Turk Thorac J 2018; 19(4): 220-5 DOI: 10.5152/TurkThoracJ.2018.18066

Review

Biologic Agents in the Treatment of Multicentric Castleman Disease

Konstantinos Kapriniotis, Savvas Lampridis, Sofoklis Mitsos, Davide Patrini, David R. Lawrence, Nikolaos Panagiotopoulos

Department of Thoracic Surgery, University College London Hospitals NHS Foundation Trust, London, United Kingdom

Cite this article as: Kapriniotis K, Lampridis S, Mitsos S, et al. Biologic Agents in the Treatment of Multicentric Castleman Disease. Turk Thorac J 2018; 19(4): 220-5.

Abstract

Multicentric Castleman disease (MCD) causes an extensive range of systematic symptoms and can be life-threatening if not treated promptly and appropriately. The pathophysiology of the disease remains unclear; however, interleukin 6 (IL-6) pathway and human herpesvirus 8 infection appear to play an important role. As a result, the treatment of MCD remains complex and often insufficient, although a plethora of therapeutic approaches have been used. Between these, biological agents in the form of monoclonal antibodies against specific pathogenic processes of the disease have improved survival rates significantly. In the present study, we review the clinical results of rituximab, which targets B lymphocytes, siltuximab and tocilizumab, which target the IL-6 pathway, bortezomib, which is a selective proteasome inhibitor, and anakinra, which is an interleukin 1 receptor antagonist. The introduction of these biological agents in the treatment of MCD appears to be promising in the first studies performed. However, more clinical trials are required to assess the efficacy and safety of each agent and to form therapeutic strategies that will be widely accepted.

KEYWORDS: Castleman disease, multicentric castleman disease, biological agents, human herpesvirus 8, human immunodeficiency virus

Received: *06.05.2018* ***Accepted:*** *07.08.2018*

INTRODUCTION

Castleman disease, alternatively known as angiofollicular lymph node hyperplasia, consists of a heterogeneous group of reactive lymphoproliferative disorders, which share some basic histopathological features but vary greatly in clinical manifestations, severity, treatment, and prognosis [1]. The first case of the disease was reported in 1954 by Benjamin Castleman [2] who identified a new histopathologic entity in a surgically resected mediastinal mass. Castleman et al. reported a series of similar cases over the next 2 years, confirming the diagnosis of the new disease.

Nowadays, the disease is clinically divided into two distinct subtypes: unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD). The former, which is usually asymptomatic, is effectively treated by surgical excision of the enlarged lymph node. The latter can cause a wide range of systematic symptoms, such as fever, night sweats, weight loss, peripheral edema, ascites, pleural effusion, lymphadenopathy, and organomegaly [1,3,4]. Laboratory hallmarks include anemia, leukocytosis, thrombocytosis or thrombocytopenia, increased C-reactive protein (CRP) and fibrinogen, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, and hypoalbuminemia [3]. Moreover, it has been associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome, paraneoplastic pemphigus, and an increased risk of hematologic malignancies, especially B-cell lymphomas [5]. MCD can be life-threatening if not treated promptly and appropriately, or it can be refractory to treatment. It requires combined systematic treatment, and despite recent advances in therapies that target the pathophysiology of the disease, its prognosis remains relatively poor [6,7].

Castleman disease is divided into at least four histopathological subtypes. All of these are characterized by excessive intrafollicular vascular proliferation. Most of the UCD cases belong to the hyaline vascular subtype, whereas most of the MCD cases belong to the plasma cell subtype. However, each histopathological subtype, as well as mixed variants, can be found in both UCD and MCD. The recently described plasmablastic subtype has been associated with aggressive forms of MCD, usually in the setting of human immunodeficiency virus (HIV) infection [1,3]. Castleman disease is usually a diagnosis of exclusion, as many benign and malignant diseases present with similar reactive lymph node histopathology [8].

Address for Correspondence: Savvas Lampridis, Department of Thoracic Surgery, University College London Hospitals NHS Foundation Trust, London, United Kingdom
E-mail: savvas.lampridis@nhs.net

Etiology and Pathophysiology

The etiology of MCD still remains unclear. However, there is good evidence to support the critical role of interleukin 6 (IL-6) pathway and human herpesvirus 8 (HHV-8) infection in the pathogenesis of at least a number of cases [9-11]. MCD is more frequent among patients infected by HIV, and its incidence is constantly increasing, especially after the introduction of highly active antiretroviral therapy [12]. Almost all HIV-positive MCD cases present with an HHV-8 coinfection, whereas the frequency of HHV-8 in patients with HIV-negative MCD varies in association with the prevalence of the infection in each population [9,10]. The World Health Organization proposed a classification of MCD depending on the HHV-8 infection status, characterizing MCD as either HHV-8-associated or idiopathic MCD.

