

Metabolism and Pharmacokinetics

Limited data on the metabolism and pharmacokinetics of lumiliximab have been published. The serum elimination $t_{1/2}$ in chimpanzees ($n = 2$) was estimated to be 5.6 days after a single 3-mg/kg subcutaneous dose of lumiliximab. The mean bioavailability was approximately 60%, based on historical clearance data [517270].

A phase I study was completed in allergic asthma patients ($n = 30$) randomized to receive a single intravenous dose of lumiliximab (0.05, 0.25, 1.0, 4.0, 10.0 or 15.0 mg/kg) or placebo [412124], [517256]. The mean C_{max} was dose proportional over the 4.0- to 15.0-mg/kg dose range (171 ± 14.5 to $658 \pm 56 \mu\text{g/ml}$), as was the mean AUC. At the lowest dose, lumiliximab was below the limit of quantitation in most patients, so other parameters were determined from 0.25 to 15.0 mg/kg. The mean AUC ranged from 38.1 to 6261.6 $\mu\text{g/day.ml}$ in patients receiving 0.25 and 15.0 mg/ml. Serum $t_{1/2}$ ranged from 2 to 10 days over these doses. The range of median clearance rates was 2.7 to 6.2 ml/day.kg and the range of median volume of distribution was 20.9 to 38.2 ml/kg [412124], [517256].

A generalized comparison of primatized mAbs with other forms of chimeric mAbs reported that the serum $t_{1/2}$ of 2 to 9 days for primatized mAbs is somewhat shorter than those previously reported $t_{1/2\beta}$ values in humans of 4 to 15 days for chimeric mAbs, and 3 to 24 days for humanized mAbs [471021].

Toxicity

No adverse events were noted in a study of two chimpanzees that each received a total of four 30-mg/kg (1200 mg/m^2) subcutaneous doses of lumiliximab, the initial dose being followed 7 weeks later by three biweekly doses [504688], [517270]. No effect was observed on serum total IgG or white blood cell count, and no anti-lumiliximab antibody response was observed in over a year. The absolute numbers of CD3+, CD4+ and CD8+ T-cell lymphocytes underwent minor, brief reductions relative to baseline. Absolute numbers of CD19+ and CD20+ B-lymphocytes underwent a sustained decline, and reduction of CD23+ B-cells was pronounced compared with the reduction in total B-cells. Absolute B-cell values returned to baseline value approximately 5 months after the final dose.

Clinical Development

Phase III

Allergy

A phase I study evaluated the safety, tolerability and pharmacokinetics of a single dose of lumiliximab in patients with allergic asthma [412124], [517256]. In the placebo-controlled, single-dose, sequential, dose-escalating study, patients with mild-to-moderate persistent allergic asthma ($n = 30$) were randomized to receive lumiliximab (0.05, 0.25,

1.0, 4.0, 10.0 or 15.0 mg/kg) or placebo. Mean IgE values decreased dose dependently with lumiliximab treatment. At a dose of 15 mg/kg (600 mg/m^2), mean IgE concentration began to decrease by day 8 and had decreased to 39.2% below baseline concentration by day 85. A dose of 0.05 mg/kg reduced mean IgE baseline concentration by 15.1% on day 8 and 2.4% by day 85. In the placebo group, IgE concentrations ranged from 5.3% less than baseline concentration to 10.4% greater than baseline concentration over the course of the study. Mean B-cell count decreased from baseline in patients receiving 4.0-, 10.0- or 15.0-mg/kg doses, but counts remained within the normal range (32 to 341 cells/ mm^3 for CD19+ cells). Changes in forced expiratory volume in 1 s (FEV₁) were not related to the dose of lumiliximab, and ranged from a 7% decrease to a 10% increase, respectively, after 4 and 85 days (both in the 4.0-mg/kg group). Most changes in peak FEV₁ were also within 10% of baseline values. The occurrence of symptom-free days or night-time awakenings caused by asthma was also unrelated to dose [517256].

