FDA Approval: Siltuximab for the Treatment of Patients with Multicentric Castleman Disease

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Abstract

On April 22, 2014, the FDA granted full approval to siltuximab (SYLVANT for injection; Janssen Biotech, Inc.), a chimeric human-mouse monoclonal antibody to IL6, for the treatment of patients with multicentric Castleman disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative. The approval was primarily based on the results of a randomized, double-blind trial in which 79 symptomatic patients with MCD were allocated (2:1) to siltuximab plus best supportive care (BSC) or to placebo plus BSC. The primary efficacy endpoint was the proportion of patients in each arm achieving a durable tumor and symptomatic response that persisted for a minimum of 18 weeks without treatment failure. Tumor response was based on independent review of CT scans using the revised Response Criteria for Malignant Lymphoma, and symptomatic response was defined as complete resolution or stabilization of 34 MCD-related signs and symptoms as reported by the investigator. Thirty-four percent of patients in the siltuximab arm and no patients in the placebo arm met the primary endpoint (P = 0.0012). The most common adverse reactions (>10% compared with placebo) during treatment with siltuximab were pruritus, increased weight, rash, hyperuricemia, and upper respiratory tract infection. Clin Cancer Res; 21(5); 950–4. © 2015 AACR.

Introduction

Castleman disease is a rare disorder characterized by hyperplasia of lymphoid tissue, resulting in lymphadenopathy, which may be unicentric Castleman disease (UCD) or multicentric Castleman disease (MCD). UCD may be approached by local therapy, whereas MCD requires a systemic approach. When the lymphadenopathy of Castleman disease is multicentric, it is also associated with signs and symptoms of excess IL6 secretion by germinal center B-cell lymphocytes (1–4). Patients with MCD may have symptoms of fatigue, fever, weakness, day or night sweats, anorexia, pruritus, pain, and/or dyspnea (5). The physical signs of the disease include fever, weight loss, fluid retention, edema, effusions, ascites, neuropathy, skin rashes, skin nodules, lymphadenopathy, splenomegaly, and hepatomegaly. Laboratory abnormalities may include anemia, thrombocytopenia, elevated C-reactive protein (CRP), and hypoalbuminemia.

When MCD is associated with viral infections such as human immunodeficiency virus (HIV) or human herpesvirus-8 (HHV-8; refs. 6, 7), the disease is driven more by the viral (HHV-8) IL6, rather than by endogenous IL6 secreted by the germinal center cells and is essentially a different disease which has a different pattern of response to therapy. This is especially true of antibodies to endogenous IL6, which do not bind to viral (HHV-8) IL6.

There are three different histopathologic variants: the plasma-cell variant, the hyaline vascular variant, and the mixed subtype (8). In the plasma-cell variant, there is abundant infiltration of the germinal centers with plasma cells and the IL6 levels are high. In the hyaline vascular variant, there is less of the plasma cell infiltration and lower levels of IL6. In patients with the hyaline vascular variant, clonal proliferation of lymphocytes may occur. In a fraction of patients with the hyaline vascular subtype, this may evolve into non-Hodgkin lymphoma.

Until the present time, there was no approved therapy in the United States for MCD. The following treatments have been tried: chemotherapy with steroids and/or rituximab, bortezomib, thalidomide, and autologous bone marrow transplantation following high-dose therapy. Initial responses may occur but are followed by relapse and progression of disease. A humanized mAb to the human IL6 receptor (tociluzumab) was administered to 28 patients with MCD (9). Although the authors did not report evidence of reduction of lymphadenopathy by CT scans, the dose of corticosteroids required to manage symptoms was reduced during therapy.

A phase I study of siltuximab, an anti-IL6 mAb administered by i.v. infusion, enrolled 37 patients with Castleman disease (10). Siltuximab, which binds to IL6, is different from tociluzumab, an antibody that binds to the IL6 receptor. According to central radiologic review, there was one complete response (CR) and 11 partial responses (PR). This experience led to a phase II, randomized, placebo-controlled, double-blind trial to test the efficacy and safety of siltuximab in MCD (11). The results of these trials were submitted in support of a Biologics License Application (BLA) for siltuximab for the treatment of...
patients with MCD that was not associated with HHV-8 infection. The BLA was received on August 30, 2013, and was approved on April 23, 2014. The FDA review of the BLA is summarized below.

Chemistry
Siltuximab is a glycosylated human-mouse chimeric IgG1 x mAb that is produced in Chinese hamster ovary cells. The product is supplied as 100-and 400-mg single-use vials containing a sterile, white, preservative-free, lyophilized powder.

