Prescribing and adverse event reporting information can be found on the last page of this document.

This is intended to be viewed as an electronic document and should not be printed.

Idiopathic Multicentric Castleman Disease (iMCD): Diagnostic Criteria

A booklet to help healthcare professionals diagnose iMCD

Additional guidance available online

For more information scan this code

www.thinkimcd.co.uk

This material is developed by Recordati Rare Diseases and is intended for use by healthcare professionals only.

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Urgency to diagnose:

Timely diagnosis and treatment is required to support best possible outcomes

- Overproduction of IL-6 is the most common pathological driver of iMCD and its symptoms[1-3]
- In severe cases, a life-threatening cytokine storm can occur, followed by organ failure and death[2,3]
- In a real-world, retrospective analysis of US claims data, a significantly higher proportion of patients with iMCD presented with organ failure and/or thrombotic events, and had significantly higher prevalence of several malignancies, compared with a non-iMCD matched cohort (P<0.001)[4]

Establish both of the following:

1 Enlarged lymph nodes[3]

- ≥1 cm in short-axis diameter in ≥2 lymph node stations

2 Histopathologic lymph node features consistent with the iMCD spectrum[3*]

- Requires excisional lymph node biopsy

*Histopathological guidelines for iMCD spectrum available online and at: Fajgenbaum DC, *et al. Blood.* 2017; 129:(12)1646–57.3

Add 2+ of the following, incl. 1+ laboratory result:

Clinical symptoms[3]

- Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue (≥2 CTCAE lymphoma score for B-symptoms)
- Fluid accumulation: oedema, anasarca, ascites or pleural effusion
- Large spleen and/or liver
- Eruptive cherry haemangiomatosis or violaceous papules
- Lymphocytic interstitial pneumonitis

Laboratory parameters[3]

- Elevated CRP (>10 mg/L) or ESR (>15 mm/h)*
- Anaemia (haemoglobin <12.5 g/dL for males, <11.5 g/dL for females)
- Thrombocytopaenia (platelet count <150 k/μL) or thrombocytosis (platelet count >400 k/μL)
- Hypoalbuminaemia (albumin <3.5 g/dL)
- Renal dysfunction (eGFR <60 mL/min/1.73m^2) or proteinuria total; 150 mg/24h OR 10 mg/100 ml)
- Polyclonal hypergammaglobulinaemia (total γ globulin or immunoglobulin G >1700 mg/dL)

*Evaluation of CRP is mandatory, and tracking is highly recommended, but ESR is acceptable where CRP is not available.

Exclude all of the following:

Infection-related[3]

- HHV-8 (infection can be documented by blood PCR, diagnosis of HHV-8-associated MCD requires positive LANA-1 staining by IHC, which excludes iMCD)
- Clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV (detectable EBV viral load not necessarily exclusionary)
- Inflammation and adenopathy caused by other uncontrolled infections (e.g. acute or uncontrolled CMV, toxoplasmosis, HIV, active tuberculosis)

Autoimmune/autoinflammatory[3]

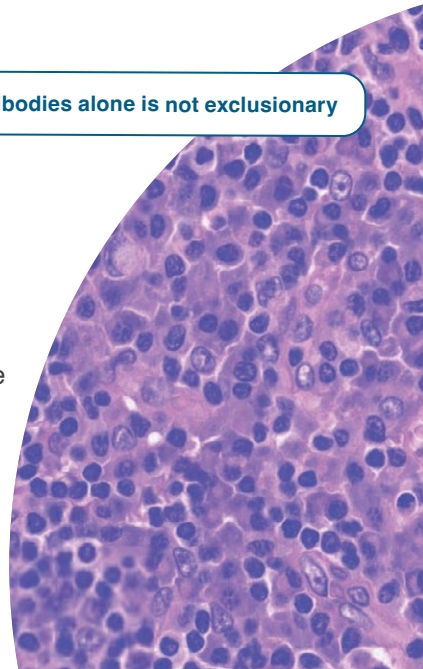
- Systemic lupus erythematosus
- Juvenile idiopathic arthritis
- Autoimmune lymphoproliferative syndrome
- Rheumatoid arthritis
- Adult-onset Still disease

Requires full clinical criteria, detection of autoimmune antibodies alone is not exclusionary

Malignant/lymphoproliferative[3]

- Lymphoma (Hodgkin and non-Hodgkin)
- Multiple myeloma
- Primary lymph node plasmacytoma
- FDC sarcoma
- POEMS syndrome (considered a disease “associated” with CD)

These disorders must be assessed at the same time as iMCD to be exclusionary



UK & IRELAND PRESCRIBING INFORMATION

SYLVANT® ▼ (siltuximab) 100mg and 400mg powder for concentrate for solution for infusion

Prescribers should refer to the Summary of Product Characteristics before prescribing.