A phase II study of lumiliximab was completed in 131 patients with seasonal allergic rhinitis resulting from ragweed pollen [517266]. Patients received four monthly intravenous infusions of lumiliximab (0.25, 1.0, 2.0 or 4.0 mg/kg) or placebo, starting 2 months prior to the onset of the pollen season. All patients in the study had moderate-to-severe ragweed-induced seasonal allergic rhinitis requiring antihistamine and/or corticosteroid therapy, and had partial symptom relief in the last two allergy seasons. No difference was noted in rhinitis symptom scores for lumiliximab and placebo patients, although lumiliximab produced dose-dependent reductions in both total and ragweed-specific IgE. The decreased levels of IgE production were sustained after the ragweed season. All study groups had a high incidence of antihistamine use, which may have confounded results of the study [517266].

CLL

A phase I study of lumiliximab as a treatment for relapsed or refractory CLL was conducted in 25 patients [527771]. This was a multiple-dose, dose-escalating, multicenter study designed to assess the safety, pharmacokinetics and efficacy of lumiliximab. Patients received lumiliximab on an outpatient basis as intravenous infusions in one of six schedules, 125, 250, 375 or 500 mg/m^2 administered once weekly for 4 weeks; 500 mg/m^2 administered three times during week 1, followed by 500 mg/m^2 once weekly for weeks 2 to 4; or 500 mg/m^2 administered three-times weekly for 4 weeks. Interim results showed the treatment to be safe and there was an indication of clinical response in patients with heavily pretreated CLL. Reductions in absolute lymphocyte count (ALC) were observed in all treatment groups (24 of 25 individuals), with a 50% or greater ALC decrease in eight out of 19 individuals (42%) enrolled in the 375- and 500- mg/m^2 weekly treatment groups. Reductions in lymphadenopathy were also observed [527771]. Final data for this study were not available at time of publication.

Side Effects and Contraindications

Adverse events were reported by all 24 patients who received lumiliximab in the phase I allergic asthma study,

but not by the six patients who received placebo [517256]. These events included ecchymosis at the injection site (in one patient in each of the 0.25-, 1.0- and 10.0-mg/kg cohorts), arthralgia and throat irritation (each in one patient in the 10.0- and 15.0-mg/kg groups). No grade 4 or serious adverse events were reported, and patients treated with lumiliximab had no apparent anti-lumiliximab antibody responses.

In the phase II study in patients with seasonal allergic rhinitis there were no infusion reactions. No relationship was apparent between dose and adverse events, and there was no difference in the rate of adverse events for lumiliximab and placebo patients. There was no T-cell depletion, and no grade 3 or 4 adverse events were related to lumiliximab treatment. One patient developed antibodies against lumiliximab, but no related adverse events were reported [517266].

The preliminary findings from a phase I study of lumiliximab in patients with relapsed or refractory CLL showed intravenous infusions of lumiliximab to be safe at doses of up to 500 mg/m² three times weekly [527771]. A total of 69 study-related adverse events were reported in 16 out of 25 individuals (64%). The most common drug-related adverse events were fatigue, nausea, headache, cough and increased sweating. Dose-limiting toxicities of grade 4 neutropenia possibly related to treatment, grade 4 headache probably related to treatment were experienced by two individuals receiving 500 mg/m².

Patent Commentary

A number of patent applications published by IDEC Pharmaceuticals Corp (now assigned to Biogen Idec Inc) make intellectual property claims relevant to lumiliximab. The PCT applications WO-09302108 and WO-09837099, published in 1993 and 1998, respectively, claim in detail the procedure for producing primatized antibodies, including the nucleic acids encoding such antibodies. A specific claim is an anti-human CD23 monoclonal antibody containing either the human γ -1 or -3 constant domain, including lumiliximab and other antibodies against immunoregulatory targets. Practical utility is claimed in the treatment or prophylaxis of disease conditions, including those conditions in which inhibition of induced IgE production is desirable, such as allergy, autoimmune and inflammatory diseases.