Nonclinical pharmacology and toxicology
Siltuximab binds to soluble human IL6 with high selectivity and affinity (KD = 34 pmol/L). Upon binding to IL6, siltuximab inhibits IL6-mediated signaling pathways in cell culture, including IL6-mediated proliferation of cell lines, IL6-stimulated production of acute phase proteins (serum amyloid A), and the secretion of IgM antibodies. Siltuximab binds human and cynomolgus monkey IL6 with similar affinity; hence, toxicology studies were conducted mainly in cynomolgus monkeys. Toxicities observed in the 6-month repeat-dose studies in cynomolgus monkeys using the intravenous route of administration were consistent with the pharmacology of siltuximab.

Findings included a trend for reduction in the size of the splenic germinal centers following KLH immunization, lower anti-KLH IgM and IgG levels in the T-dependent antigen response assay, and lower globulin levels. These effects suggest the potential for infection secondary to immune modulation. Other findings included sporadic episodes of low heart rate and blood pressure, first-dose infusion reaction in one out of 52 animals, and skin erythema with corresponding hyperkeratosis or acanthosis of minimal severity. Toxicokinetic results indicated that anti-siltuximab antibodies did not interfere with exposure or study results.

Reproductive toxicology studies consisted of a fertility study conducted in mice with an anti-mouse IL6 mAb, an embryofetal developmental study in cynomolgus monkeys with siltuximab, and an enhanced pre- and postnatal developmental (ePPND) study with a human IL6 mAb. The fertility study did not indicate any adverse fertility findings in mice. Administration of siltuximab or a human version of the antibody to pregnant monkeys did not result in maternal or fetal toxicities; however, there were significant decreases in globulin concentration in dams and infants. This may be secondary to reduction in the immunoglobulin level. The parturition, postnatal survival, or the growth and development of infants were not affected in the ePPND study. On the basis of the pharmacology of the drug and findings in animals, children born to a pregnant woman treated with siltuximab may be at increased risk of infection; hence, a pregnancy Category C has been assigned to this drug.

Clinical pharmacology
A population pharmacokinetic analysis indicated that the clearance of siltuximab in patients is 0.23 L/day (51% CV), and body weight is the only significant covariate identified for siltuximab clearance. The mean serum terminal half-life ($t_{1/2}$) for siltuximab in patients after the first i.v. infusion of 11 mg/kg is 21 days (range: 14–30 days). Binding of bioactive IL6 by siltuximab may normalize CYP450 enzyme activity that was previously downregulated by IL6. This may result in increased metabolism of CYP450 substrates compared with metabolism before treatment with siltuximab. If siltuximab is coadministered with CYP450 substrate drugs with a narrow therapeutic range, the dose of the concomitant medication may need to be adjusted. On the basis of the population pharmacokinetic analysis, no initial dosage adjustment is necessary for patients with baseline mild to severe renal impairment ($\text{CLCr} > 15 \text{ mL/minute}$) or for patients with baseline mild to moderate hepatic impairment (Child-Pugh Class A and B). Patients with baseline severe hepatic impairment (Child-Pugh Class C) were not included in clinical trials.

Within the serum siltuximab exposure range observed following administration of 11 mg/kg i.v. every 3 weeks, no exposure–response relationships between serum CRP and siltuximab exposure or between durable tumor and symptomatic response rate and siltuximab exposure were identified. Following siltuximab dosing, 0.2% (1/411) of patients tested positive for anti-siltuximab antibodies. Further immunogenicity analyses of the single positive sample revealed a low titer of anti-siltuximab antibodies with nonneutralizing capabilities.

Clinical Trial
Design
Seventy-nine patients with symptomatic MCD associated with measurable disease who did not have infections with HIV or HHV-8 were randomly allocated (2:1) to siltuximab with best supportive care (BSC) or to placebo with BSC. Patients with HIV or HHV-8 infections were excluded from the trial because in a nonclinical study, siltuximab did not bind to virally produced IL6. Patients received siltuximab 11 mg/kg or placebo i.v. every 3 weeks until treatment failure, discontinuation of treatment, withdrawal from the study, or until 48 weeks after the last subject started study treatment. Patients who met the criteria for treatment failure were allowed to cross-over from the placebo arm to the siltuximab arm.

The primary endpoint was the proportion of patients achieving a tumor and symptomatic response (CR and PR) which is durable (that persisted for a minimum of 18 weeks) without treatment failure. Treatment failure is defined as:

- a. A sustained increase from baseline in disease-related symptoms (grade 3 or higher) symptom despite BSC;
- b. Onset of any new disease-related (grade 3 or higher) symptom despite BSC;
- c. Sustained (at least 3 weeks) deterioration if performance status (PS) by more than 1 point (ECOG PS) despite BSC;
- d. Radiologic progression; and
- e. Initiation of any other therapy.

