NHS England evidence review:

Adalimumab monotherapy for deficiency of adenosine deaminase 2 (DADA2)

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of adalimumab 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 they have a confirmed diagnosis of DADA2, or where there is a strong clinical suspicion of DADA2 and genetic testing results are awaited.

Adalimumab is a TNF inhibitor, also known as anti-TNF therapy, used to prevent strokes and other vasculitic complications. Adalimumab is delivered via subcutaneous injection, which allows patients to self-administer at home.

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, i.e. methotrexate. Currently used TNF inhibitors include etanercept, adalimumab, infliximab, certolizumab or golimumab but none are licensed or commissioned in England by the NHS for use in DADA2. Adalimumab 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 adalimumab more than others and the dose of adalimumab used.

This review includes studies where adalimumab is known to be the TNF inhibitor that patients received. Outcomes for patients who have received the TNF inhibitor etanercept 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 adalimumab 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 3 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 the TNF inhibitor etanercept are considered in a separate evidence review.

Six papers were identified for inclusion in this review on adalimumab monotherapy. Two studies were retrospective cohort studies (Andriessen et al 2023 and Li et al 2023) but were treated as retrospective case series for analysis as relevant data were described on an individual patient basis. Total sample sizes for the cohorts were 29 and 30 patients and nine patients from each study were treated with adalimumab and were included in this review. The remaining four studies were retrospective case series (Cooray et al 2021, Deuitch et al 2022, Melo et al 2023 and Nihira et al 2021), in which not all patients in the series were in scope (i.e. some patients were treated with other TNF inhibitors), and relevant data were mainly described on an individual patient basis. Included sample sizes ranged from three to fourteen. It is unclear whether there may be overlap of patients included in Andriessen et al (2023), Li et al (2023 and Deuitch et al (2022) as some patients from the Andriessen et al (2023) and Li et al (2023) cohorts were included in the National Institutes of Health cohort.

Across six retrospective case series, a total of 46 patients with DADA2 were treated with adalimumab. 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 ischemic events). Where reported in the included studies, the proportion of males ranged between 43% and 75%, and the median age at symptom onset ranged between five and fourteen years. The follow-up durations varied across studies, ranging between two months and more than 10 years.

The studies were published between 2019 and 2023 and were conducted in Brazil (Melo et al 2023), China (Li et al 2023), the Netherlands (Andriessen et al 2023), Japan (Nihira et al 2021), the UK (Cooray et al 2021) and one had a coordinating centre in the US with collaborating centres in other unspecified locations (Deuitch et al 2022). No comparator studies were identified. The included retrospective case series reported results 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 identified studies reported on relevant subgroups of patients that would benefit more from treatment with adalimumab.

In terms of clinical effectiveness:

- **Number of ischaemic events (critical outcome).**
- Three retrospective case series provided very low certainty evidence of fewer ischaemic events, including strokes, following initiation of treatment with adalimumab in patients with DADA2 at median of 12, 20 and 36 months follow-up / outcome measurement. One retrospective case series provided very low certainty evidence that two patients had recurrent ischaemic event symptoms without MRI abnormalities

  following initiation of treatment with adalimumab, one of whom had had a history of stroke before treatment with adalimumab. No other patients in the series reported ischaemic events before or after treatment at between 2 months and more than 10 years follow-up. Statistical significance was not reported for any of the studies.

[1] Baseline was any period before the initiation of adalimumab. Treatments received before the initiation of adalimumab varied widely between studies.

- **Disease activity/response (critical outcome).**
- Four retrospective case series provided very low certainty evidence of reduced DADA2 disease activity following initiation of treatment with adalimumab at median follow-up/ treatment times of 20 and 36 months or between two months and greater than ten years of follow-up. One retrospective case series provided very low certainty evidence of reduced clinical vasculitic disease activity after a median of 12 months following adalimumab treatment initiation in patients with DADA2. One retrospective case series provided very low certainty evidence that neutropenia, lymphopenia and hypogammaglobulinemia were not resolved by adalimumab in patients with DADA2, but one patient no longer had thrombocytopenia. Statistical significance was not reported for any of the studies.

- **Symptom alleviation (critical outcome).**
- Two retrospective case series provided very low certainty evidence of an improvement in some DADA2 symptoms following initiation of treatment with adalimumab: cutaneous symptoms, fever, PAN-like rash, arthralgia, IBD-like disease, aphthous stomatitis and livedo. The studies provided very low certainty evidence that more patients with DADA2 had seizures/paralysis on treatment with adalimumab. Numbers were small and statistical tests of significance were not reported.

- **Steroid use reduction (important outcome).**
- Three retrospective case series provided very low certainty evidence of steroid use reduction following initiation of treatment with adalimumab in patients with DADA2 at a median of 12, 17 and 20.2 months follow-up/ treatment; no statistical comparisons were reported.

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

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

- **Change in acute phase reactants (important outcome).**
- Three retrospective case series provided very low certainty evidence that median CRP and ESR levels improved in patients with DADA2 after initiation of treatment with adalimumab. One case series provided very low certainty evidence of an improvement in serum amylase A levels in patients with DADA2 following initiation of treatment with adalimumab, with all patients having levels within the normal range when on treatment. Follow-up durations ranged from 2 months to >10 years; no statistical measures were reported.

In terms of safety:

- One retrospective case series provided very low certainty evidence that no adverse events were observed following treatment with adalimumab in patients with DADA2; details were limited. Two retrospective case series provided very low certainty evidence that there were no deaths related to adalimumab therapy during the followup period. Median follow-up was less than 24 months for safety reporting.

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 adalimumab more than the wider population of interest.

Dose of adalimumab used:

- In one case series (Cooray et al 2021), patients received 40mg of adalimumab via subcutaneous injection every 14 days. Patients received a variety of concomitant treatments including aspirin, methotrexate, glucocorticoids and G-CSF.
- The dose of adalimumab was not reported in the other five case series in this review.

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

Limitations:

All of the outcomes reported were classed as very low certainty evidence. All of the included studies presented observed results only which increases selection bias and Type I errors. Limitations reducing certainty for the outcomes in case series included uncertainty about whether the inclusion of participants was complete or consecutive and uncertainty about the direct relevance of the population selected, particularly as none of the studies included information about the participating hospitals or centres. No patients or clinicians were blinded in any of the studies, which could increase uncertainty around the clinically reported outcomes (i.e. 'Disease response/activity,' 'Symptom alleviation'). All of the data were presented as single-patient data which was extracted from tables; no summary statistics or statistical analyses were included. A lack of comparator was also a limitation across all six retrospective case series.

Conclusion:

This evidence review includes six retrospective case series. All of the studies provided noncomparator data and the evidence for all the outcomes of interest was of very low certainty. These studies provided data on adalimumab for the treatment of DADA2 for the critical outcomes of number of ischaemic events, disease activity/response and symptom alleviation. Patients reported fewer new ischaemic events following treatment with adalimumab and less clinical disease activity using composite DADA2 disease activity measures at median follow-ups/treatments of 20 months and 36 months. Some clinical symptoms of DADA2 were reduced following treatment with adalimumab: cutaneous symptoms, fever, PAN-like rash, arthritis/ arthralgia, IBD-like disease, aphthous stomatitis and livedo; whilst adalimumab treatment had no effect on others: thrombocytopenia, neutropenia, lymphopenia and hypogammaglobulinemia. Increases in two symptoms (anaemia and seizures/paralysis) were reported in a small number of patients after starting treatment with adalimumab.

These studies also provided data on adalimumab for the treatment of DADA2 for the important outcomes of steroid use reduction and changes in acute phase reactants. No evidence was found for quality of life or hospitalisation. The included studies provided evidence of steroid use reduction and improved median serum C-reactive protein (CRP)

and erythrocyte sedimentation rates (ESR) levels in patients with DADA2 following stabilisation of adalimumab therapy.

Safety outcomes were reported narratively. One study reported no adverse events. Two studies each reported a single death during follow-up; neither were directly related to adalimumab therapy.

No evidence on cost effectiveness was identified.

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, for a range of pre-specified critical and important outcomes, suggesting that adalimumab may be an effective treatment for DADA2, but it is not possible to draw any conclusions about the effectiveness of adalimumab 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 adalimumab compared with standard care?
2. In patients with deficiency of adenosine deaminase type 2, what is the safety of adalimumab compared with standard care?
3. In patients with deficiency of adenosine deaminase type 2, what is the cost effectiveness of adalimumab compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from adalimumab more than the wider population of interest?
5. From the evidence selected, what dose of adalimumab 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

Six papers were identified for inclusion (Andriessen et al 2023, Cooray et al 2021, Deuitch et al 2022, Li et al 2023, Melo et al 2023 and Nihira et al 2021). Two studies were

retrospective cohort studies (Andriessen et al 2023 and Li et al 2023) but were treated as retrospective case series for analysis as relevant data were described on an individual patient basis. The remaining four studies were retrospective case series, in which not all patients in the series were in scope (i.e. some patients were treated with other tumour necrosis factor (TNF) inhibitors), and relevant data were mainly described on an individual patient basis. It is unclear whether there may be overlap of patients in Andriessen et al (2023), Li et al (2023) and Deuitch et al (2022) as some patients from the Andriessen et al (2023) and Li et al (2023) cohorts were included in National Institutes of Health report.

No comparative evidence was identified comparing adalimumab monotherapy versus best supportive care alone. No studies were identified that reported quality of life (QoL) or hospitalisation. No cost effectiveness studies were identified for inclusion in this review. No studies were identified reporting on relevant subgroups of patients that would benefit more from treatment with adalimumab.

