NHS England evidence review:

Etanercept monotherapy for deficiency of adenosine deaminase 2 (DADA2)

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of etanercept monotherapy compared to standard care for the treatment of deficiency of adenosine deaminase type 2 (DADA2).

DADA2 is a rare, inherited disorder caused by autosomal recessive mutations in the ADA2 gene. Vasculitis is one of the most predominant features of DADA2. Patients are in scope for this review if they have a confirmed diagnosis of DADA2, or where there is a strong clinical suspicion of DADA2 and genetic testing results are awaited.

Etanercept is a tumour necrosis factor (TNF) inhibitor, also known as anti-TNF therapy, used to prevent strokes and other vasculitic complications.

Standard care for DADA2 is best supportive care alone, or with a TNF inhibitor (given lifelong), with or without immunoglobulin replacement therapy. Best supportive care can include, but is not limited to, antibiotics, antivirals, corticosteroids, antipyretics, analgesics or synthetic disease-modifying anti-rheumatic drugs (DMARDs) for anti-drug antibodies such as methotrexate. Currently used TNF inhibitors include etanercept, adalimumab, infliximab, certolizumab or golimumab but none are licenced or commissioned in England for use in DADA2. Etanercept is the least immunogenic of the TNF inhibitors and is delivered via subcutaneous injection, which allows patients to self-administer at home.

The review scope included the identification of possible subgroups of patients within the included studies who might benefit from etanercept more than others and the dose of etanercept used.

This review includes studies where etanercept is known to be the TNF inhibitor that patients received. Outcomes for patients who have received the TNF inhibitor adalimumab are considered in a separate evidence review.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of etanercept monotherapy (herein referred to as etanercept) compared to standard care for the treatment of deficiency of adenosine deaminase type 2 (DADA2). The searches for evidence published since January 2013 were conducted on 3rd October 2023 and identified 363 potential references. These were screened using their titles and abstracts and 23 full text papers potentially relating to the use of tumour necrosis factor (TNF) inhibitors for DADA2 were obtained and assessed for relevance. Papers relating to patients who have received the TNF inhibitor adalimumab are considered in a separate evidence review.

Nine papers were identified for inclusion in this review on etanercept. Four papers were retrospective case series that included whole populations of in scope patients, i.e. patients with DADA2 who received etanercept (Celikel et al 2023, Kisla Ekinci et al 2022, Melo et al 2023, Tanatar et al 2020). One paper was a systematic review (Kasap Cuceoglu et al 2021) and two papers were retrospective cohort studies (Andriessen et al 2023, Li et al 2023), but these papers were treated as retrospective case series due to only a proportion of patients in each paper being in scope for population (i.e. patients with DADA2) and/or who were treated with etanercept (34.6%, 24.14% and 43.33%, respectively) and relevant data were mainly described on an individual patient basis. Two papers were retrospective case series (Cooray et al 2021, Deuitch et al 2022) that included a proportion of in scope patients treated with etanercept (16% and 69% of the study populations respectively). It was unclear whether there may be overlap of patients included in Li et al (2023) and Deuitch et al (2022) as some patients from Li et al (2023) had previously been reported in Deuitch et al (2022).

All nine papers provided non-comparative evidence for a total sample size of 77 patients with DADA2 and individual study sample sizes ranged between five and 18 patients. Populations varied within and across studies in terms of the proportion of patients presenting with different phenotypes (vasculopathy, immunodeficiency, and hematologic manifestations) and symptoms (e.g. cutaneous involvement, fever, and stroke). Where reported in the included studies, the proportion of males ranged between 33.3% and 100%. Where reported, the median age at disease/symptom onset ranged between four and 11 years, and median age at diagnosis ranged between five and 15 years. The follow-up durations varied across studies, including at three months after starting etanercept, at median time on treatment of one year, during the next nine or 12 months of etanercept treatment, at median 20.2 months after diagnosis of DADA2, after a median of 74 months, or follow-up of the whole cohort between two months and greater than 10 years. As treatment was ongoing, this review has reported outcomes by treatment duration where studies did not report length of follow-up. The duration of treatment or follow-up of patients on etanercept was not always stated, with timepoints sometimes representing all treated patients.

The studies were published between 2020 and 2023 and were conducted in Brazil (Melo et al 2023), China (Li et al 2023), The Netherlands (Andriessen et al 2023), Turkey (Celikel et al 2023, Kasap Cuceoglu et al 2021, Kisla Ekinci et al 2022, Tanatar et al 2020), the UK (Cooray et al 2021) and the USA (Deuitch et al 2022). Deuitch et al (2022) also stated other collaborating groups were involved but did not specify where they were located; study authors were based in the USA, Canada and China. No comparator studies were identified comparing etanercept versus standard care, all outcomes presented were extracted from

small, retrospective, case series and results were reported compared to baseline[1]. No evidence was identified for the important outcomes quality of life (QoL) or hospitalisation.

No evidence relating to cost effectiveness was identified. None of the included studies reported on relevant subgroups of patients that would benefit more from treatment with etanercept.

In terms of clinical effectiveness:

- **Number of ischaemic events (critical outcome).**
- Four retrospective case series provided very low certainty evidence that the number of ischaemic events (including central nervous system (CNS) and non-CNS strokes) were reduced by 80% to 100% after initiation of etanercept. Follow-up durations varied between one year, at a median of 20.2 months after diagnosis of DADA2, after median 74 months, or follow-up was described as for the whole cohort between two months and >10 years. Details were often limited or not presented for all patients, and statistical measures were not reported.

- **Disease activity/response (critical outcome).**
- Seven retrospective case series provided very low certainty evidence on disease activity/response. Four retrospective case series reported that between 92.3% and 100% of patients were in complete/clinical remission (defined differently across studies) or had complete control of disease[2] after initiation of etanercept at median 20.2 months after diagnosis of DADA2 or between median follow-up of 23 to 56 months. One retrospective case series reported that patients did not show improvements in anaemia, lymphopenia, and hypogammaglobulinemia at follow-up of the whole cohort between two months and >10 years. One retrospective case series reported improvements in median Paediatric Vasculitis Activity Score (PVAS)[3] (reduction from baseline of 29 to 1.0 after median 74 months follow-up). Complete control of disease was reported after initiation of etanercept in one retrospective case series, but disease status before treatment with etanercept was not reported, which prevented comparisons to be made. No statistical measures were reported for any outcomes.

- **Symptom alleviation (critical outcome).**
- Six retrospective case series provided very low certainty evidence that symptoms (e.g. skin and musculoskeletal findings) generally improved or resolved at three months after initiation of etanercept, at one year follow-up, at median follow-up of 23, or at follow-up of whole cohort between two months and >10 years after initiation of

[1] Baseline defined as before the initiation of etanercept. Treatments received before the initiation of etanercept varied widely between studies.
[2] Response to treatment was considered complete when clinical and laboratory remission could be achieved; partial when either clinical or laboratory remission could be achieved, but not both; and absent when neither clinical nor laboratory remission could be achieved. Clinical remission was defined as the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation. Laboratory remission was defined as normalisation of CRP levels in the local laboratory. The authors also stated that 3 of 18 (16.7%) patients relapsed during follow-up, but it was unclear what the sequence of events was as to when patients relapsed and when they were in remission as no further details were reported.
[3] The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across 9 organ systems and a score of 0 indicating absent activity. The 'before' score was assessed at first presentation to the centre and the 'after' score at the most recent clinic visit after treatment with etanercept.

etanercept. Details were limited and mainly presented narratively, and no statistical measures were reported.

- **Steroid use reduction (important outcome).**
- Four retrospective case series provided very low certainty evidence that steroid use was discontinued in all or nearly all patients after initiation of etanercept, with one case series reporting that glucocorticoids had *"little effect"* on DADA2 symptoms. Follow-up durations were between the next nine to 12 months of etanercept treatment, after

  median time on etanercept treatment of one year, at median 20.2 months follow-up after diagnosis of DADA2, or after median 74 months follow-up. Details were limited and not always provided for all patients, and no statistical measures were reported.

- **Quality of life (QoL) (important outcome).**
- No evidence was identified for this outcome.

- **Hospitalisation (important outcome).**
- No evidence was identified for this outcome.

- **Change in acute phase reactants (important outcome).**
- Four retrospective case series provided very low certainty evidence relating to acute phase reactants. Four retrospective case series provided very low certainty evidence that median C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels improved in patients after initiation of etanercept, but where normal ranges were reported, these differed within and/or across studies. One of these case series reported serum amyloid A (SAA) levels in patients after initiation of etanercept, which were indicated to be within the normal range, but SAA levels were not reported at baseline. Follow-up durations were at 3 months, after median time on etanercept of one year, at median 20.2 months after diagnosis of DADA2 and after median 74 months follow-up.

In terms of safety:

- **Adverse effects.**
- Four retrospective case series provided very low certainty evidence on safety. Two of these case series reported that no adverse events were observed in patients after initiation of etanercept, but details were limited and narratively described. Two retrospective case series each reported one death in a patient with DADA2 after initiation of etanercept but neither appeared to be directly related to etanercept treatment. Follow-up durations were at three months after starting etanercept, at median 3.5 years to after 74 months, or at median time on etanercept treatment of one year.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients that may benefit from etanercept more than the wider population of interest.

Dose of etanercept used:

- Two retrospective case series reported that patients with DADA2 were administered varying doses of etanercept, ranging from 400µg/kg twice weekly to 50 mg weekly. Seven retrospective case series did not report the dose of etanercept used in the studies.

Please see the results table (section 5) in the review for further details of outcomes.

Limitations:

No studies were identified that provided comparative evidence between etanercept versus standard care on any critical or important outcomes. Non-comparative evidence on the treatment of DADA2 patients with etanercept was available from nine retrospective case series, which reported results compared to baseline. The certainty in the outcomes reported was very low for all nine case series due to very serious risk of bias and very serious indirectness because of the lack of a relevant treatment comparison. There are a number of factors that reduced confidence in the outcomes, including the lack of detail about the study populations, for example, limited details about baseline demographics and characteristics. Incomplete follow-up and missing data for included patients was a particular limitation of the case series and it was unclear whether the recruitment of study participants was consecutive (with the exception of one retrospective case series) or complete. Other limitations include the small sample sizes, which may reflect the rarity of the condition or difficulties in early diagnosis. One author highlighted the lack of diagnostic criteria for DADA2 alongside the limited access to functional assays and genetic sequencing in middle income countries which may also account for the low numbers of patients. No patients or clinicians were blinded in any of the studies, which could increase uncertainty around the more subjective outcomes such as the assessment of symptoms and clinical signs.

The main focus of most of the included studies was the clinical, genetic and laboratory findings of DADA2 patients with various pathogenic variants in the ADA2 gene rather than the clinical effectiveness and safety of etanercept. Outcome data were often limited, presented individually for patients in a table, or reported narratively, and some outcomes were not clearly defined. None of the included studies performed statistical analysis to aid interpretation of the findings. Given the limitations of the evidence about the clinical effectiveness and safety of etanercept in people with DADA2, it is difficult to draw conclusions.

Conclusion:

This review included non-comparative evidence from nine retrospective case series for patients with DADA2 who received etanercept. No comparator studies were identified that compared etanercept with standard care, all outcomes presented were extracted from small, retrospective case series and the results reported were compared to baseline. The nine case series provide very low certainty evidence relating to the critical and important outcomes of number of ischaemic events, disease activity/response and symptom alleviation, steroid use reduction, and change in acute phase reactants. Outcomes were mainly descriptive with no statistical measures reported. The case series reported reductions in ischaemic events and acute phase reactants in patients with DADA2 after treatment with etanercept. Narrative descriptions of symptom alleviation suggested improvements in symptoms, and reductions in steroid use were also reported. In terms of disease activity/response, the findings were mixed, with some studies reporting improvements in disease activity and other studies reporting no improvement. Where reported, etanercept appeared to be well tolerated in patients with DADA2. Two studies

each reported one death of a patient on etanercept, but neither appeared to be directly related to etanercept treatment. No evidence was identified for the important outcomes of quality of life (QoL) or hospitalisation. There was no evidence on cost effectiveness or on any subgroups of patients who may benefit more than others from treatment with etanercept.

Limitations reducing the certainty in the outcomes included the lack of detail about the study populations, incomplete follow-up and missing data for included patients, and uncertainty about whether the recruitment of study participants was consecutive and complete.

Although all the studies provide very low certainty evidence of the outcomes, there was congruence in the results reported. The studies identified in this review provide evidence that treatment with etanercept, which is delivered via subcutaneous injection and allows patients to self-administer at home, may improve disease activity and symptoms in patients with DADA2. However, the limitations of the studies, descriptive nature of the outcomes and lack of comparative data (the included retrospective case series reported results compared to baseline) limit the potential to draw any conclusions about the effectiveness of etanercept compared with standard care.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In patients with deficiency of adenosine deaminase type 2, what is the clinical effectiveness of etanercept compared with standard care?
2. In patients with deficiency of adenosine deaminase type 2, what is the safety of etanercept compared with standard care?
3. In patients with deficiency of adenosine deaminase type 2, what is the cost effectiveness of etanercept compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from etanercept more than the wider population of interest?
5. From the evidence selected, what dose of etanercept was used?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 3rd October 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Nine papers were identified for inclusion (Andriessen et al 2023, Celikel et al 2023, Cooray et al 2021, Deuitch et al 2022, Kasap Cuceoglu et al 2021, Kisla Ekinci et al 2022, Li et al 2023, Melo et al 2023, Tanatar et al 2020). Four were retrospective case series that

included whole populations of in scope patients (Celikel et al 2023, Kisla Ekinci et al 2022, Melo et al 2023, Tanatar et al 2020. One paper was a systematic review (Kasap Cuceoglu et al 2021) and two were retrospective cohort studies (Andriessen et al 2023, Li et al 2023), but were treated as retrospective case series due to only a proportion of patients in each paper being in scope for population (i.e. patients with DADA2) and/or treatment (i.e. patients treated with etanercept), and relevant data were mainly described on an individual patient basis. Two papers were retrospective case series (Cooray et al 2021, Deuitch et al 2022) that included a proportion of in scope patients treated with etanercept. It was unclear whether there may be overlap of patients included in Li et al (2023) and Deuitch et al (2022) as some patients from Li et al (2023) had previously been reported in Deuitch et al (2022).

No comparative evidence was identified comparing etanercept versus standard care, all case series reported results compared to baseline. No studies were identified that reported quality of life (QoL) or hospitalisation. No cost effectiveness studies were identified for inclusion in this review. None of the included studies reported on relevant subgroups of patients that would benefit more from treatment with etanercept.