IL-6 Signaling Pathway

Several studies suggest that the lymph node enlargement, the specific histopathological alterations, and the systematic symptoms reported in MCD are all secondary to proinflammatory hypercytokinemia. Among many cytokines that have been proposed to play a role in MCD, overproduction of IL-6 appears to be the critical point in the pathogenesis of the disease [10,11,13]. IL-6 is produced by a wide range of immunocompetent cells, including lymphocytes, monocytes/macrophages, endothelial cells, and fibroblasts, and performs multiple immunoregulating activities. The most important of these include: (1) induction of B lymphocyte proliferation and differentiation, leading to diffuse lymph node enlargement, (2) synthesis and release of hepatic acute phase factors responsible for the systematic symptoms of MCD, (3) induction of hepcidin production in the liver, which mediates anemia of chronic disease, and (4) stimulation of vascular endothelial growth factor (VEGF) expression, which causes the characteristic excessive intrafollicular angiogenesis [14]. Both experimental models and clinical studies provide strong evidence for the important role of the IL-6 pathway in MCD. Yoshizaki et al. [11] reported that IL-6 is mainly produced by the germinal centers of hyperplastic lymph nodes, whereas lymph node hyperplasia, plasma levels of acute phase proteins, and clinical symptoms were correlated to serum IL-6 concentration. Moreover, van Gameren et al. [13] conducted a phase I and II study to examine the safety of recombinant human IL-6 when administered to patients with cancer. The main side effects reported were identical to an MCD-like syndrome, and most of the clinical and laboratory abnormalities were dose dependent. Similar results were obtained by Brandt et al. [10] who used a genetically modified mouse model that overproduced IL-6. Shortly after the genetic modification, mice presented with symptoms and histopathological changes typical of MCD. The exact etiology of IL-6 pathway dysregulation remains indistinct. In patients positive with HHV-8, viral infection appears to play the most significant role. In patients with idiopathic MCD, multiple factors have been suggested to contribute, including viral infections other than HHV-8, genetic aberrations in the IL-6 pathway, autoimmune phenomena, and ectopic IL-6 production by malignant cells [9].

HHV-8 Infection

HHV-8, alternatively known as Kaposi sarcoma-associated herpes virus, was first isolated from an HIV-associated Kaposi sarcoma biopsy sample in 1994 [10]. Since then, its involvement in the pathogenesis of various diseases, including Kaposi sarcoma, primary effusion lymphoma, and a proportion of MCD cases, has been well documented [9,12,15]. HHV-8 primarily infects CD20+/IgM+ B lymphocytes in the mantle zone of the affected lymph node. Soulier et al. [9] were the first to investigate HHV-8 prevalence in excised lymph nodes from patients with MCD, using polymerase chain reaction and Southern blot analysis. All patients positive with HIV were HHV-8-positive as well, whereas HHV-8 frequency among patients negative with HIV was estimated at 41%. Subsequent studies confirmed the strong association between HIV and HHV-8 in MCD. However, the HIV-negative group was more heterogeneous when examined for HHV-8 infection [16,17]. Furthermore, Stebbing et al. [14] reported that there is a correlation between HHV-8 plasma levels and disease activity in patients positive with HIV. Therefore, they proposed HHV-8 plasma levels as a potential biomarker for disease exacerbations. Consistent with the previous study, Casper et al. [18] reported three patients who improved clinically after having antiviral treatment with ganciclovir. HHV-8 encodes a viral form of IL-6 (vIL-6), mostly during the lytic phase of the viral proliferation. It remains controversial whether vIL-6 alone can cause MCD. However, vIL-6 also induces human IL-6 expression, which is potent enough to cause MCD, alone or synergistically with vIL-6 [19]. Finally, vIL-6 upregulates VEGF expression as well, contributing to the intranodular capillary proliferation reported in the disease [20].