The use of a primatized anti-CD23 antibody to deplete undesired cells by specified methods is represented in WO-09302108, and WO-00044788 claims the use of lumiliximab in allergy and neoplasm. In 2002, the application WO-00204021 disclosed the 'Treatment of B-cell malignancies using combination of B-cell depleting antibody and immune modulating antibody'. Similar claims were made in WO-00222212 and in the 2003 application, WO-03039486.

The most recent application is WO-2004001007, which discloses methods for producing concentrated buffered antibody formulations and therapeutic uses thereof.

Current Opinion

An unmet medical need exists in the treatment of both allergic asthma and CLL, due in part to patient-to-patient

variation in response to therapies [564128], [564129]. Preclinical studies have established that lumiliximab can downregulate IgE in PBMCs and induce apoptosis in both CLL cells and fludarabine-resistant SKW cells. A caveat, however, is that the majority of these results have been presented not in peer-reviewed literature, but as conference abstracts. Thus a sufficient understanding of the preclinical development data, and its relevance in a clinical setting, cannot be assured based on the compiled results provided to date. An example of preclinical data that would be useful for evaluation purposes, but has not been reported, is the identity of the binding site of lumiliximab on CD23. This would help to establish that lumiliximab actually inhibits IgE binding to CD23, but could also portend potentially adverse effects, such as the proteolysis of the receptor with concomitant release of soluble CD23.

To date, lumiliximab has been studied in a limited number of patients. A single phase II trial in 131 seasonal allergic rhinitis patients produced unremarkable preliminary results and no phase II studies have yet been performed in CLL patients. A thorough evaluation of lumiliximab with comparison of results with marketed products and those currently in the clinical development process will not be possible until additional studies of lumiliximab are complete.

Humanized monoclonal antibody therapeutics that are potentially competitive with lumiliximab have been launched for both conditions. For the treatment of allergy-related asthma, one such therapeutic is the IgG1 κ anti-IgE mAb omalizumab (Xolair), developed through a collaborative effort between Genentech Inc, Novartis AG, Tanox Inc and Sankyo Co Ltd. For the treatment of CLL, lumiliximab is likely to face competition from a number of other products. These include alemtuzumab (Millenium & ILEX Partners), which has demonstrated overall response rates ranging from 42 to 89%, and complete response rates ranging from 4 to 50% [517254] and rituximab (Biogen Idec Inc/Genentech Inc/F Hoffmann-La Roche/Zenyaku Kogyo Co Ltd), both commercially available. Oblimersen (Genasense; Genta Inc/Sanofi-Aventis), is a pro-apoptotic antisense oligonucleotide against Bcl-2, under development for a variety of solid and hematological tumors, including CLL [569702]. Combination regimens containing these agents have also shown promise in CLL, as have chemotherapeutics such as fludarabine and cyclophosphamide [564120]. To gain regulatory approval and, subsequently, market share, clinical studies of lumiliximab will need to demonstrate that the drug is at least equivalent to or, for at least some patients, superior to these drugs.

Seikagaku was a partner in the development of lumiliximab for allergy, and Taisho was a partner in the study of lumiliximab in CLL. Both collaborations, however, have been discontinued (December 2003 and September 2003, respectively) [506490], [520057]. These events, along with alterations in company priorities and resources that often occur in the aftermath of mergers, might delay or derail the development of lumiliximab by Biogen Idec.

Development history

By October 2001, phase I/II trials in allergic asthma were underway [424553], [469858], and by January 2002, IDEC had initiated a phase I/II pilot study in seasonal allergic rhinitis [437633]. In September 2002, a phase I trial in CLL was initiated [489005]. In February 2003, the US FDA awarded Orphan Drug status to lumiliximab as a treatment for CLL [564118].

