Clinical Commissioning Policy:

Tocilizumab for Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) refractory or intolerant to previous lines of therapy (Adults) [2334]

Summary

Tocilizumab is recommended to be available as a routine commissioning treatment option for neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) refractory or intolerant to previous lines of therapy within the criteria set out in this document.

The policy is restricted to adults aged ≥18 years old[1] in line with the findings of the evidence review.

Committee discussion

Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed here.

What we have decided

NHS England has carefully reviewed the evidence to treat neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), which is refractory or intolerant to previous lines of therapy, with tocilizumab. 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 here.

Links and updates to other policies

This document relates to the neuromyelitis optica service specification for (adults and adolescents).

Plain language summary

About neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are a collection of very rare, severely disabling

[1] Tocilizumab may be used in children aged two years old and above via NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children).

disorders of the central nervous system. The condition is an autoimmune disorder, meaning that the body's own immune system inappropriately attacks its central nervous system, usually the spinal cord and visual nerves by causing inflammation there.

Patients with NMOSD will often have specific antibodies present in their blood, called aquaporin-4 antibodies (AQP4-IgG). These patients can be referred to as having 'AQP4-IgG positive' disease. Whilst the majority of patients with NMOSD will have detectable levels of AQP4-IgG, a very small proportion will not have detectable levels, and these patients can be referred to as either 'Ab negative phenotype' or 'AQP4-IgG negative' patients. Despite the absence of measurable antibodies, these patients present very similarly and may be indistinguishable to those with antibodies. These patients can all be referred to as having NMOSD. MOGAD is associated with the presence of myelin oligodendrocyte glycoprotein (MOG) antibodies.

NMOSD and MOGAD are commonly characterised by repeated relapses of inflammation of the visual nerve (optic neuritis) and inflammation of the spinal cord (longitudinally extensive transverse myelitis). Patients become significantly more impaired and disabled with each subsequent relapse. All patients with AQP4-IgG positive disease and around 45% of patients with MOGAD will have chronic relapsing disease.

Diagnostic criteria for NMOSD differs depending on the AQP4-IgG status, the current NMOSD diagnostic criteria for adults were developed in 2015 (Wingerchuk et al). Criteria differs dependent on AQP4-IgG status.

Diagnosis of AQP4-IgG positive NMOSD requires all of the following:

- At least one core clinical characteristic[2]
- Positive test for AQP4-IgG using best available detection method
- Exclusion of alternative diagnosis

Diagnostic criteria for NMOSD without AQP4-IgG or unknown AQP4-IgG status requires all of the following:

- At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting the following criteria:
    - At least one core clinical characteristic must be optic neuritis, acute myelitis with longitudinal extensive transverse myelitis or acute postrema syndrome
    - Dissemination in space (two or more different core clinical characteristics)
    - Fulfilment of additional MRI requirements[3], as applicable
- Negative tests for AQP-4 IGG using best available detection method or testing unavailable
- Exclusion of alternative diagnosis

The international MOGAD Panel published proposed MOGAD criteria in 2023[4] which extended the phenotype outside of NMOSD.

Disability and disease progression in NMOSD and MOGAD are directly correlated with disease relapses and therefore relapse prevention is the mainstay of treatment. All patients

[2]Defined in Wingerchuck et al 2015.
[3] Defined in Wingerchuck et al 2015.
[4] Prof Brenda Banwell, MD Prof Jeffrey L Bennett, MD PhD Prof Romain Marignier, MD PhD Prof Ho Jin Kim, MD PhD Prof Fabienne Brilot, PhD Prof Eoin P Flanagan, MB BCh et al (2023) Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria, The Lancet Neurology, Vol 22 Issue 3, P268-282.

with AQP4-IgG positive disease and patients with relapsing MOGAD or AQP4-IgG negative disease are at risk of profound disability with each subsequent relapse.

About current treatment

First line treatment for both NMOSD and MOGAD is corticosteroids, usually prednisolone, which can be given in combination with either azathioprine, mycophenolate or methotrexate.

