Clinical Commissioning Policy:

Siltuximab for idiopathic multicentric Castleman disease (adults) [2124]

Summary

Siltuximab is recommended to be available as a routine commissioning treatment option for idiopathic multicentric Castleman disease (iMCD) within the criteria set out in this document. Siltuximab is licensed for use in adults with iMCD.

The policy is restricted to adults as there is insufficient evidence to confirm safety in pre-pubescent children and therefore siltuximab is not recommended to be used in those age groups not included in the policy. Siltuximab may be used in post-pubescent children via NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children).

Committee discussion

Clinical Panel considered the evidence base and the recommendation was made to progress the policy as for routine commissioning. Please see the Clinical Panel report for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed on the NHS England website.

What we have decided

NHS England has carefully reviewed the evidence to treat iMCD with siltuximab. We have concluded that there is enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed the NHS England website.

Plain language summary

About idiopathic multicentric Castleman disease

Idiopathic multicentric Castleman disease (iMCD) is a rare disorder of uncontrolled growth of cells in lymph nodes. iMCD causes lymph node enlargement, enlargement of organs such as the liver and spleen, fevers, drenching sweats, anorexia, weight loss, fatigue and impaired lung function, fluid retention (body holding onto water), and changes to blood forming cells in the body.

The disease tends to follow a responding and relapsing pattern. This means that there will be episodes following treatment where the disease responds and can be in remission (symptom improvement, low level of disease), followed by episodes of disease and symptom return (relapse). Some patients go on to develop treatment resistance (no response to a treatment that the patient previously responded well to). Untreated or partially treated disease can lead to multi-organ failure, a requirement for intensive care support in hospital, and even death.

No cause has been identified for iMCD (hence the term idiopathic), and in order to receive a diagnosis of iMCD other conditions, particularly human immunodeficiency virus (HIV) and human herpesvirus-8 (HHV8), need to be excluded. Multicentric means presence of enlarged lymph nodes in at least two different sites. The disease can be classified as severe or non-severe depending on performance status (how fit or frail a patient is), the degree of kidney dysfunction, anaemia (low levels of haemoglobin in the blood), and fluid retention.

Current standard treatment

There is no currently nationally commissioned standard of care for treatment of iMCD in the UK and there are no treatment options approved by the National Institute for Health and Care Excellence (NICE). Until recently, there was no agreement on what features of disease were needed to confirm a diagnosis and what constituted as a treatment response. This made it extremely difficult to compare management options at different hospital sites.

Current UK treatment practice is decided at the local level with variation between hospitals. At initial presentation the treatment usually involves symptom control management. This includes managing effusions (build-up of fluid in the lungs), fevers using antipyretics, pain with analgesics (pain relief medication), and blood transfusions where required. The only licensed drug for iMCD is siltuximab; there are no other current licensed treatments. Various other medications are often used (either alone or in combination) off-label. These include immune suppression therapies such as steroids, chemotherapy, immunotherapy (e.g., rituximab) and thalidomide. Treatment is based on the disease severity. At relapse patients are often re-treated with either the initial therapy until no response, or an alternative treatment.

Proposed intervention

Siltuximab works by blocking the action of a chemical called interleukin-6 (IL-6), which is the main driver of the symptoms in iMCD. Siltuximab is an intravenous drug, which means it is given via a needle in a vein. Siltuximab is delivered in the outpatient setting as a day-case and is given over one hour once every three weeks until the patient stops responding to it.

Siltuximab received European Marketing Authorisation for the treatment of iMCD on 22 May 2014. Adverse events (side effects) that can be associated with siltuximab administration include reactions related to the infusion, rash, pruritus (itching), and infection.

Epidemiology and needs assessment

The incidence and prevalence of iMCD in the UK is unknown. iMCD is a disease predominantly of adults with reported age at presentation, extrapolated from case series, of 49 - 66 years. Distribution according to gender appears similar. There appear no specific risks according to ethnicity. There are limited data on proportion of newly diagnosed patients who require therapy or relapse rates following the current UK therapy approach. A recently published study in the USA reported an average annual incidence of 2.45 (95% CI, 0.85 - 8.60) per million and average prevalence of 6.31 (95% CI, 3.25 - 13.05) per million (Mukherjee et al. 2020). Based on ONS 2019 estimation of population in England (56.3million) the estimated incidence in England is 138 cases per year and prevalence 355 cases. In the US study, 58.9% patients required hospitalisation within the first year of diagnosis, and it would be expected that all these patients would require treatment. A recent French retrospective case series review reported 3/27 (11%) patients did not require treatment at diagnosis (Oksenhendler et al. 2018). It is therefore estimated that 59 - 89% of newly diagnosed patients would require treatment (81 - 122 cases) and approximately 35 patients per year would require siltuximab treatment at relapse. The estimated annual total number of patients to receive siltuximab is 116 - 157 patients.

Severe iMCD can lead to multiorgan failure requiring critical care support due to the cytokine storm; in some patients this can be fatal. Untreated disease is also eventually fatal. Reported 5-year survival for iMCD is 55 – 77%. iMCD may also present with episodic flares of symptoms prior to developing more sustained clinical disease. Affected patients may respond to treatment but the disease usually follows a responding and relapsing course with the development of treatment resistance.