The TNF inhibitor etanercept, 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	29 patients with genetically confirmed DADA2 Total cohort: N=29 Adalimumab: n=9 **Subgroups** • Stoke / no stroke • Vasculopathy phenotype / hematologic phenotype	**Intervention** Adalimumab, dose not stated. Median treatment time unknown. **Comparison** No Comparator **Concomitant treatments** Concomitant treatments included methotrexate, GCSF, filgrastim, IVIG and nanogam.	Mean follow-up not reported. Patients followed-up for between two months and >10 years[a] **Critical outcomes** • Number of ischaemic events • Disease response/activity • Anaemia • Thrombocytopenia • Neutropenia • Lymphopenia • Hypogammaglobulinemia • Symptom alleviation • Cutaneous involvement (except eczema) • Fever • PAN-like rash/other cutaneous vasculitis • Arthralgia • IBD-like disease • Aphthous stomatitis
Cooray et al 2021 Retrospective case Series	31 patients with genetically confirmed DADA2 Total cohort: N=31 Adalimumab: n=14	**Intervention** Adalimumab, 40mg every 14 days	Median (range) treatment time (months): 12 (0 to 59) **Critical outcomes** • Number of ischaemic events

Study	Population	Intervention and comparison	Outcomes reported
Specialist centre, UK	No subgroups reported	Total follow-up after adalimumab initiation: 261 patient-months **Comparison** No Comparator **Concomitant treatments** Concomitant treatments included aspirin, methotrexate, glucocorticoids and G-CSF.	• Patients experiencing ischaemic events • Patients experiencing CNS ischaemic events • Patients experiencing non-CNS ischaemic events • Disease activity/response • PVAS score **Important outcomes** • Steroid use reduction • Change in acute phase reactants • CRP level • CRP levels outside of normal range • ESR level • ESR levels outside of normal range • SAA level • SAA levels outside of normal range • Safety
Deuitch et al 2022 Retrospective Case Series Multicentre, locations not stated (coordinating centre US, authors from US, Canada and China)	31 patients with genetically confirmed DADA2 Total cohort: N=31 Adalimumab: n=7 No subgroups reported	**Intervention** Adalimumab, dose not stated Median (range) treatment time (months): 17 (4 to 60) **Comparison** No Comparator **Concomitant treatments** Concomitant treatments included IVIG and prednisone.	Median (range) treatment time (months): 17 (4 to 60) **Critical outcomes** • Symptom alleviation • Livedo • Arthritis, livedo and racemosa • Other symptoms **Important outcomes** • Steroid use reduction • Change in acute phase reactants • Median CRP

Li et al 2023 Retrospective cohort study (assessed as a case series as data presented individually for each patient) Multicentre (17 hospitals), China	30 patients with genetically confirmed DADA2 Total cohort: N=30 Adalimumab: n=9 No subgroups reported	**Intervention** Adalimumab, dose not stated Median treatment time unknown. **Comparison** No Comparator **Concomitant treatments** Concomitant treatments included mycophenolate mofetil, glucocorticoids, methotrexate NSAIDS, tacrolimus, thalidomide and IVIG.	Median (range) follow-up (months): 20.2 (5 to 36)[b] **Critical outcomes** • Number of ischaemic events • Disease activity/response **Important outcomes** • Steroid use reduction • Change in acute phase reactants • CRP level • Elevated CRP levels • ESR level • Elevated ESR levels
Study	**Population**	**Intervention and comparison**	**Outcomes reported**
Melo et al 2023 Retrospective case Series Multicentre (10 centres), Brazil	18 patients with genetically confirmed DADA2 Total cohort: N=18 Adalimumab: n=4 No subgroups reported	**Intervention** Adalimumab, dose not stated Median treatment time unknown. **Comparison** No Comparator **Concomitant treatments** Concomitant treatments (or previous treatments) included steroids, azathioprine, rituximab, mycophenolate and sirolimus.	Median (range) follow-up (months): 20 (12 to 24) **Critical outcomes** • Disease activity/response **Important outcomes** • Safety
Nihira et al **2021** Retrospective case Series Multicentre, Japan	Eight patients with genetically confirmed DADA2 Total cohort: N=8 Adalimumab: n=3 No subgroups reported	**Intervention** Adalimumab, dose not stated Median (range) treatment time (years): 3 (2.75 to 5) **Comparison** No Comparator **Concomitant treatments** Concomitant treatments included methotrexate and subcutaneous immunoglobulin.	Median (range) follow-up (months): 36 (23 to 48) **Critical outcomes** • Number of ischaemic events • Disease activity/response

Abbreviations CNS: central nervous system; CRP: C reactive protein; DADA2: Deficiency of Adenosine Deaminase-2; ESR: erythrocyte sedimentation rate; G-CSF: Granulocyte colony stimulating factor; IBD: Inflammatory bowel disease; IQR: interquartile range; n: number; IVIG: intravenous immunoglobulin; mg: milligrams; NSAIDs: non-steroidal anti-inflammatory drugs; PAN: polyarteritis nodosa; PVAS: Paediatric Vasculitis Activity Score; SAA: serum amylase A; UK: United Kingdom; US: United States
a Follow-up period for full cohort of 29 patients. Follow-up details for nine patients receiving adalimumab were not available separately b Follow-up period for full cohort of 30 patients. Follow-up details for nine patients receiving adalimumab were not available separately

5. Results

In patients with deficiency of adenosine deaminase type 2, what is the clinical effectiveness and safety of adalimumab 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 treatment with adalimumab. Three retrospective case series reported the number of patients with ischaemic events (including stroke) at a median of 20.2 months, 36 months or between 2 and >10 years follow-up. One case series reported CNS and non-CNS ischaemic events at a median of 12 months treatment. All outcomes are compared to baseline.[2] **Between two months and >10 years follow-up:** • One retrospective case series (Andriessen et al 2023) (n=9) reported that two patients, one with a history of stroke, *"developed gait disorder, diplopia and dysarthria while on TNF-inhibition [adalimumab] without abnormalities on MRI"*. None of the other patients providing data had evidence of ischaemic events before adalimumab or after initiation of adalimumab; no tests of statistical significance were performed. **(VERY LOW)** **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) (n=14) reported that prior to adalimumab treatment, 11 patients (79%) had a total of 24 ischaemic events.[2] During the follow-up period, following initiation of adalimumab, two patients reported two total ischaemic events. No statistical tests were performed. **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=14) reported that prior to adalimumab treatment, five patients (36%) had a total of 13 central nervous system (CNS) ischaemic events. During the follow-up period, following initiation of adalimumab, one patient reported one CNS ischaemic event. No statistical tests were performed. **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=14) reported that prior to adalimumab treatment, seven (50%) patients had a total of 11 non-CNS ischaemic events. During the follow-up period, following initiation of adalimumab, one patient reported one non-CNS ischaemic event. No statistical tests were performed. **(VERY LOW)** **At median 20.2 months follow-up (range 23 to 48 months):** • One retrospective case series (Li et al 2023) (n=9) reported that *"… no patients have had a stroke during the time they have been on treatment".* No further details were provided, and no summary statistics were performed. **(VERY LOW)** **At median 36 months follow-up (range 23 to 48 months):** • One retrospective case series (Nihira et al 2021) (n=3) reported that "*no patient[s] had a cerebral infarction or haemorrhage after starting treatment".*

[2] Baseline was any period before the initiation of adalimumab. Treatments received before the initiation of adalimumab varied widely between studies.

Outcome	Evidence statement

[2] This outcome included both CNS and non-CNS (arteries supplying viscera and peripheries) ischaemic events. Ischaemic events were diagnosed based on clinical features together with brain MRI/MRA and/or other imaging modalities such as ultrasound scan, CT-angiography or selective visceral catheter arteriography where indicted.

	No further details were provided, and no summary statistics were performed. **(VERY LOW)** **Three retrospective case series provided very low certainty evidence of fewer ischaemic events, including strokes, following initiation of treatment with adalimumab in patients with DADA2 at median of 12, 20 and 36 months, 36 months follow-up/ outcome measurement. One retrospective case series provided very low certainty evidence that two patients had recurrent ischaemic event symptoms without MRI abnormalities following initiation of treatment with adalimumab, one of whom had had a history of stroke before treatment with adalimumab. No other patients in the series reported ischaemic events before or after treatment at between 2 months and more than 10 years follow-up. Statistical significance was not reported for any of the studies.**
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. Six retrospective case series provided non-comparative evidence relating to disease activity/response in patients with DADA2 after initiation of treatment with adalimumab. Three retrospective case series reported the disease response at a median of 20 months, 20.2 months, 36 months follow-up; median 12 months or 17 months of adalimumab treatment; or between 2 and >10 years follow-up . Disease activity/response was measured differently in each study, but all studies that used a *composite* variable or haematological measures to evaluate response to treatment are included here. All outcomes are compared to baseline. **At 2 months to >10 years follow-up:** • One retrospective case series (Andriessen et al 2023) (n=8) reported that more patients had anaemia following treatment with adalimumab (before adalimumab, 2/8 (25%); after initiation of adalimumab, 3/8 (38%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had thrombocytopenia following treatment with adalimumab (before adalimumab, 1/8 (13%); after initiation of adalimumab, 0/8 (0%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that neutropenia was not resolved with adalimumab treatment (before adalimumab, 3/8 (38%); after initiation of adalimumab, 3/8 (38%); neutropenia persisted in the same three patients). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that lymphopenia was not resolved with adalimumab treatment (before adalimumab, 2/8 (25%); after initiation of adalimumab, 2/8 (25%); lymphopenia persisted in the same two patients). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that hypogammaglobulinemia was not resolved with adalimumab treatment (before adalimumab, 1/8 (13%); after initiation of adalimumab, 1/8 (13%); hypogammaglobulinemia persisted in the same patient). **(VERY LOW)** **At median 12 months treatment (range 0 to 59 months):**

	• One retrospective case series (Cooray et al 2021) reported that prior to adalimumab treatment, median PVAS scores[3] were 17.5 (IQR 13.5 to 31.3). After a median of 12 months following initiation of adalimumab treatment, median PVAS scores reduced (improved) to 2.0 (IQR 1.0 to 4.0). **(VERY LOW)**

Outcome	**Evidence statement**

[3] The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across nine 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.

