Reference no: 2319
Publication date: 26 February 2025

Clinical commissioning policy:

# Etanercept and adalimumab for the treatment of deficiency of adenosine deaminase type 2 (aged 5 years and older) [2319]

## Summary

Etanercept and adalimumab are both recommended to be available as routine commissioning treatment options for deficiency of adenosine deaminase type 2 (DADA2) within the criteria set out in this document.

This policy has been restricted to those aged 5 years[1] and older in line with the findings from the evidence review. Note that both etanercept and adalimumab are not licensed in children or adults for DADA2 and therefore this is an off-label use of both drugs.

## Committee discussion

Clinical Panel agreed with the policy and recommended this proceeds as a routine commissioning policy. The evidence and reported outcomes were considered carefully. Panel members discussed the very low certainty of the evidence but agreed that clinical benefit can be seen particularly in relation to ischaemic events and other critical outcomes.

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

The Clinical Priorities Advisory Group committee papers can be accessed here: www.england.nhs.uk/publication/etanercept-and-adalimumab-for-the-treatment-of-deficiency-of-adenosine-deaminase/

## What we have decided

NHS England has carefully reviewed the evidence to treat DADA2 with etanercept or adalimumab. We have concluded that there is enough evidence to make both treatments available at this time.

The evidence review which informs this commissioning position can be accessed here: www.england.nhs.uk/publication/etanercept-and-adalimumab-for-the-treatment-of-deficiency-of-adenosine-deaminase/

# Plain language summary

## About deficiency of adenosine deaminase type 2

Deficiency of adenosine deaminase type 2 (DADA2) is a rare, inherited disorder caused by autosomal recessive mutations in the ADA2 gene. Deficiency of ADA2 disrupts the integrity of the blood vessel wall and impairs differentiation of specific cells called macrophages. This results in a predominance of a specific type of macrophages that secrete proteins that

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

cause inflammation such as tumour necrosis factor (TNF), an important mediator of vasculitis.

DADA2 is characterised by abnormal inflammation, and immune system dysfunction. Inflammatory features include intermittent fevers, rash, pain and or inflammation in the muscles and the joints. Problems with normal blood cell development may also begin early in life or in late adulthood, and include severe anaemia, low white blood cells, or low blood platelets.

Vasculitis is one of the most predominant features of DADA2 and often begins early in childhood, with many patients experiencing early-onset strokes or peripheral vascular disease before the age of 10. In severe cases these strokes can be debilitating, leading to irreversible brain damage, and the peripheral vascular disease can lead to loss of fingers, toes, testicles or damage to organs such as the kidneys and liver. High blood pressure and organomegaly (enlarged organs) are also often seen in early childhood and persist into adulthood. Patients are highly susceptible to infections and cancers as a result of their immunodeficiency. Untreated, the disease can lead to permanent disability or death.

### About current treatment

The only commissioned treatment for DADA2 is hematopoietic stem cell transplant (HSCT). HSCT is considered a curative treatment, but this is only an option for patients with either severe bone marrow failure and/or problems regulating the immune system who fail to respond to standard of care treatment. Whilst HSCT can be successful for patients with DADA2, the procedure itself is associated with 20% chance of death.

### About etanercept and adalimumab

Etanercept and adalimumab are both from a class of drugs called TNF inhibitors. These drugs block the action of the protein TNF, which is responsible for the inflammation seen in DADA2.

Etanercept is licensed for use in rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, axial spondylarthritis, and plaque psoriasis. It is not licensed for use in DADA2.

Adalimumab is licensed for use in several medical conditions including Crohn’s disease, ulcerative colitis and certain types of arthritis such as rheumatoid arthritis and ankylosing spondylitis. It is not licensed for use in DADA2.

Both etanercept and adalimumab are given subcutaneously, which means an injection into the skin. This means patients can self-administer the medication at home rather than attending hospital for repeated infusions.

Etanercept is a recombinant drug, so it is less likely for patients to develop an immune reaction to the drug.  This means that patients can stay on the treatment lifelong without the risk of forming anti-drug antibodies, a common problem with TNF inhibitors, that would lead to reduced effectiveness.

## Epidemiology and needs assessment

As DADA2 is an autosomal recessive condition it affects males and females equally, although there is a higher prevalence of disease in populations with a high degree of consanguinity or in populations with founder variants, for example, the p.Gly47Arg founder variant in Israeli, Georgian-Jewish and Turkish populations (Aksentijevich et al, 2019).

The incidence and prevention of DADA2 in the UK in unknown. Jee et al estimated a carrier frequency of at least 1 in 236 individuals, corresponding to an expected DADA2 disease prevalence of ~1 in 222,000 individuals (Jee et al, 2022). Based on ONS 2019 estimation of the population of England being 56 million, this would equate to a prevalence of ~253 cases and estimated incidence of 2-3 new cases/year. However, due to the rarity of the condition and the non-specific symptoms, most patients will be misdiagnosed. It would be expected that most diagnosed patients would require treatment. The estimated overall mortality is 8%, although this is likely to be higher due to mis- or underdiagnosis. Therefore, it is estimated that there are approximately 30 diagnosed patients who would require treatment with this policy every year.