PRESENTATION: Siltuximab, 100 mg or 400 mg freeze-dried white powder for concentrate.
INDICATION: Treatment of adult patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus- 8 (HHV8) negative.
POSOLOGY & ADMINISTRATION: This medicinal product should be administered by qualified healthcare professionals and under appropriate medical supervision. **Adults**: Recommended dose 11mg/kg siltuximab given over 1 hour as an intravenous infusion administered every 3 weeks until treatment failure. Haematology laboratory tests should be performed prior to each dose for first 12 months, then every third cycle. Consider delaying treatment if: absolute neutrophil count <1.0x10^9/L; platelet count <75x10^9/L for first administration or <50x10^9/L for subsequent administration; or haemoglobin ≥170g/L (10.6 mmol/L). Withhold treatment if severe infection or any severe non-haematological toxicity. Restart at the same dose after recovery. Discontinue if severe infusion-related reaction, anaphylaxis, severe allergic reaction or cytokine release syndrome. Consider discontinuation if more than 2 dose delays due to treatment-related toxicities during first 48 weeks. **SPECIAL POPULATIONS**: **Elderly Patients**: No dose adjustment required. **Renal & Hepatic impairment**: No studies. **Paediatric population**: The safety and efficacy of siltuximab in children aged 17 years and younger has not been established. No data available. **CONTRAINDICATIONS**: Severe hypersensitivity to active substance or any excipient. **SPECIAL WARNINGS & PRECAUTIONS**: **Traceability**: In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded. **Concurrent active serious infections**: Infections, including localised infections, should be treated prior to administering SYLVANT. Serious infections, including pneumonia and sepsis, were observed during clinical studies. Hypoglobulinaemia was observed in 4% to 11.3% of patients in the clinical study. Two cases of reactivated hepatitis B have been reported on concomitant use with high dose dexamethasone, and bortezomib, melphalan and prednisone. Monitor for serious infections as SYLVANT may mask signs and symptoms of acute inflammation, including suppression of fever and acute-phase reactants such as C-reactive protein (CRP). **Vaccinations**: Do not administer live, attenuated vaccines concurrently or within 4 weeks prior to initiating SYLVANT. **Lipid parameters**: Triglyceride and cholesterol elevations observed, manage as per current guidelines for hyperlipidaemia. **Infusion reactions and hypersensitivity**: Mild to moderate infusion reactions may improve following slowing of or stopping the infusion. Upon resolution, reinitiating the infusion at a lower infusion rate and therapeutic administration of antihistamines, paracetamol, and corticosteroids may be considered. Discontinue in patients who have severe infusion related hypersensitivity reactions (e.g., anaphylaxis). The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medicinal product should be available to treat anaphylaxis if it occurs. **Malignancy**: Immunomodulatory medicinal products may increase the risk of malignancy. On the basis of limited experience with siltuximab the present data do not suggest any increased risk of malignancy. **Gastrointestinal perforation**: Gastrointestinal (GI) perforation has been reported in siltuximab clinical trials. Use with caution in patients at increased risk of GI perforation. Promptly evaluate patients presenting with symptoms that may be associated with or suggestive of GI perforation. **Hepatic impairment**: Transient or intermittent mild to moderate elevation of hepatic transaminase levels or other liver function tests have been reported. Monitor patients with known hepatic impairment or elevated transaminase or bilirubin levels. **INTERACTIONS**: Binding bioactive IL-6 by siltuximab may result in increased metabolism of CYP450 substrates. It is recommended to monitor the effect or concentration of CYP450 substrates that have a narrow therapeutic index (e.g., warfarin, cyclosporine or theophylline). Exercise caution when siltuximab is co-administered with medicinal products that are CYP3A4 substrates where a decrease in effectiveness would be undesirable (e.g., oral contraceptives). **WOMEN OF CHILDBEARING POTENTIAL**: Effective contraception must be used during and up to 3 months after treatment. **PREGNANCY**: Not recommended. **BREAST-FEEDING**: No data. Risk to newborn / infant cannot be excluded. **FERTILITY**: Effects on fertility have not been evaluated in humans. **ADVERSE REACTIONS**: **Very common (≥1/10)**: Upper respiratory tract infection, urinary tract infection, nasopharyngitis, neutropenia, thrombocytopenia, hypertriglyceridaemia, hyperuricaemia, dizziness, headache, oropharyngeal pain, hypertension, nausea, abdominal pain, vomiting, constipation, diarrhoea, gastroesophageal reflux disease, mouth ulceration, rash, pruritus, eczema, arthralgia, pain in extremity, renal impairment, localised oedema, weight increased. **Common (≥1/100 to <1/10)**: Anaphylactic reaction, hypercholesterolaemia. **Prescribers should refer to the summary of product characteristics in relation to other adverse reactions.** **LEGAL CLASSIFICATION**: POM. **PRESENTATIONS**, **PACK SIZES**, **MARKETING AUTHORISATION NUMBER(S)**: SYLVANT 100 mg powder for concentrate for solution for infusion, 1 vial per pack: PLGB 44185/0006 (UNITED KINGDOM), EU/1/14/928/001 (REPUBLIC OF IRELAND). SYLVANT 400mg powder for concentrate for solution for infusion, 1 vial per pack: PLGB 44185/0007 (UNITED KINGDOM), EU/1/14/928/002 (REPUBLIC OF IRELAND). **UK BASIC NHS COST**: SYLVANT 100 mg powder for concentrate for solution for infusion, 1 vial per pack: £502.15. SYLVANT 400mg powder for concentrate for solution for infusion, 1 vial per pack: £2009.81. **MARKETING AUTHORISATION HOLDER (UNITED KINGDOM)**: Recordati UK Ltd., Breakspear Park, Breakspear Way, Hemel Hempstead, HP2 4TZ, United Kingdom. **MARKETING AUTHORISATION HOLDER (REPUBLIC OF IRELAND)**: Recordati Netherlands B.V., Beechavenue 54, 1119PW Schiphol-Rijk, Netherlands. **FURTHER INFORMATION IS AVAILABLE UPON REQUEST FROM**: Recordati UK Ltd, Breakspear Park, Breakspear Way, Hemel Hempstead, HP2 4TZ, United Kingdom. **DATE PRESCRIBING INFORMATION LAST REVISED**: December 2024 (version 3.0).