The tumour necrosis factor (TNF) inhibitor adalimumab, for the treatment of DADA2, is considered in a separate evidence review.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Andriessen et al 2023 Retrospective cohort study (assessed as a case series as data presented individually for each patient) Multi-centre (seven university hospitals), The Netherlands	N=29 patients (from 23 families) with DADA2 Etanercept: n=7 (n=22 patients received out of scope interventions) Male: 4 (57.14%) Median (IQR) age at study inclusion (years): 19 (14 to 31) Median (IQR) age at disease onset (years): 5 (4 to 7.5) No relevant subgroups reported	**Intervention** Etanercept: dose not stated Duration of treatment not stated **Comparison** No comparator Two patients received concomitant treatment of nanogam or cuvitru	Follow-up between two months and >10 years (whole cohort) **Critical outcomes** • Number of ischaemic events • MRI-confirmed stroke before and after initiation of etanercept • Disease activity/response • Number (%) patients with anaemia, lymphopenia, hypogammaglobulinemia before and after initiation of etanercept • Symptom alleviation • Number (%) patients with cutaneous involvement (except eczema), eczema, fever, PAN-like rash, arthralgia/arthritis, aphthous stomatitis, before and after initiation of etanercept
Celikel et al 2023	n=6 children with DADA2	**Intervention** Etanercept: dose not stated	Median (IQR) follow-up (months): 23 (18 to 29.5)

Study	Population	Intervention and comparison	Outcomes reported

Retrospective case series One centre, Turkey	Etanercept: n=6 Male: 4 (67%) Median (IQR) age at symptom onset (years): 5 (1.88 to 7.75) Median (IQR) age at diagnosis (years): 7.75 (5.63 to 10.25) No relevant subgroups reported	Duration of treatment not stated **Comparison** No comparator No information about any concomitant treatment	**Critical outcomes** • Disease activity/response • Number of patients in clinical remission[a] before and after initiation of etanercept • Symptom alleviation • Number of patients with seizures before and after initiation of etanercept
Cooray et al 2021 Retrospective case series One specialist centre, UK	N=31 patients with DADA2 Etanercept: n=5 Male: 5/5 (100%) Median (IQR) age at symptom onset (years): 5 (3 to 11) Median (IQR) current age (years):[b] 20 (16 to 21) Median (IQR) duration of disease activity prior to etanercept treatment (months): 78 (28 to 136) No relevant subgroups reported	**Intervention** Etanercept doses: • 400µg/kg twice weekly or • 800 µg/kg weekly or • 25mg twice weekly or 50mg weekly if >12 years old Number of patients receiving each dose not stated **Comparison** No comparator No information about any concomitant treatment Other treatments received after etanercept treatment included glucocorticoid and aspirin (one patient) and azathioprine (one patient). Three patients did not receive any other treatments after etanercept	Median (range) etanercept treatment (months): 74 (12 to 84) **Critical outcomes** • Ischaemic events • Number of patients experiencing CNS and non-CNS ischaemic events before and after initiation of etanercept • Disease activity/response • Median (IQR) PVAS[c] before and after initiation of etanercept **Important outcomes** • Steroid use reduction • Change in acute phase reactants • Median (IQR) CRP before and after initiation of etanercept • Median (IQR) ESR before and after initiation of etanercept[d] after initiation of etanercept • Median (IQR) SAA **Safety** • Adverse events

Deuitch et al 2022 Retrospective case series National Institutes of Health, USA and collaborating groups (not specified) (authors were based in USA, Canada and China)	N=31 patients with DADA2[e] Etanercept: n=9 Patient sex not stated Median (IQR) age before treatment (years) (n=4): 6 (5 to 7) Median (IQR) age after treatment (years) (n=9): 11 (10 to 15)	**Intervention** Etanercept: dose not stated **Comparison** No comparator One patient received concomitant IVIG and clonazepammira, one patient received concomitant hydroxychloroquine, anakinra, and IVIG. Five patients received only etanercept	Median (range) etanercept treatment (n=8): 1 year (6 months to 5 years) **Critical outcomes** • Symptom alleviation • Number of patients with symptoms before and/or after initiation of etanercept **Important outcomes** • Steroid use reduction • Change in acute phase reactants

Study	**Population**	**Intervention and comparison**	**Outcomes reported**
	No relevant subgroups reported		• Median (IQR) CRP before and after initiation of etanercept **Safety** • Deaths
Kasap Cuceoglu et al 2021 Retrospective case series One paediatric rheumatology unit, Turkey	n=18 children with DADA2 Etanercept: n=18 Patient sex not stated Median (IQR) age at symptom onset (years): 4 (2 to 6) Median (IQR) age at diagnosis (years): 5.5 (3.5 to 8) No relevant subgroups reported	**Intervention** Etanercept: dose not stated Duration of treatment not stated **Comparison** No comparator No information about any concomitant treatment	Median (IQR) follow-up (years): 3.5 (2 to 5) **Critical outcomes** • Disease activity/response • Number of patients in complete remission (not defined) after etanercept • Number of patients who relapsed after initiation of etanercept **Important outcomes** **Safety** • Deaths

Kisla Ekinci et al 2022 Retrospective case series One paediatric rheumatology unit, Turkey	n=5 children with DADA2 Etanercept: n=5 Male: 3 (60%) Median (IQR) age at symptom onset (years): 7 (6.5 to 8) Median (IQR) age at diagnosis (years): 8.5 (7 to 9) Median (IQR) age at study inclusion (years): 9 (8 to 10) No relevant subgroups reported	**Intervention** Etanercept: dose not stated **Comparison** No comparator One patient was also receiving monthly IVIG replacement. No concomitant treatments stated for the other patients	Where reported, outcomes were described as during the next 9 months or 12 months of etanercept treatment **Critical outcomes** • Number of ischaemic events • Number of patients with neurological symptoms before and after initiation of etanercept • Disease activity/response • Number of patients in complete remission (not defined) • Symptom alleviation • Patients with improvements or complete resolution of symptoms after initiation of etanercept **Important outcomes** • Steroid use reduction • Steroid use after initiation of etanercept
Li et al 2023 Retrospective cohort study (given only 13 of 30 patients were in scope, this has been treated as a case series)	N=30 children with DADA2[e] Etanercept: n=13 Male: 9 (69.2%) Median (IQR) age at symptom onset (years): 4.2 (2.3 to 4.9)	**Intervention** Etanercept: dose not stated Duration of treatment not stated **Comparison** No comparator	Median (range) follow-up (months): 20.2 (5 to 36) after diagnosis of DADA2 (whole cohort) **Critical outcomes** • Number of ischaemic events • Disease activity/response

Study	**Population**	**Intervention and comparison**	**Outcomes reported**

Seventeen rheumatology centres, China	Median (IQR) age of diagnosis (years): 7.9 (5.3 to 11.8)[f] No relevant subgroups reported	Six patients received concomitant treatment with one or more of the following: NSAIDs, glucocorticoids, methotrexate, thalidomide, hydroxychloroquine, cyclophosphamide, and mycophenolate mofetil	• Number of patients in complete remission[g] after initiation of etanercept • Number of patients in partial remission[h] after initiation of etanercept • Symptom alleviation **Important outcomes** • Steroid use reduction • Change in acute phase reactants • Median (IQR) CRP before and after initiation of etanercept • Median (IQR) ESR before and after initiation of etanercept
Melo et al 2023 Retrospective case series Ten centres, Brazil	N=18 patients with DADA2 Etanercept: n=9 Male: 3 (33.3%) Additional baseline characteristics reported but not separately for in scope patients No relevant subgroups reported	**Intervention** Etanercept: dose not stated Duration of treatment not stated **Comparison** No comparator Four patients received one or more of the following: steroids during flares, azathioprine, mycophenolate, cyclophosphamide as induction therapy, and/or IVIG	Median (range) follow-up (months): 56 (36 to 72) **Critical outcomes** • Disease activity/response • Number of patients with complete control of disease[j] after initiation of etanercept

Tanatar et al 2020 Retrospective case series One centre, Turkey	n=5 patients (three families) with DADA2 Etanercept: n=5 Male: 2 (40%) Median (IQR) age at symptom onset (years): 11 (11 to 12) Median (IQR) age at diagnosis (years): 15 (14 to 16) All patients had mild to severe vasculopathy No relevant subgroups reported	**Intervention** Four patients received 25mg subcutaneously per week One patient received 50mg subcutaneously per week One patient had previously received infliximab before the diagnosis of DADA2 with a 'partial response Duration of treatment not stated **Comparison** No comparator One patient received concomitant fresh frozen plasma for six months. No concomitant treatments	Median (IQR) follow-up (months): 8 (6 to 16) **Critical outcomes** • Symptom alleviation • Systemic inflammation before and after initiation of etanercept • Resolution of symptoms after initiation of etanercept **Important outcomes** • Change in acute phase reactants • Number of patients with normal acute phase reactants after initiation of etanercept **Safety** • Number of patients with recurrent infections and requiring IVIG treatment after initiation of etanercept
Study	**Population**	**Intervention and comparison**	**Outcomes reported**
		were described for the remaining patients	

Abbreviations
CNS: central nervous system; CRP: C-reactive protein; DADA2: Deficiency of adenosine deaminase type 2; ESR: erythrocyte sedimentation rate; IQR: interquartile range; IVIG: intravenous immunoglobulin; MRI: magnetic resonance imaging; NSAIDs: nonsteroidal anti-inflammatory drugs; PAN: polyarteritis nodosa; PVAS: Paediatric Vasculitis Activity Score; SAA: serum amyloid A; TNF: Tumour necrosis factor.

a. Defined as the absence of active vasculitis, recovery/stabilisation of disease-related organ damage and absence of systemic inflammation.
b. Current age was reported at the time of the study data collection.
c. The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across 9 organ systems and a score of 0 indicating absent activity. The 'before' score was assessed at first presentation to the centre and the 'after' score at the most recent clinic visit after treatment with etanercept. d. The authors did not provide a definition for SAA, but it has been presumed to be serum amyloid A.
e. It is unclear whether there may be overlap of patients included in Li et al (2023) and Deuitch et al (2022) as some patients from Li et al (2023) had previously been reported in Deuitch et al (2022).
f. There was a discrepancy in the figure reported for age of diagnosis in the supplementary table; reported as 7.1.0, which we have interpreted as being 7.1 years.
g. Defined as persistent control of inflammatory parameters with no disease's flares or complications in the absence of any steroid treatment.
h. Defined as good control of disease activity with sporadic relapses and need of steroid on demand or increased steroid dosage.
i. Response to treatment was considered complete when clinical and laboratory remission could be achieved; partial when clinical or laboratory remission could not be achieved; and absent when neither clinical nor laboratory remission could be achieved. Clinical remission was defined as the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation. Laboratory remission was defined as normalisation of CRP levels in the local laboratory.

5. Results

In patients with deficiency of adenosine deaminase type 2, what is the clinical effectiveness and safety of etanercept compared with standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Number of ischaemic events **Certainty of evidence:** Very low	This is an important outcome to patients as ischaemic events are a detrimental effect of DADA2 and prevention of ischaemic events is an indication of successful treatment. Four retrospective case series provided non-comparative evidence relating to ischaemic events in patients with DADA2 after initiation of etanercept. All four case series reported results compared to baseline[4]. One retrospective case series reported the number of patients with neurological symptoms for the one year followup after initiation of etanercept. Three retrospective case series reported the number of patients with ischaemic events (including stroke) at a median of 20.2 months follow-up after diagnosis of DADA2, after median 74 months, or between two months and >10 years after treatment with etanercept. MRI-confirmed strokes after adequate disease control (not defined) **At follow-up of the whole cohort between two months and >10 years:[4]** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 6 of 7 (85.7%) patients with DADA2 had MRI-confirmed strokes prior to treatment with etanercept. After adequate disease control (not defined) with etanercept, none of the 7 (0%) patients experienced an MRI-confirmed stroke. No statistical measures were reported. **(VERY LOW)** Neurological symptoms **At one-year follow-up:** • One retrospective case series (Kisla Ekinci et al 2022) (n=5) reported that 1 patient with DADA2 had neurological symptoms prior to treatment with etanercept. The same patient was described as *"neurologically symptomfree"* after initiation of etanercept.[5] No further details were provided and no statistical measures were reported. **(VERY LOW)** Stroke/stroke activity **At median 20.2 months follow-up after diagnosis of DADA2:[6]** • One retrospective case series (Li et al 2023) (n=13) reported that *"… no patients have had a stroke during the time they have been on treatment"* . No further details were provided and no statistical measures were reported. **(VERY LOW)** Ischaemic events **After median 74 months follow-up:**

[4] Duration of follow-up of etanercept patients not stated.
[5] No comments relating to ischaemic events after etanercept were made for the remaining four patients.
[6] Follow-up period for full cohort of 30 patients. Follow-up duration for 13 patients receiving etanercept was not available separately.

	• One retrospective case series (Cooray et al 2021) (n=5) reported that 5 of 5 (100%) patients with DADA2 reported experiencing a total of 11 CNS ischaemic events prior to treatment with etanercept. After initiation of

[4] Baseline defined as before the initiation of etanercept. Treatments received before the initiation of etanercept varied widely between studies.

Outcome	**Evidence statement**

	etanercept, none of the 5 patients (0%) had experienced a CNS ischaemic event. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=5) reported that 2 of 5 (40%) patients with DADA2 reported experiencing one non-CNS ischaemic event each prior to treatment with etanercept. After initiation of etanercept, 1 of 5 (20%) patients had experienced a non-CNS ischaemic event[7] (one patient who had events before etanercept). No statistical measures were reported. **(VERY LOW)** **Four retrospective case series provided very low certainty evidence on ischaemic events in patients with DADA2. All four case series reported reductions in the number of patients with DADA2 who experienced ischaemic events (including CNS and non-CNS strokes) after initiation of etanercept, compared to baseline. Follow-up durations varied between one year followup, a median of 20.2 months after diagnosis of DADA2, after median 74 months, or was described for the whole cohort between two months and >10 years. No statistical measures were reported.**

[7] One patient developed digital necrosis resulting in a partial amputation due to poor compliance with etanercept. This patient had both CNS and non-CNS ischaemic events before treatment with etanercept.

Disease activity/response **Certainty of evidence:** Very low	This outcome is important to patients as objective measures of functioning of affected organs. Given the progressive nature of DADA2, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression. Seven retrospective case series provided non-comparative evidence relating to disease activity/response in patients with DADA2 after initiation of etanercept. All seven case series reported results compared to baseline[4]. Disease activity/response was defined differently across the studies, including using the PVAS, or defined as number of patients in clinical remission or having complete control of disease. Follow-up durations varied, including the next 9 months of treatment, at a median of 20.2 months after diagnosis of DADA2, or at median 23 months to after 74 months. **During the next 9 months of etanercept treatment:** • One retrospective case series (Kisla Ekinci et al 2022) (n=5) reported that for 1 patient with DADA2, etanercept resulted in *"complete remission of the disease for the next 9 months"* (not further defined).[8] No further details were provided and no statistical measures were reported. **(VERY LOW)** **At follow-up of the whole cohort between two months and >10 years:[5]** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 1 of 7 (14.3%) patients with DADA2 had anaemia before treatment with etanercept. After initiation of etanercept 1 of 7 (14.3%) patients had anaemia (the same patient with anaemia prior to treatment). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 1 of 7 (14.3%) patients with DADA2 had lymphopenia before treatment with etanercept. After initiation of etanercept 1 of 7 (14.3%) patients had lymphopenia (the same patient with lymphopenia prior to treatment). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 4 of 7 (57.1%) patients with DADA2 had hypogammaglobulinemia before treatment with etanercept. After initiation of etanercept 4 of 7 patients (57.1%) had hypogammaglobulinemia (the same patients with hypogammaglobulinemia prior to treatment). No statistical measures were reported. **(VERY LOW)** **At median 20.2 months follow-up after diagnosis of DADA2:[7]** • One retrospective case series (Li et al 2023) (n=13) reported that before etanercept, no patients were in complete or partial remission. After initiation of etanercept, 12 of 13 (92.3%) patients with DADA2 had complete

Outcome	Evidence statement

[8] No comments relating to disease activity/response after etanercept were made for the remaining four patients.

	remission[9] and 1 of 13 (1.7%) patients with DADA2 had partial remission[10] . No statistical measures were reported. **(VERY LOW)** **At median 23 months follow-up:** • One retrospective case series (Celikel et al 2023) (n=6) reported that 6 of 6 (100%) patients with DADA2 were in clinical remission[11] after initiation of etanercept. The authors stated that *"after the initiation of [etanercept], clinical findings improved and inflammation was suppressed in 6 patients".* No statistical measures were reported. **(VERY LOW)** **At median 3.5 years follow-up:** • One retrospective case series (Kasap Cuceoglu et al 2021) (n=18) reported that 17 of 18 (94.5%) patients with DADA2 were in complete remission (not further defined) after initiation of etanercept. The authors also stated that 3 of 18 (16.7%) patients relapsed during follow-up.[12] No statistical measures were reported. **(VERY LOW)** **At median 56 months follow-up:** • One retrospective case series (Melo et al 2023) (n=9) reported that all 9 patients (100%) with DADA2 had complete control of disease[13] after initiation of etanercept. No statistical measures were reported. **(VERY LOW)** **After median 74 months follow-up:** • One retrospective case series (Cooray et al 2021) (n=5) reported that the median PVAS[14] was 29 (IQR 21 to 30) in patients with DADA2 before treatment. After initiation of etanercept, the PVAS reduced to 1 (IQR 0 to 2), indicating improvement. No statistical measures were reported. **(VERY LOW)** **Seven retrospective case series provided very low certainty evidence on disease activity/response in patients with DADA2. Four retrospective case series reported that between 92.3% and 100% patients with DADA2 were in remission (defined differently across studies) or had complete control of disease after initiation of etanercept at median 20.2 months after diagnosis of DADA2 or between a median of 23 and 56 months follow-up, compared to baseline. One retrospective case series reported that, compared to baseline, patients with DADA2 did not show improvements in anaemia, lymphopenia, and hypogammaglobulinemia at follow-up of the whole cohort between two months and >10 years. One retrospective case series reported improvements in median PVAS after median 74 months follow-up, compared to baseline.**

[9] Defined as persistent control of inflammatory parameters with no disease's flares or complications in the absence of any steroid treatment.
[10] Defined as good control of disease activity with sporadic relapses and need of steroid on demand or increased steroid dosage.
[11] Clinical remission defined as the absence of active vasculitis, recovery/stabilisation of disease-related organ damage and absence of systemic inflammation. Response to treatment was considered complete when clinical and laboratory remission could be achieved; partial when clinical or laboratory remission could not be achieved; and absent when neither clinical nor laboratory remission could be achieved. Clinical remission was defined as the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation. Laboratory remission was defined as normalisation of CRP levels in the local laboratory.
[12] , It was unclear what the sequence of events was as to when patients relapsed, when they were in remission and when the patient died as no further details were reported.
[13] Response to treatment was considered complete when clinical and laboratory remission could be achieved; partial when clinical or laboratory remission could not be achieved; and absent when neither clinical nor laboratory remission could be achieved. Clinical remission was defined as the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation. Laboratory remission was defined as normalisation of CRP levels in the local laboratory.
[14] The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across 9 organ systems and a score of 0 indicating absent activity. The 'before' score was assessed at first presentation to the centre and the 'after' score at the most recent clinic visit after treatment with etanercept.