Implementation

NHS England will routinely commission siltuximab in accordance with the patient pathway for patients meeting all the following inclusion criteria, and none of the exclusion criteria.

Inclusion criteria

Individuals who:

- have a diagnosis of iMCD based on clinical, laboratory and pathological findings[1] **AND**
- have measurable disease with grade I (or greater) symptoms according to the National Cancer Institute Common Terminology Criteria for Adverse Events **AND**
- have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 to 2 **AND**
- are adult patients[2].

[1] Diagnostic criteria as defined in the International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease (Fajgenbaum et al., 2017)

[2] This policy is applicable to adults (≥18 years) due to lack of safety data in children. Post-pubescent access is permitted as outlined in NHS England Policy 170001/P Commissioning Medicines for Children in Specialised Services

Exclusion criteria

- Individuals with contraindications to siltuximab, as outlined in the summary of product characteristics (SmPC) **OR**
- Individuals who have acquired human immunodeficiency virus (HIV) and are seropositive, have acquired human herpesvirus-8 (HHV8) infection or have other clinically significant infections including active hepatitis B[3] or C.

Starting criteria

The decision to initiate treatment with siltuximab and management of the patient should be by physicians with significant experience in the treatment of iMCD. Confirmation of the diagnosis and initiation of siltuximab should be agreed at a regional lymphoma/ myeloma multi-disciplinary team (MDT) which includes at least one consultant with active and credible expertise in Castleman disease. Haematology laboratory tests should be performed prior to each dose of siltuximab therapy for the first 12 months and every third dosing cycle thereafter.

Before administering the infusion, the prescriber should consider delaying treatment if the treatment criteria outlined in the SmPC are not met.

Stopping criteria

A decision to stop using siltuximab should be made by the treating clinician along with the patient and carers (if applicable).

Serious adverse events e.g., anaphylaxis, severe allergic reaction, or cytokine release syndrome related to the infusion **OR**

no evidence of clinical (biochemical, lymph node size, symptomatic) response within three months of starting treatment **OR**

disease progression (as outlined in diagnostic criteria[1]).

Dose

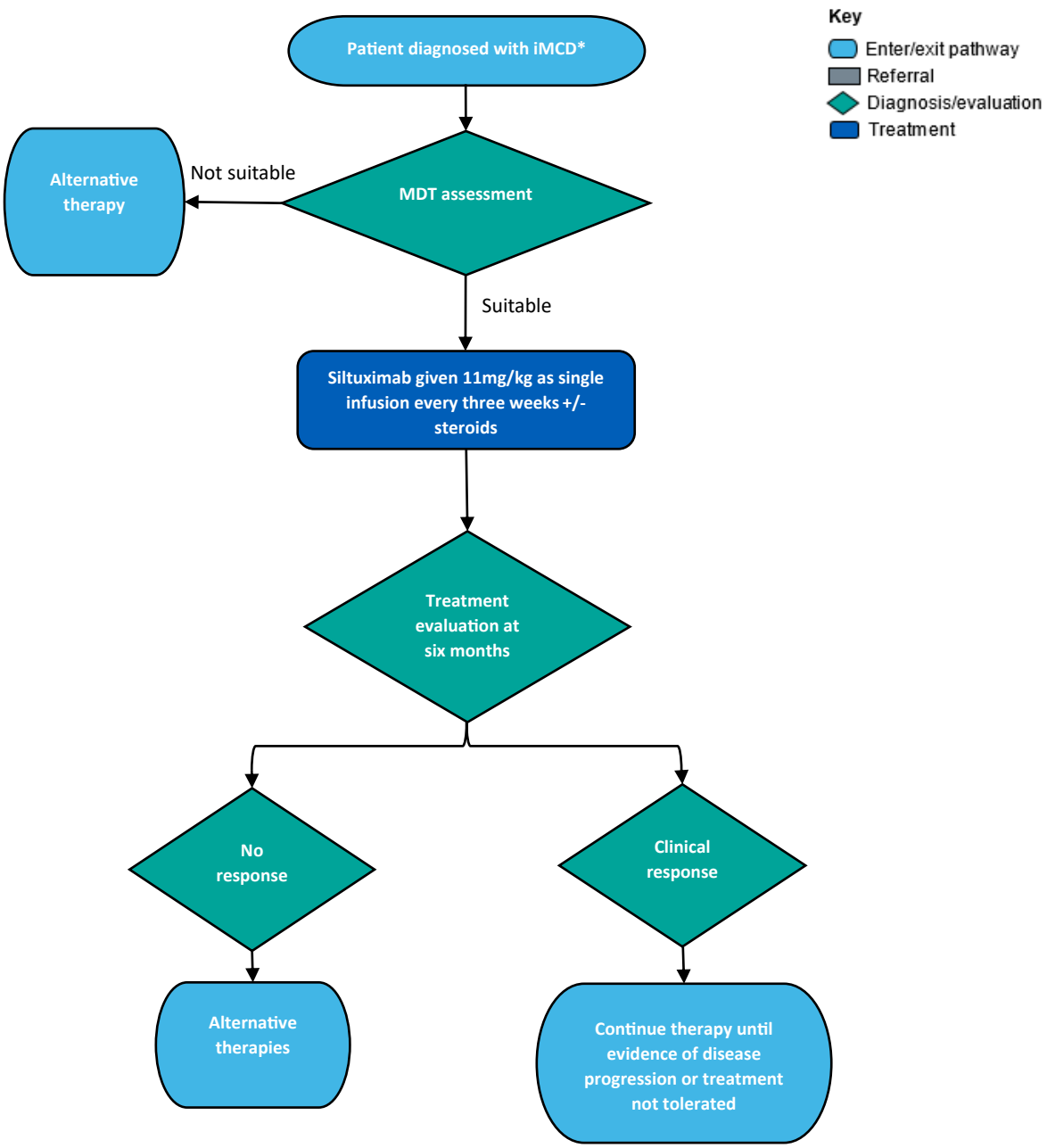
It is recommended that siltuximab is given at a dose of 11mg/kg as a single intravenous infusion every three weeks.