Targeted Therapies

Surgical resection of the enlarged mass provides radical treatment to the majority of patients with UCD. Radiotherapy is an important alternative when surgical resection is contraindicated or technically challenging [21]. The treatment of MCD still remains complex and often insufficient as the diagnosis of the disease can sometimes be delayed, and the pathogenetic onset of each case is usually different among patients [4,8]. Moreover, MCD is a rare clinical entity, and therefore, there is a lack of randomized controlled trials (RCTs) to support clinical practice. Only one RCT has been published to date, evaluating siltuximab (anti-IL-6 monoclonal antibody) safety and efficacy in patients with idiopathic MCD [6]. The rest of the knowledge that constitutes the basis of our clinical practice lies mostly upon case series, case reports, and expert opinions. As a result, multiple therapeutic approaches have been used, including conventional cytotoxic chemotherapy (single-agent or combined), antiviral treatment, glucocorticoids, thalidomide, interferon-alpha, and molecular targeted therapies. Determination of HHV-8 status is very important for the selection of the appropriate therapeutic strategy [9]. Below, we summarize current clinical data regarding the use of biological agents (monoclonal antibodies) in the treatment of MCD.

Targeting B Lymphocytes

Rituximab

Rituximab is a chimeric monoclonal antibody that was initially (approximately 20 years ago) approved for use in low-grade non-Hodgkin's follicular lymphoma. It targets CD20 antigens on the surface of B lymphocytes, leading to their destruction mostly via complement activation and antibody-

dependent cell mediated cytotoxicity [22]. It has now been used for many B-cell mediated and autoimmune diseases, such as non-Hodgkin lymphomas (NHLs), chronic lymphocytic leukemia, rheumatoid arthritis, and Wegener's granulomatosis [23]. Moreover, it has been used off-label as first-line treatment in HIV-positive/HHV-8-positive MCD, alone or in combination with conventional chemotherapeutics (e.g., etoposide) and antiviral treatment (e.g., ganciclovir) [24]. In addition, it has been used as second-line treatment, along with combined conventional chemotherapeutics (e.g., CHOP) in HIV-negative/HHV-8-negative MCD, when the disease is refractory to anti-IL-6 treatment [25].

Most of the clinical evidence regarding rituximab use in MCD comes from both prospective and retrospective studies in patients positive with HIV/HHV-8. Bower et al. [24] conducted a single-group, phase II trial in which 21 patients with HIV-positive/HHV-8-positive MCD participated. Each patient received 4 doses of 375 mg/m^2 of body surface area at weekly intervals, without having any other treatment prior to this. Twenty patients showed clinical response to the treatment, with resolution of symptoms. Fourteen patients had partial radiological response (assessed by the Response Evaluation Criteria in Solid Tumors), and most of the patients presented with improvement in a number of hematological and viral markers, including hemoglobin, platelet count, and HHV-8 viral load. In addition, after 2 years, the overall survival rate was 95%, and the relapse-free survival rate was 79%. Similarly, Gerard et al. [7] published a prospective, phase II trial in which 24 patients were treated with the same dose of rituximab as in the study described above. Participants had been effectively treated with conventional chemotherapy in the past, but they became chemotherapy-dependent, with at least one exacerbation of the disease when chemotherapy was withdrawn. All patients received at least one dose of rituximab. Twenty-two of them exhibited sustained remission of the disease off chemotherapy at day 60 after the first dose (primary endpoint), and 17 participants showed sustained remission of the disease off chemotherapy at day 365 after the first dose (secondary endpoint). The estimated 1-year overall survival, event-free survival, and disease-free survival rates were 92%, 71%, and 77%, respectively. Moreover, rituximab has been found to reduce significantly the incidence of NHL, a potentially fatal complication occurring frequently in the setting of HIV-positive/HHV-8-positive MCD [26].

Two retrospective studies aimed to assess the effect of rituximab-based therapies on overall survival. Hoffmann et al. [27] examined 52 patients with HIV-positive MCD, some of whom received rituximab (alone or in combination with conventional chemotherapeutics), and some others did not. A predominance in sustained complete remission rate (91% vs 41% after 1 year) and overall survival rate was reported in the rituximab-treated group compared with the group of patients who received conventional chemotherapy (with or without antiviral agents). In a similar study of 61 HIV-positive MCD cases by Bower et al. [28], the overall survival rates reached 94% at 2 years and 90% at 5 years in the rituximab-treated group compared with 42% and 33%, respectively, in the group of patients who did not receive rituximab. Moreover, the investigators reported 24 patients with Kaposi sarcoma at the time of MCD diagnosis. Nine of them suffered progression of Kaposi sarcoma after 3 months of rituximab therapy, and all of them except for one required systemic liposomal anthracycline chemotherapy. In conclusion, despite their limitations, both studies suggest that rituximab has dramatically improved survival rates in HIV-positive MCD.