	Complete control of disease was reported after initiation of etanercept, but disease status before etanercept was not reported, which prevented

Outcome	Evidence statement
	comparisons to be made. No statistical measures were reported for any outcomes.

Symptom alleviation **Certainty of evidence:** Very low	This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. Six retrospective case series provided non-comparative evidence relating to symptom alleviation (defined as resolution of symptoms, symptom alleviation after initiation of etanercept, or patients with individual symptoms such as seizures) in patients with DADA2 after initiation of etanercept. All six case series reported results compared to baseline[4]. Follow-up durations were at 3 months after initiation of etanercept, at one year follow-up, at median between one year, or at follow-up of the whole cohort between two months and >10 years. Systemic inflammation (not defined) **At 3 months after initiation of etanercept:** • One retrospective case series (Tanatar et al 2020) (n=5) reported that 4 of 5 (80%) patients with DADA2 had systemic inflammation before treatment with etanercept, and this resolved in all 4 (100%) patients at three months after treatment with etanercept. No statistical measures were reported. **(VERY LOW)** Resolution of symptoms **At 3 months after initiation of etanercept:** • One retrospective case series (Tanatar et al 2020) (n=5) reported that *"at the 3rd month of etanercept treatment, all the symptoms resolved"* in patients with DADA2. All patients had at least one symptom before treatment. No further details were provided and no statistical measures were reported. (**VERY LOW**) Symptom alleviation **At follow-up of whole cohort between two months and >10 years:[5]** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 5 of 7 (71.4%) patients with DADA2 had cutaneous involvement (except eczema) before treatment with etanercept. After initiation of etanercept none of 7 patients had cutaneous involvement (except eczema). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 1 of 7 (14.3%) patients with DADA2 had eczema before treatment with etanercept. After initiation of etanercept, 3 of 7 (42.8%) patients had eczema including one patient with pre-existing eczema. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 2 of 7 (28.6%) patients with DADA2 had fever before treatment with etanercept. After initiation of etanercept no patients had fever. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 4 of 7 (57.1%) patients with DADA2 had PAN-like rash or other cutaneous vasculitis before treatment with etanercept. After initiation of etanercept no patients had PAN-like rash or other cutaneous vasculitis. No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 2 of 7 (28.6%) patients with DADA2 had arthralgia/arthritis[15] before treatment with etanercept. After initiation of etanercept 1 of 7 patients 14.3%) had

[15] Spelled as 'artritis' in the paper; assumed to be arthritis

Outcome	Evidence statement
	arthralgia/arthritis (one patient with pre-existing arthralgia/arthritis). No statistical measures were reported. **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=7) reported that 3 of 7 (42.9%) patients with DADA2 had aphthous stomatitis before treatment with etanercept. After initiation of etanercept no patients had aphthous stomatitis. No statistical measures were reported. **(VERY LOW)** **At median time on etanercept treatment of one year:** • One retrospective case series (Deuitch et al 2022) (n=9[16]) reported that 2 of 9 (22.2%) patients with DADA2 had mild flare with fever prior to treatment with etanercept. Both patients were reported to be *"clinically well"* after initiation of etanercept. No further details were provided and no statistical measures were reported. **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=9[17]) reported that before treatment with etanercept, 1 of 9 (11.1%) patients with DADA2 had some livedo. After initiation of etanercept, the same patient had minimal livedo and Raynaud's. No further details were provided and no statistical measures were reported. **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=9[17]) reported that after the initiation of etanercept, 1 patient was *"clinically well"* but with some pancytopenia, and 1 patient was *"clinically well"* but some gait disorders remained. Symptoms before starting treatment were not reported for these two patients and no further details were provided. **(VERY LOW)** **At one year after the initiation of etanercept:** • One retrospective case series (Kisla Ekinci et al 2022) (n=5[17]) reported that 2 of 5 patients (40%) had complete resolution of symptoms (skin symptoms in n=2, fever in n=1, inflammatory attacks in n=1) after initiation of etanercept; 2 of 5 patients (40%) had improvement in symptoms (skin symptoms in n=2, musculoskeletal in n=1, constitutional symptoms in n=1); and for 1 of 5 patients (20%) (the patient described as being in complete remission) no comment on symptomatic involvement was made. No statistical measures were reported. **(VERY LOW)** Number of seizures **At median 23 months follow-up:** • One retrospective case series (Celikel et al 2023) (n=6) reported that 2 of 6 (33.3%) patients with DADA2 had seizures before treatment with etanercept. After initiation of etanercept, 1 patient (16.7%) experienced seizures but it was not clear if this patient had experienced seizures before initiation of etanercept. No statistical measures were reported. **(VERY LOW)** **Six retrospective case series provided very low certainty evidence that, compared to baseline, symptoms generally improved or resolved in patients with DADA2 after initiation of etanercept at 3 months after initiation of etanercept, at one year follow-up, at median follow-up between one year and at median 23 months, or follow-up of the whole cohort between two months and >10 years. Details were mainly presented narratively and no statistical measures were reported.**
Important outcomes	

[16] Information on symptoms both before and after commencing treatment with etanercept was available for three patients, and after commencing treatment only for two patients.
[17] No comment on symptomatic involvement was made for one patient. The patient was described as experiencing symptoms before etanercept.

Steroid use reduction **Certainty of evidence:** Very low	This outcome is important to those patients receiving steroids because steroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders.

Outcome	Evidence statement
	Four retrospective case series provided non-comparative evidence relating to steroid use reduction in patients with DADA2 after initiation of etanercept. All four case series reported results compared to baseline[4]. Follow-up durations were between the next 9 or 12 months of etanercept treatment, after median time on etanercept treatment of one year, at median 20.2 months follow-up after diagnosis of DADA2, or after median 74 months. **During the next 9 or 12 months follow-up:** • One retrospective case series (Kisla Ekinci et al 2022) (n=5) reported that treatment with etanercept resulted *"in cessation of systemic steroids and methotrexate"* in one patient.[18] No further details were provided and no statistical measures were reported. **(VERY LOW)** **After median time on etanercept treatment of one year:** • One retrospective case series (Deuitch et al 2022) (n=9[19]) reported that 3 patients who were treated with etanercept were receiving steroids (prednisone, dose not stated) before anti-TNF inhibitor treatment. After initiation of etanercept, all patients discontinued steroids; 1 patient was receiving hydroxychloroquine, anakinra, and IVIG in addition to etanercept. No further details were provided and no statistical measures were reported. **(VERY LOW)** **At median 20.2 months follow-up after diagnosis of DADA2:[7]** • One retrospective case series (Li et al 2023) (n=13) provided information in a table suggesting that 12 of the 13 patients (92.3%) who received etanercept were receiving glucocorticoids (dose not stated) before antiTNF inhibitor treatment. After initiation of etanercept, 5 of the 13 patients (38.5%) were on glucocorticoids; the remaining 7 patients on glucocorticoids before initiation of etanercept discontinued glucocorticoid treatment. The authors note that the glucocorticoids had *"little effect"* on DADA2 symptoms. No statistical measures were reported. **(VERY LOW)** **After median 74 months follow-up:** • One retrospective case series (Cooray et al 2021) (n=5) reported that 4 of 5 (80%) patients received steroids prior to treatment with etanercept and 1 of 5 (20%) patients continued to receive steroids after initiation of etanercept. No statistical measures were reported. **(VERY LOW)** **Four retrospective case series provided very low certainty evidence that steroid use was discontinued in all or nearly all patients with DADA2 after initiation of etanercept compared to baseline, with one case series suggesting that glucocorticoids had *"little effect"* on DADA2 symptoms. Follow-up durations were between the next 9 or 12 months of etanercept treatment, after median time on etanercept treatment of one year, at median 20.2 months follow-up after diagnosis of DADA2, or after median 74 months follow-up. Details were limited and not always reported for all patients, and no statistical measures were reported.**

[18] No comments relating to steroid use reduction after etanercept were made for the remaining four patients.

[19] Information on treatment both before and after commencing treatment with etanercept was available for four patients.

Quality of life **Certainty of evidence:** Not applicable	This is an important outcome for patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Disease specific quality of life measures are also useful for this purpose. **No evidence was identified for this outcome.**
Hospitalisation **Certainty of evidence:**	This outcome is important for patients as it may represent either disease progression or treatment toxicity. It may have a bearing on the patient's quality of life ad inform their treatment decision making.

Outcome	**Evidence statement**
Not applicable	**No evidence was identified for this outcome.**

Change in acute phase reactants **Certainty of evidence:** Very low	This outcome is important to patients as normalisation of acute phase reactants is associated with a reduction in symptoms and improved quality of life for patients. This is particularly important in children as normalisation of acute phase reactants in linked to improvements in growth. Four retrospective case series provided non-comparative evidence relating to change in acute phase reactants (i.e. normal APR, CRP, ESR, SAA) in patients with DADA2 after treatment with etanercept. All four case series reported results compared to baseline[4]. Follow-up durations were at 3 months, after median time on etanercept of one year, at median 20.2 months after diagnosis of DADA2 and after median 74 months. Normal APRs (not defined) **At 3 months follow-up:** • One retrospective case series (Tanatar et al 2020) (n=5) reported that *"at the 3rd month of etanercept treatment,… APRs were normal"*. No further details were provided and statistical measures were not reported. (**VERY LOW**) Change in CRP levels **After median time on etanercept of one year:** • One retrospective case series (Deuitch et al 2022) (n=9[20]) reported an improvement in CRP levels[21] in patients with DADA2 after initiation of etanercept, reflected in the reduction in median CRP levels from 50.3 mg/L (IQR 33.5 to 56.4; n=4 patients) to 0.35 mg/L (IQR 0.2 to 0.4; n=7 patients). No statistical measures were reported. **(VERY LOW)** **At median 20.2 months follow-up after diagnosis of DADA2:[7]** • One retrospective case series (Li et al 2023) (n=13) reported that 12 of 13 (92.3%) patients with DADA2 had elevated CRP levels at presentation, all were within the normal reference range after initiation of etanercept. Improvements were also reflected in the reduction in median CRP levels from 33.4 mg/L (IQR 18 to 60) to 5.7 mg/L (IQR 4.9 to 6.5) at. No statistical measures were reported. **(VERY LOW)** **After median 74 months follow-up:** • One retrospective case series (Cooray et al 2021) (n=5) reported that 4 of 5 patients with DADA2 in whom data were available before etanercept had elevated CRP levels[22]. After initiation of etanercept, data were available for all 5 patients which indicated that CRP levels improved and 4 patients were within normal reference range. Improvements were reflected in the reduction in median CRP levels from baseline: 65 mg/L (IQR 45.5 to 95) to 3 mg/L (IQR 1.8 to 4.5).[23] No statistical measures were reported. **(VERY LOW)** Change in ESR levels **At median 20.2 months follow-up after diagnosis of DADA2:[7]** • One retrospective case series (Li et al 2023) (n=13) reported that 9 of 13 (69.2%) patients with DADA2 had elevated ESR levels before treatment with etanercept, all were within the normal reference range after initiation of etanercept. Improvements were also reflected in the reduction in ESR levels

Outcome	**Evidence statement**

[20] CRP levels were not available in five patients before etanercept or in two patients after initiation of etanercept.
[21] Normal CRP levels were defined as 0.00 to 4.99 mg/L.
[22] Elevated CRP levels were not further defined, but laboratory ranges were reported to vary at each centre.
[23] Data were only available in four patients before treatment with etanercept, but were available for all five patients after treatment.

	from baseline of 38.5 mm/hr (IQR 19 to 51) to 10 mm/hr (IQR 8 to 13). No statistical measures were reported. **(VERY LOW)** **After median 74 months follow-up:** • One retrospective case series (Cooray et al 2021) (n=3) reported that 3 of 5 patients with DADA2 in whom data were available before etanercept had elevated ESR levels.[24] After initiation of etanercept, data were available for 2 patients which indicated that ESR levels improved and 1 patient was within normal reference range. Improvements in ESR levels in patients with DADA2 after initiation of etanercept were reflected in the reduction in median ESR levels from baseline: 100 mm/hr (IQR 60 to 103.5) to 6 mm/hr (IQR 4.5 to 7.5) at follow-up. No statistical measures were reported. **(VERY LOW)** Change in SAA levels[26] **After median 74 months follow-up:** • One retrospective case series (Cooray et al 2021) (n=3) reported SAA levels in 3 patients with DADA2 after initiation of etanercept: median 10.1 mg/L (IQR 8.6 to 11.3). These values were indicated to be within the normal range although normal ranges were not specified. SAA levels at baseline were not assessed or were missing and no statistical measures were reported. **(VERY LOW)** **Four retrospective case series provided very low certainty evidence relating to acute phase reactants in patients with DAD2 after treatment with etanercept compared to baseline. Four retrospective case series reported that median CRP and ESR levels improved in patients with DADA2 after initiation of etanercept, but where normal ranges were reported, these differed within and/or across studies. One of these case series reported SAA levels in patients with DADA2 but only after initiation of etanercept (SAA levels were not available at baseline). Follow-up durations were at 3 months, after median time on etanercept of one year, at median 20.2 months after diagnosis of DADA2 and after median 74 months follow-up.**
Safety	

[24] Elevated ESR levels were not further defined, but laboratory ranges were reported to vary at each centre.
[26] The authors did not provide a definition for SAA, but it has been presumed to be serum amyloid A.