	At median 20 months follow-up (range 12 to 24 months): • One retrospective case series (Melo et al 2023) reported that 100% of patients (4/4) achieved complete remission[4] following initiation of treatment with adalimumab. **(VERY LOW)** **At median 20.2 months follow-up (range 5 to 36 months):** • One retrospective case series (Li et al 2023) reported that the majority of patients were in complete remission[5] (CR: 7, 78%; PR: 2, 22%; NR: 0, 0%) after initiation of adalimumab treatment when compared to baseline (CR: 0, 0%; PR: 3, 33%; NR: 6, 67%). No statistical tests were performed. **(VERY LOW)** **At median 36 months follow-up (range 23 to 48 months):** • One retrospective case series (Nihira et al 2021) reported that 100% of patients (3/3) achieved complete response following initiation of treatment with adalimumab. No further details were provided, and no summary statistics were performed. **(VERY LOW)** **Four retrospective case series provided very low certainty evidence of reduced DADA2 disease activity following initiation of treatment with adalimumab at median follow-up/ treatment times of 20 and 36 months or between two months and greater than ten years of follow-up. One retrospective case series provided very low certainty evidence of reduced clinical vasculitic disease activity after a median of 12 months following adalimumab treatment initiation in patients with DADA2. One retrospective case series provided very low certainty evidence that neutropenia, lymphopenia and hypogammaglobulinemia were not resolved by adalimumab in patients with DADA2, but one patient no longer had thrombocytopenia. Statistical significance was not reported for any of the studies.**

[4] Complete remission: clinical (the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation) AND laboratory (normalisation of CRP levels in local laboratory) control achieved; Partial remission: clinical OR laboratory control achieved; Absent remission: Neither clinical nor laboratory control achieved

[5] Complete remission (CR): persistent control of inflammatory parameters with no disease's flares or complications in the absence of any steroid treatment; Partial remission (PR): good control of disease activity with sporadic relapses and need of steroid on demand or increased steroid dosage; No remission (NR): little or absent response with persistence of systemic flares and/or complications

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. Two retrospective case series provided non-comparative evidence relating to symptom alleviation in patients with DADA2 after initiation of treatment with adalimumab. One retrospective case series reported symptom alleviation at followup in the range of 2 months to >10 years, whilst the other case series reported outcomes following a median of 17 months of treatment. All outcomes are compared to baseline. **At 2 months to >10 years follow-up:** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had cutaneous symptoms following treatment with adalimumab (before adalimumab, 6/8 (75%); after initiation of adalimumab, 0/8 (0%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had fever following treatment with adalimumab (before adalimumab, 4/8 (50%); after initiation of adalimumab, 0/8 (0%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had PAN-like rash and other cutaneous vasculitis's following treatment with adalimumab (before adalimumab, 2/8 (25%); after initiation of adalimumab, 0/8 (0%)). **(VERY LOW)**

Outcome	**Evidence statement**

	• One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had arthralgia following treatment with adalimumab (before adalimumab, 3/8 (38%); after initiation of adalimumab, 1/8 (13%). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had symptoms of IBD-like disease following treatment with adalimumab (before adalimumab, 1/8 (13%); after initiation of adalimumab 0/8 (0%)). **(VERY LOW)** • One retrospective case series (Andriessen et al 2023) (n=8) reported that fewer patients had symptoms of aphthous stomatitis following treatment with adalimumab (before adalimumab, 4/8 (50%); after initiation of adalimumab, 1/8 (13%)). **(VERY LOW)** **At median 17 months treatment (range 4 to 60 months):** • One retrospective case series (Deuitch et al 2022) (n=7) reported that livedo was noted in one patient prior to adalimumab. Following initiation of adalimumab, clinicians noted the patient was *"clinically well, some livedo"*[6]. **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=7) reported that one patient had arthritis, livedo and racemosa symptoms prior to treatment; after initiation of adalimumab the livedo and racemosa resolved and the arthritis was downgraded to *"mild joint pain".* **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=7) reported follow-up symptoms for three patients with no baseline data. After initiation of adalimumab, one patient was *"clinically well",* one patient was *"clinically well with come neutropenia"* and one patient was reporting the symptoms of seizures and paralysis. **(VERY LOW)** • One retrospective case series (Deuitch et al 2022) (n=7) reported follow-up symptoms for two patients reported to be *"not in flare"*[7] at baseline. After initiation of adalimumab, one patient was *"clinically well"* and one patient had concurrent gastroenteritis. **(VERY LOW)** **Two retrospective case series provided very low certainty evidence of an improvement in some DADA2 symptoms following initiation of treatment with adalimumab: <u>cutaneous symptoms, fever, PAN-like rash, arthralgia, IBD-like disease, aphthous stomatitis and livedo</u>. The studies provided very low certainty evidence that more patients with DADA2 had <u>seizures/paralysis</u> on treatment with adalimumab. Numbers were small and statistical tests of significance were not reported.**
Important outcomes	

[6] Definition of "*clinically well*" was not provided by authors
[7] Definition of *"not in flare"* was not provided by authors

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. Three retrospective case series provided non-comparative evidence relating to steroid use reduction in patients with DADA2 after initiation of treatment with adalimumab. Three retrospective case series reported steroid use reduction at a median of 12, 17 and 20.2 months follow-up /treatment. All outcomes are compared to baseline. **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) (n=14) reported fewer patients were taking steroids after initiating adalimumab treatment (before adalimumab treatment: n=10 (71.4%), after initiation of adalimumab treatment: one patient remained on steroids (7.1%) and *"one patient is being weaned off steroids"*). No statistical comparisons were reported. **(VERY LOW)**

Outcome	Evidence statement
	At median 17 months treatment (4 to 60 months): • One retrospective case series (Deuitch et al 2022) (n=7) reported that fewer patients were taking steroids (prednisone) after commencing adalimumab treatment (before adalimumab: n=2 (28.6%), after initiation of adalimumab: n=1 (14.3%)). No statistical comparisons were reported. **(VERY LOW)** **At median 20.2 months follow-up (range 5 to 36 months):** • One retrospective case series (Li et al 2023) (n=9) reported that fewer patients were taking glucocorticoids after commencing adalimumab treatment (before adalimumab: n=9 (100%), after initiation of adalimumab: n=4 (44%)). No statistical comparisons were reported. **(VERY LOW)** **Three retrospective case series provided very low certainty evidence of steroid use reduction following initiation of treatment with adalimumab in patients with DADA2 at a median of 12, 17 and 20.2 months follow-up /treatment; no statistical comparisons were reported.**
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:** Not applicable	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 and inform their treatment decision making. **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. Three retrospective case series provided non-comparative evidence relating to changes acute phase reactants (SAA, CRP and ESR) in patients with DADA2 after initiation of treatment with adalimumab. Three retrospective case series reported changes in acute phase reactants at 12, 17 and 20.2 months follow-up /treatment. All outcomes are compared to baseline. <u>C-reactive protein (CRP)</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) reported a reduction in median CRP after initiation of adalimumab treatment (Before: n=14; 21 mg/L (IQR 11 to 125 mg/L); After: n=13; 5 mg/L (IQR 4 to 5 mg/L)[8]). **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=14) reported that prior to adalimumab treatment, 10/14 patients (71.4%) reported CRP levels outside of normal range[9]; following initiation of adalimumab treatment, 1/13 patients (7.7%) had CRP levels outside of normal range. **(VERY LOW)** **At median 17 months treatment (range 4 to 60 months):** • One retrospective case series (Deuitch et al 2022) reported a reduction in median CRP after initiation of adalimumab treatment (Before: n=4; 9.7

Outcome	**Evidence statement**

[8] Some patients CRP levels were indicated as being <5 (too low to measure) following adalimumab treatment; for statistical summary the level of 5 mg/L was used

[9] CRP levels >10 mg/L were indicated as being out of target range

	mg/L (IQR 9.2 to 16.7 mg/L); After: n=7; 8.0 mg/L (IQR 1.6 to 8.3 mg/L)). **(VERY LOW)** **At median 20.2 months follow-up (range 5 to 36 months):** • One retrospective case series (Li et al 2023) reported that the median CRP levels had decreased following initiation of treatment with adalimumab (Before: n=9; 40 mg/L (IQR 33 to 49 mg/L); After adalimumab:[10] 8 mg/L (IQR 8 to 8 mg/L)). No statistical tests were performed. **(VERY LOW)** • One retrospective case series (Li et al 2023) (n=9) reported that all nine (100%) patients had elevated CRP levels before adalimumab. Following initiation of adalimumab, two patients (22.2%) had elevated CRP levels. No statistical tests were performed. **(VERY LOW)** <u>Erythrocyte sedimentation rate (ESR)</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) reported a reduction in median ESR after initiation of adalimumab treatment (Before (n=14): 52 mm/hr (IQR 29 to 104 mm/hr); After (n=13): 9 mm/hr (IQR 5 to 14 mm/hr)). **(VERY LOW)** • One retrospective case series (Cooray et al 2021) reported that prior to adalimumab treatment, 10/14 DADA2 patients (71.4%) reported ESR levels outside of normal range[11]; following initiation of adalimumab treatment, one patient (7.7%) had ESR levels outside of normal range. **(VERY LOW)** **At median 20.2 months follow-up (range 5 to 36 months):** • One retrospective case series (Li et al 2023) reported median ESR levels had decreased following initiation of treatment with adalimumab (Before: n=9; 44 mm/hr (IQR 22 to 49 mm/hr); After: n=9; 8 mm/hr (IQR 8 to 8 mm/hr)). No statistical tests were performed. **(VERY LOW)** • One retrospective case series (Li et al 2023) reported that 5/9 (55.6%) patients had elevated ESR levels before adalimumab. Following initiation of adalimumab, all patients had ESR levels within the reference range. No statistical tests were performed. **(VERY LOW)** <u>Serum amylase A (SAA)</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) reported a beneficial reduction in median serum amylase A after initiation of adalimumab treatment (Before: n=10, 85.0 mg/L (IQR 17.2 to 96.0 mg/L); After: n=7, 7.0 mg/L (IQR 4.8 to 12.2 mg/L)). **(VERY LOW)** • One retrospective case series (Cooray et al 2021) (n=10) reported that prior to adalimumab treatment, seven patients (70%) reported serum amylase A levels outside of normal range; following initiation of adalimumab treatment, no patients (0%) had SAA levels outside of normal range (normal ranges were not specified). **(VERY LOW)** **Three retrospective case series provided very low certainty evidence that median <u>CRP and ESR levels</u> improved in patients with DADA2 after initiation of treatment with adalimumab. One case series provided very low certainty evidence of an improvement in <u>serum amylase A levels</u> in patients with DADA2 following initiation treatment with adalimumab, with all patients having levels within the normal range when on treatment. Follow-up durations ranged from 2 months to >10 years; no statistical measures were reported.**
Safety	

[10] Some patients had CRP levels below detectable levels (<8 mg/L). These were coded as 8 mg/L to calculate median and IQR

[11] CRP levels >10 mg/L were indicated as being out of target range

Safety outcomes **Certainty of evidence:**	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