Rituximab is commissioned for patients either with AQP4-IgG positive disease or those with MOGAD or AQP4-IgG negative disease that fulfil the NMOSD 2015 diagnostic criteria who are refractory to first line treatment (Wingerchuk et al, 2015).

Recently immunoglobulin (Ig) therapy has been approved by NHS England for patients with NMOSD (AQP4 IgG positive and negative disease) who have failed or intolerant to ≥ three previous therapies and patients with MOGAD who are refractory to at least two treatments.

All commissioned treatments for NMOSD and MOGAD are off-label. There are currently no licensed treatments available for NMOSD or MOGAD with a positive recommendation from NICE.

About tocilizumab

Tocilizumab is a humanized monoclonal antibody that targets the IL- 6 receptor. It is licensed and NICE approved in rheumatoid arthritis, juvenile Idiopathic arthritis, giant cell arteritis and severe COVID-19 infection. Tocilizumab can be delivered intravenously or subcutaneously.

Tocilizumab is not licensed in NMOSD or MOGAD. Tocilizumab is proposed as a treatment for patients with NMOSD or MOGAD who are refractory or intolerant to previous lines of commissioned therapy. This means that patients continue to relapse despite treatment. It can be given as monotherapy or in combination with steroids. It is proposed as an alternative option to Ig therapy for those eligible.

Epidemiology and needs assessment

NMOSD is associated with a much higher prevalence in people of Afro-Caribbean and East Asian ethnicity compared to White and has a much higher female to male ratio of up to 9:1. Meanwhile, for MOGAD, the split between females and males is much closer to 1:1 and there is no significant racial split in incidence and prevalence. MOGAD is, however, more common in children whereas NMOSD is more common in adults (Hor et al, 2020).

An annual report of the Oxford NMO Service demonstrated a current prevalence of 145 patients with AQP4-IgG positive NMOSD, 111 patients with MOGAD, and 28 patients with AQP4-IgG negative disease (Annual Report, 2018).

It is estimated that <5-10% over 5 years would be refractory or intolerant to previous therapies and need treatment with tocilizumab. This would equate to roughly **17** patients a year (9 AQP4-IgG positive NMOSD and 8 MOGAD), of which 4 are estimated to be children. AQP4-IgG negative disease is extremely rare, so it is not anticipated to be included in the annual incidence but may present occasionally (O'Connell et al, 2020).

Implementation

Inclusion criteria

All patients aged ≥ 18 years old with a confirmed diagnosis[5] of:

- neuromyelitis optica spectrum disorder (NMOSD)

  OR

- myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)

AND WHO EITHER

- are intolerant[6] to previous lines of therapy including rituximab or two other immunosuppressants

  OR

- have had at least one relapse on rituximab or two other immunosuppressants

Exclusion criteria

Patients who meet any of the following contraindications are not eligible for treatment with tocilizumab under this policy:

- contraindications to tocilizumab as outlined in the summary of product characteristics (SmPC)
- monophasic AQP4-IgG negative disease and monophasic MOGAD

Starting criteria

Patients should be given clear, written information outlining treatment with tocilizumab and the potential side effects. Informed consent must be taken before starting treatment. Patients of reproductive age should be appropriately counselled regarding current best practice around potential need for contraception and drug wash out.

Patients need to be discussed with the National NMO multidisciplinary team (MDT) which must include at least two neurological consultants[7] with expertise in the disease who decide that tocilizumab is the most appropriate treatment option. Appropriate data must be shared with the NMO service for the purposes of audit and governance.

[5] According to the latest diagnostic criteria.
[6] Defined as having a contra-indication, anaphylaxis or development of autoantibodies to previous lines of therapy.
[7] If the Commissioning Medicines for Children policy is being used, then the use of tocilizumab must be discussed at the National NMO multidisciplinary team (MDT). At least two consultants must be involved from the relevant subspecialty with active and credible expertise in the relevant field, including at least one consultant paediatrician or a consultant with a Certificate of Completion of Training (CCT) which includes training in caring for children. In some specialities, it may be the case that medical consultants are trained in both adult and paediatric medicine. The MDT should include a paediatric pharmacist and other professional groups appropriate to the disease area.