Treatment of HIV-positive MCD with rituximab-based therapies has significantly improved survival; however, the potential benefit of maintenance therapy is low. In a prospective cohort study, 84 patients with HIV-positive MCD were treated with risk-stratified rituximab-based therapy [28]. Four patients died of refractory HIV-positive MCD, while the rest achieved clinical remission. The median follow-up for these patients was 6.9 years. The 5-year overall survival for the 80 patients was 92%. Eighteen patients relapsed, including five with concomitant HHV8-associated lymphoma at relapse, with a median time to first relapse of 30 months (maximum 10 years). Moreover, all patients were successfully retreated with rituximab-based therapy. Therefore, the high risk of developing HHV8-associated lymphoma, the relatively low relapse rate and the high salvage rates at relapse, reduce the potential benefit of maintenance therapy.

Targeting IL-6 Pathway

IL-6 plays a critical role in the pathogenesis of both idiopathic and HHV-8-associated MCD, as described above. Therefore, the investigators tried to target the IL-6 signaling pathway, IL-6 or IL-6 receptor (IL-6R), in order to provide an etiologic therapy for MCD. Beck et al. [29] were the first to administer a murine anti-IL-6 antibody (BE-8) in a case of MCD. Symptoms improved within 24 h after administration and improvement of laboratory markers followed after a few weeks. However, symptoms and laboratory abnormalities recurred within a few days after therapy cessation. Since then, two more monoclonal antibodies targeting IL-6 pathway have been used in the treatment of MCD, siltuximab (anti-IL-6) and tocilizumab (anti-IL-6R), which are discussed in more detail below.

Siltuximab

Siltuximab is a chimeric monoclonal antibody that binds to IL-6 with high affinity and, therefore, prevents IL-6 binding to its receptor (IL-6R). It has been the only drug approved for the treatment of idiopathic MCD in the United States and Europe so far. The first clinical data regarding siltuximab use in MCD were published in 2010 by van Rhee et al. [30] who examined 23 patients negative with HIV/HHV-8 with symptomatic MCD or unresectable UCD. The interim results of this phase I clinical trial showed that 18 (78%) patients exhibited clinical benefit response (CBR, a combination of certain clinical and laboratory indicators, as defined by the investigators of the study) after siltuximab administration. The CBR rate was 100% (11 patients) in the group who received a higher dose of siltuximab (12 mg/kg). Moreover, 11 (52%) patients experienced radiologic tumor response (complete or partial), as defined by the modified Cheson criteria, whereas hemoglobin increase (0.2-4.7 g/dL) was reported in 19 patients. Finally, neither dose-limiting toxicities nor treatment-related deaths were reported, whereas only three patients experienced grade 3 or higher adverse events.

The final results of this study, mainly focusing on the evaluation of siltuximab safety, were published by Kurzrock et al. [31] in 2013. Sixty-seven patients with NHL, multiple myeloma, or symptomatic Castleman disease were enrolled in this cohort study and received siltuximab at a dose of 3, 6, 9, or 12 mg/kg weekly, every 2 or 3 weeks for a median of 8.5 (maximum 60.5) months. No dose-related toxicities associated with siltuximab administration were reported, whereas the most frequent all-grade adverse events possibly linked to siltuximab administration were thrombocytopenia (25%), neutropenia (19%), hypertriglyceridemia (19%), leukopenia (18%), hypercholesterolemia (15%), and anemia (10%). Grade 3 or greater adverse events reasonably related to siltuximab included neutropenia (11 patients), thrombocytopenia (3 patients), sepsis (1 patient), and hyperlipidemia (1 patient). An extension of the initial phase I trial, including 19 patients, was published by van Rhee et al. [32] in 2015. The median duration of treatment for all patients was 5.1 (range 3.4-7.2) years. Neither evidence of cumulative toxicities nor treatment discontinuations were reported. In addition, all patients were alive at the time of the publication. Grade 3 or greater adverse events reasonably attributed to siltuximab were leukopenia, lymphopenia, and a serious case of polycythemia (1 patient in each event).