It is worth nothing that DADA2 has now been added to the Generation Study gene list. This will likely increase the incidence of DADA2 in the future as more people get diagnosed, but the size of this increase is uncertain at present.

# Implementation

Etanercept and adalimumab are both recommended treatment options at the same point in the treatment pathway for patients with DADA2. Both treatments are given lifelong.

The choice between starting a patient on etanercept vs adalimumab should be a joint decision made between the patient and their treating consultant after a discussion on the pros and cons of both therapies, subject to the patient meeting all the relevant inclusion criteria and none of the exclusion criteria in this policy.

## Inclusion criteria

All patients aged 5 years and older with a diagnosis of deficiency of adenosine deaminase type 2 (DADA2) as confirmed by:

- a genetic result of DADA2 by a sensitive PCR/next generation sequencing based method[2]

  **OR**

- biochemical evidence of serum or plasma ADA2 enzyme deficiency whilst awaiting genetic confirmation[3]

## Exclusion criteria

Patients with contraindications to either etanercept or adalimumab, as outlined in the summary of product characteristics (SmPC), are not eligible for treatment with that drug under this policy.

## Starting criteria

Genetic confirmation (typically blood, occasionally saliva) by a sensitive PCR/next generation sequencing based method to confirm a diagnosis of DADA2 prior to initiating treatment.

Patients should be given clear, written information outlining treatment with etanercept/adalimumab and the potential side effects, including an increased risk of infection. Informed consent must be taken before starting treatment with either drug.

[2] See starting criteria
[3] Normal ADA2 enzymatic activity excludes the diagnosis of DADA2

Patients need to be discussed at a multidisciplinary team (MDT) meeting which must include at least two consultants[4] with expertise in the disease (typically but not exclusively immunology and rheumatology) who decide that etanercept or adalimumab is the most appropriate treatment option. The MDT should include other professional groups appropriate to the disease and organ area (e.g. neurology for stroke; haematology for cytopenia).

Given that genetic testing can take at least three months, patients with clinical suspicion of the diagnosis and who have been found to have low ADA2 enzyme activity can start treatment whilst awaiting genetic confirmation, subject to MDT approval.

## Stopping criteria

A decision to stop using etanercept/adalimumab 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 insufficient response to treatment as determined by MDT. Insufficient response would be defined as ongoing evidence of autoinflammation (elevation of acute phase reactions e.g. CRP, ESR, serum amyloid A) and/or vasculitis disease progression (ischaemic events including strokes or peripheral ischaemia or others e.g. vasculitic ulcers).

## Monitoring

Prior to commencing treatment, the patient should be screened for tuberculosis (QuantiFERON assay, or equivalent assay) and chest X-ray.

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 every three to six months. Regular monitoring of blood markers (CBC with differential, ESR, CRP, liver function and kidney function) should be arranged at clinical review. Follow-up of other laboratory and imaging studies should be guided by the patient's disease manifestations and baseline findings (Lee et al, 2023).

Etanercept/adalimumab drug level and antidrug antibody monitoring (e.g. every 6-12 months) and antidrug antibody prophylaxis (e.g. with methotrexate or other nonbiological DMARD) should be considered[5]. Clinicians may consider switching treatment between etanercept or adalimumab in patients who develop drug resistance to either agent (with or without antidrug antibodies).

## Dose

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

[4] If the Commissioning Medicines for Children policy is being used, then the use of the drug must be discussed at a specialised MDT meeting. At least two consultants must be involved from the relevant subspecialty with active and credible expertise in the relevant field. 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.

[5] Please refer to the international consensus statement on the evaluation and management of DADA2 for further details on monitoring requirements of DADA2.

Both etanercept and adalimumab are administered subcutaneously. The choice of drug should be a joint decision between the patient and their treating clinician.

## Paediatrics (<18 years old)

### Etanercept

Etanercept is given subcutaneously at a dose of either 0.4mg/kg twice weekly (max. per dose 25mg) or 0.8mg/kg once weekly (max. per dose 50mg)[6].

### Adalimumab

Body weight 10 to <30 kg

Adalimumab is given subcutaneously at a dose of 20 mg every other week.

Body weight ≥30 kg and above

Adalimumab is given subcutaneously at a dose of 40 mg every other week.