Stopping criteria

A decision to stop using tocilizumab should be made by the treating clinician if one of the following occur:

- a serious adverse event e.g., anaphylaxis or severe allergic reaction **OR**
- patient decides to stop treatment **OR**
- evidence of intolerance or refractory disease as evidenced by continuing disease relapse[8] (taking into account therapeutic lag[9] and the option of add on therapies[10])

Monitoring

Prior to commencing treatment, the patient should be screened for tuberculosis (QuantiFERON assay, or equivalent assay and chest x-ray) and hepatitis B virus. A formal medical review to assess the tolerability of and response to treatment should take place at three months. Patients with controlled disease should be followed by experienced clinicians at least annually or sooner depending on tolerance and disease activity.

Monitor lipid profile 4-8 weeks after starting treatment and then as indicated. Monitor hepatic transaminases before starting treatment, every 4-8 weeks for first 6 months of treatment, then every 12 weeks thereafter.

Monitor neutrophil and platelet count before starting treatment, 4-8 weeks after starting treatment and then as indicated.

Dose

The use of tocilizumab in this patient cohort is off-label and Trust policy regarding off-label use of medicines should apply.

Tocilizumab can be delivered subcutaneously or intravenously. The choice of administrative route should be a joint decision between the patient and their treating clinician.

Tocilizumab should be given as monotherapy with the exception of concomitant corticosteroids[11].

Intravenous

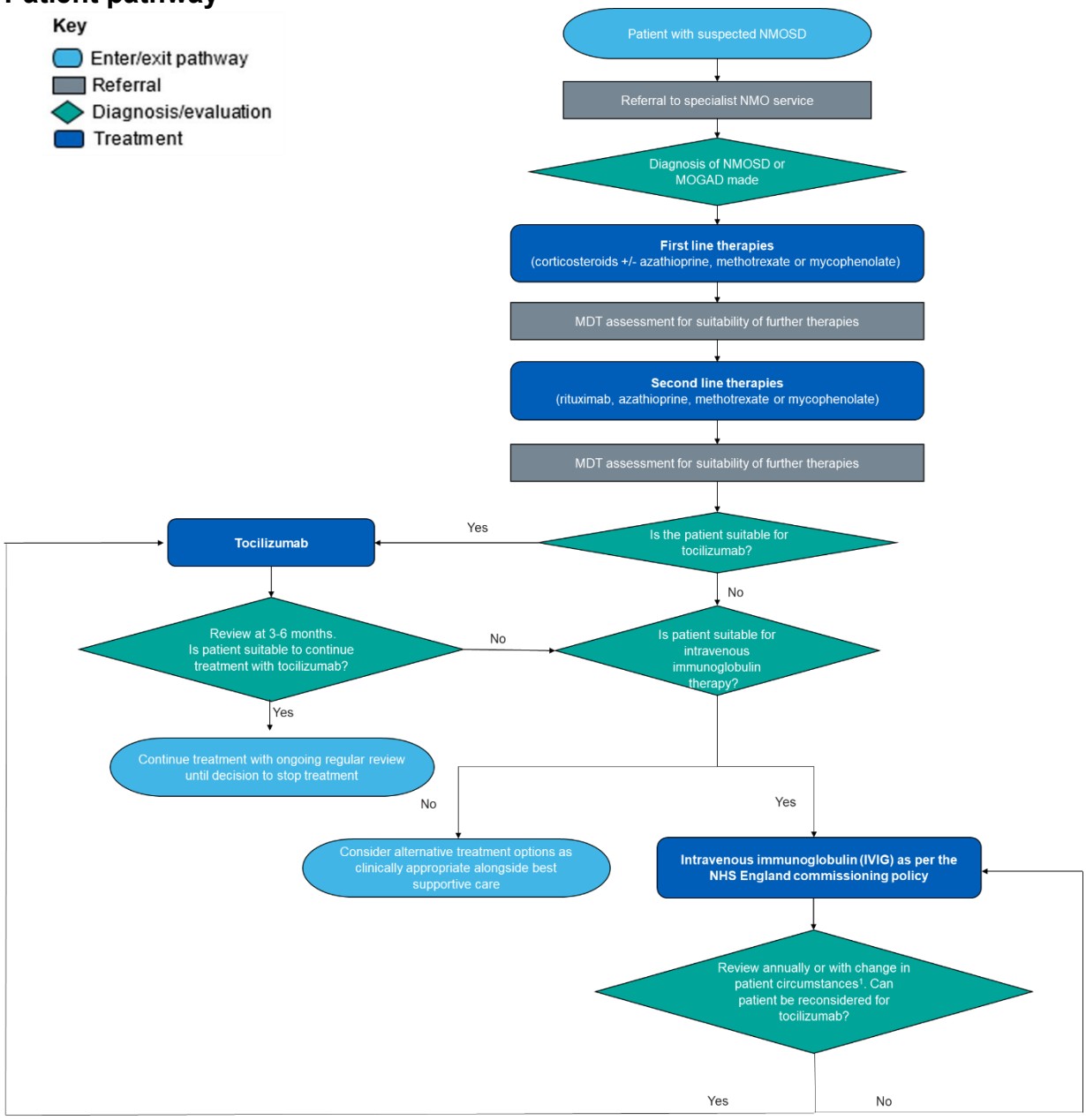
Tocilizumab should be given at a dose of 8mg/kg intravenously every four weeks (for individuals whose body weight is more than 100kg, doses exceeding 800mg per infusion are not recommended).