Van Rhee et al. [6] also conducted a randomized, double-blind, placebo-controlled trial in which siltuximab efficacy was compared with best supportive care in patients with HIV-negative/HHV-8-negative MCD. Siltuximab was administered intravenously at a dose of 11 mg/kg every 3 weeks. Eighteen (34%) out of 53 patients who received siltuximab had durable radiologic tumor response (according to the Cheson criteria) and symptomatic response (as defined by the authors in the study), with a median response duration of 383 (range 232-676) days. One patient experienced complete response, whereas the other 17 patients had only partial response. None of the 26 patients in the placebo group showed radiologic tumor response or symptomatic response. Furthermore, similar incidence of grade 3 or greater adverse events was reported in each group, but specific adverse events, such as pruritus, maculopapular rash, weight gain, upper respiratory tract infection, and localized edema, were reported more frequently in the siltuximab group. Three (6%) patients experienced adverse events reasonably attributed to siltuximab administration (lower respiratory tract infection, anaphylactic reaction, and sepsis). In conclusion, siltuximab has been proven to be a potent and considerably safe drug, which improved significantly life expectancy in patients with idiopathic MCD.

In a study conducted by Yu et al. [33], siltuximab was shown to have a greater proportion of complete responses and longer progression-free survival for HIV-negative/HHV-8-negative MCD compared to rituximab. Twenty-one patients received siltuximab intravenously at a dose of 11 mg/kg every three or six weeks. A dose of 375 mg/m^2 of rituximab was administered intravenously to 25 patients once a week for four weeks. Siltuximab was associated with a significantly higher rate of complete response than rituximab or rituximab-based therapies (p=0.034). Moreover, it controlled and improved the clinical manifestations and progression-free survival in cases where rituximab failed. However, patients treated with siltuximab might need lifelong administration of the medication, as relapse has been reported on cessation of IL-6 receptor therapy with tocilizumab.

Tocilizumab

Tocilizumab is a humanized IL-6R antagonist, which blocks the IL-6 signaling pathway very effectively. It has been approved for the treatment of idiopathic MCD in Japan and moderately to severely active rheumatoid arthritis in adults worldwide. The first data regarding tocilizumab use in MCD were published by Nishimoto et al. [33] in 2000. The investigators administered tocilizumab in seven patients with HIV-negative/HHV-8-negative MCD at a dose of 50-100 mg either once or twice weekly. Fever and fatigue resolved immediately after tocilizumab administration, whereas laboratory markers, such as hemoglobin, CRP, and albumin, started to improve within a few days. After 3 months of treatment, hypergammaglobulinemia, lymphadenopathy, and renal dysfunction in the setting of secondary amyloidosis improved significantly. However, recurrence of the disease was reported 2 weeks after therapy cessation. No severe adverse events were reported, except for self-limited, transient neutropenia in two patients.

Thereafter, Nishimoto et al. [34] published an open-label phase II trial to evaluate the safety and efficacy of tocilizumab in 28 patients with MCD (26 with idiopathic MCD and 2 with HIV-negative/HHV-8-positive MCD). The investigators administered eight tocilizumab infusions at a dose of 8 mg/kg every 2 weeks, and afterwards, dose and treatment intervals were adjusted to each patient individually for the next 16 weeks. Within the initial phase of administration (16 weeks), lymphadenopathy was markedly improved, recorded as a reduction of the mean short-axis from 10 mm to 9.1 mm. After 1 year of treatment, this was further reduced to 8.6 mm. In addition to lymphadenopathy alleviation, inflammatory markers, hemoglobin level, and nutritional status (total and high-density lipoprotein cholesterol levels and body mass index) were also improved significantly after treatment with tocilizumab. Regarding the safety of the drug, no severe adverse events were reported. The most common adverse events possibly attributed to tocilizumab treatment were flu-like symptoms, such as cough, rhinorrhea, and pharyngitis. Moreover, no patients developed malignancies, and only one patient who suffered from chronic myelomonocytic leukemia experienced exacerbation of secondary disease. In 2007, Nishimoto et al. [35] published an extension of the prospective trial, in which they examined the efficacy and safety of tocilizumab in a long-term, >5 years, follow-up. Tocilizumab was initially administered to 35 patients, from whom 30 (86%) continued to have tocilizumab for >5 years at doses and intervals as stated above. The effect of tocilizumab on lymphadenopathy, constitutional symptoms, and laboratory markers was sustained. In addition, pulmonary diffuse lymphoid hyperplasia, identified in 31 patients initially, improved dramatically over the 5-year period, as examined by two independent radiologists in high-resolution computed tomography scans. Finally, the most frequent adverse events were similar to those reported in the initial phase of the study, with the majority of them classified as not severe. Several case reports and case series published thereafter described similar effects of tocilizumab on symptoms and laboratory markers. In addition to this, some studies supported the efficacy of tocilizumab when used as treatment for complications attributed to MCD, such as renal failure, myelofibrosis, pulmonary hypertension, glomerulonephritis, cardiomyopathy, and autoimmune hemolytic anemia [36-42].