A complete response for this combined endpoint was defined as complete disappearance of all measurable and evaluable disease using the revised criteria for malignant lymphoma (12), and resolution of 34 clinicians reported baseline physical signs and symptoms attributed to MCD as defined by the MCD-related overall symptom score (11), which is sustained for at least 18 weeks. The overall symptom score was calculated with each cycle of therapy as the sum of the investigator-determined severity grades (NCI-Common Terminology Criteria for Adverse Events v 4.0) of MCD-related signs and symptoms. PR for this combined endpoint was defined as a $>50\%$ decrease in the sum of the product of the diameters of index lesion(s), with at least stable disease in all other evaluable disease in the absence of treatment failure, which is sustained for at least 18 weeks.
If the primary endpoint achieved a statistically significant difference in the proportion of patients achieving a durable tumor and symptomatic response, the following secondary endpoints were analyzed in a fixed order at a two-sided 5% level of significance: (i) tumor response by central review; (ii) median time to treatment failure on each arm; (iii) percentage of patients on each arm who were anemic within 2 weeks before study treatment on each arm who showed an increase in hemoglobin level at week 13 of 1.5 g/dL or more over baseline; (iv) median time to improvement in the MCD symptom scale as reported by patients; (v) median time to improvement in the Functional Assessment of Chronic Illness Therapy Fatigue score (FACIT-F); and (vi) the proportion of patients on each arm who were corticosteroid free for at least 9 consecutive weeks during the blinded treatment period.

**Demographics**

The median age was 48 years. Sixty-six percent of patients were male, 48% Asian, 39% white, and 4% black. Thirty-three percent had the hyaline vascular subtype, 23% the plasmacytic subtype, and 44% the mixed subtype. Of the 79 patients on the protocol, 78.5% (62/79) had >4 symptoms of MCD before initiation of therapy, and 58% had received at least one prior treatment. The baseline features of the patients entered onto the siltuximab and placebo arms are summarized in Table 1.

**Efficacy**

Eighteen patients (34.0%; 95% confidence intervals, 11.1%–54.8%) on the siltuximab arm had a durable tumor and symptomatic response (1 CR and 17 PRs) compared with no patients on the placebo arm \( (P = 0.0012) \); calculated with an exact Cochran–Mantel–Haenszel test adjusted for baseline corticosteroid use). There were eight responses in 13 patients with the plasmacytic subtype, 10 responses in 12 patients with the mixed subtype, and no responses in 18 patients with the hyaline vascular subtype. The median duration of tumor and symptomatic response could not be reliably estimated because only one of the 18 responders had lost the response at the time of the data cutoff.

The results for each of the secondary endpoints are shown in Table 2. The results of three of the six secondary endpoints were statistically significant. The percentage of patients on the siltuximab and placebo arms with a partial tumor response or better was 38% and 4%, respectively. With 422 days of follow-up, the time to treatment failure was not reached on the siltuximab arm and was 134 days on the placebo arm. The percentage of patients who were anemic at baseline with an increase in hemoglobin \( \geq 1.5 \text{g/dL} \) at 13 weeks was 61% on the siltuximab arm compared with 0% on the placebo arm.

**Safety**

In the randomized trial, the median duration of treatment was 375 days in the siltuximab arm and 152 days in the placebo arm.

The median number of completed infusions was more than double in the siltuximab group (19 infusions) compared with the placebo group (8 infusions). To control for the disparate number of infusions, the per patient incidence of adverse reactions occurring during the first eight infusions is shown in Table 3. Only adverse reactions that occurred in \( >3\% \) of patients on the siltuximab arm are presented. The most common adverse reactions \( (>10\% \text{ compared with placebo}) \) during treatment with siltuximab were pruritus, increased weight, rash, hyperuricemia, and upper respiratory tract infection. There were no adverse events leading to death, and the percentage of patients who discontinued because of adverse events was 23% on the siltuximab arm and 39% on the placebo arm.

Over 750 patients have been treated with siltuximab. One patient had an anaphylactic reaction. In the randomized trial, infusion reactions were seen in 8% of patients on the siltuximab arm (one grade 3 and the rest grade 1 or 2) and in no patients on the placebo arm.

The safety of long-term administration of siltuximab was addressed in an extension study derived from the initial phase I dose-finding study in patients with MCD who were benefiting...
Skin disorders in enrolling subjects (i) were the biological mechanism of the disease; (ii) the company succeeded in the enrolment, and the median duration of treatment was 5.1 years (range, 3.4–7.2 years). The most common adverse reactions (>20%) were upper respiratory tract infection (63%), diarrhea (32%), pain in extremities (21%), arthralgia (21%), and fatigue (21%). No cumulative toxicities or deaths were reported.

