Spotlight in Clinical Response

Molecular Cancer Therapeutics

Sustained Remission of Multicentric Castleman Disease in Children Treated with Tocilizumab, an Anti-Interleukin-6 Receptor Antibody

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Abstract

Multicentric Castleman Disease (MCD) is an idiopathic lymphoproliferative disorder, reported exceptionally in children and generally believed to be an autoinflammatory disease resulting in an increase of interleukin-6 secretion. Previous studies in adult patients suggested a beneficial role of the anti-interleukin-6 receptor antibody tocilizumab on the clinical and biologic disease manifestations of MCD. Here, we describe the efficacy and safety of tocilizumab in two children with MCD, which was diagnosed on the basis of clinical and histologic findings. In both cases, tocilizumab was administered intravenously at a dose of 8 mg/kg every 2 weeks. The tocilizumab treatment alleviated fever and restored growth rate in both patients. The patients' hypergammaglobulinemia, high C-reactive protein, and high erythrocyte sedimentation rates normalized simultaneously. Nevertheless, splenomegaly persisted in the first patient, and a secondary hepatic node appeared in the second patient. The side effects, essentially sustained thrombocytopenia, were mild in both cases. For the first patient, following an initial 10-month period, the interval between infusions was increased. This patient benefited from sustained remission for a period of 3 years. Tocilizumab was effective and safe in these two children with MCD. *Mol Cancer Ther; 11(8); 1623–6. ©2012 AACR.*

Introduction

Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder with benign hyperplastic lymph nodes, which is reported only exceptionally in children. The main systemic symptoms of the disease are fever, fatigue, splenomegaly, and hepatomegaly, skin rash, and severe growth retardation. Abnormal laboratory findings include anemia, hypergammaglobulinemia, and increased levels of acute phase proteins. Dysregulated overproduction of interleukin-6 (IL-6) by the affected lymph nodes is thought to be responsible for the systemic manifestations of the disease (1–3). Previous studies in adults showed that the anti–IL-6 and anti–IL-6 receptor antibody (tocilizumab) alleviated symptoms and biochemical abnormalities in patients with MCD (4–6).

To the best of our knowledge, very little is known about the long-term effects of tocilizumab, especially in pediatric patients. We describe the efficacy and safety of tocilizumab in 2 children with MCD.

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Patients and Methods

Patient 1

A 6.5-year-old white boy was hospitalized following a 3-week-period of fever associated with chills, arthralgia, and an inflammatory syndrome, but with no infection. Still disease was originally diagnosed. Although a prednisolone treatment initially led to a partial clinical improvement, all of the symptoms recurred when the steroid dose was reduced, and the patient developed serious growth retardation.

At the age of 13.5 years, the patient was hospitalized as a consequence of fatigue, diffuse abdominal pain, and elevated biologic inflammatory markers. Abdominal ultrasonography and an abdominal CT scan revealed a steatosic hepatomegaly, multiple mesenteric and retroperitoneal lymphadenopathies, a large, infiltrative tissue mass located between the pancreatic tail and the splenic hilum, and a homogeneous splenomegaly. A mixed type of MCD was diagnosed on the basis of a biopsy and histologic examinations of the tissue mass. HIV and KSHV serology and KSHV PCR in biopsies were negative. The patient received combined chemotherapy [6 courses of rituximab (375 mg/m^2), cyclophosphamide (500 mg/m^2), and vinblastine (4 mg/m^2)] for 5 months, with no clinical response.

An IL1-RA agonist (Anakinra) was taken for a period of 2 years and 3 months. This treatment improved the patient's general status, clinical symptoms, and decreased the size of his lymph nodes and the acute phase proteins level (Fig. 1). However, occasional fever peaks indicated that control of the disease was possibly incomplete.