Targeting Other Signaling Pathways

Bortezomib

Bortezomib is a selective proteasome inhibitor, which is believed to reduce IL-6 production possibly via inhibition of nuclear factor-κB. It has been approved for treatment of relapsing multiple myeloma and mantle cell lymphoma in the USA and Europe. A limited number of case reports regarding bortezomib use in MCD have been published so far. Hess et al. [43] reported a case of a 48-year-old female patient with recurrent, treatment-refractory HIV-negative/HHV-8-negative MCD. After bortezomib administration, the patient exhibited significant alleviation of symptoms, improvement of general performance status (as defined by the Eastern Cooperative Oncology Group), improvement of inflammatory markers, and loss of transfusion dependency for >1 year. Furthermore, no severe adverse events were reported during the treatment period. In addition, Wang et al. [44] and Sobas et al. [45] treated two cases of Castleman disease associated to POEMS syndrome using bortezomib in combination with thalidomide and dexamethasone, respectively. Both patients experienced disease remission, which lasted for 2 and >4, respectively, without any severe adverse events during this period. Finally, Yuan et al. [46] and Khan et al. [47] published two cases of MCD in the setting of multiple myeloma, which were treated with bortezomib and dexamethasone (followed by maintenance treatment with thalidomide in the second case). Both patients remained in partial disease remission when examined after 18 and 24 months, respectively.

Anakinra

Anakinra is an interleukin 1 (IL-1) receptor antagonist. IL-1 is an IL-6 up-regulator via activation of the nuclear factor-κB pathway. Therefore, it has been used in the treatment of several IL-6-mediated diseases. Officially, it has been approved for the treatment of rheumatoid arthritis and cryopyrin-associated periodic syndromes in the USA and Europe. Similar to bortezomib, only a small number of case reports regarding anakinra use in MCD have been published thus far. Galeotti et al. [48] reported a case of a 13-year-old boy who suffered from treatment-refractory MCD. Initially, the patient received a combination of conventional chemotherapy (cyclophosphamide and vinblastine) with rituximab, which proved to be inefficient. Thereafter, he received anakinra and responded immediately, experiencing a rapid resolution of symptoms and improvement of laboratory markers. Similarly, El-Osta et al. [49] reported a case of a 61-year-old woman with MCD refractory to previous therapies (cladribine, rituximab, steroids, etanercept, and anti-IL-6 monoclonal antibody) who experienced both clinical and laboratory remission of the disease after anakinra administration for 1 week.

CONCLUSION

Multicentric Castleman disease is a rare systematic disorder, which was characterized by aggressive development and poor prognosis during the past decades. The introduction of biological agents targeting the pathophysiology of the disease improved survival rates significantly. Rituximab, mainly used in HHV-8-positive MCD cases, and IL-6/IL-6R antagonists, mainly used in idiopathic MCD cases, have geared the disease course toward a relapsing-remitting pattern. However, further studies, especially RCTs, are required to assess the efficacy and safety of each agent and implement a therapeutic strategy that will be widely accepted. Moreover, targeting new mechanisms in the pathophysiology of the disease may benefit patients with MCD refractory to current therapies. For example, abnormally high levels of IL-10 and VEGF have been reported in many MCD cases, rendering these two molecules rather appealing therapeutic candidates in the future [50]. Finally, combinational approaches may minimize the proportion of non-responding patients and, therefore, improve therapeutic outcomes.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.P., K.K., D.R.L.; Design - K.K., S.L., S.M., D.P.; Supervision - D.R.L., N.P.; Literature Search - K.K., S.L., S.M., D.P.; Writing Manuscript - K.K., S.L., S.M., D.P., D.R.L., N.P.; Critical Review - K.K., S.L., S.M., D.P., D.R.L., N.P.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Cronin DMP, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol 2009;16:236-46. [CrossRef]
2. Castleman B, Towne VW. Case records of the Massachusetts General Hospital: Case No. 40231. N Engl J Med 1954;250:1001-5. [CrossRef]
3. Liu AY, Nabel CS, Finkelman BS, et al. Idiopathic multicentric Castleman's disease: a systematic literature review. Lancet Haematol 2016;3:e163-75. [CrossRef]
4. Dispenzieri A, Armitage JO, Loe MJ, et al. The clinical spectrum of Castleman's disease. Am J Hematol 2012;87:997-1002. [CrossRef]
5. Larroche C, Cacoub P, Soulier J, et al. Castleman's disease and lymphoma: report of eight cases in HIV-negative patients and literature review. Am J Hematol 2002;69:119-26. [CrossRef]
6. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014;15:966-74. [CrossRef]
7. Gérard L, Bérezné A, Galicier L, et al. Prospective Study of Rituximab in Chemotherapy-Dependent Human Immunodeficiency Virus-Associated Multicentric Castleman's Disease: ANRS 117 CastlemaB Trial. J Clin Oncol 2007;25(:3350-6.
8. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129:1646-57. [CrossRef]
9. Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 1995;86:1276-80.
10. Brandt SJ, Bodine DM, Dunbar CE, et al. Dysregulated interleukin 6 expression produces a syndrome resembling Castleman's disease in mice. J Clin Invest 1990;86:592-9. [CrossRef]
11. Yoshizaki K, Matsuda T, Nishimoto N, Kuritani T, Taeho L, Aozasa K, et al. Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. Blood 1989;74:1360-7.
12. Powles T, Stebbing J, Bazeos A, Hatzimichael E, Mandalia S, Nelson M, et al. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. Ann Oncol 2009;20:775-9. [CrossRef]