## Adults (≥18 years old)

### Etanercept

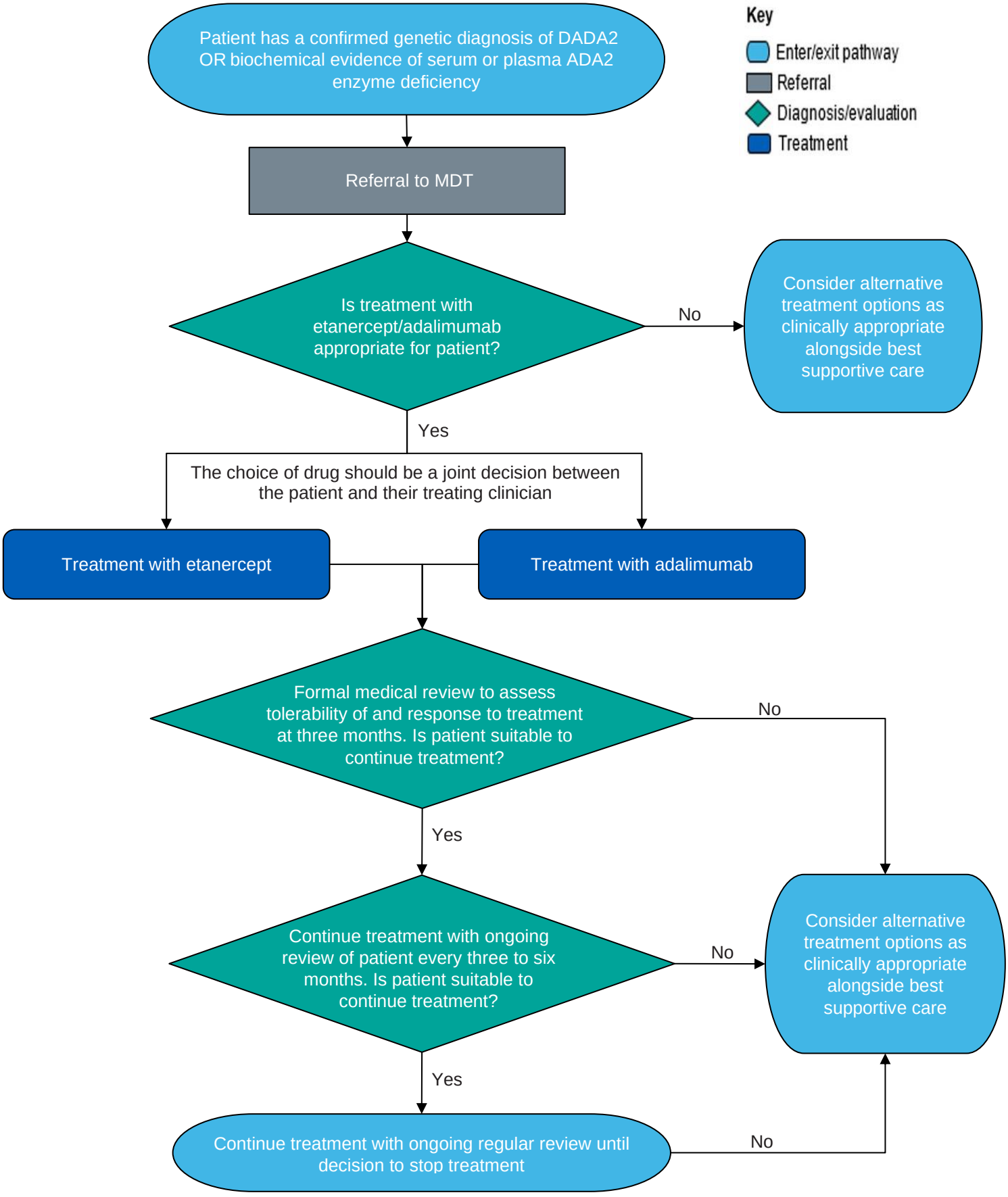
Etanercept is given subcutaneously at a dose of either 25mg twice weekly or 50mg once weekly[6].

### Adalimumab

Adalimumab is given subcutaneously at a dose of 40mg every other week.

[6] Choice of dose frequency of etanercept should be a joint decision between the patient and their treating clinician.

## Patient pathway



## 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 etanercept and adalimumab 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

Adalimumab and etanercept will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of Specialised Immunology services.

Where both treatment options are equally clinically suitable, the treatment option with the lowest acquisition cost should be used. Where suitable and available, biosimilar medicines should be used in the first instance.

## Audit requirements

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. |
| Immunodeficient | Patients with hypogammaglobulinemia, lymphopenia, and/or evidence of recurrent infection and/or opportunistic infection. Patients with this phenotype may be diagnosed with common variable immunodeficiency. |

## References

Aksentijevich I, Sampaio Moura N, Barron K. Adenosine Deaminase 2 Deficiency. 2019 Aug 8. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544951/

Jee H, Huang Z, Baxter S, Huang Y, Taylor ML, Henderson LA, Rosenzweig S, Sharma A, Chambers EP, Hershfield MS, Zhou Q, Dedeoglu F, Aksentijevich I, Nigrovic PA, O'Donnell-Luria A, Lee PY. Comprehensive analysis of ADA2 genetic variants and estimation of carrier frequency driven by a function-based approach. J Allergy Clin Immunol. 2022 Jan;149(1):379-387. doi: 10.1016/j.jaci.2021.04.034. Epub 2021 May 15. PMID: 34004258; PMCID: PMC8591146.

Lee PY, Davidson BA, Abraham RS, et al. Evaluation and Management of Deficiency of Adenosine Deaminase 2: An International Consensus Statement. *JAMA Netw Open.* 2023;6(5):e2315894. doi:10.1001/jamanetworkopen.2023.15894