Safety outcomes **Certainty of evidence:** Very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. Four retrospective case series provided non-comparative evidence relating to safety in patients with DADA2 after initiation of etanercept. All four case series reported results compared to baseline[4]. Follow-up durations were at 3 months after starting etanercept, at median 3.5 years to after 74 months, or at median time on etanercept treatment of one year. Safety **At 3 months after starting etanercept:** • One retrospective case series (Tanatar et al 2020) (n=5) reported that *"none of the patients suffered from recurrent infections and required intravenous immunoglobulin (IVIG) treatment"*. No further details were provided and statistical measures were not reported. (**VERY LOW**) Adverse events **After median 74 months follow-up:**

Outcome	Evidence statement
	• One retrospective case series (Cooray et al 2021) (n=5) reported that no adverse reactions were reported in patients with DADA2 after initiation of etanercept. **(VERY LOW)** Number of deaths **At median time on etanercept treatment of one year:** • One retrospective case series (Deuitch et al 2022) (n=9[25]) reported that 1 patient died after commencing treatment with etanercept due to complications of liver disease. No further details were provided. **(VERY LOW)** **At median 3.5 years follow-up:** • One retrospective case series (Kasap Cuceoglu et al 2021) (n=18) reported that 1 patient died due to pulmonary haemorrhage.[26] No statistical measures were reported. **(VERY LOW)** **Four retrospective case series provided very low certainty evidence on safety. Two retrospective case series reported that there were no adverse events observed in patients with DADA2 after initiation of etanercept compared to baseline, but details were limited and narratively described. Two retrospective case series each reported one death in a patient with DADA2 after initiation of etanercept but neither appeared to be directly related to etanercept treatment. Follow-up durations were at 3 months after starting etanercept, at median 3.5 years to after 74 months, or at median time on etanercept treatment of one year.**

[25] Information on symptoms both before and after commencing treatment with etanercept was available for three patients, and after commencing treatment only for two patients.
[26] , It was unclear what the sequence of events was as to when patients relapsed, when they were in remission and when the patient died as no further details were reported.

Abbreviations
ADA2: adenosine deaminase type 2 gene; APR: acute phase reactants; CNS: central nervous system; CRP: C-reactive protein; DADA2: Deficiency of adenosine deaminase type 2; ESR: erythrocyte sedimentation rate; IQR: interquartile range; IVIG: intravenous immunoglobulin; mg/L: milligram**s** per litre; mm/hr: millimetre per hour; MRI: magnetic resonance imaging; PAN: polyarteritis nodosa; PVAS: Paediatric Vasculitis Activity Score; SAA: serum amyloid A; TNF: Tumour necrosis factor.

In patients with deficiency of adenosine deaminase type 2, what is the cost effectiveness of etanercept compared with standard care?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of patients that may benefit from etanercept more than the wider population of interest?

Outcome	Evidence statement
Subgroups	**No evidence was identified regarding any subgroups of patients that may benefit from etanercept more than the wider population of interest.**

From the evidence selected, what dose of etanercept was used?

Outcome	Evidence statement

Dose of etanercept	Evidence about dose of etanercept, which is delivered via subcutaneous injection and allows patients to self-administer at home, was reported in two retrospective case series. • One retrospective case series (Cooray et al 2021) (n=5) reported etanercept doses of: 400 µg/kg twice weekly, or 800 µg/kg weekly, or 25 mg twice weekly or 50 mg weekly if >12 years old. The number of patients receiving each dose was not stated. Other treatments received after etanercept treatment included glucocorticoid and aspirin (one patient) and azathioprine (one patient). Three patients did not receive any other treatments after initiation of etanercept. • One retrospective case series (Tanatar et al 2020) (n=5) reported that four patients received 25 mg subcutaneously per week and one patient received 50 mg subcutaneously per week. One patient received concomitant fresh frozen plasma for six months. No concomitant treatments were described for the remaining patients. Etanercept doses were not reported in the seven remaining retrospective case series (Andriessen et al 2023, Celikel et al 2023, Deuitch et al 2022, Kasap Cuceoglu et al 2021, Kisla Ekinci et al 2022, Li et al 2023, Melo et al 2023). **Two retrospective case series reported that patients with DADA2 were provided with varying doses of etanercept, ranging from 400µg/kg twice weekly to 50 mg weekly. Seven retrospective case series did not report the dose of etanercept used in the studies.**
Abbreviations DADA2: Deficiency of adenosine deaminase type 2; kg: kilogram; mg: milligram; µg: microgram.	

6. Discussion

This evidence review examines the clinical effectiveness, safety and cost effectiveness of etanercept compared to standard care for the treatment of deficiency of adenosine deaminase type 2 (DADA2). The critical outcomes of interest were number of ischaemic events, disease activity/response and symptom alleviation. Important outcomes were steroid use reduction, quality of life, hospitalisation, change in acute phase reactants and safety. Evidence on cost effectiveness was also sought.

No studies were identified that provided comparative evidence on any critical or important outcomes. Evidence for the clinical effectiveness and safety of etanercept was available from nine retrospective case series (Andriessen et al 2023, Celikel et al 2023, Cooray et al 2021, Deuitch et al 2022, Kasap Cuceoglu et al 2021, Kisla Ekinci et al 2022, Li et al 2023, Melo et al 2023, Tanatar et al 2020). Andriessen et al (2023) and Li et al (2023) were retrospective cohort studies, but were treated as case series as only a proportion of patients in each paper were in scope (24.14% and 43.33%, respectively) and relevant data were mainly described on an individual basis. One paper was a systematic review (Kasap Cuceoglu et al 2021) but was also treated as a retrospective case series as only data relating to patients with DADA2 who were treated with etanercept were extracted. It is unclear whether there may be overlap of patients included in Li et al (2023) and Deuitch et al (2022) as Li et al (2023) reported that twelve patients in their cohort had previously been reported in the literature, including in Deuitch et al (2022). No comparator studies were identified that compared etanercept with standard care, all outcomes presented were extracted from small, retrospective case series and the results reported were compared to baseline. No evidence was identified for the important outcomes of quality of life (QoL) or hospitalisation, and no cost effectiveness studies were identified. None of the identified studies reported on relevant subgroups of patients that would benefit more from treatment

with adalimumab. No information about what the minimal clinically important thresholds or differences might be was reported for the outcomes considered.

All nine retrospective case series provided non-comparative evidence and sample sizes ranged from five to 18 patients with DADA2. The studies were conducted in Brazil (Melo et al 2023), China (Li et al 2023), The Netherlands (Andriessen et al 2023), Turkey (Celikel et al 2023, Kasap Cuceoglu et al 2021, Kisla Ekinci et al 2022, Tanatar et al 2020), the UK (Cooray et al 2021), the USA (Deuitch et al 2022). Between them, the nine included studies reported outcomes on a total of 77 patients with DADA2, but there may have been some overlap in the populations included in Li et al (2023) and Deuitch et al (2022), which means that the actual total number of included patients may have been less than this.

Demographic details were limited in the included studies. Where reported, the number of males ranged from 33.3% to 100%, and the age of symptom/disease onset was during childhood (between four and 11 years). Where clinical information was provided, populations varied within and across studies in terms of the proportion of patients presenting with different phenotypes (vasculopathy, immunodeficiency and hematologic manifestations) and symptoms (e.g. cutaneous involvement, fever, stroke). One study included both in scope and out of scope populations (Kasap Cuceoglu et al 2021), and five studies included both in scope and out of scope interventions (Andriessen et al 2023, Cooray et al 2021, Deuitch et al 2022, Li et al 2023, Melo et al 2023); only data on patients with DADA2 who were treated with etanercept were extracted. The follow-up durations or treatment durations at which outcomes were reported varied across studies, including at three months after starting etanercept, at median time on treatment of one year, during the next nine or 12 months of etanercept treatment, at median 20.2 months after diagnosis of DADA2, after median 74 months, or at follow-up of the whole cohort between two months to greater than 10 years. As treatment was ongoing, this review has reported outcomes by treatment duration where studies did not report length of follow-up. The duration of treatment or follow-up of patients on etanercept was not always stated, with timepoints sometimes representing all treated patients.

Only two case series reported what dose of etanercept was used, either calculated according to body weight or as a standard dose.

Where reported, concomitant treatments varied across and within the studies. Patients in one retrospective case series were reported as receiving current tumour necrosis factor (TNF) inhibitor (Andriessen et al 2023), but the narrative suggested that some patients may have also previously received another TNF inhibitor. It was therefore unclear whether the outcomes reported were specifically for treatment with etanercept and this study was downgraded due to indirectness. Concomitant non-TNF inhibitor treatments reported in some patients in the studies included azathioprine, intravenous immunoglobulin (IVIG) replacement, clonazepammira, hydroxychloroquine, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, methotrexate, thalidomide, cyclophosphamide, mycophenolate mofetil (MMF) and frozen fresh plasma.

Where reported, treatments received prior to etanercept (and in some cases prior to the diagnosis of DADA2) also varied across and within the studies and included corticosteroids, cyclophosphamide, azathioprine, MMF, methotrexate, colchicine, thalidomide, tocilizumab, IVIG, hydroxychloroquine, and cyclosporine.

Considerable potential overlap was found between the definitions of the critical outcomes ‘Disease activity/response’ and ‘Symptom alleviation’ and it was agreed that composite

measures such as the Paediatric Vasculitis Activity Score (PVAS) and any conditions measured objectively (i.e., anaemia using blood tests) would be reported as 'Disease activity/response'. Any change in individual clinical symptoms, such as fever or rash, would be reported as 'Symptom alleviation'.

The nine retrospective case series reported outcomes for patients with DADA2 who received etanercept for the critical outcomes of ischaemic events, disease activity/response and symptom alleviation, and the important outcomes of steroid use reduction and change in acute phase reactants. Many of the composite measures of 'Disease activity/response' were poorly defined in the papers, reported as, for example, *"complete response"* or *"clinically well"* with no further details provided. One retrospective case series (Li et al 2023) defined *"complete remission"* as "*persistent control of inflammatory parameters with no disease flares or complications in the absence of any steroid treatment*"; but no further details were provided. The lack of clear parameters and differences in the variables used to compile these composite measures make direct comparison difficult. For the critical outcome of 'Number of ischaemic events' much of the data provided was narrative with little or no information provided regarding diagnosis clinically or through imaging. Other variables, particularly steroid use reduction and safety, were also only reported as narrative description. One study (Cooray et al 2021) reported one outcome measure as 'SAA' which was not defined but was assumed to represent serum amyloid A.

The certainty in the outcomes reported was very low for all nine retrospective case series due to very serious risk of bias and very serious indirectness because of the lack of a relevant treatment comparison. There are a number of factors that reduced confidence in the outcomes, including the lack of detail about the study populations, for example, limited details about baseline demographics and characteristics. Incomplete follow-up and missing data for included patients was a particular limitation of the case series and it was unclear whether the recruitment of study participants was consecutive (with the exception of Deuitch et al 2022) or complete. Other limitations include the small sample sizes, which may reflect the rarity of the condition or difficulties in early diagnosis. Melo et al (2023) highlighted the lack of diagnostic criteria for DADA2 alongside the limited access to functional assays and genetic sequencing in middle income countries which may also account for the low numbers of patients.

The main focus of most of the included studies was the clinical, genetic and laboratory findings of DADA2 patients with various pathogenic variants in the *ADA2* gene rather than the clinical effectiveness and safety of etanercept. As such, outcome data were often limited, presented individually for patients in a table, or reported narratively. Furthermore, none of the included studies performed statistical analysis to aid interpretation of the findings. No patients or clinicians were blinded in any of the studies, which could increase uncertainty around the more subjective outcomes such as the assessment of symptoms and clinical signs. Given the limitations of the evidence and the lack of comparative data (the included retrospective case series reported results compared to baseline), it is difficult draw any conclusions about the clinical effectiveness and safety of etanercept in people with DADA2 compared with standard care.

7. Conclusion

This review included non-comparative evidence from nine retrospective case series assessing patients with DADA2 who received etanercept, which is delivered via subcutaneous injection and allows patients to self-administer at home. No comparator studies were identified that compared etanercept with standard care, all outcomes presented were extracted from small, retrospective, case series and results were reported compared to baseline. The nine case series provide very low certainty evidence relating to the critical and important outcomes of number of ischaemic events, disease activity/response and symptom alleviation, steroid use reduction, and change in acute phase reactants. Outcomes were mainly descriptive with no statistical measures reported. The case series reported reductions in ischaemic events and acute phase reactants in patients with DADA2 who were treated with etanercept. Narrative descriptions of symptom alleviation suggested improvements in symptoms, and reductions in steroid use were also reported. In terms of disease activity/response, the findings were mixed, with some studies reporting improvements in disease activity and other studies reporting no improvement. Where reported, etanercept appeared to be well tolerated in patients with DADA2. Two studies each reported one death of a patient on etanercept, but neither appeared to be directly related to etanercept treatment. No evidence was identified for the important outcomes of quality of life (QoL) or hospitalisation. There was no evidence on cost effectiveness or on any subgroups of patients who may benefit more than others from treatment with etanercept.

Limitations reducing the certainty in the outcomes included the lack of detail about the study populations, incomplete follow-up and missing data for included patients, and uncertainty about whether the recruitment of study participants was consecutive and complete. Although all the studies provided very low certainty evidence of the outcomes, there was congruence in the results reported. The studies identified in this review provide evidence that treatment with etanercept may reduce ischaemic events and improve disease activity and symptoms in patients with DADA2. However, the limitations of the studies, the descriptive nature of the outcomes and lack of comparative data limit (the included retrospective case series reported results compared to baseline) the potential to draw any conclusions about the effectiveness of etanercept compared with standard care.

Appendix A PICO Document

The review questions for this evidence review are:

1. In patients with deficiency of adenosine deaminase type 2, what is the clinical effectiveness of etanercept compared with standard care?
2. In patients with deficiency of adenosine deaminase type 2, what is the safety of etanercept compared with standard care?
3. In patients with deficiency of adenosine deaminase type 2, what is the cost effectiveness of etanercept compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from etanercept more than the wider population of interest?
5. From the evidence selected, what dose of etanercept was used?

P-Population and Indication	All patients with a confirmed diagnosis of deficiency of adenosine deaminase type 2 (DADA2) or where there is a strong clinical suspicion of DADA2 and genetic testing results are awaited. [This may also be referred to in the literature as: • ADA2 deficiency • Sneddon syndrome • Polyarteritis nodosa • Early onset lacunar stroke • Monogenic vasculitis]
I-Intervention	Etanercept monotherapy [Etanercept may be given alongside immunoglobulin (Ig) replacement therapy and/or supportive care.] [Supportive care can include but is not limited to antibiotics, antivirals, corticosteroids, antipyretics, analgesics or synthetic DMARDs for anti-drug antibodies e.g., methotrexate.] [Biosimilars should be included]
C-Comparator	Standard care [Standard care is best supportive care alone or could also be best supportive care with another TNF inhibitor (such as adalimumab, infliximab, certolizumab, golimumab) +/- Ig replacement therapy.] [Haematopoietic stem cell transplantation is not a valid comparator as patients not all patients eligible for TNF inhibitors would be eligible for HSCT.]
O-Outcomes	**Clinical Effectiveness** Minimally clinically important differences (MCIDs) are not known unless stated. Outcomes reported at 12 months are of particular clinical interest. Outcomes should be sustained for at least six months. *Critical to decision-making:* • **Number of ischaemic events**

	This is an important outcome to patients as ischaemic events are a detrimental effect of DADA2 and prevention of ischaemic events is an indication of successful treatment. [Ischaemic events can be diagnosed based on clinical features together with brain magnetic resonance imaging/angiography (MRI/MRA); and/or other imaging modalities such as ultrasound scan, computed tomography (CT)-angiography, or selective visceral catheter arteriography. Ischaemic events can be categorised as either CNS (stroke) or non-CNS (arteries supplying viscera and peripheries).] • **Disease activity/ response** *This outcome is important to patients as objective measures of functioning of affected organs. Given the progressive nature of DADA2, disease activity results might not be expected to return to normal following treatment, however, stabilisation may indicate treatment has successfully limited disease progression.* [Disease activity or response may be measured by but not limited to, symptoms such as livedoid rash, fever, joint pain, peripheral vascular disease, cutaneous ulceration and neurological features. Scoring systems such as the paediatric vasculitis activity score (PVAS) may also be used to assess vasculitic activity or the Birmingham vasculitis activity score (BVAS).] • **Symptom alleviation** *This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.* [Other terms used to describe or indicate symptom alleviation include but are not limited to symptoms, symptomatic response, alleviating disease symptoms. Symptom alleviation seen before six months may be significant to patients.] *Important to decision-making:* • **Steroid use reduction** *This outcome is important to those patients receiving steroids because steroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders.* • **Quality of life** *This is an important outcome for patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Disease specific quality of life measures are also useful for this purpose.*

	[Examples of quality-of-life tools include but are not limited to QLQ-OV28, QLQ-C30, EQ-5D and SF-36.] • **Hospitalisation** *This outcome is important to patients as it may represent either disease progression or treatment toxicity. It may have a bearing on the patient's quality of life and inform their treatment decision making.* [This is all cause hospitalisation.] • **Change in acute phase reactants** *This outcome is important to patients as normalisation of acute phase reactants is associated with a reduction in symptoms and improved quality of life for patients. This is particularly important in children as normalisation of acute phase reactants is linked to improvements in growth.* [Acute phase reactants include, but are not limited to CRP and ESR] **Safety** *These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.* [Infection control would be of particular interest in this patient group.] **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library and the TRIP database were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2013 to 3 October 2023.