By 1995, IDEC had entered into a development and marketing agreement with Seikagaku Corp, worth up to US \$26 million, for primatized anti-allergy antibodies. Under the agreement, IDEC was to receive research and development support, milestone payments and opportunities to profit from future product sales. IDEC and Seikagaku were to share co-exclusive rights to all products arising from the collaboration, with IDEC retaining US marketing rights and Seikagaku obtaining marketing rights in Asia and Europe [178382]. In April 2002, the agreement was extended; Seikagaku was to share the costs of development of lumiliximab in asthma and other allergic diseases. Financial terms of the entire collaboration were valued at US \$60 million, subject to the achievement of development objectives [449406]. However, in December 2003, Seikagaku terminated its agreement with Biogen Idec [520057].

In 1999, Taisho signed a development and marketing agreement with IDEC for the development of anti-CD23 antibodies; an alliance covering Europe and Asia [319612]. In September 2003, Taisho decided to withdraw from the development of IDEC-152 to focus on its own in-house pipeline [506490].

Developer	Country	Status	Indication	Date	Reference
Biogen Idec Inc	US	Phase II	Allergic rhinitis	12-NOV-03	512976
Biogen Idec Inc	US	Phase II	Asthma	12-NOV-03	512976
Biogen Idec Inc	US	Phase I	Chronic lymphocytic leukemia	12-NOV-03	512976
Biogen Idec Inc	US	Discovery	Allergy	12-NOV-03	512976
Seikagaku Corp	Japan	Discontinued	Asthma	24-DEC-03	520057
Seikagaku Corp	Western Europe	Discontinued	Allergy	24-DEC-03	520057
Taisho Pharmaceutical Co Ltd	Japan	Discontinued	Asthma	22-SEP-03	506490
Taisho Pharmaceutical Co Ltd	Western Europe	Discontinued	Allergy	22-SEP-03	506490

Literature classifications

Key references relating to the technology are classified according to a set of standard headings to provide a quick guide to the bibliography. These are as follows:

Chemistry: References which discuss synthesis and structure-activity relationships.

Biology: References which disclose aspects of the drug's pharmacology in animals.

Metabolism: References which discuss metabolism, pharmacokinetics and toxicity.

Clinical: Reports of clinical phase studies in volunteers providing, where available, data on the following: whether the experiment is placebo-controlled or double- or single-blind; number of patients; dosage.

Chemistry

Study Type	Result	Reference
Synthesis and SAR.	Cynomolgus macaques were immunized with soluble human CD23. Anti-CD23 antibody-producing cells were fused to produce hybridoma cell lines, five of which were selected by ELISA (5E8, 6G5, 2C8, B3B11 and 3G12). The primatization of 5E8 and 6G5 was performed by cloning the primate Ig light and heavy chain variable regions into a mammalian expression vector containing human γ chain and λ light chain constant regions. Antibodies were expressed in CHO cells and isolated by centrifugation followed by protein A column purification. Of the isotypes of primatized 5E8, only the p5E8G1 version was as effective as the primate mAb parent in an <i>in vitro</i> assay of IgE suppression, and was selected for further development as lumiliximab.	527764

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
<i>In vitro</i>	CD23 binding.	Unspecified cell model.	Lumiliximab binds CD23 with a K_d value of 0.12 nM.	504688
<i>In vitro</i>	Activity.	SKW and CCL cell lines treated with lumiliximab (0.1 to 10 μ g/ml).	Incubation with lumiliximab induced apoptosis in ~ 10 and > 60% of cells at 0.1 and 10 μ g/ml, respectively.	504688

Biology (continued)