Outcome	**Evidence statement**
Very low	a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. Two retrospective case series provided non-comparative evidence relating to safety in patients with DADA2 after initiation of treatment with adalimumab. One retrospective case series reported the disease response at a median of 20.2 months follow-up and the other at a median of 12 months of treatment. <u>Adverse Events</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) stated that *"no adverse events were reported with adalimumab or etanercept"* following a median of 12 months of treatment. **(VERY LOW)** <u>Deaths</u> **At median 12 months treatment (range 0 to 59 months):** • One retrospective case series (Cooray et al 2021) reported that one patient had bone marrow failure and died of complications of sepsis and bowel perforation; the patient had one dose of adalimumab. **(VERY LOW)** **At median 20 months follow-up (range 12 to 24 months):** • One retrospective case series (Melo et al) reported that one patient, treated with adalimumab, died during the follow-up period due to disseminated staphylococcal infection. **(VERY LOW)** **One retrospective case series provided very low certainty evidence that no <u>adverse events</u> were observed following treatment with adalimumab in patients with DADA2; details were limited. Two retrospective case series provided very low certainty evidence that two patients died during the followup period, but there was no evidence that these <u>deaths</u> related to adalimumab therapy. Median follow-up was less than 24 months for safety reporting.**
Abbreviations CNS: central nervous system; CR: complete remission; CRP: C reactive protein; CT: computerised tomography; DADA2: Deficiency of Adenosine Deaminase-2; ESR: erythrocyte sedimentation rate; hr: hour; IBD: Inflammatory bowel disease; IQR: interquartile range; n: number; L: litre; mg: milligrams; mm: millimetres; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; NR: no remission; PAN: polyarteritis nodosa; PR: partial remission; Pt: patient; PVAS: Paediatric Vasculitis Activity Score; SAA: serum amylase A; TNF: Tumour Necrosis Factor	

In patients with deficiency of adenosine deaminase type 2, what is the cost effectiveness of adalimumab 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 adalimumab more than the wider population of interest?

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

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

Outcome	Evidence statement
Dose of adalimumab	In one case series (Cooray et al 2021), patients received 40mg of adalimumab via subcutaneous injection every 14 days. Patients received a variety of concomitant treatments including aspirin, methotrexate, glucocorticoids and G-CSF. The dose of adalimumab was not reported in the other five case series in this review (Andriessen et al 2023, Deuitch et al 2022, Li et al 2023, Melo et al 2023 and Nihira et al 2021).
Abbreviations G-CSF: Granulocyte colony stimulating factor; mg: milligram	

6. Discussion

This evidence review examines the clinical effectiveness, safety and cost effectiveness of adalimumab 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. Evidence on patients who received the TNF inhibitor etanercept is considered in a separate review.

Six papers were included in this review: two retrospective cohort studies (Andriessen et al 2023 and Li et al 2023) and four retrospective case series (Cooray et al 2021, Deuitch et al 2022, Melo et al 2023 and Nihira et al 2021). All relevant data were described on an individual patient basis and, thus, all studies were analysed as retrospective case series. No comparator studies were identified. The included retrospective case series reported results compared to baseline. Baseline was defined as any period before the initiation of adalimumab; treatments received before the initiation of adalimumab varied widely between studies.

The sample sizes of the patients treated with adalimumab in the selected studies varied from three patients to fourteen patients, and median duration of follow-up or treatment duration at which outcomes were reported ranged from 2 to 36 months, or in one study a range of 2 months to >10 years. As treatment was ongoing, this review has reported outcomes by treatment duration where studies did not report length of follow-up. One retrospective case series followed patients with DADA2 from seven university hospitals in the Netherlands (Andriessen et al 2023) for between two months and over ten years. The cohort included 29 patients with DADA2, nine of whom received adalimumab. Another retrospective case series (Cooray et al 2021) followed 31 DADA2 patients referred to a single paediatric specialist hospital in the UK, of whom 14 received treatment with adalimumab; outcomes were reported after a median of 12 months of adalimumab treatment. One retrospective case series in China (Li et al 2023) followed 30 DADA2 patients for a median of 20.2 months; nine patients received adalimumab anti-TNF monotherapy. Melo et al (2023) and Nihira et al (2021) reported on national cohorts in Brazil

(N=18, 4 on adalimumab) and Japan (N=8, 3 on adalimumab) with median follow-up times of 20 months and 36 months, respectively. Finally, Deuitch et al (2022) reported a National Institutes of Health collaboration cohort of 31 DADA2 patients from the US and collaborating centres (locations were not stated), of whom seven received adalimumab treatment; outcomes were reported after a median of 17 months of adalimumab treatment. It is possible that there may be overlap of patients included in Andriessen et al (2023) and Deuitch et al (2022) as some patients from Andriessen et al (2023) have been included in National Institutes of Health cohorts. In addition, Li et al (2023) reported that twelve patients in their cohort had previously been reported in the literature, including in Deuitch et al (2022).

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 ischemic events). Limited demographic details were provided; where reported in the included studies, the proportion of males ranged between 43% and 75%, and the median age at symptom onset ranged between five and fourteen years. Concomitant treatments varied across and within the studies; examples include intravenous immunoglobulin (IVIG), mycophenolate mofetil, glucocorticoids, methotrexate, thalidomide and non-steroidal anti-inflammatory drugs (NSAIDs).

Evidence was identified for all the critical outcomes of interest for this review. No evidence was identified for the important outcomes of quality of life or hospitalisation, or for cost effectiveness.

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., haematological measures) would be reported as 'Disease activity/response'. Any change in individual clinical symptoms, such as fever or rash, would be reported as 'Symptom alleviation'.

Many of the composite measures of ‘Disease activity/response’ were poorly defined in the reports. Authors reported *“complete response”* and *“clinically well”* with no further details. One 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”*; no further details were given. 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 amylase A. Evidence on adalimumab dosing was available from one retrospective case series; dose of adalimumab was not reported for five studies. None of the identified studies reported on relevant subgroups of patients that would benefit more from treatment with adalimumab. No evidence on cost effectiveness was identified. No specific detail about what the minimal clinically important thresholds or differences might be was reported for the outcomes considered.

All of the outcomes reported were classed as very low certainty evidence. All of the included studies presented observed results only which increases selection bias and Type I errors. Limitations reducing certainty for the outcomes in case series included uncertainty about whether the inclusion of participants was complete or consecutive and uncertainty about the direct relevance of the population selected, particularly as none of the studies included information about the participating hospitals or centres. No patients or clinicians were blinded in any of the studies, which could increase uncertainty around the clinically reported outcomes (i.e. 'Disease response/activity,' 'Symptom alleviation'). All of the data were presented as single-patient data which was extracted from tables; no summary statistics or statistical analyses were included. A lack of comparator was also a limitation across all six retrospective case series.

7. Conclusion

This evidence review includes six retrospective case series. All of the studies provided noncomparator data and the evidence for all the outcomes of interest was of very low certainty. These studies provided data on adalimumab for the treatment of DADA2 for the critical outcomes of number of ischaemic events, disease activity/response and symptom alleviation. Patients reported fewer new ischaemic events following treatment with adalimumab and less clinical disease activity using composite DADA2 disease activity measures at median follow-ups/treatments of 20 months and 36 months. Some clinical symptoms of DADA2 were reduced following treatment with adalimumab: cutaneous symptoms, fever, PAN-like rash, arthritis/arthralgia, IBD-like disease, aphthous stomatitis and livedo; whilst adalimumab treatment had no effect on others: thrombocytopenia, neutropenia, lymphopenia and hypogammaglobulinemia. Increases in two symptoms (anaemia and seizures/paralysis) were reported in a small number of patients after starting treatment with adalimumab.

These studies also provided data on adalimumab for the treatment of DADA2 for the important outcomes of steroid use reduction and changes in acute phase reactants. No evidence was found for quality of life or hospitalisation. The included studies provided evidence of steroid use reduction and improved median serum C-reactive protein (CRP) and erythrocyte sedimentation rates (ESR) levels in patients with DADA2 following stabilisation of adalimumab therapy.

Safety outcomes were reported narratively. One study reported no adverse events. Two studies each reported a single death during follow-up; neither were directly related to adalimumab therapy. One study provided information on dose adalimumab: 40mg of adalimumab via subcutaneous injection every 14 days.

The risk of bias was generally high, with limitations reducing the certainty in the outcomes including the lack of blinding in relation to more subjective outcomes, selection bias in relation to non-consecutive and incomplete inclusion of study participants and the lack of any statistical analyses. There was also some uncertainty about the length of follow-up for some of the studies, as only median treatment length was reported, or no median follow-up was reported with a large range in follow-up times.

No evidence on cost effectiveness was identified.

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, for a range of pre-specified critical and important outcomes, suggesting that adalimumab may be an effective treatment for DADA2, but it is not possible to draw any conclusions about the effectiveness of adalimumab 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 adalimumab compared with standard care?
2. In patients with deficiency of adenosine deaminase type 2, what is the safety of adalimumab compared with standard care?
3. In patients with deficiency of adenosine deaminase type 2, what is the cost effectiveness of adalimumab compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from adalimumab more than the wider population of interest?
5. From the evidence selected, what dose of adalimumab 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	Adalimumab monotherapy [Adalimumab 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	**<u>Clinical Effectiveness</u>** 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 selfperceived 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 preprints
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 ten 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.