One search was performed to identify studies on the use of TNF inhibitors for DADA2. After consideration of the evidence available, NHS England commissioned evidence reviews on the TNF inhibitors etanercept and adalimumab.

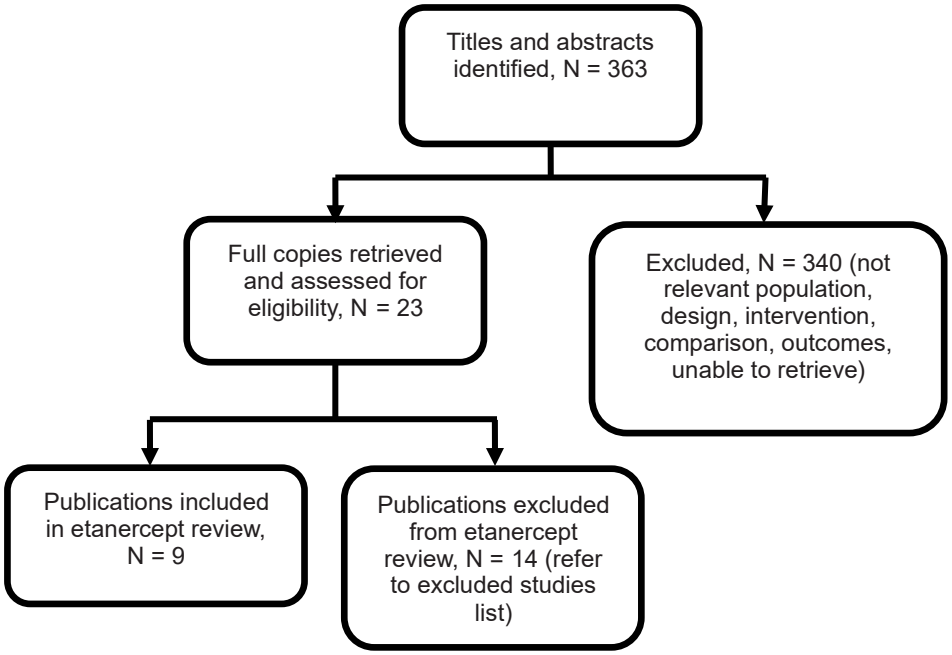
Medline search strategy:

1	Adenosine Deaminase/df [Deficiency] 2
	adenosine deaminase*.ti,kf. and deficien*.mp.
3	(dada-2 or dada2 or ada-2 or ada2).ti,kf.
4	(Deficien* adj3 (adenosine deaminase 2 or adenosine deaminase2 or "ada 2" or ada2)).ab.
5	Sneddon Syndrome/
6	Polyarteritis Nodosa/
7	Stroke, Lacunar/
8	Adenosine Deaminase/ and Vasculitis/
9	(Sneddon syndrome or Polyarteritis nodosa or lacunar stroke or ((Monogenic or adenosine deaminase) adj5 vasculitis)).ti,ab,kf.
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	Tumor Necrosis Factor-alpha/ai [Antagonists & Inhibitors]
12	tumor necrosis factor inhibitors/ or adalimumab/ or certolizumab pegol/ or infliximab/ or Etanercept/
13	Antibodies, Monoclonal/
14	(antitnf or anti-tnf or anti-tumo?r necrosis factor? or ((tnf or tumo?r necrosis factor?) adj3 (inhibitor? or antagonist? or blocker?))).ti,ab,kf.
15	(etanercept or enbrel or adalimumab or humira or infliximab or remicade or remicade or remisma or certolizumab or cimzia or golimumab or simponi).ti,ab,kf.
16	11 or 12 or 13 or 14 or 15
17	10 and 16
18	exp animals/ not humans/
19	17 not 18
20	limit 19 to (english language and yr="2013 -Current")

Appendix C Evidence selection

The literature search identified 363 potential references. These were screened using their titles and abstracts and 23 references potentially relating to the use of TNF inhibitors for DADA2 were obtained and assessed for relevance. Of these, nine references contained outcomes that could be extracted for etanercept and are included in this evidence review. Six references were included in the evidence review on adalimumab for DADA2. The 14 references excluded from this evidence review on etanercept are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Ombrello AK, Qin J, Hoffmann PM, Kumar P, Stone D, Jones A, et al. Treatment Strategies for Deficiency of Adenosine Deaminase 2. New England Journal of Medicine. 2019;380(16):1582-4.	Excluded due to out of scope publication type (i.e. letter describing case series)
Cooray S, Omyinmi E, Hong Y, Papadopoulou C, Harper L, Al-Abadi E, et al. Anti-tumour necrosis factor treatment for the prevention of ischaemic events in patients with deficiency of adenosine deaminase 2 (DADA2). Rheumatology. 2021;60(9):4373-8.	Included in this review on etanercept for DADA2
Li GM, Han X, Wu Y, Wang W, Tang HX, Lu MP, et al. A Cohort Study on Deficiency of ADA2 from China. Journal of Clinical Immunology. 2023;43(4):835-45.	Included in this review on etanercept for DADA2

Appendix D Excluded studies table

Study reference	Reason for exclusion
Alabbas F, Alanzi T, Alrasheed A, Essa M, Elyamany G, Asiri A, et al. Genotype and Phenotype of Adenosine Deaminase 2 Deficiency: a Report from Saudi Arabia. Journal of Clinical Immunology. 2023;43(2):338-49.	No PICO defined outcomes (Appendix A).

Barron KS, Aksentijevich I, Deuitch NT, Stone DL, Hoffmann P, Videgar-Laird R, et al. The Spectrum of the Deficiency of Adenosine Deaminase 2: An Observational Analysis of a 60 Patient Cohort. Frontiers in Immunology. 2021;12:811473.	No PICO defined outcomes. No results for patients treated with etanercept, only pooled anti-TNF outcomes.
Conticini E, Sota J, Falsetti P, Lamberti A, Miracco C, Guarnieri A, et al. Biologic drugs in the treatment of polyarteritis nodosa and deficit of adenosine deaminase 2: A narrative review. Autoimmunity Reviews. 2021;20(4):102784.	Narrative review. Out of scope as described by PICO (Appendix A).
Do N, Ringold S, Brandling-Bennett H. Cutaneous polyarteritis nodosa in pediatric patients successfully treated with TNF-alpha inhibitor and methotrexate: Case series and literature review. Pediatric Dermatology. 2019;36(6):932-5.	Incorrect population, patients did not have confirmed DADA2.
Ginsberg S, Rosner I, Slobodin G, Rozenbaum M, Kaly L, Jiries N, et al. Infliximab for the treatment of refractory polyarteritis nodosa. Clinical Rheumatology. 2019;38(10):2825-33.	Incorrect intervention. Patients treated with infliximab not etanercept.
Hadjadj J, Canzian A, Karadag O, Contis A, Maurier F, Sanges S, et al. Use of biologics to treat relapsing and/or refractory polyarteritis nodosa: data from a European collaborative study. Rheumatology. 2022;62(1):341-6.	Incorrect population, patients with DADA2 were excluded.
Nihira H, Izawa K, Ito M, Umebayashi H, Okano T, Kajikawa S, et al. Detailed analysis of Japanese patients with adenosine deaminase 2 deficiency reveals characteristic elevation of type II interferon signature and STAT1 hyperactivation. Journal of Allergy & Clinical Immunology. 2021;148(2):550-62.	Incorrect intervention: patients treated with adalimumab not etanercept.
Ombrello AK, Qin J, Hoffmann PM, Kumar P, Stone D, Jones A, et al. Treatment Strategies for Deficiency of Adenosine Deaminase 2. New England Journal of Medicine. 2019;380(16):1582-4.	Incorrect publication type: letter describing case series.
Sahin S, Adrovic A, Barut K, Ugurlu S, Turanli ET, Ozdogan H, Kasapcopur O. Clinical, imaging and genotypical features of three deceased and five surviving cases with ADA2 deficiency. Rheumatology International. 2018;38(1):129-36.	No PICO defined outcomes, only survival reported.
Samson M, Puéchal X, Devilliers H, Ribi C, Cohen P, Bienvenu B, et al. Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors. Autoimmunity reviews. 2014;13(9):945?53.	Incorrect population, patients did not have confirmed DADA2.
Sharma A, Naidu G, Sharma V, Jha S, Dhooria A, Dhir V, et al. Deficiency of Adenosine Deaminase 2 in Adults and Children: Experience From India. Arthritis & Rheumatology. 2021;73(2):276-85.	No PICO defined outcomes. No results for patients treated with etanercept, only pooled anti-TNF outcomes.
Verschoof MA, van Meenen LCC, Andriessen MVE, Brinkman DMC, Kamphuis S, Kuijpers TW, et al. Neurological phenotype of adenosine deaminase 2 deficient patients: a cohort study. European Journal of Neurology. 2023;16:16.	No PICO defined outcomes. No results for patients treated with etanercept, only pooled anti-TNF outcomes.
Study reference	**Reason for exclusion**
Wang W, Zhang T, Zheng W, Zhong L, Wang L, Li J, et al. Diagnosis and management of adenosine deaminase 2 deficiency children: the experience from China. Pediatric Rheumatology Online Journal. 2021;19(1):44.	Case report. Out of scope as described by PICO (Appendix A).

Zhang B, Xu N, Chen J, Zhang S, Huang X, Shen M, Zeng X. Treatment and Outcome in Deficiency of Adenosine Deaminase 2: A Literature Review. Journal of Investigational Allergology & Clinical Immunology. 2021;32(1):13-22.	No PICO defined outcomes. No results for patients treated with etanercept only pooled anti-TNF outcomes.

Appendix E Evidence Table

For abbreviations see list after table. For the JBI checklist for case series see Appendix F.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Andriessen MVE, Legger GE, Bredius RGM, van Gijn ME, Hak AE, Muller P, et al. Clinical Symptoms, Laboratory Parameters and LongTerm Follow-up in a National DADA2 Cohort. Journal of Clinical Immunology. 2023;43(7):1581-96. **Study location** Seven university hospitals in the Netherlands **Study type** Retrospective cohort study **Study aim** To assess the clinical, laboratory and genetic characteristics of Dutch patients with DADA2 and to report on response to TNF inhibitor for patients with different phenotypes and the relation between	Patients with DADA2 (biallelic pathogenic variants in the ADA2 gene) **Inclusion criteria** Patients with a diagnosis of DADA2 followed up in seven university hospitals in the Netherlands or identified through the Dutch national immunodeficiency database. Patients were diagnosed by ADA2 gene sequencing and ADA2 enzyme activity **Exclusion criteria** None stated **Total sample size** N=29 (from 23 families); n=7 patients receiving etanercept **Baseline characteristics** (n=7 receiving etanercept) Male: 4 (57.14%) Median (IQR) age at study inclusion (years): 19 (14 to 31)	**Intervention** Etanercept: dose not stated Duration of treatment not stated **Comparison** No comparator **Concomitant treatments** Two patients received concomitant treatment of nanogam or cuvitru	Follow-up of the whole cohort between two months and >10 years; duration of follow-up of patients receiving etanercept not stated. Outcomes after the initiation of etanercept were presented in a table for individual patients. **Critical outcomes** **Number of ischaemic events** (n=7) *MRI-confirmed stroke after adequate*	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. Yes 4. Unclear 5. No 6. No 7. Yes 8. Yes 9. No 10. N/A **Other comments**: This study collected data retrospectively from the immunology departments at seven Dutch university hospitals and by searching the Eurofever Registry and Dutch national immunodeficiency database. The paper presents data for each patient and has therefore been treated as a case series.

ADA2 residual activity and phenotype			*disease control,*[27] *n/total (%)* • Before etanercept: 6/7 (85.7) • After initiation of etanercept: 0/7 (0) **Disease activity/response** (n=7) *Anaemia, n/total (%)* • Before etanercept: 1/7 (14.3) • After initiation of etanercept: 1/7 (14.3) (the same patient) *Lymphopenia, n/total (%)* • Before etanercept: 1/7 (14.3) • After initiation of etanercept: 1/7 (14.3) (the same patient)	The focus of the paper concerns the clinical

Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

[27] No definition provided for adequate disease control.

Study dates Not stated	Median (IQR) age at disease onset (years): 5.0 (4 to 7.59) Symptoms: • Cutaneous involvement: 4 (57.14%) • Fever: 2 (28.6%) • Stroke: 6 (85.71%) • PAN-like rash or other cutaneous vasculitis: 5 (71.43%) • Systemic vasculitis: 0 (0%) • Recurrent infections: 3 (42.86%) • Arthralgia/arthritis: 5 (71.43%) • IBD-like symptoms: 0 (0%) • Aphthous stomatitis: 3 (42.86%) • (Hepato)splenomegaly: 4 (57.14%) • Malignancy (all types, including basal cell carcinoma): 1 (14.29%)		*Hypogammaglobulinemia, n/total (%)* • Before etanercept: 4/7 (57.1) • After initiation of etanercept: 4/7 (57.1) (the same patients) **Symptom alleviation** (n=7) *Cutaneous involvement (except eczema), n/total (%)* • Before etanercept: 5/7 (71.4) • After initiation of etanercept: 0/7 (0) *Eczema, n/total (%)* • Before etanercept: 1/7 (14.3) • After initiation of etanercept: 3/7 (42.8) (including one patient with preexisting eczema) *Fever, n/total (%)* • Before etanercept: 2/7 (28.6) • After initiation of etanercept: 0/7 (0) *PAN-like rash/ other cutaneous vasculitis, n/total (%)* • Before etanercept: 4/7 (57.1) • After initiation of etanercept: 0/7 (0) *Arthralgia/arthritis[28], n/total (%)* • Before etanercept: 2/7 (28.6) • After initiation of etanercept: 1/7 (14.3) (one patient with pre-existing arthralgia/arthritis)	presentation of patients and diagnosis of DADA2. It was unclear whether patients were recruited consecutively and whether all patients treated at the seven university hospitals in the same time period were included. Three out of 32 known DADA2 patients did not give informed consent to be included in the study, but it was unclear whether these patients were receiving etanercept. The authors reported that the study *"provides an in-depth overview of almost all known DADA2 patients in the Netherlands."* Limited data were provided on patient demographics, but clear clinical information was presented. Patients included in the study received different treatments, with seven of 29 patients receiving etanercept at the time of the study. Percentages were not reported in the paper but have been calculated for the outcomes reported from the individual data presented for these

[28] Spelled 'artritis' in the paper; assumed to be arthritis.

				patients. The remaining patients received out of scope

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Aphthous stomatitis, n/total (%) • Before etanercept: 3/7 (42.9) • After initiation of etanercept: 0/7 (0)	treatments (e.g. HCT, splenectomy). The paper reports patients by current TNF inhibitor and the narrative suggests that some patients may have also previously received another TNF inhibitor. It is therefore unclear whether the outcomes reported are specifically for treatment with etanercept. Side effects of TNF inhibitors were reported, but only indicated for patients who received other TNF inhibitors (e.g. infliximab). The paper also reports that “EBV-related malignancies, herpes labialis, varicella zoster infections and warts were reported in this cohort (data not shown).” It is not clear when this was measured. There is insufficient information to conclude that this was assessed in patients who received etanercept. Patients were treated at seven Dutch university hospitals and data were also collected from the Dutch national immunodeficiency dataset. The study dates were not

				reported and it is unclear whether data from the

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				hospitals may have been duplicated in the registry. **Source of funding:** The authors stated that the study received no financial support. The Dutch Eurofever cohort was in part financially supported by Novartis and SOBI.