Study Type	Effect Studied	Experimental Model	Result	Reference
<i>In vitro</i>	Activity.	CLL cells from patients treated with lumiliximab.	Apoptosis was mediated by activation of caspase-3 and -9, and was accompanied by cleavage of PARP. Lumiliximab induced marked downregulation of XIAP, Bcl-x _L and Mcl-1, but expression of cIAP-1, cIAP-2, survivin and Bcl-2 remained unchanged.	473757 484178 515913
<i>In vivo</i>	Efficacy.	SCID mice (n = 10) injected with SKW cells, treated on days 1, 3, 5, 7, 9 and 11 with intraperitoneal injections of either lumiliximab (400 µg), a combination of lumiliximab (200 µg) plus rituximab (200 µg), or placebo.	On day 60, 40% of mice treated with lumiliximab and 70% treated with the combination of lumiliximab and rituximab had survived, compared with 0% of controls.	471021
<i>In vivo</i>	Efficacy.	SCID mice injected with SKW cells.	On day 45, 100% of control mice were dead, while 50 and 90% of mice treated with lumiliximab alone and in combination with rituximab, respectively, were alive.	504688

Metabolism

Study Type	Effect Studied	Model Used	Result	Reference
<i>In vivo</i>	Pharmacokinetics.	Chimpanzees (n = 2) given a single 3-mg/kg subcutaneous dose followed 7 weeks later by three doses.	The serum elimination t _{1/2} was estimated to be 5.6 days after a single dose, and mean bioavailability was estimated to be ~ 60%, based on historical clearance data.	517270
<i>In vivo</i>	Pharmacokinetics.	Phase I, allergic asthma patients given a single intravenous dose of lumiliximab (0.05, 0.25, 1.0, 4.0, 10.0 or 15.0 mg/kg) or placebo.	Mean C _{max} was dose proportional over the 4.0 to 15.0 mg/kg dose range (171 ± 14.5 to 658 ± 56 µg/ml), as was mean AUC. Other parameters were determined from the 0.25 to 15.0 mg/kg doses. Ranges were as follows: mean AUC = 38.1 to 6261.6 µg/day.ml; serum t _{1/2} = 2 to 10 days; median Cl _t = 2.7 to 6.2 ml/day.kg; and median Vd = 20.9 to 38.2 ml/kg.	412124 517256

Clinical

Effect Studied	Model Used	Results	Reference
Efficacy and safety.	Phase I, placebo-controlled, single-dose, sequential, dose-escalating study in patients with mild-to-severe allergic asthma (n = 30). Patients were randomized to receive lumiliximab (0.05, 0.25, 1.0, 4.0, 10.0 or 15.0 mg/kg) or placebo.	At a dose of 15 mg/kg, mean IgE concentration began to decrease by day 8 and decreased to 39.2% below baseline concentration by day 85. A dose of 0.05 mg/kg reduced mean IgE baseline concentration by 15.1% at day 8 and 2.4% by day 85. Mean B-cell count decreased from baseline in patients receiving 4.0 to 15.0 mg/kg doses, but remained within the normal range. Changes in FEV ₁ and peak FEV were dose related, and were also within 10% of baseline values. The occurrence of symptom-free days or night-time awakenings caused by asthma was also unrelated to dose.	517256
Efficacy and safety.	Phase I, multiple-dose, dose-escalating study in patients with relapsed or refractory CLL (n = 25). Lumiliximab was administered as intravenous infusions in one of the following schedules: 125, 250, 375 or 500 mg/m ² administered once weekly for 4 weeks; 500 mg/m ² administered three times during week 1, followed by 500 mg/m ² once weekly for weeks 2 to 4; or 500 mg/m ² three-times weekly for 4 weeks.	Interim results showed the treatment to be safe. An indication of clinical response was observed in patients with heavily pretreated CLL. Reductions in ALC were observed in all treatment groups (24/25 individuals), with a ≥ 50% ALC decrease in 8/19 (42%) individuals enrolled in the 375- and 500-mg/m ² weekly treatment groups. Reductions in lymphadenopathy were also observed.	527771

Clinical (continued)