Monitoring

The monitoring requirements for siltuximab are in the SmPC and should be followed accordingly. Disease monitoring is as stated above in the starting criteria.

[3] Active hepatitis infection can be described as hepatitis B surface antigen and core antibody positive, surface antibody negative (Hepatitis B (chronic): diagnosis and management | Guidance | NICE, 2022)

Patient pathway



*As per the diagnostic criteria in the International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease.

Governance arrangements

This policy should be used in conjunction with the service specification for Specialised Chemotherapy Services B15/S/a.

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

Siltuximab for the treatment of iMCD will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of specialised Immunology and Allergy services.

Audit requirements

All patients receiving siltuximab for iMCD should be registered with the international ACCELERATE registry for Castleman disease (www.cdcn.org). The information is collected to inform future revisions of this policy.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base, then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

Given due regard to the need to eliminate discrimination, harassment, and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Corticosteroids	Corticosteroids are synthetically produced steroids that are mainly used to reduce inflammation and suppress the immune system.
Disease response	This is defined as reduction in lymph node size, improvement in biochemical markers (haemoglobin, platelet level, CRP, ESR, ferritin, renal and liver dysfunction), and improvement in symptoms.
Human herpesvirus 8 (HHV-8)	A herpesvirus that contributes to the development of Kaposi sarcoma, an otherwise rare form of cancer sometimes seen in AIDS patients, and to some B-cell lymphomas.
Human immunodeficiency virus (HIV)	A virus that attacks the body's immune system. There is currently no effective cure for HIV, and once someone acquires HIV, they live with HIV for life. However, there is now effective medication which reduces the viral load and stops the transmission of HIV to others.
International, evidence-based consensus diagnostic criteria for HHV-8 negative/idiopathic multicentric Castleman disease	An international working group comprising 34 paediatric and adult pathology and clinical experts in iMCD and related disorders from 8 countries, including 2 physicians that are also iMCD patients, was convened to establish iMCD diagnostic criteria.
Multidisciplinary Team (MDT)	MDTs consist of practitioners and professionals from health, care and allied disciplines and sectors that work together to provide holistic, person-centred and coordinated care and support.
Office of National Statistics (ONS)	A British government department which researches and publishes social and economic statistics, including trade figures and the Retail Price Index. ONS also publishes the results of the census (= an official count of the population).
Post-pubescent children	This policy refers to post-pubescent children in line with the considerations outlined in the Commissioning Medicines for Children in Specialised Services policy. (NHS England 170001/P, 2017).

References

Dong, Y. et al (2018) "Effectiveness of rituximab-containing treatment regimens in idiopathic multicentric Castleman disease" Annals of Hematology 97(9):1641 – 1647

Fajgenbaum, D., Uldrick, T., Bagg, A., Frank, D., Wu, D., Srkalovic, G., Simpson, D., Liu, A., Menke, D., Chandrakasan, S., Lechowicz, M., Wong, R., Pierson, S., Paessler, M., Rossi, J., Ide, M., Ruth, J., Croglio, M., Suarez, A., Krymskaya, V., Chadburn, A., Colleoni, G., Nasta, S., Jayanthan, R., Nabel, C., Casper, C., Dispenzieri, A., Fosså, A., Kelleher, D., Kurzrock, R., Voorhees, P., Dogan, A., Yoshizaki, K., van Rhee, F., Oksenhendler, E., Jaffe, E., Elenitoba-Johnson, K. and Lim, M., 2017. International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease. Blood, 129(12), pp.1646-1657.

Mukherjee, S. et al. (2020) "A Longitudinal Population Level Analysis of Healthcare Resource Utilization, Comorbidity, and Survival in Idiopathic Multicentric Castleman Disease Patients" Blood 136 (Supplement 1):11

Oksenhendler, E. et al. (2018) "The full spectrum of Castleman disease: 273 patients studied over 20 years" British Journal of Haematology 180(2):202-216.