### Discussion

The approval of siltuximab was notable for several reasons: (i) it is the first FDA approval of a treatment for MCD and first approval of an anti-IL6 antibody; (ii) the treatment targets the pathophysiological mechanism of the disease; (iii) the company succeeded in enrolling sufficient numbers of patients in a randomized trial despite the rarity of the disease; and (iv) the trial met its pre-specified primary endpoint as well as three secondary endpoints. MCD is a disease of lymphadenopathy accompanied by signs and symptoms associated with elevated levels of IL6. One of the most interesting aspects of the randomized trial design was the composite primary endpoint composed of tumor response by CT scan combined with changes in signs and symptoms of the disease. This endpoint was designed to capture all of the major defining hallmarks of the disease: lymphadenopathy and clinician-reported signs and symptoms of excessive IL6 exposure.

The fact that the disease is defined by dramatic symptomatology as well as equally notable physical findings which arise from increased levels of IL6, as well as the extreme rarity of the disease, provided challenges for the design of the trial as well as the analysis of the results by the FDA.

The trial was supported by 38 hospitals in the following countries: Canada, United States, Brazil, Finland, Norway, United Kingdom, France, Spain, the Netherlands, Germany, Belgium, Hungary, Israel, Egypt, Jordan, Russia, Korea, China, India, Hong Kong, Taiwan, Malaysia, Australia, and New Zealand. This provided challenges in terms of the real-time review of the histopathology as part of eligibility assessment. There were challenges as well as for the real-time review of the responses or progression of the lymphadenopathy, symptoms and signs following administration of the siltuximab. This required seven medical monitors with responsibilities around the world. Special measures were required for obtaining histopathologic material from countries in which the export of such samples is tightly regulated. These measures allowed the entry onto a pivotal trial of 79 patients who were randomized 2:1: siltuximab plus standard of care was compared with placebo plus standard of care.

The review was complicated by the composite primary endpoint that was used to capture the effect of siltuximab on the cardinal features of the disease: the signs and symptoms arising from increased IL6 levels, as well as lymphadenopathy, effusions, and enlargement of the spleen and liver. The response of the signs and symptoms of MCD was measured by investigator assessment.

The major finding of the trial was a durable tumor and symptomatic response rate of 34% in the siltuximab arm versus 0% in the placebo arm. Durable tumor and symptomatic responses were seen consistently across all histopathologic subgroups except for the hyaline vascular subgroup. Although the analysis of secondary endpoints in this subgroup must be considered exploratory, some of the results suggest that siltuximab may reduce the severity of the anemia in MCD in the hyaline vascular subgroup as well. Similarly, the median time to treatment failure in the hyaline vascular subgroup was 206 days on the siltuximab arm and 70 days on the placebo arm.

The most common adverse reactions with siltuximab in the randomized trial were pruritis, increased weight, rash, hyperuricemia, and upper respiratory tract infection. Although infusion reactions were reported in 4.8% of patients receiving monotherapy, the median number of completed infusions and the duration of treatment in the siltuximab arm was more than double the placebo arm. There were no adverse events leading to death, and more patients on the placebo arm discontinued treatment due to adverse events. In addition, patients on the phase 1 extension study continued siltuximab infusions for a median of 5.1 years. This result not only suggests that patients with MCD receiving siltuximab are deriving benefit, but also that the toxicity profile is acceptable for this patient population.

<table>
<thead>
<tr>
<th>Table 3. Per-patient incidence (expressed as a percentage of total enrolled on arm) of common adverse reactions during initial eight infusions</th>
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<tbody>
<tr>
<td><strong>Siltuximab, all grades (n = 53)</strong></td>
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<tr>
<td>Skin disorders</td>
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<tr>
<td>Rash</td>
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<td>Pruritis</td>
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<tr>
<td>Skin: increase in pigmentation</td>
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<td>Eczema</td>
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<td>Psoriasis</td>
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<td>Dry skin</td>
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<td>Lower respiratory tract infections</td>
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<td>Upper respiratory tract infections</td>
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<td>Thrombocytopenia</td>
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<td>Edema</td>
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<td>Constipation</td>
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<td>Oropharyngeal pain</td>
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<td>Weight gain</td>
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<td>Hypotension</td>
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Infusions of siltuximab are well tolerated and many patients remain on therapy for years. Siltuximab provides symptomatic relief to a substantial number of patients with MCD for whom there is no other approved therapy.

**Disclosure of Potential Conflicts of Interest**
No potential conflicts of interest were disclosed.

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**References**

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