Effect Studied	Model Used	Results	Reference
Efficacy and safety.	Phase II, multiple-dose, dose-escalating, placebo-controlled study in 131 patients with seasonal allergic rhinitis, who received four monthly intravenous infusions of lumiliximab (0.25, 1.0, 2.0 or 4.0 mg/kg) or placebo, starting 2 months prior to onset of the pollen season.	Preliminary results indicate that lumiliximab was well tolerated, with no drug-related grade 3 or 4 adverse events. One patient developed anti-lumiliximab antibodies. No difference was noted in rhinitis symptom scores for lumiliximab and placebo patients, although lumiliximab produced dose-dependent reductions in both total and ragweed-specific IgE. The decreased levels of IgE production were sustained after the ragweed season.	517266

Associated patent

Title Recombinant antibodies for human therapy.

Assignee IDEC Pharmaceuticals Corp

Publication WO-09302108 04-FEB-93

Priority US-19910735064 25-JUL-91

Inventors Newman RA, Hanna N, Raab RW.

Associated references

178382 IDEC Pharmaceuticals Corp *ANNUAL REPORT* 1994

317457 **Antibody-mediated CD4 stripping contributes to reduced cell surface CD4 density following administration of clenoliximab to patients with rheumatoid arthritis.** Hepburn TW, Davis CB, Elliot MJ, Totoritis MC, Luggen ME *ARTHRITIS RHEUM* 1998 **40** 9 Suppl S159

319612 **Taisho, Seikagaku, IDEC to codevelop anti-allergy drugs.** *PHARMA JPN* 1999 **1640** 5

338079 **Treatment of rheumatoid arthritis with a primatized anti-CD4 monoclonal antibody, SB-210396 (IDEC-CE9.1). Results of an open label extension study in patients responding to induction therapy.** Tesser JRP, Wiesenhutter C, Levy R, Schiff M, Lipani J, Solinger A, MacDonald B, Elliott M, Singh K *ARTHRITIS RHEUM* 1997 **40** 9 Suppl S224

404493 **American Academy of Allergy, Asthma and Immunology - 57th Annual Meeting (Part III), New Orleans, LA, USA.** Lieberman P *IDDB MEETING REPORT* 2001 March 16-21

412124 **Results of a phase I, single-dose, dose-escalating trial of a primatized anti-CD23 monoclonal antibody (IDEC-152) in patients with allergic asthma.** Busse WW, Rosenwasser LJ, Lizambri RG, Olejnik A, Totoritis MC *J ALLERGY CLIN IMMUNOL* 2001 **107** 2 Abs 354

412387 **Anti-CD23 monoclonal antibody (IgE inhibition involves the Fc portion of the molecules).** Yabuuchi S, Nakamura T, Kloetzer WS, Reff ME *J ALLERGY CLIN IMMUNOL* 2001 **107** 2 Abs 597

424553 **Drug development pipeline: IDEC-152.** IDEC Pharmaceuticals Corp *COMPANY COMMUNICATION* 2001 October 04

432438 **Induction of apoptosis by IDEC-152 (Anti-CD23) in lymphoma cells.** Pathan N, Hariharan K, Hopkins M, Saven A, Reff M, Hanna N, Grint P *BLOOD* 2001 **98** 11 Suppl 1 Abs 1545

432863 **American Society of Hematology - 43rd Annual Meeting (Part III) - OVERNIGHT REPORT, Orlando, FL, USA.** Veryard C *IDDB MEETING REPORT* 2001 December 7-11

437633 **IDEC Pharmaceuticals Corp.** *HAMBRECHT & QUIST* 2002 Suppl January 7-10 25

447539 **Induction of apoptosis by IDEC-152 (anti-CD23) in chronic lymphocytic leukemia.** Pathan N, Hariharan K, Berquist L, Hopkins M, Saven A, Reff M, Grint P, Hanna N *PROC AM ASSOC CANCER RES* 2002 **43** 93 Abs 4982

449406 **IDEC to continue IDEC-152 alliance with Seikagaku.** IDEC Pharmaceuticals Corp *PRESS RELEASE* 2002 April 25