13. van Gameren MM, Willemse PH, Mulder NH, et al. Effects of recombinant human interleukin-6 in cancer patients: a phase I-II study. Blood 1994;84:1434-41.
14. Stebbing J, Adams C, Sanitt A, et al. Plasma HHV8 DNA predicts relapse in individuals with HIV-associated multicentric Castleman disease. Blood 2011;118:271-5. [CrossRef]
15. Nador R, Cesarman E, Chadburn A, et al. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood 1996;88:645-56.
16. Yamasaki S, Iino T, Nakamura M, et al. Detection of human herpesvirus-8 in peripheral blood mononuclear cells from adult Japanese patients with multicentric Castleman's disease. Br J Haematol 2003;120:471-7. [CrossRef]
17. Suda T, Katano H, Delsol G, et al. HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. Pathol Int 2001;51:671-9. [CrossRef]
18. Casper C, Nichols WG, Huang ML, et al. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. Blood 2004;103:1632-4. [CrossRef]
19. Polizzotto MN, Uldrick TS, Wang V, et al. Human and viral interleukin-6 and other cytokines in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. Blood 2013;122:4189-98. [CrossRef]
20. Aoki Y, Jaffe ES, Chang Y, et al. Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. Blood 1999;93:4034-43.
21. Chronowski GM, Ha CS, Wilder RB, et al. Treatment of unicentric and multicentric Castleman disease and the role of radiotherapy. Cancer 2001;92:670-6. [CrossRef]
22. Naresh KN, Trivedi P, Horncastle D, Bower M. CD20 expression in the HHV-8-infected lymphoid cells in multicentric Castleman disease. Histopathology 2009;55:358-9. [CrossRef]
23. Silverman GJ, Weisman S. Rituximab therapy and autoimmune disorders: Prospects for anti-B cell therapy. Arthritis Rheum 2003;48:1484-92. [CrossRef]
24. Bower M, Powles T, Williams S, et al. Brief Communication: Rituximab in HIV-Associated Multicentric Castleman Disease. Ann Intern Med 2007;147:836. [CrossRef]
25. Ide M, Kawachi Y, Izumi Y, et al. Long-term remission in HIV-negative patients with multicentric Castleman's disease using rituximab. Eur J Haematol 2006;76:119-23. [CrossRef]
26. Gérard L, Michot JM, Burcheri S, et al. Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease. Blood 2012;119:2228-33. [CrossRef]
27. Hoffmann C, Schmid H, Müller M, et al. Improved outcome with rituximab in patients with HIV-associated multicentric Castleman disease. Blood 2011;118:3499-503. [CrossRef]
28. Bower M, Newsom-Davis T, Naresh K, et al. Clinical Features and Outcome in HIV-Associated Multicentric Castleman's Disease. J Clin Oncol 2011;29:2481-6. [CrossRef]
29. Beck JT, Hsu SM, Wijdenes J, et al. Alleviation of Systemic Manifestations of Castleman's Disease by Monoclonal Anti-Interleukin-6 Antibody. N Engl J Med 1994;330:602-5. [CrossRef]
30. van Rhee F, Fayad L, Voorhees P, et al. Siltuximab, a Novel Anti-Interleukin-6 Monoclonal Antibody, for Castleman's Disease. J Clin Oncol 2010;28:3701-8. [CrossRef]
31. Kurzrock R, Voorhees PM, Casper C, et al. A phase I, open-label study of siltuximab, an anti-IL-6 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma, multiple myeloma, or Castleman disease. Clin Cancer Res 2013;19:3659-70. [CrossRef]
32. van Rhee F, Casper C, Voorhees PM, Fayad LE, et al. A phase 2, open-label, multicenter study of the long-term safety of siltuximab (an anti-interleukin-6 monoclonal antibody) in patients with multicentric Castleman disease. Oncotarget 2015;6:30408-19. [CrossRef]