Celikel E, Aydin F, Tekin ZE, Kurt T, Sezer M, Tekgoz N, et al. Deficiency of adenosine deaminase 2 as an unrecognized cause of early-onset stroke and cranial nerve palsy. Northern Clinics of Istanbul. 2023;10(4):4117 **Study location** 1 tertiary hospital (Ankara City Hospital) in Turkey **Study type** Retrospective case series **Study aim** To evaluate the clinical, laboratory and radiological findings and prognosis of patients with DADA2 and to highlight the situations that DADA2 should be	Patients with DADA2 (predominant phenotype was vasculitis with PAN-like findings) **Inclusion criteria** Patients with a diagnosis of DADA2 followed up in a tertiary hospital rheumatology department. Five patients were diagnosed by ADA2 gene sequencing and one patient by ADA2 enzyme activity **Exclusion criteria** None stated **Total sample size** n=6 treated with etanercept **Baseline characteristics** Male: 4 (67%) Median (IQR) age at symptom onset (years): 5 (1.88 to 7.75)	**Intervention** Etanercept: dose not stated Duration of treatment not stated One patient initially started treatment with infliximab due to Behçet's-like disease. After the diagnosis of DADA2, the treatment was changed to etanercept due to the difficulty of administering infliximab Etanercept was the only listed treatment after the diagnosis of DADA2 **Comparison** No comparator **Concomitant treatments** No information on concomitant treatments	Median (IQR) follow-up (months): 23 (18 to 29.5) **Critical outcomes** **Disease activity/response** (n=6) Reported as clinical remission, which was defined as the absence of active vasculitis, recovery/stabilisation of disease-related organ damage and absence of systemic inflammation Number of patients in clinical remission after initiation of etanercept, n/total (%): 6/6 (100) The authors stated that *"after the initiation of [etanercept], clinical findings improved and inflammation was suppressed in 6 patients"* **Symptom alleviation** *Number of seizures, n/total (%)* • Before etanercept: 2/6 (33.3) • After initiation of etanercept: 1/6 (16.7)	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. No 7. Yes 8. No 9. No 10. N/A **Other comments**: This study reviewed patients treated at one centre in Turkey. The main focus of the paper concerns the presenting features and diagnosis of DADA2. It is not clear if all DADA2 patients treated at the centre in a time period were included.
Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

considered in in the differential diagnosis of patients with neurological findings **Study dates** Not stated	Median (IQR) age at diagnosis (years): 7.75 (5.63 to 10.25) • Systems involved: • Skin: 5 (83.3%) • Neurological: 4 (66.6%) • Immunological: 0 (0%) • Renal: 2 (33.33%)		It was not clear if the patient who experienced seizures after the initiation of treatment was one of those who had experienced seizures before treatment with etanercept	Limited data were provided on patient demographics, but clinical information was presented. Data were retrospectively extracted from patient records. All patients included in the study received treatment with etanercept. One patient had previously received infliximab (plus corticosteroid, cyclophosphamide) before the diagnosis of DADA2[29]. Three patients had previously received colchicine before the diagnosis of DADA2. Outcomes were reported descriptively with limited detail to aid interpretation of the result. ADA2 enzyme activity was only available for one patient at baseline (ADA2 level: 0.47 U/L). Percentages were not reported in the paper but have been calculated for the outcomes reported from the individual data presented for these patients. The paper includes a table that reports median and range ESR and CRP for each patient. It is

[29] The treatment was changed after diagnosis *"due to the difficulty of administering infliximab"*.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				not clear when these were measured and there is no comparison of values before and after treatment with etanercept was started. All patients were treated at one centre in Turkey. The study dates were not reported. It is not clear how generalisable these might be to NHS settings. **Source of funding:** The authors stated that the study received no financial support

Cooray S, Omyinmi E, Hong Y, Papadopoulou C, Harper L, Al-Abadi E, et al. Anti-tumour necrosis factor treatment for the prevention of ischaemic events in patients with deficiency of adenosine deaminase 2 (DADA2). Rheumatology. 2021;60(9):4373-8. **Study location** One specialist centre, UK (patients referred from six centres)	Patients with genetically confirmed DADA2 (confirmed bi-allelic or compound heterozygous mutations in the ADA2 gene) **Inclusion criteria** Patients referred to Great Ormond Street Hospital who had genetically confirmed DADA2. The authors stated that all their patients commenced TNF inhibitor treatment for *"significant vasculitic features"* **Exclusion criteria**	**Intervention** Etanercept Etanercept doses: • 400µg/kg twice weekly or • 800 µg/kg weekly or • 25mg twice weekly or • 50mg weekly if >12 years old Number of patients receiving each dose not stated **Comparison** No comparator	Median (range) etanercept treatment (months): 74 (12 to 84) **Critical outcomes** **Number of ischaemic events** (n=5) *Patients experiencing CNS ischaemic events, n/total (%)* • Before etanercept: 5/5 (100) [total events: n=11] • After initiation of etanercept: 0/5 (0) [total events: n=0] *Patients experiencing non-CNS ischaemic events, n/total (%)* • Before etanercept: 2/5 (40) [total events: n=2]	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. No 7. Yes 8. Yes 9. No 10. N/A **Other comments**: This study reviewed patients treated at Great Ormond
Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

Study type Retrospective case series **Study aim** To evaluate the impact of anti-TNF treatment on the occurrence of vasculitic ischaemic events in patients with DADA2 **Study dates** Not stated. Data were collected up to July 2020	None stated **Total sample size** N=31; n=5 only received TNF inhibitor treatment with etanercept **Baseline characteristics** (n=5 receiving etanercept) Male: 5/5 (100%) Median (IQR) age at symptom onset (years): 5 (3 to 11) Median (IQR) current age[30] (years): 20 (16 to 21) • Median (IQR) duration of disease activity prior to etanercept treatment (months): 78 (28 to 136)	**Concomitant treatments** Other treatments received after initiation of etanercept included aspirin (one patient) and azathioprine (one patient). Three patients did not receive any other treatments after initiation of etanercept.	• After initiation of etanercept:[31] 1/5 (20) (one patient who had events before etanercept) [total events: n=1] **Disease activity/response** Median (IQR) PVAS:[32] • Before etanercept (n=5): 29 (21 to 30) • After initiation of etanercept (n=5): 1 (0 to 2) **Important outcomes** **Steroid use reduction** (n=5) • Before etanercept: 4/5 (80%) were receiving steroids • After initiation of etanercept: 1/5 (20%) continued to receive steroids **Change in acute phase reactants** Median (IQR) CRP (mg/L):[33] • Before etanercept (n=4): 65 (45.5 to 95) • After initiation of etanercept (n=5): 3 (1.8 to 4.5) Median (IQR) ESR (mm/hr):[36] • Before etanercept (n=3): 100 (60 to 103.5)	Street Hospital, a specialist centre in the UK. Patients were referred to Great Ormand Street from six UK centres. It is not clear if all patients treated at the centre in a time period were included. Data were retrospectively extracted from patient records. The study states that 31 patients were included in the study. Of these, 27 received treatment with a TNF inhibitor, of whom five only received treatment with etanercept. Outcomes relating to patients who received etanercept were taken from the paper supplement. Outcomes were reported descriptively with no statistical comparison of scores before and after etanercept. Percentages, ranges and medians were not reported in the paper but were

[30] Current age was reported at the time of the study data collection.
[31] One patient developed digital necrosis resulting in a partial amputation due to poor compliance with etanercept. This patient had both CNS and non-CNS ischaemic events before treatment with etanercept.
[32] The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across 9 organ systems and a score of 0 indicating absent activity. The 'before' score was assessed at first presentation to the centre and the 'after' score at the most recent clinic visit after treatment with etanercept.
[33] Elevated CRP levels were not further defined, but laboratory ranges were reported to vary at each centre. [36]
Elevated ESR levels were not further defined, but laboratory ranges were reported to vary at each centre.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• After initiation of etanercept (n=2): 6 (4.5 to 7.5) Median (IQR) SAA (mg/L):[34] • Before etanercept: not done or missing data • After initiation of etanercept (n=3): 10.1 (8.6 to 11.3)[35] **Safety** The authors stated that *"no adverse reactions were reported with … etanercept*"	calculated for these patients from the data presented. All patients were referred to one UK specialist centre. It is not clear how generalisable these might be to other NHS settings. **Source of funding:** The study was supported in part by a grant from Rosetrees (a charity supporting medical research)

[34] The authors did not provide a definition for SAA, but it has been presumed to be serum amyloid A activity.

[35] These values were indicated to be within the normal range although normal ranges were not specified, and it was unclear whether values were within the normal range before initiation of etanercept as data were not available.

Deuitch NT, Yang D, Lee PY, Yu X, Moura NS, Schnappauf O, et al. TNF inhibition in vasculitis management in adenosine deaminase 2 deficiency (DADA2). Journal of Allergy & Clinical Immunology. 2022;149(5):1812-6.e6. **Study location** National Institutes of Health, USA and collaborating groups (not specified; authors were from centres in the USA, Canada and China)	Patients with DADA2 **Inclusion criteria** Patients with a diagnosis of DADA2, which was genetically confirmed in all patients **Exclusion criteria** None stated **Total sample size** N=31; n=9 patients treated with etanercept **Baseline characteristics** (n=9 treated with etanercept) Patient sex not stated	**Intervention** Etanercept: dose not stated **Comparison** No comparator **Concomitant treatments** One patient received concomitant IVIG and clonazepammira, one patient received concomitant hydroxychloroquine, anakinra, and IVIG. Seven patients received only etanercept	Median (range) etanercept treatment (n=8): 1 year (6 months to 5 years) **Critical outcomes** **Symptom alleviation** Information on symptoms both before and after commencing treatment with etanercept was available for three patients, and after commencing treatment only for two patients. *Mild flare with fever* • Before etanercept: two patients had mild flare with fever • After initiation of etanercept: both patients were *"clinically well"*	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. Yes 4. Unclear 5. No 6. No 7. Yes 8. No 9. No 10. N/A **Other comments**: This study reviewed patients treated at the National

Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

Study type Retrospective case series **Study aim** To explore the effect of TNF inhibitor treatment on the patients with DADA2 **Study dates** Not stated	Median (IQR) age before treatment (years) (n=4): 6 (5 to 7) Median (IQR) age after treatment (years) (n=9): 11 (10 to 15) • Clinical manifestations:[36] • Arthritis: 1 (11.1%) • Skin rash: 3 (33.3%) • Recurrent fever: 7 (77.8%) • Livedo: 4 (57.1%) • Stroke (haemorrhagic, ischaemic, or multiple): 5 (55.6%) • Limb numbness and weakness: 1 (11.1%) • Basal ganglia ischaemia: 1 (11.1%) • Seizures: 1 (11.1%) • Portal hypertension: 1 (11.1%) • Vasculitis: 2 (22.2%) • Hypogammaglobulinemia: 1 (11.1%) • Raynaud's: 1 (11.1%)		*Livedo* • Before etanercept: one patient had some livedo • After initiation of etanercept: the same patient had minimal livedo and Raynaud's *Other symptoms* • After initiation of etanercept: one patient was *"clinically well"* but with some pancytopenia, and one patient was *"clinically well"* but some gait disorders remained[37] **Important outcomes** **Steroid use reduction** Information on treatment both before and after commencing treatment with etanercept was available for four patients • Before etanercept: three patients who were treated with etanercept were receiving steroids (prednisone, dose not stated) before anti-TNF inhibitor treatment • After initiation of etanercept: all patients discontinued steroids, one was receiving hydroxychloroquine, anakinra, and IVIG in addition to etanercept	Institutes of Health and collaborating sites; no further details were provided but study authors were from centres in the USA, Canada and China. It was unclear whether there may be overlap of patients included in Li et al (2023) as some patients from Li et al (2023) had previously been reported in Deuitch et al (2022). It was unclear whether patients were recruited consecutively and whether all patients treated in the same time period were included. Patients included in the study received different treatments, with 9 of 31 patients receiving etanercept. The remaining patients received other TNF inhibitor drugs (e.g. adalimumab, golimumab) or treatments were not reported. Data were retrospectively extracted from patient records, but demographic and clinical information was limited.

[36] All patients experienced more than one clinical manifestation.

[37] Symptoms were not reported for these two patients before initiation of etanercept.

			Change in acute phase reactants	

Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

			Median (IQR) CRP (mg/L):[38] • Before etanercept (n=4): 50.3 (33.5 to 56.4) • After initiation of etanercept (n=7): 0.35 (0.2 to 0.4) **Safety** One patient died after commencing treatment due to complications of liver disease	The paper includes a table that reports CRP for DADA2 patients, but otherwise outcomes were reported descriptively with limited detail to aid interpretation of the result. Percentages, ranges and medians were not reported in the paper but were calculated for patients receiving etanercept from the data presented. It is unclear where all patients were treated and study dates were not reported. It is not clear how generalisable these findings might be to NHS settings. **Source of funding:** The Intramural Research Program of the National Human Genome Research Institute
Kasap Cuceoglu M, Sener S, Batu ED, Kaya Akca U, Demir S, Sag E, et al. Systematic review of childhood-onset polyarteritis nodosa and DADA2. Seminars in Arthritis & Rheumatism. 2021;51(3):559-64.	Patients with DADA2 **Inclusion criteria** Children aged 0 to 18 years with a diagnosis of DADA2 followed up at a rheumatology unit. DADA2 was genetically confirmed in all patients	**Intervention** Etanercept: dose not stated Duration of treatment not stated. **Comparison** No comparator	Median (IQR) follow-up (years): 3.5 (2 to 5) **Critical outcomes** **Disease activity/response** (n=18) Number of patients in complete remission (not further defined) at follow-up: 17/18 (94.5%)	This study was appraised using the JBI checklist for case series as the systematic review conducted as part of this study was not in scope. 1. Yes 2. Yes 3. Yes 4. Unclear

[38] Normal CRP levels: 0.00 to 4.99 mg/L.

	Exclusion criteria			

Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

Study location One paediatric rheumatology unit (Hacettepe University) in Turkey **Study type** Retrospective case series **Study aim** To define the differential features of paediatric PAN and DADA2 patients in one centre and in the literature **Study dates** 2010 to 2020	None stated **Total sample size** n=18 treated with etanercept **Baseline characteristics** Patient sex not stated Median (IQR) age at symptom onset (years): 4 (2 to 6) Median (IQR) age at diagnosis (years): 5.5 (3.5 to 8) • Systems involved: • Skin: 18 (100%) • Gastrointestinal: 11 (61.6%) • Neurologic: 10 (55.5%) • Renal: 2 (11.1%) • Testicular: 1 (5.6%) • Cardiac: 1 (5.6%) • Pulmonary: 0 (0%) • Eye: 2 (11.1%)	**Concomitant treatments** No information on concomitant treatments	The authors also stated that 3/18 patients (16.7%) relapsed during follow-up.[39] **Important outcomes** **Safety** The authors stated that one patient died due to pulmonary haemorrhage[42]	5. Unclear 6. Yes 7. Yes 8. No 9. No 10. N/A **Other comments**: This study included a systematic review of the literature and also described patients with PAN (n=34) or DADA2 (n=18) treated at one centre in Turkey. The systematic review focused on the differential features of PAN and DADA2. Only data relating to the treatment of patients with DADA2 were extracted. It is not clear if all patients treated at the centre in a time period were included. Data were retrospectively extracted from patient records. All DADA2 patients included in the study received treatment with etanercept. Prior to treatment with etanercept, 10 (55.5%) DADA2 patients used corticosteroids, 3 (16.6%) patients received cyclophosphamide, 4 (22.2%)

[39] It was unclear what the sequence of events was in terms of patients in complete remission, those who relapsed and the patient who died during follow-up as no further details were reported.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

				patients were treated with azathioprine, 3 (16.7%) patients received MMF, 1 (5.6%) patient used methotrexate. 6 (33.3%) DADA2 patients were treated with colchicine in addition to the primary immunosuppressive treatment. Outcomes were reported descriptively with limited detail to aid interpretation of the result. The authors reported that one patient died and the cause of death was *"pulmonary haemorrhage in DADA2 patient"*, but no further details were reported. The paper includes a table that reports median ESR and CRP, and PVAS for DADA2 patients. It is not clear when these were measured. There is insufficient information to conclude that these were assessed after treatment with etanercept was started. All patients were treated at one centre in Turkey between 2010 and 2020. It is not clear how generalisable these might be to NHS settings. **Source of funding:**

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				No statement on funding was included. The authors declared that they had no conflicts of interest.