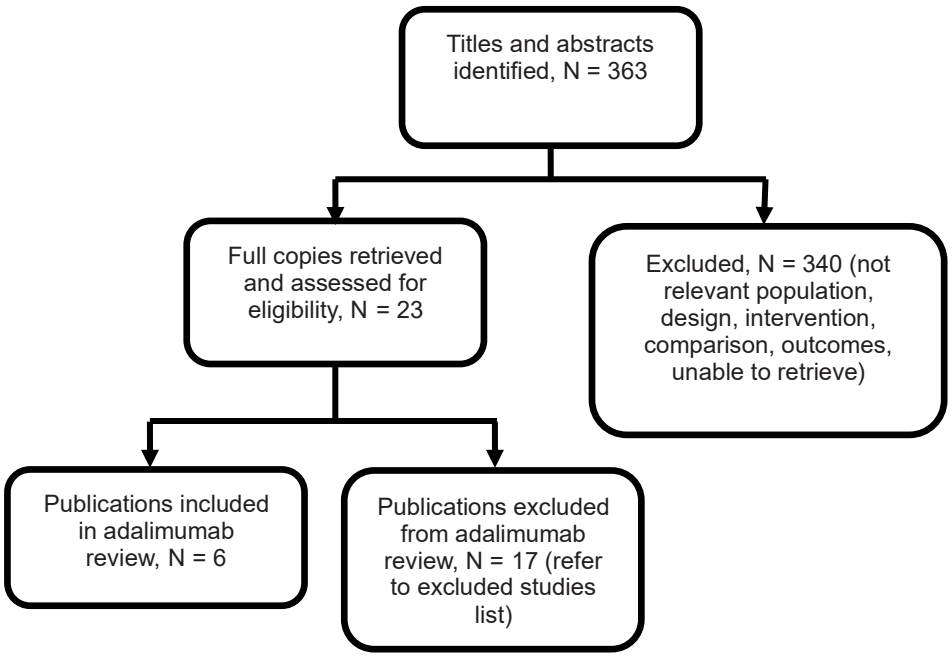
Medline search strategy:

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, six references contained outcomes that could be extracted for adalimumab and are included in this evidence review. A further ten references were included in the evidence review on etanercept for DADA2. The 17 references excluded from this evidence review on adalimumab are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale
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.	No results for patients treated with adalimumab, only pooled anti-TNF outcomes and patients treated with etanercept. Included in the review on etanercept for DADA2.
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 adalimumab 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 adalimumab 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 adalimumab, only pooled anti-TNF outcomes.
Celikel E, Aydin F, Tekin ZE, Kurt T, Sezer M, Tekgoz N, et al. Deficiency of adenosine deaminase 2 as an unrecognized cause of earlyonset stroke and cranial nerve palsy. Northern Clinics of Istanbul. 2023;10(4):411-7.	Incorrect intervention. Patients treated with etanercept not adalimumab.
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 adalimumab.
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.
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.	Incorrect intervention. Patients treated with etanercept not adalimumab.
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.	Incorrect intervention. Patients treated with etanercept not adalimumab.
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.	No results for patients treated with adalimumab, only pooled anti-TNF outcomes and patients treated with etanercept.
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	Incorrect population, patients did not have confirmed DADA2.

Study reference	Reason for exclusion
MPA patients without poor-prognosis factors. Autoimmunity reviews. 2014;13(9):945?53.	
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 adalimumab, only pooled anti-TNF outcomes.
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.	Incorrect intervention. Patients treated with etanercept not adalimumab.
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 adalimumab, only pooled anti-TNF outcomes.
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 adalimumab, 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 ADA2 residual activity and phenotype	Patients with DADA2 **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=9 patients received adalimumab **Baseline characteristics** (n=9 receiving adalimumab) Male: 4 (44%) Median (IQR) age at study inclusion (years): 25 (15 to 47) Median (IQR) age at disease onset (years): 11 (1 to 16) Predominant phenotype, n (%):	**Intervention** Adalimumab, dose not stated **Comparison** No comparator **Concomitant treatments** • Three patients received adalimumab monotherapy • Three patients received concomitant treatment with methotrexate • One patient received G-CSF alongside adalimumab • One patient received both filgrastim and IVIG alongside adalimumab • One patient received concomitant treatment with nanogam	Follow-up between two months and >10 years[12] **Critical outcomes** **Number of ischaemic events** *Stroke*, n (%); n=9 Before adalimumab: 1 (11.1%) After initiation of adalimumab: 0 *Episodes of recurrent ischaemia without MRI abnormalities*, n (%); n=9 Before adalimumab: 0 After initiation of adalimumab: 2 (22.2%) One of the patients with recurrent ischaemia after initiation of adalimumab was the same patient who had had a stroke before treatment. **Disease response/activity** Haematological measures, n(%); n=8 *Anaemia* • Before adalimumab: 2 (25%) • After initiation of adalimumab: 3 (38%) • Before adalimumab two patients had anaemia; After initiation of adalimumab, one additional patient developed anaemia. *Thrombocytopenia*	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. Not applicable **Other comments**: This was a retrospective case series which included the patients from all seven university hospitals in the Netherlands. Eligible patients had a confirmed genetic diagnosis of DADA2; 29 of 32 eligible patients provided consent and were included in the case series, nine of whom started treatment with adalimumab. It is not clear if all patients treated at the

[12] Follow-up period for full cohort of 29 patients. Follow-up details for 9 patients receiving adalimumab were not available separately

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study dates Not stated	• inflammatory vasculopathy: 3 (33%) • Hematologic: 2 (22%) • Mixed: 4 (44%)		• Before adalimumab: 1 (13%) • After initiation of adalimumab: 0 (0%) *Neutropenia* • Before adalimumab: 3 (38%) • After initiation of adalimumab: 3 (38%) • Three patients had neutropenia before adalimumab, and this remained in all three patients after initiation of treatment *Lymphopenia* • Before adalimumab: 2 (25%) • After initiation of adalimumab: 2 (25%) • Two patients had lymphopenia before adalimumab, and this remained in both patients after initiation of treatment *Hypogammaglobulinemia* • Before adalimumab: 1 (13%) • After initiation of adalimumab: 1 (13%) • One patient had hypogammaglobulinemia before adalimumab, and this remained after initiation of treatment **Symptom alleviation** DADA2 Symptoms, n (%); n=8 *Cutaneous involvement (except eczema)* • Before adalimumab: 6 (75%) • After initiation of adalimumab: 0 (0%) *Fever*	centre in a time period were included. The authors note that three of the patients that initiated adalimumab have been reported previously in the literature. There is a possibility that there is some overlap in the patients reported in these tables. Data were retrospectively extracted from patient records. The data set was pre-defined and based on previously published literature on DADA2. No summary statistics were calculated. Summary statistics, in the form of percentages, medians and IQR were calculated by SPH from individual patient data in the supplementary data tables. No information was provided about the participating sites and limited data was reported for age, sex or ethnicity; it is not clear how generalisable this data might be to NHS settings.

			• Before adalimumab: 4 (50%) • After initiation of adalimumab: 0 (0%)	**Source of funding:**
Study details	**Population**	**Intervention**	**Study outcomes**	**Appraisal and Funding**

			PAN-like rash/ other cutaneous vasculitis • Before adalimumab: 2 (25%) • After initiation of adalimumab: 0 (0%) *Arthralgia* • Before adalimumab: 3 (38%) • After initiation of adalimumab: 1 (13%) *IBD-like disease* • Before adalimumab: 1 (13%) • After initiation of adalimumab: 0 (0%) *Aphthous stomatitis* • Before adalimumab: 4 (50%) • After initiation of adalimumab: 1 (13%)	The authors declare that no funds, grants, or other support were received during the preparation of the manuscript. The Dutch Eurofever cohort was in part financially supported by Novartis and SOBI.
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**	Patients with genetically confirmed DADA2 **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** None stated	**Intervention** 14 patients received adalimumab only at a dose of 40mg every 14 days Total patient months after starting adalimumab treatment: 261 **Comparison** No comparator **Concomitant treatments**	Median (range) treatment time (months): 12 (0 to 59) **Critical outcomes** **Number of ischaemic events**	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. Not applicable **Other comments**:

			Patients experiencing ischaemic events[13], n (%) [total events]; n=14 • Before adalimumab: 11 (79%) [total events: n=24] • After initiation of adalimumab: 2 (14%) [total events n=2] *Patients experiencing CNS ischaemic events, n (%) [total events]; n=14* • Before adalimumab: 5 (36%) [total events n=13]	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

[13] This outcome included both CNS and non-CNS (arteries supplying viscera and peripheries) ischaemic events. Ischaemic events were diagnosed based on clinical features together with brain MRI/MRA and/or other imaging modalities such as ultrasound scan, CT-angiography or selective visceral catheter arteriography where indicted

One specialist centre, UK (patients referred from six centres) **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	**Total sample size** N=31 n=14 received TNF inhibitor treatment with adalimumab only **Baseline characteristics** (n=14 receiving adalimumab) Male: 6 (43%) Median (IQR) age at symptom onset (years): 5 (3 to 7) Median (IQR) current age[14] (years): 12 (9 to 14) Median (IQR) duration of disease activity prior to adalimumab treatment (months): 52 (29.3 to 74.5) Median (range) CNS ischaemic events before adalimumab treatment: 0 (0 to 4)	• Eight patients received adalimumab monotherapy • Two patients take aspirin, due to nonhaemorrhagic ischaemic events • One patient was taking methotrexate alongside adalimumab • Another patient was being weaned off glucocorticoids at the time of publication • One patient continued on glucocorticoids, methotrexate and GCSF whilst awaiting allo-HSCT	• After initiation of adalimumab: 1 (7%) [total events n=1] *Patients experiencing non-CNS ischaemic events, n (%) [total events]; n=14* • Before adalimumab: 7 (50%) [total events n=11] • After initiation of adalimumab: 1 (7%) [total events n=1] **Disease activity/response** PVAS score[15], median (IQR) • Before adalimumab treatment, n=14: 17.5 (13.5 to 31.3) • After adalimumab treatment, n=13[17]: 2.0 (1.0 to 4.0) **Important outcomes** **Steroid use reduction** Before adalimumab: 10/14 (71.4%) were receiving steroids. After initiation of adalimumab: 1/14 (7.1%) remained on steroid therapy and 1/14 (7.1%) was *"being weaned off steroids"* . **Change in acute phase reactants** *CRP level, mg/L[16]; median (IQR)*	This was a retrospective case series at a specialist paediatric centre in the UK (Great Ormond Street Hospital). Eligible patients had a confirmed genetic diagnosis of DADA2. It is not clear if all potentially eligible patients were included in the study. 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 14 received treatment with adalimumab only. As this was a retrospective data collection, it was not possible to blind participants or assessors to drug treatment. There was limited reporting of patient demographics. Some characteristics related to all patients with DADA2 or

[14] Current age was reported at the time of the study data collection

[15] The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across nine 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. [17] One patient died after a single dose of adalimumab; no follow-up measures were collected for this patient.