469858 **Interim result figures: September 2002 (First half of FY2002).** Taisho Pharmaceutical Co Ltd *2ND QUARTER REPORT* 2002 November 01

471021 **Future of monoclonal antibodies in the treatment of hematologic malignancies.** Reff ME, Hariharan K, Braslawsky G *CANCER CONTROL* 2002 **9** 2 152-166

472393 **IDEC-152 (anti-CD23) triggers apoptosis of chronic lymphocytic leukemia (CLL) cells *in vitro*.** Hopkins MT, Pathan N, Chu P, Grint P, Saven A *BLOOD* 2002 **100** 11 Abs 2346

473757 **IDEC-152 (Anti-CD23) induced apoptosis in CLL cells is mediated by caspase activation and downmodulation of anti-apoptotic proteins.** Pathan N, Chu P, Scales L, Hariharan K, Hopkins M, Saven A, Leigh B, Wynne D, Grint P *BLOOD* 2002 **100** 11 Abs 3170

484178 **Mechanism of IDEC-152-induced apoptosis in chronic lymphocytic leukemia B cells.** Chu P, Scales L, Zou A, Hopkins M, Saven A, Kehry M, Giri J, Pathan N *PROC AM ASSOC CANCER RES* 2003 **44** 1 Abs 661

489005 **IDEC Pharmaceuticals Corp: 2002 Form 10-K.** IDEC Pharmaceuticals Corp *FORM 10-K* 2003 January 31

504688 **Drug Discovery Technology (Part II), Boston, MA, USA.** Kumar R *IDDB MEETING REPORT* 2003 August 10-15

506490 **Taisho to withdraw from development of anti-CD-23 antibody.** *PHARMA JPN* 2003 6 September 22

512976 **Biogen and IDEC complete merger.** Biogen Inc *PRESS RELEASE* 2003 November 12

515913 **Lumiliximab (IDEC-152), an anti-CD23 antibody, induces apoptosis *in vitro* and *in vivo* in CLL cells.** Pathan N, Zou A, Wynne D, Chu P, Thall A, Byrd J, Hanna N, Leigh B *BLOOD* 2003 **102** 11 Abs 1596

516978 **Phase I results from a multicenter trial of galiximab (anti-CD80 antibody, IDEC-114) in combination with rituximab for the treatment of follicular lymphoma.** Gordon LI, Moore JO, Cheson BD, Czuczman M, Younes A, Leonard JP, Forero-Torres A, Sweetenham JW, Chieffo N, Thall A, Leigh BR *BLOOD* 2003 **102** 11 Abs 4951

517254 **Monoclonal antibody therapy of chronic lymphocytic leukemia.** Mavromatis B, Cheson BD *J CLIN ONCOL* 2003 **21** 9 1874-1881

517256 **Allergic asthma and an anti-CD23 mAb (IDEC-152): Results of a phase I, single-dose, dose-escalating clinical trial.** Rosenwasser LJ, Busse WW, Lizambri RG, Olejnik TA, Totoritis MC *J ALLERGY CLIN IMMUNOL* 2003 **112** 3 563-570

517266 **Results of a phase II, multiple-dose, randomized trial of an anti-CD23 monoclonal antibody (IDEC-152) in patients with seasonal allergic rhinitis.** Casale TB, Busse WW, Lizambri RG, Korenblat PE, Schoenwetter WF, Weiler JM, Rosenwasser LJ, Nayak AS, Perea RM, Totoritis MC *J ALLERGY CLIN IMMUNOL* 2003 **111** 2 Suppl S75

517270 **Pharmacokinetics and pharmacodynamics of IDEC-152 antibody in chimpanzees after multiple subcutaneous doses.** Kuo B, Wey KR, Clark JK, Phan A, Leonard JE *J IMMUNOTHER* 2002 **25** 6 S5

520057 **Seikagaku to withdraw from development of SI-03401.** *PHARMA JPN* 2004 1874 11