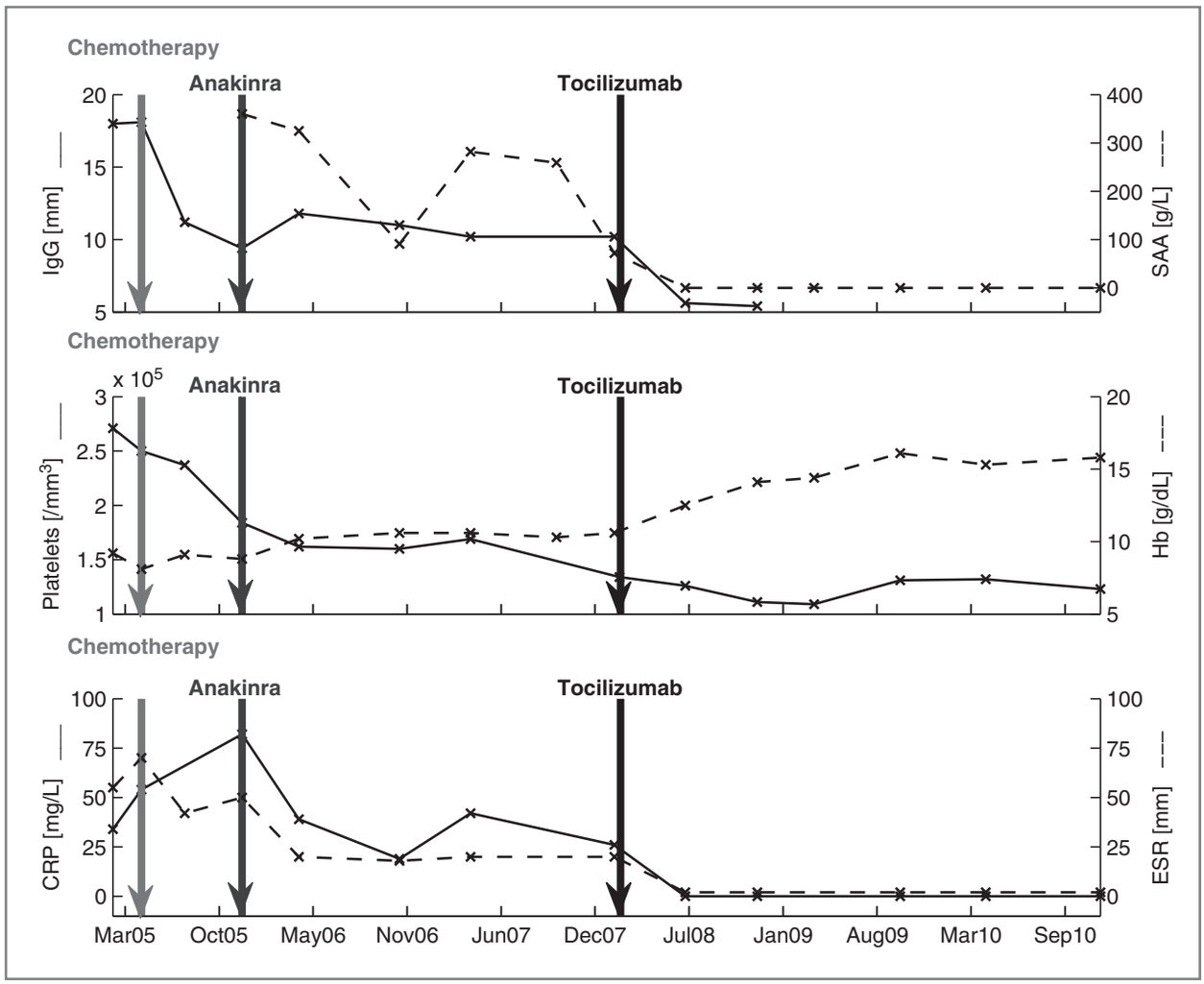

Figure 1. Representative changes in IgG, SAA protein, platelets, hemoglobin (Hb), CRP, and ESR in the first patient with multicentric Castleman disease during treatment with chemotherapy, anakinra, and tocilizumab.

At the age of 16.5 years, the authors decided to introduce a 8 mg/kg dose of tocilizumab every 2 weeks. After the first tocilizumab infusion, the fever peaks disappeared and the C-reactive protein (CRP), erythrocyte sediment rate (ESR), and hemoglobin levels normalized. After 6 months of treatment, all clinical symptoms had disappeared and the patient's general status improved markedly, with weight gain and normalized growth. The steroid administration was stopped. The size of the lymph nodes also decreased, but the splenomegaly persisted. The average SAA protein level decreased from 360 mg/L to less than 5 mg/L ($N < 15$ mg/L), the average IgG level decreased from 18 g/L to 5.62 g/L ($N = 6.55 – 12.17$ mg/L), and the IL-6 level increased from 17 pg/L to 150 pg/L. After 10 months of treatment, as the patient's clinical and biologic conditions continued to improve, we increased the administration intervals to once every 3 weeks for a period of 5 months, and then to once every 4 weeks for a period of 1 year, and finally to once every 5 weeks.

This boy has now been under tocilizumab treatment for a period of 3 years, with good efficacy and a good level of tolerance, apart from occasional headaches. The observed side effects were low platelet counts and low fibrin levels, with no macrophage activation syndrome (Fig. 1) and an episode of herpes zoster. The fibrinogen decreased from 4–5 g/L to 1.4–1.8 g/L.