[16] CRP levels >10 mg/L were indicated as being out of target range

			• Before adalimumab, n=14: 21 (11 to 125)	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

			• After initiation of adalimumab, n=13: 5 (4 to 5)[17] *CRP levels outside of normal range, n (%)* • Before adalimumab, n=14: 10 (71.4%) • After initiation of adalimumab, n=13: 1 (7.7%) *ESR level, mm/hr; median (IQR)* • Before adalimumab, n=14: 52 (29 to 104) • After initiation of adalimumab, n=13: 9 (5 to 14) *ESR levels outside of normal range, n (%)* • Before adalimumab, n=14: 10 (71.4%) • After initiation of adalimumab, n=13: 1 (7.7%) *SAA level, mg/L; median (IQR)[20]* • Before adalimumab, n=10: 85.0 (17.2 to 96.0) • After initiation of adalimumab, n=7: 7.0 (4.8 to 12.2) *SAA levels outside of normal range, n (%)* • Before adalimumab, n=10: 7 (70%) • After initiation of adalimumab, n=7: 0 (0%) **Safety**	patients treated with any TNF inhibitor rather than to only patients who received adalimumab. There was limited clinical information about the patients, with some descriptions of individual patients but with a lack of clear information about the cohort of patients as a whole. Outcomes are reported as before and after adalimumab treatment. One patient had bone marrow failure and died of complications of sepsis and bowel perforation, after having received a single dose of adalimumab; "after" treatment outcomes were not available for this patient. Some data were only available in the commentary or with limited detail in the supplementary tables. Summary statistics, in the form of medians and IQR were calculated by SPH from individual patient data in the supplementary data tables.

[17] Some patients CRP levels were indicated as being <5 (too low to measure) following adalimumab treatment; for statistical summary the level of 5 mg/L was used [20] SAA was not defined but is assumed to be serum amylase A

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			The authors stated that "*no adverse events were reported with adalimumab or etanercept".* One patient had bone marrow failure and died of complications of sepsis and bowel perforation during the study period; the patient had one dose of adalimumab.	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:** All work at Great Ormand Street Institute of Child Health is supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The study was also supported in part by a grant from Rosetrees (a charity supporting medical research).

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, US and collaborating groups (locations not stated, (authors were from centres	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=7 received TNF inhibitor treatment with adalimumab only **Baseline characteristics** (n=7 treated with adalimumab)	**Intervention** Adalimumab: dose not stated **Comparison** No comparator **Concomitant treatments** One patient received concomitant IVIG and prednisone. Six patients received only adalimumab.	Median (range) adalimumab treatment (months): 17 (4 to 60) **Critical outcomes** **Symptom alleviation** Before adalimumab, n=4, after initiation of adalimumab, n=7. *Livedo* • Before adalimumab: livedo was noted in one patient • After initiation of adalimumab: clinicians noted the patient was "*clinically well*[18]*, some livedo*" *Arthritis, livedo and racemosa* • Before adalimumab: one patient had arthritis, livedo and racemosa	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. Not applicable **Other comments**: This study included patients that were referred the National Institutes of Health (NIH)

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

[18] Definition of "*clinically well"* not provided by authors

in the US, Canada and China) **Study type** Retrospective case series **Study aim** To explore the effect of TNF inhibitor treatment on the patients with DADA2 **Study dates** Not stated	Patient sex not stated Median (IQR) age before treatment (years) (n=4): 14 (7 to 22) Median (IQR) age after treatment (years) (n=7): 12 (7 to 26) Clinical manifestations:[19] • Arthritis / arthralgia: 2 (29%) • Skin ulcerations: 1 (17%) • Recurrent fever: 3 (43%) • Livedo: 2 (29%) • Stroke (haemorrhagic, ischaemic, or multiple): 5 (71%) • Childhood PAN: 2 (29%) • Seizures: 1 (11.1%) • Hypogammaglobulinemia: 2 (29%)		• After initiation of adalimumab: the livedo and racemosa resolved and the arthritis was downgraded to "*mild joint pain*" *Other symptoms* • Before adalimumab: Three patients did not have data available. • After initiation of adalimumab: one patient was "*clinically well with some neutropenia*"; one patient was "*clinically well";* one patient reported *seizures and paralysis* • Before adalimumab: two patients were reported to be "*not in flare*[20]" • After initiation of adalimumab: one patient had concurrent gastroenteritis, one was "*clinically well"* **Important outcomes** **Steroid use reduction** • Before adalimumab: 2/7 (28.6%) were receiving steroids (prednisone, dose not stated). • After initiation of adalimumab: 1/7 (14.3%) continued to received steroids (along with IVIG), the other had discontinued steroids	through its collaborating centres; no further information was provided but study authors were from the US, Canada and China. The authors note that a larger cohort of 60 DADA2 patients have been identified at the NIH but that this study used only 31 patients on the basis of *"sample availability for functional studies, and on the novelty of their variants in the* ADA2 *gene."* It is not clear if the selected cohort is representative of all DADA2 patients. Data were retrospectively extracted from patient records. Limited data was reported for age, sex or ethnicity. All patients included in this report received treatment with adalimumab. Outcomes were reported descriptively with limited detail to aid interpretation of the result, particularly around symptoms. No summary statistics were calculated.

[19] All patients experienced more than one clinical manifestation
[20] Definition of "*flare"* not provided by authors

			Change in acute phase reactants	

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

			Median (IQR) CRP (mg/L):[21] • Before adalimumab (n=4): 9.7 (9.2 to 16.7) • After initiation of adalimumab (n=7): 8.0 (1.6 to 8.3)	Summary statistics, in the form of percentages, medians and IQR were calculated by SPH from individual patient data in the supplementary data tables. No information was provided about the participating sites; it is not clear how generalisable this might be to NHS settings. **Source of funding:** The research was supported by the Intramural Research Program of the National Human Genome Research Institute and individual grants from National Key Research and Development Project, the National Natural Science Foundation of China and the Zhejiang Provincial Natural Science Foundation of China. The authors declared 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.	Patients with DADA2 **Inclusion criteria** Patients with biallelic variants in the ADA2 gene, plus at least one of the following: systemic	**Intervention** Adalimumab, dose not stated. Duration of treatment not stated **Comparison**	Median (range) follow-up (months): 20.2 (5 to 36) after diagnosis of DADA2[22] **Critical outcomes** **Number of ischaemic events** The authors reported that *"… no patients have had a stroke during the time they*	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. No 4. Unclear 5. Unclear

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

[22] Follow-up period for full cohort of 30 patients. Follow-up details for 9 patients receiving adalimumab were not available separately

	inflammation, vasculitis, humoral immunodeficiency,			

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

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	haematologic abnormalities, and low level of ADA2 enzymatic activity **Exclusion criteria** None stated **Total sample size** N=30 n=9 treated with adalimumab only **Baseline characteristics** (n=9 treated with adalimumab) Male: 5 (55.6%) Median (IQR) age at symptom onset (years): 5.3 (2.3 to 7.1) Median (range) age of diagnosis (years): 7.6 (6.2 to 12.1) Systems involved, n (%) • Inflammatory: 9 (100%) • Skin: 8 (88.9%) • Musculoskeletal: 3 (33.3%) • Gastrointestinal: 3 (33.3%) • Neurological: 5 (55.6%) • Renal: 0 (0%)	No comparator **Concomitant treatments** • Three patients received adalimumab monotherapy • One patient was taking mycophenolate mofetil alongside adalimumab • One patient was taking glucocorticoids only alongside adalimumab • One patient was taking glucocorticoids and methotrexate alongside adalimumab • One patient was taking glucocorticoids, methotrexate, NSAIDs and thalidomide alongside adalimumab • One patient was taking glucocorticoids and tacrolimus (FK506) alongside adalimumab • One patient was taking thalidomide	*have been on treatment"* (no further details were provided) **Disease activity/response** *Remission rates*[23] n (%), n=9 Before adalimumab • Complete remission: 0 (0%) • Partial remission: 3 (33.3%) • No remission: 6 (66.7%) After initiation of adalimumab • Complete remission: 7 (77.8%) • Partial remission: 2 (22.2%) • No remission: 0 (0%) **Important Outcomes** **Steroid use reduction** • Before adalimumab: 9/9 (100%) patients were receiving glucocorticoids (dose not stated). • After initiation of adalimumab: 4/9 patients (44%) were on glucocorticoids; 5/9 (56%) discontinued glucocorticoid treatment. The authors note that the glucocorticoids had "*little effect"* on DADA2 symptoms. **Change in acute phase reactants** n=9 All nine (100%) patients had elevated CRP levels before adalimumab. Following	6. No 7. Yes 8. No 9. No 10. Not applicable **Other comments**: This was a retrospective case series which recruited patients across 17 centres in China. Eligible patients had a confirmed genetic diagnosis of DADA2. The authors note that 12 patients have been reported previously in the literature, including in Deuitch et al 2022. There is a possibility that there is some overlap in the patients reported in these tables. Data were retrospectively extracted from patient records. Limited data was reported for some demographic variables. All patients included in this report received treatment with adalimumab. Outcomes were reported descriptively with limited detail

[23] Complete remission: persistent control of inflammatory parameters with no disease's flares or complications in the absence of any steroid treatment; Partial remission: good control of disease activity with sporadic relapses and need of steroid on demand or increased steroid dosage; No remission: little or absent response with persistence of systemic flares and/or complications.

			initiation of adalimumab, two patients (22.2%) had elevated CRP levels.	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

		and IVIG alongside adalimumab	*CRP (mg/L), median (IQR); n=9* • Before adalimumab: 40 (33 to 49) • After initiation of adalimumab:[24] 8 (8 to 8) Five (55.6%) patients had elevated ESR levels at presentation. All patients were within the normal reference range after initiation of adalimumab. *ESR (mm/hr), median (IQR); n=9* • Before adalimumab: 44 (22 to 49) • After initiation of adalimumab: 11 (10 to 16)	to aid interpretation of the result. No summary statistics were calculated. Duration of follow-up was reported for the whole cohort but not separately for patients receiving adalimumab. Summary statistics, in the form of percentages, medians and IQR were calculated by SPH from individual patient data in the supplementary data tables. No information was provided about the participating sites; it is not clear how generalisable this might be to NHS settings. **Source of funding:** The work was supported by individual funding grants from the National Natural Science Foundation of China and from the Zhejiang Provincial Natural Science Foundation of China. The authors declare no conflicts of interest.
Melo A, de Carvalho LM, Ferriani VPL, Cavalcanti A, Appenzeller S, Oliveira VR, et al. A Brazilian nationwide	Patients with DADA2	**Intervention** Adalimumab Dose not stated	Median (range) follow-up (months): 20 (12 to 24) **Critical Outcomes** **Disease activity/response**	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes

[24] Some patients had CRP levels below detectable levels (<8 mg/L). These were coded as 8 mg/L to calculated median and IQR