527747 **Chronic lymphocytic leukemia: Advances in biology and therapeutics.** Aksentjevich I, Flinn IW *CURR OPIN ONCOL* 2003 **15** 1 16-22

527764 ***In vitro* IgE inhibition in B cells by anti-CD23 monoclonal antibodies is functionally dependent on the immunoglobulin Fc domain.** Nakamura T, Kloetzer WS, Brams P, Hariharan K, Chamat S, Cao X, LaBarre MJ, Chinn PC, Morena RA, Shestowsky WS, Li YP *et al* *INT J IMMUNOPHARMACOL* 2000 **22** 2 131-141

527771 **Interim results from a phase I study of lumiliximab (IDEC-152, anti-CD23 antibody) therapy for relapsed or refractory CLL.** Byrd JC, O'Brien IF, Kipps TJ, Weiss MA, Reid J, Wynne D, Leigh BR *BLOOD* 2003 **102** 11 Abs 248

527774 **CD23 quantification in chronic lymphocytic leukemia and the effects of anti-CD23 therapy on its levels.** Jilani I, O'Brien S, Kantarjian H, Caiyo J, Giles F, Ferrajoli A, Keating M, Albitar M *BLOOD* 2003 **102** 11 Abs 5170

529904 **Lumiliximab (IDEC-152), an anti-CD23 antibody, induces apoptosis *in vitro* and *in vivo* in CLL cells.** Pathan NI, Zou A, Chu P, Wynne D, Leigh B, Hanna N *PROC AM ASSOC CANCER RES* 2004 **45** Abs 703

531819 **Lumiliximab (IDEC-152), an anti-CD23 antibody induces apoptosis in drug-resistant lymphoma cells.** Zou A, Hariharan K, Murphy T, Scales L, Kehry MR, Leigh B, Hanna N, Pathan NI *PROC AM ASSOC CANCER RES* 2004 **45** Abs 2131

564119 **Inflammation in allergic asthma: Initiating events, immunological response and risk factors.** Ferreira MA *RESPIROLOGY* 2004 **9** 1 16-24

564120 **Current approach to diagnosis and management of chronic lymphocytic leukemia.** Shanafelt TD, Call TG *MAYO CLINIC PROCEEDINGS* 2004 **79** 3 388-398

564122 **From bench to bedside: Discovering rules for antibody design, and improving serotherapy with monoclonal antibodies.** Isaacs JD *RHEUMATOLOGY* 2001 **40** 7 724-738

564125 **Antibody humanization: A case of the 'Emperor's new clothes'?** Clark M *IMMUNOLOGY TODAY* 2000 **21** 8 397-402

564126 **Human antibody effector function.** Burton DR, Woof JM *ADV IMMUNOL* 1992 **51** 1-84

564118 **Cumulative list of all products that have received US Orphan Products Designation.** US Food and Drug Administration *INTERNET SITE* (<http://www.fda.gov/orphan/designat/list.htm>)

564128 **Moving towards individualized medicine with pharmacogenomics.** Evans WE, Relling MV *NATURE* 2004 **429** 6990 464-468

564129 **Pharmacogenomics - drug disposition, drug targets, and side effects.** Evans WE, McLeod HL *NEW ENGL J MED* 2003 **348** 6 538-549

564130 **CD23 (the low-affinity IgE receptor) as a C-type lectin: A multidomain and multifunctional molecule.** Kijimoto-Ochiai S *CELL MOL LIFE SCI* 2002 **59** 4 648-664

564835 **The low-affinity receptor for IgE.** Conrad DH, Kilmon MA, Studer EJ, Cho S *BIOCHEM SOC TRANS* 1997 **25** 2 393-397

569702 **Phase 3 trial of Genasense plus chemotherapy in patients with advanced chronic lymphocytic leukemia achieves primary endpoint.** Genta Inc *PRESS RELEASE* 2004 November 08