Patient 2

A 7-year-old white girl was hospitalized following a 3-week-period of fever, accompanied by multiple superficial adenopathies and an inflammatory syndrome, but no infection. She had a polyclonal hypergammaglobulinemia. The IgG serum level was 25.6 g/L. An abdominal CT scan revealed multiple mesenteric and precaval lumbar and retroperitoneal lymphadenopathies. Histologic analysis of the liver and cervical lymph node biopsies revealed a nonspecific inflammatory reaction. The patient received 3 infusions of immunoglobulin, with no observed efficacy.

During a 2-year follow-up period, she still experienced recurrent fever peaks, multiple superficial adenopathies, and developed serious growth retardation.

At the age of 10.8 years, she was hospitalized in our department for additional tests. The abdominal ultrasonography revealed a hepatomegaly, a splenomegaly, and multiple mesenteric, retroperitoneal, and hilum liver lymphadenopathies. Biopsies of the inguinal lymph nodes were carried out surgically; 3.8 years after disease onset, the diagnosis of MCD with plasma cell type was confirmed. HIV and KSHV serology and KSHV PCR in the inguinal lymph nodes biopsies were negative.

It was decided to introduce a 8 mg/kg dose of tocilizumab every 2 weeks. The patient's general status improved quickly, the fever peaks disappeared, and we observed a decrease in her inflammatory parameters (Fig. 2). However, the multiple deep adenopathies were not modified and a 7-mm diameter hepatic node appeared. She had a mild thrombopenia, but sustained (Fig. 2). The patient's fibrinogen level decreased from 5–6 g/L to 2–3 g/L, and the serum IL-6 level increased from 50 pg/mL to 3194 pg/mL.

Discussion

Castleman disease is a very rare lymphoproliferative disorder, for which no standard treatment exists. A variety of approaches, including surgery, radiation, steroids, antiviral therapies, specific antibodies such as rituximab (7), and chemotherapy have been tested with MCD, with variable results. Previous studies in adults have reported that blockage of the IL-6 signal is effective in treating MCD (4–6). Here, we report, for the first time, 2 cases of children with MCD, which was improved by tocilizumab treatment.

MCD is linked to excessive production of IL-6 in the germinal centers (1). It has been suggested that KSHV could contribute by inducing the secretion of the human IL-6 analog viral IL-6 (8). Furthermore, KSHV infection is present in 100% of Castleman Disease cases when associated with HIV infection and in 41% of other cases (9). This association was not found in our patients.

It was first reported in 1994 that treatment with a murine anti-IL-6 antibody improved the signs and symptoms associated with Castleman Disease (10). A phase I trial suggested that tocilizumab was effective in patients with MCD (4). Then, in a multicenter prospective study, tocilizumab was administered to ($n = 28$) patients with MCD. Within 16 weeks, the tocilizumab treatment consistently improved the patients' lymphadenopathy (5). Van Rhee and colleagues have treated in 2010 in a phase I study 23 patients with Castleman Disease with siltuximab, a novel anti-IL6 monoclonal antibody (6). Siltuximab was safe and effective in this study.

We first reported a case of MCD (see Patient 1 above) in 2008, in the form of an initial report on the partial efficacy of an IL1-RA agonist, Anakinra, for the treatment of this disease (11). In 2008 we obtained formal approval to use tocilizumab. This treatment alleviated the patient's fever, restored his growth rate, and normalized his inflammatory parameters. Tocilizumab may also prevent the