	Inclusion criteria Patients of any age with a diagnosis of DADA2. All			

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

multicenter study on deficiency of deaminase2 (DADA2). Advances in Rheumatology. 2023;63(1):23. **Study location** Ten centres in Brazil **Study type** 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	patients carried pathogenic mutations in the ADA2 gene **Exclusion criteria** None stated **Total sample size** N=18 n=4 received TNF inhibitor treatment with adalimumab only **Baseline characteristics** (n=4 treated with adalimumab) Male: 3 (75%) Syndromic Presentation, n (%) • Recurrent Stroke: 1 (25%) • PAN: 2 (50%) • ALPS-like: 1 (25%) Region of Brazil, n (%) • Recife: 2 (50%) • São Paulo: 2 (50%) Additional baseline characteristics reported for the whole cohort but not separately for in scope patients	One patient also received rituximab and had a partial response to the drug; no further information was given as to the order of drug treatment. Duration of treatment not stated **Comparison** No comparator **Concomitant treatments** It is unclear from the literature if these drugs were concomitant therapy, or all drug treatments ever taken by patients to manage DADA2 symptoms • Two patients were taking steroids for acute management • One patient was taking steroids for acute symptoms and azathioprine for longterm management of DADA2 • One patient had a	"*[Patients A-D] achieved complete clinical control after adalimumab was initiated (median follow-up of 20 months; min 12; max 24 months"*[25] Number of patients with complete remission[26] achieved: 4/4 (100%) **Important Outcomes** **Safety** One patient (n=4), treated with adalimumab, died during the follow-up period due to disseminated staphylococcal infection.	3. No 4. Unclear 5. Unclear 6. No 7. No 8. No 9. No 10. Not applicable **Other comments**: This retrospective case series examined the clinical, genetic and therapeutic data of DADA2 patients across 10 centres in Brazil. All patients with a genetic diagnosis of DADA2 were eligible for inclusion but it is not clear if all patients treated at the centre across the time period were included. Data were retrospectively extracted from patient records. Limited data was reported for age, sex or ethnicity. All patients included in this report received treatment with adalimumab. Outcomes were reported descriptively with limited detail to aid interpretation of the

[25] "*complete clinical control"* was defined as the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation

[26] Complete remission: clinical (the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation) AND laboratory (normalisation of CRP levels in local laboratory) control achieved; Partial remission: clinical OR laboratory control achieved; Absent remission: Neither clinical nor laboratory control achieved

		history of rituximab,		

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

		azathioprine, mycophenolate and sirolimus for long-term management and steroids for acute management of symptoms		result, particularly around disease response. No summary statistics were calculated. All patients came from across Brazil. No information was provided about the participating sites; it is not clear how generalisable this might be to NHS settings. **Source of funding:** This paper was supported by the Center for Rare and Immunological Disorders – Hospital 9 de Julho/DASA. The authors declare no conflicts of interest.
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. **Study location** Japan	Patients with a genetic diagnosis of DADA2 **Inclusion criteria** Patients diagnosed with DADA2 between 2016 and 2019 in Japan. Patients were screened using plasma ADA2 activity and diagnosis was confirmed by genetic analysis. **Exclusion criteria** None stated **Total sample size** N=8	**Intervention** Adalimumab Dose not stated Median (range) treatment time (years): 3 (2.75 to 5) **Comparison** No comparator **Concomitant treatments** • Two patients received adalimumab monotherapy	Median (range) follow-up (months): 36 (23 to 48) **Critical outcomes** **Number of ischaemic events** The authors reported that *"No patient had a cerebral infarction or haemorrhage after starting treatment"* (no further details were provided) **Disease activity/response** Number of patients with complete response: 3/3 (100%) (no further details were provided)	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. No 4. Unclear 5. Unclear 6. No 7. Yes 8. No 9. No 10. Not applicable **Other comments**:

		• One patient was taking methotrexate		This retrospective case series examined the clinical and

Study details	Population	Intervention	Study outcomes	Appraisal and Funding

Study type Retrospective case series **Study aim** To assess the clinical and genetic characteristics of Japanese patients with DADA2 **Study dates** January 2016 and December 2019	n=3 received TNF inhibitor treatment with adalimumab only **Baseline characteristics** (n=3 treated with adalimumab) Male: 2 (67%) Median (range) age at symptom onset (years): 9 (0.17 to 12) Median (range) age at diagnosis (years): 12 (0.083 to 17) Median (range) age at data collection (years): 15 (2 to 21) Symptoms: • Stroke: 1 (33%) • Rash: 3 (100%) • Fever: 2 (67%) • Renal infarction / hypertension: 2 (67%)	and subcutaneous immunoglobulin alongside adalimumab		genetic characteristics of DADA2 patients across Japan. All patients with a genetic diagnosis of DADA2 were eligible for inclusion. Eight patients were included in the retrospective case series; three patients were treated with adalimumab only. It is not clear if all patients treated at the centre across the time period were included. Data were retrospectively extracted from patient records. Limited demographic data was reported. All patients included in this report received treatment with adalimumab. Outcomes were reported descriptively with limited detail to aid interpretation of the result, particularly around disease response. No summary statistics were calculated. Participating centres referred patients from across Japan for genetic testing. No information was provided about the participating sites; it is not clear how generalisable this might be to NHS settings. **Source of funding:**

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				The research was supported by grants from the Ministry of Health, Labour and Welfare of Japan, the Japan Agency for Medical Research and Development and a research grant from the Morinaga Hoshikai. The authors declare no conflicts of interest.

Abbreviations allo-HSCT: allogeneic haematopoietic stem cell transplantation; ALPS: Autoimmune Lymphoproliferative Syndrome; CNS: central nervous system; CRP: C reactive protein; CT: computerised tomography; DADA2: Deficiency of Adenosine Deaminase-2; ESR: erythrocyte sedimentation rate; FK506: tacrolimus; G-CSF: Granulocyte colony stimulating factor; hr:
hour; IBD: Inflammatory bowel disease; IQR: interquartile range; n: number; IVIG: intravenous immunoglobulin; L: litre; mg: milligrams; mm: millimetres; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; NHS: National Health Service; NIH: National Institutes of Health; NIHR: National Institute for Health and Care Research; NSAIDs: non-steroidal anti-inflammatory drugs; PAN: polyarteritis nodosa; PVAS: Paediatric Vasculitis Activity Score; SAA: serum amylase A; SPH: Solutions for Public Health; TNF: Tumour Necrosis Factor; TNFi: TNF-inhibitor; UK: United Kingdom; US: United States

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 adalimumab compared with standard care?

For abbreviations and footnotes see end of tables.

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Adalimumab	Comparator	Result		
Number of ischaemic events (4 case series)									
Number of ischaemic events n (%) at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	0	*Stroke* Before adalimumab: 1 (11.1%) After initiation of adalimumab: 0 *Episodes of recurrent ischaemia without MRI abnormalities* Before adalimumab: 0 After initiation of adalimumab: 2 (22.2%) One of the patients with recurrent ischaemia after initiation of adalimumab was the same patient who had had a stroke before treatment.	Critical	Very low
Patients experiencing[B] ischaemic events[C] n (%) [total events] at median (range) 12 months treatment (0 to 59 months)									

1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	14	0	• Before adalimumab: 11 (79%) [total events: n=24] • After initiation of adalimumab: 2 (14%) [total events n=2]	Critical	Very low
Patients experiencing CNS ischaemic events[C] n (%) [total events] at median (range) 12 months treatment (0 to 59 months)									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	14	0	• Before adalimumab: 5 (36%) [total events n=13] • After initiation of adalimumab: 1 (7%) [total events n=1]	Critical	Very low
Patients experiencing non-CNS ischaemic events[C] n (%) [total events] at median (range) 12 months treatment (0 to 59 months)									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	14	0	• Before adalimumab: 7 (50%) [total events n=11] • After initiation of adalimumab: 1 (7%) [total events n=1]	Critical	Very low
Number of ischaemic events at median (range) 20.2 months follow-up (5 to 36 months)[D]									
1 retrospective case series Li et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	9	0	The authors reported that *"… no patients have had a stroke during the time they have been on treatment"* (no further details were provided)	Critical	Very low
Number of ischaemic events at median (range) 36 months follow-up (23 to 48 months)									

1 retrospective case series Nihira et al 2021	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	3	0	The authors reported that *"No patient had a cerebral infarction or haemorrhage after starting treatment"* (no further details were provided)	Critical	Very low
Disease activity/response (6 case series)									
Number of patients, n (%) with anaemia at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 2 (25%) • After initiation of adalimumab: 3 (38%) • Before adalimumab two patients had anaemia; following initiation of treatment, one additional patient developed anaemia.	Critical	Very low
Number of patients, n (%) with thrombocytopenia at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 1 (13%) • After initiation of adalimumab: 0 (0%)	Critical	Very low
Number of patients, n (%) with neutropenia at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 3 (38%) • After initiation of adalimumab: 3 (38%) • Three patients had neutropenia before adalimumab, and this remained in all three patients after initiation of treatment	Critical	Very low

Number of patients, n (%) with lymphopenia at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 2 (25%) • After initiation of adalimumab: 2 (25%) • Two patients had lymphopenia before adalimumab, and this remained in both patients after initiation of treatment	Critical	Very low
Number of patients, n (%) with hypogammaglobulinemia at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 1 (13%) • After initiation of adalimumab: 1 (13%) • One patient had hypogammaglobulinemia before adalimumab, and this remained after initiation of treatment	Critical	Very low
PVAS Score[E], median (IQR) (lower scores indicate an absence of disease activity) at median (range) 12 months treatment (0 to 59 months)									
1 retrospective case series	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	14	0	• Before adalimumab: 17.5 (13.5 to 31.3)	Critical	Very low
Cooray et al 2021							• After initiation of adalimumab: 2.0 (1.0 to 4.0)		
Remission[F] n (%) at median (range) 20 months follow-up (12 to 24 months)									

1 retrospective case series Melo et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	4	0	Number of patients with complete remission achieved: 4/4 (100%) *"[Patients A-D] achieved complete clinical control after adalimumab was initiated (median follow-up of 20 months; min 12; max 24 months"*	Critical	Very low
Remission[G], n (%) at median (range) 20.2 months follow-up (5 to 36 months)[D]									
1 retrospective case series Li et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	9	0	*Before adalimumab* • Complete remission: 0 (0%) • Partial remission: 3 (33.3%) • No remission: 6 (66.7%) *After initiation of adalimumab* • Complete remission: 7 (77.8%) • Partial remission: 2 (22.2%) • No remission: 0 (0%)	Critical	Very low
Disease response n (%) at median (range) 36 months follow-up (23 to 48 months)									
1 retrospective case series Nihira et al 2021	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	3	0	Number of patients with complete response: 3/3 (100%) (no further details were provided)	Critical	Very low