Subcutaneous

Tocilizumab should be given at a dose of 162mg subcutaneously weekly.

[8] Refers to current disease relapse being potentially too disabling to allow ongoing relapses.
[9] Therapeutic lag is defined as 3 months.
[10] Add on therapies include prednisolone and other non-corticosteroid immunotherapy. A maximum of two add on therapies can be used in addition to tocilizumab.
[11] Tocilizumab may be given concomitantly with other immunosuppressants during the switchover period only.

Patient pathway



1. For example: New risk factor for IVIG identified, contraindication to IVIG, patient relocating away from a centre able to provide IVIG where SC tocilizumab may be more suitable.

Governance arrangements

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.

The use of tocilizumab is off-label; Trust policy regarding unlicensed medicines should apply.

Any provider organisation treating patients with these interventions 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.

Mechanism for funding

Tocilizumab will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of Neuromyelitis Optica service (adults and adolescents) (D04/S(HSS)/b).

Audit requirements

Data should be submitted annually to the National NMO Service for audit purposes. Data will be reviewed through use of prior approval forms. 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

Autoimmunity	A misdirected immune response that occurs when the immune system goes awry and attacks the body itself.

References

Hor, J.Y. et al. (2020) ‘Epidemiology of Neuromyelitis Optica spectrum disorder and its prevalence and incidence worldwide’, Frontiers in Neurology, 11. doi:10.3389/fneur.2020.00501.

O’Connell K, Hamilton-Shield A, Woodhall M, et al., Prevalence and incidence of neuromyelitis optica spectrum disorder, aquaporin-4 antibody-positive NMOSD and MOG antibody-positive disease in Oxfordshire, UK. Accepted 21 May 2020, J Neurol Neurosurg Psychiatry 2020;0:1–3. doi:10.1136/jnnp-2020-323158

Oxford University Hospitals NHS Foundation Trust Diagnostic and Advisory Service for Neuromyelitis Optica (NMO) Annual Report 2018. Oxford University Hospitals NHS Foundation Trust; (2018).

Uzawa, A. et al. (2013) ‘Cerebrospinal fluid interleukin-6 and glial fibrillary acidic protein levels are increased during initial neuromyelitis optica attacks’, Clinica Chimica Acta, 421, pp. 181–183. doi:10.1016/j.cca.2013.03.020.

Wingerchuk, D.M. et al. (2015) ‘International consensus diagnostic criteria for Neuromyelitis Optica Spectrum Disorders’, Neurology, 85(2), pp. 177–189. doi:10.1212/wnl.0000000000001729.