Adverse events should be reported. (UK) Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. (Ireland) Healthcare professionals are requested to report suspected adverse reactions to HPRA via their website https://www.hpra.ie/. Adverse events should also be reported to Recordati UK Ltd by telephone: +44 (0)1491 414 333 or email: RRDpharmacovigilance@recordati.com.

Abbreviations: CD, Castleman Disease; **CMV**, cytomegalovirus; **CRP**, C-reactive protein; **CTCAE**, Common Terminology Criteria for Adverse Events; **EBV**, Epstein-Barr virus; **eGFR**, estimated glomerular filtration rate; **ESR**, erythrocyte sedimentation rate; **FDC**, follicular dendritic cell; **HHV-8**, human herpesvirus-8; **HIV**, human immunodeficiency virus; **IHC**, immunohistochemical staining; **IL-6**, interleukin-6; **iMCD**, idiopathic multicentric CD; **LANA-1**, latency-associated nuclear antigen; **PCR,** polymerase chain reaction; **POEMS**, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin changes.

References: 1. Fajgenbaum DC. *Blood.* 2018; 132(22): 2323-30. 2. van Rhee F, *et al. Clin Adv Hem & Onc.* 2010; 8(7): 486-98. 3. Fajgenbaum DC, *et al. Blood.* 2017; 129:(12)1646–57. 4. Mukherjee S, *et al. Leukemia.* 2022; 36(10): 2539-43.

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