Symptom alleviation (2 case series)									
Number of patients, n (%) with cutaneous involvement at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 6 (75%) • After initiation of adalimumab: 0 (0%)	Critical	Very low
Number of patients, n (%) with fever at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 4 (50%) • After initiation of adalimumab: 0 (0%)	Critical	Very low
Number of patients, n (%) with PAN-like rash/ other cutaneous vasculitis at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 2 (25%) • After initiation of adalimumab: 0 (0%)	Critical	Very low
Number of patients, n (%) with arthralgia at follow-up between two months and >10 years[A]									

1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 3 (38%) • After initiation of adalimumab: 1 (13%)	Critical	Very low
Number of patients, n (%) with IBD-like disease at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 1 (13%) • After initiation of adalimumab: 0 (0%)	Critical	Very low
Number of patients, n (%) with aphthous stomatitis at follow-up between two months and >10 years[A]									
1 retrospective case series Andriessen et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	0	• Before adalimumab: 4 (50%) • After initiation of adalimumab: 1 (13%)	Critical	Very low
Number of patients with livedo at median (range) 17 months treatment (4 to 60 months)									
1 retrospective case series Deuitch et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	0	• Before adalimumab: livedo was noted in one patient • After initiation of adalimumab: clinicians noted the patient was "*clinically well[a], some livedo*"	Critical	Very low

Number of patients with arthritis, livedo and racemosa at median (range) 17 months treatment (4 to 60 months)									
1 retrospective case series Deuitch et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	0	• Before adalimumab: one patient had arthritis, livedo and racemosa • After initiation of adalimumab: the livedo and racemosa resolved and the arthritis was downgraded to *"mild joint pain"*	Critical	Very low
Number of patients with other DADA2 symptoms at median (range) 17 months treatment (4 to 60 months)									
1 retrospective case series Deuitch et al 2022	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	0	• Before adalimumab: Three patients did not have data available.[d] • After initiation of adalimumab: one patient was *"clinically well with some neutropenia";* one patient was *"clinically well";*	Critical	Very low
							one patient reported seizures and paralysis • Before adalimumab: two patients were reported to be *"not in flare"*[b] • After initiation of adalimumab: one patient had concurrent gastroenteritis, one was *"clinically well"*		
Steroid use reduction (3 case series)									
Steroid use n (%) at median (range) 12 months treatment (0 to 59 months)									

1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	14	0	• Before adalimumab: 10/14 (71.4%) were receiving steroids. • After initiation of adalimumab: 1/14 (7.1%) remained on steroid therapy and 1/14 (7.1%) was “being weaned off steroids”.	Important	Very low
Steroid use n (%) at median (range) 17 months treatment (4 to 60 months)									
1 retrospective case series Deuitch et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	7	0	• Before adalimumab: 2/7 (28.6%) were receiving steroids (prednisone, dose not stated). • After initiation of adalimumab: 1/7 (14.3%) continued to received steroids (along with IVIG), the other had discontinued steroids	Important	Very low
Steroid use n (%) at median (range) 20.2 months follow-up (5 to 36 months)[D]									
1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	0	• Before adalimumab: 9/9 (100%) patients were receiving glucocorticoids (dose not stated). • After initiation of adalimumab: 4/9 patients (44%) were on glucocorticoids; 5/9 (56%)	Important	Very low

							discontinued glucocorticoid treatment.		
Change in acute phase reactants (4 case series)									
Median (IQR) CRP levels, mg/L (benefit is indicated by a lower result) at median (range) 12 months treatment (0 to 59 months)									

1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	Before treatment, n=14; After treatment, n=13	0	• Before adalimumab: 21 (11 to 125) • After initiation of adalimumab: 5 (4 to 5)[c]	Important	Very low
Number of patients, n (%) with CRP levels outside of normal range at median (range) 12 months treatment (0 to 59 months)									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	Before treatment, n=14; After treatment, n=13	0	• Before adalimumab: 10 (71.4%) • After initiation of adalimumab: 1 (7.7%)	Important	Very low
Median (IQR) ESR levels, mm/hr (benefit is indicated by a lower result) at median (range) 12 months treatment (0 to 59 months)									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	Before treatment, n=14; After treatment, n=13	0	• Before adalimumab: 52 (29 to 104) • After initiation of adalimumab: 9 (5 to 14)	Important	Very low
Number of patients, n (%) with ESR levels outside of normal range at median (range) 12 months treatment (0 to 59 months)									
1 retrospective case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	Before treatment, n=14; After treatment, n=13	0	• Before adalimumab: 10 (71.4%) • After initiation of adalimumab: 1 (7.1%)	Important	Very low
Median (IQR) serum amylase A levels, mg/L (benefit is indicated by a lower result) at median (range) 12 months treatment (0 to 59 months)									
1 retrospective case series	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	Before treatment, n=10; After	0	• Before adalimumab : 85.0 (17.2 to 96.0)	Important	Very low

Cooray et al 2021					treatment, n=7		• After initiation of adalimumab: 7.0 (4.8 to 12.2)		
Number of patients, n (%) with serum amylase A levels outside of normal range at median (range) 12 months treatment (0 to 59 months)									
1 case series Cooray et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	Before treatment, n=10; After treatment, n=7	0	• Before adalimumab: 7 (70%) • After initiation of adalimumab: 0 (0%)	Important	Very low
Median (IQR) CRP levels, mg/L (benefit is indicated by a lower result) at median (range) 17 months treatment (0 to 60 months)									
1 retrospective case series Deuitch et al 2022	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	Before treatment, n=4; After treatment, n=7	0	• Before adalimumab: 9.7 (9.2 to 16.7) • After initiation of adalimumab: 8.0 (1.6 to 8.3)	Important	Very low
Median (IQR) CRP levels, mg/L (benefit is indicated by a lower result) at median (range) 20.2 months follow-up (5 to 36 months)[D]									
1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	0	• Before adalimumab: 40 (33 to 49) • After initiation of adalimumab[d]: 8 (8 to 8)	Important	Very low
Number of patients, n (%) with elevated CRP levels at median (range) 20.2 months follow-up (5 to 36 months)[D]									
1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	0	All nine (100%) patients had elevated CRP levels before adalimumab. Following initiation of adalimumab, two patients (22.2%) had elevated CRP levels.	Important	Very low
Median (IQR) ESR levels, mm/hr (benefit is indicated by a lower result) at median (range) 20.2 months follow-up (5 to 36 months)[D]									

1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	0	• Before adalimumab: 44 (22 to 49) • After initiation of adalimumab: 11 (10 to 16)	Important	Very low
Number of patients, n (%) with elevated ESR levels at median (range) 20.2 months follow-up (5 to 36 months) [D]									
1 retrospective case series Li et al 2023	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	9	0	Five (55.6%) patients had elevated ESR levels at presentation. All patients were within the normal reference range after initiation of adalimumab.	Important	Very low
Safety (2 case series)									
Number of deaths during median (range) 12 months treatment (0 to 59 months)									
1 retrospective case series Cooray et al 2021	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	14	0	One patient had bone marrow failure and died of complications of sepsis and bowel perforation during the study period; the patient had one dose of adalimumab.	Important	Very low
Number of adverse events during median (range) 12 months treatment (0 to 59 months)									
1 retrospective case series Cooray et al 2021	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	14	0	The authors stated that "*no adverse events were reported with adalimumab or etanercept*".	Important	Very low
Deaths during follow-up of median (range) 20 months (12 to 24 months)									
1 retrospective case series Melo et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	4	0	One patient, treated with adalimumab, died during the followup period due to disseminated staphylococcal infection.	Important	Very low

Abbreviations
CNS: central nervous system; CRP: C reactive protein; CT: computerised tomography; DADA2: Deficiency of Adenosine Deaminase-2; ESR: erythrocyte sedimentation rate; hr: hour; IBD: Inflammatory bowel disease; IQR: interquartile range; n: number; IVIG: intravenous immunoglobulin; L: litre; mg: milligrams; mm: millimetres; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; PAN: polyarteritis nodosa; Pt: patient; PVAS: Paediatric Vasculitis Activity Score; TNF: Tumour Necrosis Factor; TNFi: TNF-inhibitor

1 Risk of bias: very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion) and the lack of any statistical analysis or summary statistic.
2 Indirectness: serious indirectness due to lack of comparator group
3 Risk of bias: very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion), lack of blinding of patients and clinicians and the lack of any statistical analysis or summary statistic.

A This is the follow-up period for the full cohort; follow-up times for the nine patients that received adalimumab were not detailed separately.
B This outcome included both CNS and non-CNS (arteries supplying viscera and peripheries) ischaemic events.
C Ischaemic events were diagnosed based on clinical features together with brain MRI/MRA and/or other imaging modalities such as ultrasound scan, CT-angiography or selective visceral catheter arteriography where indicted.
D This is the follow-up period for the full cohort; median follow-up was not provided for the nine patients that received adalimumab.
E The Paediatric Vasculitis Activity Score (PVAS) is scored from 0 to 63 with higher scores indicating clinical vasculitic disease activity across nine 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
F Complete remission: clinical (the absence of fever and control of the skin manifestation and/or of signs of lymphoproliferation) AND laboratory (normalisation of CRP levels in local laboratory) control achieved; Partial remission: clinical OR laboratory control achieved; Absent remission: Neither clinical nor laboratory control achieved.
G Complete remission: persistent control of inflammatory parameters with no disease's flares or complications in the absence of any steroid treatment; Partial remission: good control of disease activity with sporadic relapses and need of steroid on demand or increased steroid dosage; No remission: little or absent response with persistence of systemic flares and/or complications.

a Definition of "*clinically well*" not provided by authors b
Definition of "*flare*" not provided by authors
c Some patients CRP levels were indicated as being <5 (too low to measure) following adalimumab treatment; for statistical summary the level of 5 mg/L was used d
Some patients had CRP levels below detectable levels (<8 mg/L). These were coded as 8 mg/L to calculate median and IQR

Glossary

Term	Definition
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.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
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).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
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.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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