33. Yu L, Tu M, Cortes J, et al. Clinical and pathological characteristics of HIV- and HHV-8-negative Castleman disease. Blood 2017;129:1658-68. [CrossRef]
34. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005;106:2627-32. [CrossRef]
35. Nishimoto N, Honda O, Sumikawa H, et al. A Long-Term (5-Year) Sustained Efficacy of Tocilizumab for Multicentric Castleman's Disease and the Effect on Pulmonary Complications. Blood 2007;110:646.
36. Turcotte LM, Correll CK, Reed RC, et al. Sustained remission of severe Multicentric Castleman disease following multiagent chemotherapy and tocilizumab maintenance. Pediatr Blood Cancer 2014;61:737-9. [CrossRef]
37. Kawabata H, Kotani S, Matsumura Y, et al. Successful treatment of a patient with multicentric Castleman's disease who presented with thrombocytopenia, ascites, renal failure and myelofibrosis using tocilizumab, an anti-interleukin-6 receptor antibody. Intern Med 2013;52:1503-7. [CrossRef]
38. Man L, Goudar RK. Reversal of cardiomyopathy with tocilizumab in a case of HIV-negative Castleman's disease. Eur J Haematol 2013;91:273-6. [CrossRef]
39. Otani N, Morishita Y, Oh I, et al. Successful treatment of a mesangial proliferative glomerulonephritis with interstitial nephritis associated with Castleman's disease by an anti-interleukin-6 receptor antibody (tocilizumab). Intern Med 2012;51:1375-8. [CrossRef]
40. Galeotti C, Boucheron A, Guillaume S, et al. Sustained remission of multicentric Castleman disease in children treated with tocilizumab, an anti-interleukin-6 receptor antibody. Mol Cancer Ther 2012;11:1623-6. [CrossRef]
41. Yuzuriha A, Saitoh T, Koiso H, et al. Successful treatment of autoimmune hemolytic anemia associated with multicentric Castleman disease by anti-interleukin-6 receptor antibody (tocilizumab) therapy. Acta Haematol 2011;126:147-50. [CrossRef]
42. Taniguchi K, Shimazaki C, Fujimoto Y, et al. Tocilizumab is effective for pulmonary hypertension associated with multicentric Castleman's disease. Int J Hematol 2009;90:99-102. [CrossRef]
43. Hess G, Wagner V, Kreft A, et al. Effects of bortezomib on pro-inflammatory cytokine levels and transfusion dependency in a patient with multicentric Castleman Disease. Br J Haematol 2006;134:544-5. [CrossRef]
44. Wang X, Ye S, Xiong C, et al. Successful Treatment with Bortezomib and Thalidomide for POEMS Syndrome Associated with Multicentric Mixed-type Castleman's Disease. Jpn J Clin Oncol 2011;41:1221-4. [CrossRef]
45. Sobas MA, Alonso Vence N, Diaz Arias J, et al. Efficacy of bortezomib in refractory form of multicentric Castleman disease associated to poems syndrome (MCD-POEMS variant). Ann Hematol 2010;89:217-9. [CrossRef]
46. Yuan Z, Dun X, Li Y, et al. Treatment of multicentric Castleman's Disease accompanying multiple myeloma with bortezomib: a case report. J Hematol Oncol 2009;2:19. [CrossRef]
47. Khan AA, Siraj F, Bhargava M, et al. Successful treatment of multicentric Castleman's disease accompanying myeloma with bortezomib. BMJ Case Rep 2012;2012:bcr2012007646.
48. Galeotti C, Tran TA, Franchi-Abella S, et al. IL-1RA Agonist (Anakinra) in the Treatment of Multifocal Castleman Disease. J Pediatr Hematol Oncol 2008;30:920-4. [CrossRef]
49. El-Osta H, Janku F, Kurzrock R. Successful treatment of Castleman's disease with interleukin-1 receptor antagonist (Anakinra). Mol Cancer Ther 2010;9:1485-8. [CrossRef]
50. Cohen JC, Boerwinkle E, Mosley TH, et al. Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease. N Engl J Med 2006;354:1264-72. [CrossRef]