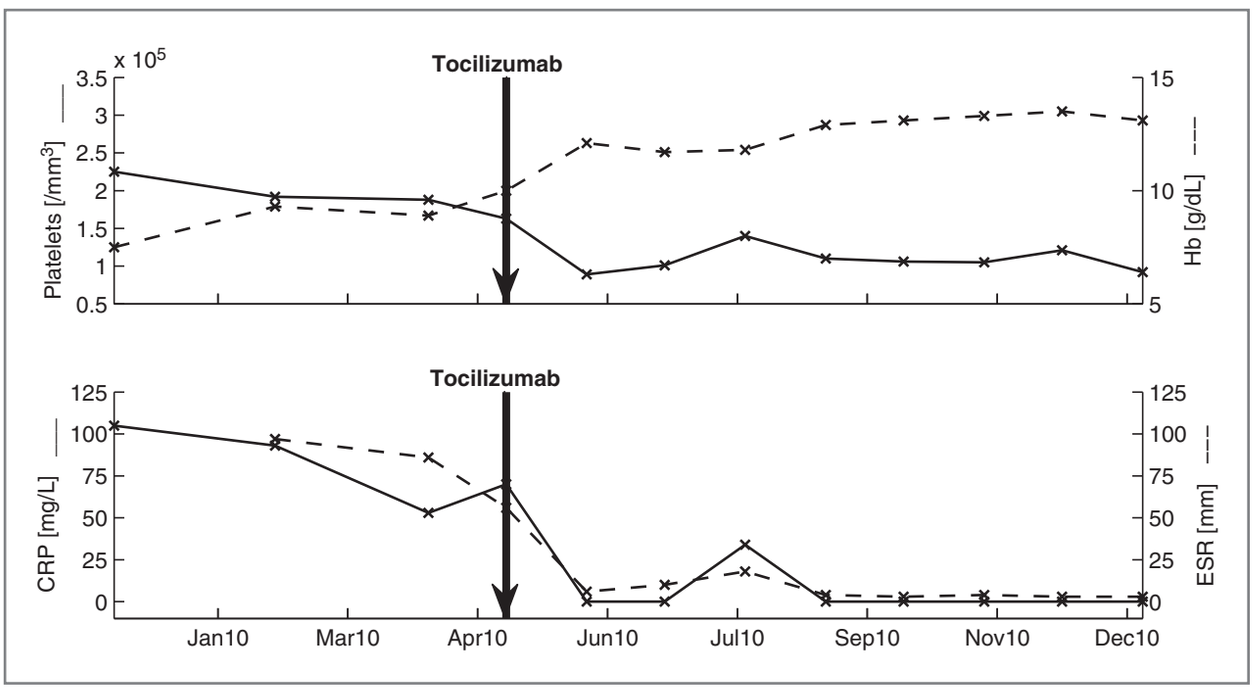

Figure 2. Representative changes in platelets, hemoglobin (Hb), CRP, and ESR in the second patient with Castleman disease during treatment with tocilizumab.

development of secondary amyloidosis associated with MCD because the treatment decreases the levels of SAA protein, a causative factor of this disorder. But the splenomegaly persisted. The infusion intervals were increased after the first 10 months because the patient had sustained remission. He has now been treated for a period of 3 years.

In the case of the second patient, we had received approval to treat her with tocilizumab when the diagnosis was made in May 2010. The tocilizumab treatment alleviated her fever, restored her growth parameters and hemoglobin level, and normalized her inflammatory parameters. Nevertheless, the multiple deep adenopathies persisted and a 7-mm diameter hepatic node appeared. This patient has been treated once every 2 weeks over the last 8 months.

In clinical trials, tocilizumab has been shown to have a good tolerance profile (12). Infections, hypertension during infusion, headache, an increase in liver enzyme levels, blood cholesterol levels, and thrombocytopenia were the most commonly observed adverse side effects. The more serious adverse side effects were serious infections, gastrointestinal perforations, and hypersensitivity reactions, including anaphylaxis and neutropenia (13). The side effects observed in our patients were mild. Sustained thrombocytopenia and hypofibrinemia are possibly side effects of tocilizumab. One of our patients developed intercostal herpes zoster after 10 months of treatment. The IL-6 level increased after treatment with tocilizumab in both patients. However, in 2008, Nishimoto and colleagues found that the free serum IL-6 increased because the IL6R-mediated consumption of IL-6 was inhibited by the unavailability of tocilizumab-free IL6R (14).

To the best of our knowledge, this study describes the first pediatric cases of MCD treated with tocilizumab and also provides the second report based on long-term follow-up data. Harada and colleagues reported the successful long-term administration of tocilizumab (3 years) for the treatment of a 46-year-old man with an interstitial lung disease due to MCD (15). The follow-up period of our first patient is now substantial, and we have observed that the residual effects of the drug allowed the infusion rates to be adapted to the context of long-term administration.

Conclusions

Tocilizumab is effective and seems to be safe in children with MCD.

Disclosure of Potential Conflicts of Interest

I. Koné-Paut received educational and research grants and consulting fees from Chugai-Roche; C. Galeotti received educational grant from Chugai-Roche; S. Guillaume received educational grant and consulting fees from Chugai-Roche; and A. Boucheron does not disclose any financial interest, direct or indirect.

Authors' Contributions

Conception and design: C. Galeotti, I. Koné-Paut
Development of methodology: C. Galeotti
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Galeotti, A. Boucheron, S. Guillaume
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Galeotti, S. Guillaume
Writing, review, and/or revision of the manuscript: C. Galeotti, A. Boucheron, S. Guillaume, I. Koné-Paut
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Galeotti, S. Guillaume
Study supervision: C. Galeotti, S. Guillaume, I. Koné-Paut

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