Kisla Ekinci RM, Anlas O, Ozalp O. Clinical presentation of children with Deficiency of Adenosine deaminase 2: A case series. European Journal of Medical Genetics. 2022;65(8):104555. **Study location** One paediatric rheumatology unit in Adana, Turkey **Study type** Retrospective case series **Study aim** To report details of five patients with DADA2 from five unrelated families **Study dates** Not stated	Patients with DADA2 **Inclusion criteria** All patients had G47R mutation in at least one allele. The authors stated that all patients could be classified as vasculitis phenotype **Exclusion criteria** None stated **Total sample size** n=5 treated with etanercept **Baseline characteristics** Male: 3 (60%) Median (range) age at symptom onset (years): 7 (6.5 to 8) Median (range) age at diagnosis (years): 8.5 (7 to 9) Median (range) age at study inclusion (years): 9 (8 to 10) • Systems involved: • Skin: 5 (100%) • Musculoskeletal: 4 (80%)	**Intervention** Etanercept Dose not stated **Comparison** No comparator **Concomitant treatments** One patient was also receiving monthly IVIG replacement. No concomitant treatments stated for the other patients.	Where reported, outcomes were described as during the next 9 months or 12 months of etanercept treatment **Critical outcomes** **Number of ischaemic events** For one patient, etanercept was described as resulting in the patient being *"neurologically symptom-free for the 1 year follow-up"*. This patient was reported as having neurological symptoms prior to etanercept No comments relating to ischaemic events after etanercept were made for other patients **Disease activity/response** For one patient etanercept was described as resulting in *"complete remission of the disease for the next 9 months"* (not further defined) No comments relating to disease activity/response after etanercept were made for other patients **Symptom alleviation** (n=5) Symptom alleviation up to 1 year after the initiation of etanercept was described for individual patients, n/total (%).	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. No 7. Yes 8. No 9. No 10. N/A **Other comments**: This study reviewed patients treated at one centre in Turkey. Much of the paper concerns the presenting features of DADA2. It is not clear if all patients treated at the centre in a time period were included. Data were retrospectively extracted from patient records. All patients included in the study received treatment with etanercept.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• Haematological: 3 (60%) • Neurological: 2 (40%) • Gastrointestinal: 3 (60%)		2/5 patients (40%) were stated to have complete resolution of symptoms (skin symptoms in n=2, fever in n=1, inflammatory attacks in n=1) 2/5 patients (40%) were stated to have improvement in symptoms (skin symptoms in n=2, musculoskeletal in n=1, constitutional symptoms in n=1) In 1/5 patients (20%) (the patient described as being in complete remission) no comment on symptomatic involvement was made **Important outcomes** **Steroid use reduction** For one patient etanercept was described as resulting *"in cessation of systemic steroids and methotrexate"* No comments relating to steroid use after etanercept were made for other patients	The study was written up as a series of case reports describing individual patients. Descriptive comments relating to individual patients were extracted as the type of information included in the reports was similar for all patients. Outcomes were reported descriptively with limited detail. No statistical comparison of outcomes before and after etanercept was conducted. The authors reported that one patient had recurrent history of arterial stroke and transient ischaemic attack, but no further details were reported. The authors stated that they could not perform ADA2 enzyme activity in patients as *"it was not routinely performed and affordable in our country".* All patients were treated at one centre in Turkey (study dates not reported). It is not clear how generalisable these might be to NHS settings. **Source of funding:**

				The authors stated that no funding was received. The
Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

				authors declared that they had no conflicts of interest.
Li GM, Han X, Wu Y, Wang W, Tang HX, Lu MP, et al. A Cohort Study on Deficiency of ADA2 from China. Journal of Clinical Immunology. 2023;43(4):835-45. **Study location** 17 rheumatology centres in China **Study type** Retrospective cohort study **Study aim** To describe the clinical and genetic features of DADA2 in Chinese patients **Study dates** January 2015 to December 2021	Patients with DADA2 **Inclusion criteria** Patients with biallelic variants in the ADA2 gene, plus at least one of the following: systemic inflammation, vasculitis, humoral immunodeficiency, haematologic abnormalities, and low level of ADA2 enzymatic activity **Exclusion criteria** None stated **Total sample size** N=30; n=13 treated with etanercept **Baseline characteristics** (n=13 treated with etanercept) Male: 9 (69.2%) Median (range) age at symptom onset (years): 4.2 (2.3 to 4.9) Median (range) age of diagnosis (years): 7.9 (5.3 to	**Intervention** Etanercept Dose not stated Duration of treatment not stated. **Comparison** No comparator **Concomitant treatments** Six patients received concomitant treatment with one or more of the following: NSAIDs, glucocorticoids, methotrexate, thalidomide, hydroxychloroquine, cyclophosphamide, and mycophenolate mofetil	Median (range) follow-up (months): 20.2 (5 to 36) after diagnosis of DADA2[41] Outcomes after the initiation of etanercept were presented in a table for individual patients. **Critical outcomes** **Number of ischaemic events** The authors reported that *"… no patients have had a stroke during the time they have been on treatment"* (no further details were provided) **Disease activity/response** *Remission, n/total (%)* (n=13) Before etanercept: no patients were in complete or partial remission After initiation of etanercept Complete remission:[45] 12/13 (92.3%) Partial remission:[42] 1/13 (1.7%) **Symptom alleviation** The authors reported that etanercept *"significantly reduced fever episodes, vasculitis…"*	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. No 4. Unclear 5. Unclear 6. Yes 7. Yes 8. No 9. No 10. N/A **Other comments**: This study reviewed patients treated at 17 centres in China. Although this was a cohort study, given only 13 of 30 patients were in scope, this has been treated as a case series. The authors note that 12 patients from the whole cohort have been reported previously

[41] Follow-up period for full cohort of 30 patients. Follow-up duration for 13 patients receiving etanercept was not reported separately, [45] Defined as persistent control of inflammatory parameters with no disease's flares or complications in the absence of any steroid treatment.
[42] Defined as good control of disease activity with sporadic relapses and need of steroid on demand or increased steroid dosage.

	11.8)[40]		**Important outcomes**	in the literature, including in Deuitch et al 2022. There is a

Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

[40] There was a discrepancy in the figure reported for age of diagnosis in the supplementary table; reported as 7.1.0, which we have interpreted as being 7.1 years.

	• Systems involved: • Musculoskeletal: 6 (46.2%) • Skin: 13 (100%) • Gastrointestinal: 2 (15.4%) • Neurological: 10 (76.9%) • Renal: 0 (0%) • Other (headache or myositis): 3 (23.1%)		**Steroid use reduction** (n=13) • Before etanercept: information provided in a table suggests that 12 of the 13 patients (92.3%) who received etanercept were receiving glucocorticoids (dose not stated) before anti-TNF inhibitor treatment. • After initiation of etanercept: 5 of the 13 patients (38.5%) were on glucocorticoids; the remaining 7 who were on glucocorticoids before initiation of etanercept discontinued glucocorticoid treatment. The authors note that the glucocorticoids had "*little effect"* on DADA2 symptoms. **Change in acute phase reactants** Twelve (92.3%) patients had elevated CRP levels before etanercept. All patients were within the normal reference range after etanercept: Median (IQR) CRP (mg/L): • Before etanercept (n=13): 33.4 (18 to 60) • After initiation of etanercept (n=13): 5.7 (4.9 to 6.5) Nine (69.2%) patients had elevated ESR levels before etanercept. All patients were within the normal reference range after initiation of etanercept: Median (IQR) ESR (mm/hr):	possibility that there is some overlap in the patients reported in these tables. Data were retrospectively extracted from patient records. 13 of 30 patients included in the study received treatment with etanercept. The remaining patients received infliximab or adalimumab. Twelve of the 13 patients treated with etanercept had received previous treatment with glucocorticoids, methotrexate, thalidomide, cyclophosphamide, tocilizumab, mycophenolate mofetil, IVIG, hydroxychloroquine, or cyclosporine. Outcomes were reported descriptively for all patients with limited detail to aid interpretation of the results for in scope patients. None of the patients treated with etanercept died during the study treatment period. Duration of follow-up was reported for the whole cohort but not separately for patients receiving etanercept. The paper includes a table that reports median ESR and CRP

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• Before etanercept (n=13): 38.5 (19 to 51) • After initiation of etanercept (n=13): 10.0 (8 to 13)	for each patient. Ranges and percentages were calculated based on the data provided. All patients were treated at 17 centres in China between January 2015 and December 2021. It is not clear how generalisable these might be to NHS settings. **Source of funding:** One author was supported by grants from The National Natural Science Foundation of China and from Zhejiang Provincial Natural Science Foundation of China.
Melo A, de Carvalho LM, Ferriani VPL, Cavalcanti A, Appenzeller S, Oliveira VR, et al. A Brazilian nationwide multicenter study on deficiency of deaminase2 (DADA2). Advances in Rheumatology. 2023;63(1):23. **Study location** Ten centres in Brazil **Study type**	Patients with DADA2 **Inclusion criteria** Patients of any age with a diagnosis of DADA2. All patients carried pathogenic mutations in the ADA2 gene **Exclusion criteria** None stated **Total sample size** N=18; n=9 patients treated with etanercept	**Intervention** Etanercept Dose not stated Duration of treatment not stated. **Comparison** No comparator **Concomitant treatments** Four patients received one or more of the following: steroids during	Median (range) follow-up (months): 56 (36 to 72) **Critical outcomes** **Disease activity/response** (n=9)	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. No 4. Unclear 5. Unclear 6. No 7. No 8. No 9. No 10. N/A

			Complete control of disease:[43] 9/9 (100%)	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

[43] Response to treatment was considered complete when clinical and laboratory remission could be achieved; partial when clinical or laboratory remission could not be achieved; and absent when neither clinical nor laboratory remission could be achieved. Clinical remission was defined as the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation. Laboratory remission was defined as normalisation of CRP levels in the local laboratory.

Retrospective case series **Study aim** To describe clinical, genetic and therapeutic data in Brazilian patients with confirmed DADA2 **Study dates** January 2019 to December 2022	**Baseline characteristics** (n=9 treated with etanercept) Male: 3 (33.3%) Additional baseline characteristics reported for whole cohort but not separately for in scope patients	flares, azathioprine, mycophenolate, cyclophosphamide as induction therapy, and/or IVIG		**Other comments**: This study reviewed patients treated at 10 centres in Brazil. Data were retrospectively extracted from patient records. Nine patients included in the study received treatment with etanercept. The remaining out of scope patients received adalimumab, certolizumab or infliximab. It is not clear if all patients treated at the centre in a time period were included. Outcomes were reported descriptively with limited detail to aid interpretation of the result. The paper includes a table that reports therapeutic intervention and response per patient for treatments used for long-term management and acute management. patients. Of the four patients who received steroids for flares, one achieved partial response and three achieved complete response; three patients received azathioprine but not achieved response to

				treatment; two patients received mycophenolate with

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				one patient achieving additional benefit and one patient not achieving a response; two patients received cyclophosphamide as induction therapy, with neither patient achieving a response; one patient received IVIG and achieved partial response. Patients were treated at 10 centres in Brazil between January 2019 to December 2022. It is not clear how generalisable these might be to NHS settings. **Source of funding:** Centre for Rare and Immunological Disorders of the Hospital 9 de Julho.

Tanatar A, Karadag SG, Sozeri B, Sonmez HE, Cakan M, Kendir Demirkol Y, Aktay Ayaz N. ADA2 Deficiency: Case Series of Five Patients with Varying Phenotypes. Journal of Clinical Immunology. 2020;40(2):253-8. **Study location** One training hospital in Istanbul, Turkey **Study type**	Patients with DADA2 **Inclusion criteria** Patients with a diagnosis of DADA2 followed up in a training hospital rheumatology unit. DADA2 was genetically confirmed in all patients **Exclusion criteria** None stated **Total sample size** n=5 treated with etanercept **Baseline characteristics**	**Intervention** Etanercept Four patients received 25mg subcutaneously per week One patient received 50mg subcutaneously per week One patient had previously received infliximab before the diagnosis of DADA2 with a 'partial response.	Median (range) follow-up (months): 8 (6 to 16), unless otherwise stated **Critical outcomes** **Symptom alleviation** (n=5) Systemic inflammation (no definition provided), n/total (%): • Before etanercept: 4/5 (80%) • At 3 months after initiation of etanercept: 0/5 (100%) All patients were reported to have at least one symptom before treatment.	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. No 7. Yes 8. Yes 9. No 10. N/A **Other comments**:
Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

Retrospective case series **Study aim** To describe the clinical features, genotype and treatment approaches of patients with confirmed DADA2 with dissimilar phenotypes **Study dates** Not stated	Male: 2 (40%) Median (IQR) age at symptom onset (years): 11 (11 to 12) Median (IQR) age at diagnosis (years): 15 (14 to 16) Systems involved: • Musculoskeletal: 5 (100%) • Skin: 4 (80%) • Gastrointestinal: 3 (60%) • Neurological:[44] 3 (60%) • Ocular: 3 (60%) • Renal: 3 (60%) • Haematological: 2 (40%) • Immunological: 2 (40%) • Cardiac: 1 (20%) All patients had mild to severe vasculopathy	Etanercept was the only listed treatment after the diagnosis of DADA2 Duration of treatment not stated. **Comparison** No comparator **Concomitant treatments** One patient received concomitant fresh frozen plasma for six months. No concomitant treatments were described for the remaining patients	The authors stated that *"at the 3rd month of etanercept treatment, all the symptoms resolved"* **Important outcomes** **Change in acute phase reactants** The authors stated that *"at the 3rd month of etanercept treatment,… APRs were normal"* **Safety** The authors stated that *"None of the patients suffered from recurrent infections and required intravenous immunoglobulin (IVIG) treatment"*	This study reviewed patients treated at one centre in Turkey. It is not clear if all patients treated at the centre in a time period were included. Data were retrospectively extracted from patient records. All patients included in the study received treatment with etanercept. All patients were reported to have absence of ADA2 activity in the plasma prior to treatment with etanercept. Outcomes were reported descriptively with limited detail to aid interpretation of the result. Percentages were not reported in the paper but were calculated based on the data provided. The paper includes a table that reports highest ESR and CRP for each patient, and serum amyloid A for 3 patients. It is not clear when these were measured. Patients were described as having normal

[44] There was a discrepancy in the number of patients reported to have neurological involvement: n=2 reported in the abstract and n=3 reported in the table. We have reported the figure presented in the table.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				APRs after treatment with etanercept. All patients were treated at one centre in Turkey. The study dates were not reported. It is not clear how generalisable these might be to NHS settings. **Source of funding:** The authors stated that there were no financial relationships to disclose.

Abbreviations

ADA2: adenosine deaminase type 2 gene; APR: acute phase reactant; CNS: central nervous system; CRP: C-reactive protein; DADA2: Deficiency of adenosine deaminase type 2; EBV: Epstein-Barr virus; ESR: erythrocyte sedimentation rate; HCT: haematopoietic cell transplantation; IBD: inflammatory bowel disease; IQR: interquartile range; IVIG: intravenous immunoglobulin; kPa: kilopascals; MMF: mycophenolate mofetil; MRI: magnetic resonance imaging; n: number; N/A: not applicable; NHS: National Health Service; NSAIDs: nonsteroidal anti-inflammatory drugs; PAN: polyarteritis nodosa; PVAS: Paediatric Vasculitis Activity Score; SAA: serum amyloid A; TNF: Tumour necrosis factor; U/L: units per litre.

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

In patients with deficiency of adenosine deaminase type 2, what is the clinical effectiveness and safety of TNF inhibitors compared with standard care?

For abbreviations and footnotes see end of table.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Etanercept	Comparator	Result		
Number of ischaemic events (4 case series)									
Number of patients with MRI-confirmed strokes after adequate disease control[A] (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept: 6/7 (85.7%) After initiation of etanercept: 0/7 (0%)	Critical	Very low
Number of patients with neurological symptoms for the one-year follow-up									
1 retrospective case series Kisla Ekinci et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	Before etanercept: one patient with neurological symptoms[a] After initiation of etanercept: the same patient was described as being *"neurologically symptomfree"*	Critical	Very low
Number of patients with stroke at median 20.2 months follow-up (range 5 to 36) after diagnosis of DADA2[C]									

1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	13[b]	0	The authors reported that *"no patients have had a stroke during the time they have been on treatment"*	Critical	Very low
Number of patients with ischaemic events (n/total, %) after median 74 months follow-up (range 12 to 84)									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	*Patients experiencing CNS ischaemic events* Before etanercept: 5/5 (100%) [total events: n=11] After initiation of etanercept: 0/5 (0%) [total events: n=0] *Patients experiencing non-CNS ischaemic events*: Before etanercept: 2/5 (40%) [total events: n=2] After initiation of etanercept 1/5 (20%) (one patient who had events before etanercept) [total events: n=1][c]	Critical	Very low
Disease activity/response (7 case series)									
Disease remission (n) during the next 9 months of etanercept treatment									
1 retrospective case series Kisla Ekinci et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	For one patient etanercept was described as resulting in *"complete remission of the disease for the next 9 months"* (not further defined)	Critical	Very low
Number of patients with anaemia (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									

1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept: 1/7 (14.3%) After initiation of etanercept: 1/7 (14.3%) (the same patient)	Critical	Very low
Number of patients with lymphopenia (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept: 1/7 (14.3%) After initiation of etanercept: 1/7 (14.3%) (the same patient)	Critical	Very low
Number of patients with hypogammaglobulinemia (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept 4/7 (57.1%) After initiation of etanercept: 4/7 (57.1%) (the same patients)	Critical	Very low
Number of patients in complete or partial remission (n/total, %) at median 20.2 months follow-up (range 5 to 36) after diagnosis of DADA2[C]									
1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	13[b]	0	Before etanercept: no patients were in complete or partial remission After initiation of etanercept: Complete remission:[d]12/13 (92.3%) Partial remission:[e] 1/13 (1.7%)	Critical	Very low
Number of patients in clinical remission[D] (n/total, %) at median 23 months follow-up (IQR 18 to 29.5)									

1 retrospective case series Celikel et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	6	0	Number of patients in clinical remission after initiation of etanercept: 6/6 (100%) The authors stated that *"after the initiation of [etanercept], clinical findings improved and inflammation was suppressed in 6 patients"*	Critical	Very low
Number of patients in complete remission (n/total, %) at median 3.5 years follow-up (IQR 2 to 5)									
1 retrospective case series Kasap Cuceoglu et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	18	0	Number of patients in complete remission (not further defined) at follow-up: 17/18 (94.5%) The authors also stated that 3/18 patients (16.7%) relapsed during follow-up[f]	Critical	Very low

Number of patients with complete control of disease[E] (n/total, %) at median 56 month follow-up (range 36 to 72)									
1 retrospective case series	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	9	0	After etanercept: 9/9 (100%)	Critical	Very low

Melo et al 2023									
PVAS[F] (median, IQR) after median 74 months follow-up (range 12 to 84) [lower scores indicate benefit]									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	Before etanercept: 29 (21 to 30) After initiation of etanercept: 1 (0 to 2)	Critical	Very low
Symptom alleviation (6 case series)									
Number of patients with cutaneous involvement (except eczema) (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									

1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept: 5/7 (71.4%) After initiation of etanercept: 0/7 (0%)	Critical	Very low
Number of patients with eczema (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept: 1/7 (14.3%) After initiation of etanercept: 3/7 (42.8%) (including one patient with pre-existing eczema)	Critical	Very low
Number of patients with fever (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept: 2/7 (28.6%) After initiation of etanercept: 0/7 (0%)	Critical	Very low
Number of patients with PAN-like rash or other cutaneous vasculitis (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept: 4/7 (57.1%) After initiation of etanercept: 0/7 (0%)	Critical	Very low
Number of patients with arthralgia/arthritis (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept: 2/7 (28.6%) After initiation of etanercept: 1/7 (14.3%) (one patient with preexisting arthralgia/arthritis)	Critical	Very low

Number of patients with aphthous stomatitis (n/total, %) at follow-up of the whole cohort between two months and >10 years[B]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	7	0	Before etanercept: 3/7 (42.9%) After initiation of etanercept: 0/7 (0%)	Critical	Very low
Systemic inflammation (not defined) (n/total, %) at 3 months after initiation of etanercept									
1 retrospective case series Tanatar et al 2020	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	Before etanercept: 4/5 (80%) At 3 months after initiation of etanercept treatment: 0/5 (100%)	Critical	Very low
Resolution of symptoms (n) at 3 months after initiation of etanercept									
1 retrospective case series Tanatar et al 2020	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	All patients had at least one symptom before treatment. The authors stated that *"at the 3rd month of etanercept treatment, all the symptoms resolved"*	Critical	Very low
Mild flare with fever (n) after median time on etanercept treatment of one year (range 6 months to 5 years)									
1 retrospective case series Deuitch et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9[b, g]	0	Before etanercept: two patients had mild flare with fever After initiation of etanercept: both patients were *"clinically well"*	Critical	Very low

Livedo (n) after median time on etanercept treatment of one year (range 6 months to 5 years)									
1 retrospective case series	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9[b, g]	0	Before etanercept: one patient had some livedo	Critical	Very low

Deuitch et al 2022							After initiation of etanercept: the same patient had minimal livedo and Raynaud's		
Other symptoms (n) after median time on etanercept treatment of one year (range 6 months to 5 years)									
1 retrospective case series Deuitch et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9[b, g]	0	After initiation of etanercept: one patient was "*clinically well"* but with some pancytopenia, and one patient was *"clinically well"* but some gait disorders remained. Symptoms before starting treatment were not reported for these two patients.	Critical	Very low
Symptom alleviation up to one year after the initiation of etanercept (n/total, %)									
1 retrospective case series Kisla Ekinci et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	2/5 patients (40%) were stated to have complete resolution of symptoms (skin symptoms in n=2, fever in n=1, inflammatory attacks in n=1) 2/5 patients (40%) were stated to have improvement in symptoms (skin symptoms in n=2, musculoskeletal in n=1, constitutional symptoms in n=1) In 1/5 patients (the patient described as being in complete remission) no comment on symptomatic involvement was made	Critical	Very low
Symptom alleviation at median 20.2 months follow-up (range 5 to 36) after diagnosis of DADA2[C]									

1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	13[b]	0	The authors reported that etanercept *"significantly reduced fever episodes, vasculitis…"* but no further details were provided	Critical	Very low
Number of seizures (n/total, %) at median 23 months follow-up (IQR 18 to 29.5)									
1 retrospective case series Celikel et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	6	0	Before etanercept: 2/6 (33.3%) After initiation of etanercept:1/6 (16.7%). It was not clear if the patient who experienced seizures on treatment was one of those who had experienced seizures before treatment with etanercept	Critical	Very low
Steroid use reduction (4 case series)									
Steroid use (n) during the next 9 months or 12 months of etanercept treatment									
1 retrospective case series Kisla Ekinci et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	For one patient etanercept was described as resulting *"in cessation of systemic steroids and methotrexate"*[h]	Important	Very low
Steroid use reduction (n) after median time on etanercept treatment of one year (range 6 months to 5 years)									

1 retrospective case series Deuitch et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9[b, i]	0	Before etanercept: three patients who were treated with etanercept were receiving steroids (prednisone, dose not stated) before anti-TNF inhibitor treatment. After initiation of etanercept: all patients discontinued steroids, one was receiving hydroxychloroquine, anakinra, and IVIG in addition to etanercept	Important	Very low
Steroid use reduction (n/total, %) at median 20.2 months follow-up (range 5 to 36) after diagnosis of DADA2[C]									
1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	13[b]	0	Before etanercept: information provided in a table suggests that 12 of the 13 patients (92.3%) who received etanercept were receiving glucocorticoids (dose not stated) before anti-TNF inhibitor treatment. After initiation of etanercept: 5 of the 13 patients (38.5%) were on glucocorticoids; the remaining 7 patients on glucocorticoids before initiation of etanercept discontinued glucocorticoid treatment The authors note that the glucocorticoids had *"little effect"* on DADA2 symptoms	Important	Very low
Steroid use (n/total, %) after median 74 months follow-up (range 12 to 84)									

1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	Before etanercept: 4/5 (80%) were receiving steroids After initiation of etanercept: 1/5 (20%) continued to receive steroids	Critical	Very low
Change in acute phase reactants (5 case series)									
Normal acute phase reactants (n/N, %) at 3 months after starting etanercept									
1 retrospective case series Tanatar et al 2020	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	The authors stated that *"at the 3rd month of etanercept treatment,… APRs were normal"*	Important	Very low
Change in CRP (mg/L) (median, IQR) after median time on etanercept of one year (range 6 months to 5 years) [lower levels indicate benefit]									
1 retrospective case series Deuitch et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9[b]	0	Before etanercept (n=4): 50.3 (33.5 to 56.4)[j] After initiation of etanercept (n=7): 0.35 (0.2 to 0.4)	Important	Very low
Change in CRP (mg/L) (median, IQR) at median 20.2 months follow-up (range 5 to 36) after diagnosis of DADA2[C] [lower levels indicate benefit]									
1 retrospective case series	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	13[b]	0	Before etanercept: 33.4 (18 to 60)[k]	Important	Very low
Li et al 2023							After initiation of etanercept: 5.7 (4.9 to 6.5)		
Change in ESR (mm/hr) (median, IQR) at median 20.2 months follow-up (range 5 to 36) after diagnosis of DADA2[C] [lower levels indicate benefit]									
1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	13[b]	0	Before etanercept: 38.5 (19 to 51)[l] After initiation of etanercept: 10.0 (8 to 13)	Important	Very low

Change in CRP (mg/L) (median, IQR) after median 74 months follow-up (range 12 to 84) [lower levels indicate benefit]									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	Before etanercept (n=4): 65 (45.5 to 95) After initiation of etanercept (n=5): 3 (1.8 to 4.5)	Important	Very low
Change in ESR (mm/hr) (median, IQR) after median 74 months follow-up (range 12 to 84) [lower levels indicate benefit]									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	3	0	Before etanercept (n=3): 100 (60 to 103.5) After initiation of etanercept (n=2): 6 (4.5 to 7.5)	Important	Very low
Change in SAA (mg/L) (median, IQR) after median 74 months follow-up (range 12 to 84) [lower levels indicate benefit]									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	3	0	Before etanercept: Not assessed or missing data After initiation of etanercept (n=3): 10.1 (8.6 to 11.3)[o]	Important	Very low
Safety (4 case series)									
Safety at 3 months after starting etanercept									
1 retrospective case series Tanatar et al 2020	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	The authors stated that *"None of the patients suffered from recurrent infections and required intravenous immunoglobulin (IVIG) treatment"*	Important	Very low
Number of deaths at median time on treatment of one year (range 6 months to 5 years)									
1 retrospective case series Deuitch et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9[b, g]	0	One patient died after commencing treatment due to complications of liver disease	Important	Very low
Number of deaths at median 3.5 years follow-up (IQR 2 to 5)									

1 retrospective case series Kasap Cuceoglu et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	18	0	The authors stated that one patient died due to pulmonary haemorrhage[f]	Important	Very low
Adverse events after median 74 months follow-up (range 12 to 84)									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	5	0	The authors reported that *"no adverse reactions were reported with … etanercept"*	Important	Very low

Abbreviations
ADA2: adenosine deaminase type 2 gene; APR: acute phase reactant; CNS: central nervous system; DADA2: Deficiency of adenosine deaminase type 2; ESR: erythrocyte sedimentation rate; IQR: interquartile range; IVIG: intravenous immunoglobulin; kPa: kilopascals; MRI: magnetic resonance imaging; n: number; N/A: not applicable; PAN: polyarteritis nodosa PVAS: Paediatric Vasculitis Activity Score; SAA: serum amyloid A; U/L: units per litre.

1. Risk of bias: very serious limitations due to unclear reporting of inclusion assessment and enrolment of participants (in relation to non-consecutive and/or incomplete inclusion), lack of any statistical analysis or summary statistic, and one or more of the following: unclear reporting of demographics and clinical information, lack of blinding of patients and clinicians, or unclear reporting of follow up results of cases.
2. Indirectness: serious indirectness due to lack of a comparator.
3. Indirectness: very serious indirectness due to lack of comparator and uncertainty as to whether the outcomes reported were specifically for treatment with etanercept. 4. Risk of bias: very serious limitations due to unclear enrolment of participants (in relation to non-consecutive and/or incomplete inclusion), unclear reporting of study participants (baseline data not presented separately for in-scope patients), unclear reporting of follow up results of cases and lack of any statistical analysis or summary statistic.

A. No definition provided for adequate disease control.
B. Duration of follow-up of etanercept patients not stated.
C. Follow-up period for full cohort of 30 patients. Follow-up duration for 13 patients receiving etanercept was not reported separately.
D. Clinical remission defined as the absence of active vasculitis, recovery/stabilisation of disease-related organ damage and absence of systemic inflammation.
E. Response to treatment was considered complete when clinical and laboratory remission could be achieved; partial when clinical or laboratory remission could not be achieved; and absent when neither clinical nor laboratory remission could be achieved. Clinical remission was defined as the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation. Laboratory remission was defined as normalisation of CRP levels in the local laboratory.
F. The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across 9 organ systems and a score of 0 indicating absent activity. The 'before' score was assessed at first presentation to the centre and the 'after' score at the most recent clinic visit after treatment with etanercept.

a. No comments relating to ischaemic events after etanercept were made for the remaining four patients.
b. . It was unclear whether there may be overlap of patients included in Li et al (2023) and Deuitch et al (2022) as some patients from Li et al (2023) had previously been reported in Deuitch et al (2022).
c. One patient developed digital necrosis resulting in a partial amputation due to poor compliance with etanercept. This patient had both CNS and non-CNS ischaemic events before treatment with etanercept.
d. Defined as persistent control of inflammatory parameters with no disease's flares or complications in the absence of any steroid treatment.
e. Defined as good control of disease activity with sporadic relapses and need of steroid on demand or increased steroid dosage.
f. It was unclear what the sequence of events was in terms of patients in complete remission, those who relapsed and the patient who died during follow-up as no further details were reported.
g. Information on symptoms both before and after commencing treatment with etanercept was available for three patients, and after commencing treatment only for two patients.
h. No comments relating to steroid use reduction after etanercept were made for the remaining four patients.
i. Information on treatment both before and after commencing treatment with etanercept was available for four patients j.
Normal CRP levels: 0.00 to 4.99 mg/L.
k. Twelve (92.3%) patients had elevated CRP levels at presentation, all were within the normal reference range after etanercept.
l. Nine (69.2%) patients had elevated ESR levels at presentation, all were within the normal reference range after etanercept.
m. Six (66.7%) patients had elevated CRP levels before etanercept. Elevated CRP was defined for all patients as > 5 mg/L.
n. One (11.11%) patient had elevated ESR levels before etanercept. Elevated ESR was not defined.
o. These values were indicated to be within the normal range although normal ranges were not specified. It was unclear whether values were within the normal range before initiation of etanercept as data were not available.

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.

References

Included studies

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NHS England
Wellington House
133-155 Waterloo Road
London
SE1 8UG