NHS England Evidence Review:

Rituximab for acute immune Thrombotic Thrombocytopaenic Purpura (TTP)

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Rituximab for acute immune thrombotic thrombocytopaenic purpura

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of rituximab compared to any treatment regimen that does not include rituximab in people diagnosed with acute immune thrombotic thrombocytopaenic purpura (TTP).

Rituximab is a monoclonal anti-CD20 antibody. Its use in acute immune TTP is intended to normalise the low ADAMTS13 activity levels. It may be given with or without additional treatments. In this review, its use is compared to any other treatment regimen without rituximab.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with rituximab more than others, as well as the criteria used by the included studies to define those people diagnosed with acute immune TTP who are eligible to commence treatment.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of rituximab compared to any treatment regimen that does not include rituximab in patients with acute immune thrombotic thrombocytopaenic purpura (TTP). The searches for evidence published since January 2005 were conducted on 10th May 2021 and identified 433 references. The titles and abstracts were screened and 40 full text papers were obtained and assessed for relevance.

Six studies were identified for inclusion: one systematic review and meta-analysis (SRMA), two prospective cohort studies with historical controls, two retrospective cohort studies and one retrospective case series, including between 79 and 365 participants. The SRMA included six studies in acute TTP and two of these were also included separately in this review because they reported additional outcomes of interest. Studies reported outcomes at follow-up ranging from 12 months to 4 years. Studies were based in France, Japan, the USA and two were based in the UK.

In terms of clinical effectiveness:

- **Mortality (critical)**. One SMRA, three comparative cohort studies and one case series provided very low certainty evidence. They did not provide evidence that there is a difference in mortality from the acute episode after treatment with rituximab compared with no rituximab. Fewer people in rituximab groups died than in no rituximab groups overall across studies, but none of the studies reported that there was a statistically significant difference in mortality.
- **Relapse rate (critical).** One SMRA, four comparative cohort studies and one retrospective case series provided very low certainty evidence that compared to conventional treatment, rituximab reduces the relapse rate in people with acute TTP during the first two years after treatment but no evidence that it does so at longer time points.
- **Disease response (critical).** Three comparative cohort studies and one retrospective case series reported very low certainty evidence on disease response. Three studies provided non-comparative evidence that median time to remission following rituximab treatment ranges from eight to 14 days. One study found ADAMTS13 activity was higher with rituximab than no treatment up to nine months after treatment but not at 12 months. One study reported a substantial reduction in B-cell numbers following rituximab treatment.
- **Quality of life (important).** No evidence was identified for quality of life.
- **Functional outcome measures (important).** No evidence was identified for function.
- **Hospitalisation (important).** Two comparative cohort studies and one retrospective case series provided very low certainty evidence. They did not provide evidence of a difference in length of hospital stay for what is assumed to be the acute admission with rituximab treatment compared with no rituximab. Median length of stay ranged from 16.5 days to 19 days with rituximab and nine days to 20 days with no rituximab.

In terms of safety:

- **Adverse events.** Three comparative cohort studies and one retrospective case series provided very low certainty non-comparative evidence of adverse events

following treatment with rituximab, with one patient experiencing respiratory distress and no other severe adverse events reported.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- One case series reported subgroups by early or late administration of rituximab, and by administration weekly or every three days. This provided very low certainty evidence that following early compared with late administration of rituximab: mortality may be lower (but no statistical analysis was reported); relapse free survival is not different; time to remission (from the point of admission but not from first infusion) is lower; and median length of admission is lower. No evidence of a difference was found between administration weekly or every 3 days.

In terms of criteria:

- Four comparative cohort studies and one case series reported criteria used to identify patients for inclusion in the study, but none reported criteria for eligibility to commence treatment.

Limitations:

The SRMA and four comparative studies included in this review had a high risk of bias due to factors related to their design and methods. Control groups were identified retrospectively and may have differed from the rituximab treated groups in important (confounding) factors such as disease severity and other treatments received, patients lost to follow-up were not always reported, and statistical tests were often not carried out. One non-comparative study was also included; the risk of bias was unclear due to inadequate reporting. There were differences in the target patient populations included between the studies and the overall generalisability of the studies to the NHS setting is unclear because of different healthcare settings in some studies. The certainty of the evidence from these studies was very low.

This review did not find any evidence for the important outcomes of quality of life or function or for cost-effectiveness of rituximab for acute TTP.

Conclusion:

The studies identified for this review provided very low certainty evidence relating to the effect of rituximab compared to no rituximab for the treatment of acute TTP. The studies reported fewer deaths in the rituximab groups than in the no rituximab groups overall across the studies, but none of the studies reported a statistically significant difference in mortality. The studies did not provide evidence of a difference in length of hospital stay for what is assumed to be the acute admission with rituximab treatment compared with no rituximab. The studies provided very low certainty evidence that rituximab reduces relapse rate in people with acute TTP during the first two years after treatment but not at longer time points. The studies provided very low certainty evidence that median time to remission following rituximab treatment ranges from 8 to 14 days and that no serious adverse events occurred, but no comparative evidence was identified for these outcomes. In addition, one study compared early and later administration of rituximab and provided very low certainty

evidence that time to remission (from the point of admission but not from first infusion) is lower following early compared with later administration of rituximab, as was the median length of admission. Key areas of uncertainty, including the absence of reliable comparative studies and evidence gaps for critical and important outcomes of interest, limit the conclusions that can be drawn about the balance of benefit and harm of rituximab for acute TTP, and about the clinical effectiveness and safety of rituximab.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people diagnosed with acute immune TTP, what is the clinical effectiveness of rituximab compared with no rituximab?
2. In people diagnosed with acute immune TTP, what is the safety of rituximab compared with no rituximab?
3. In people diagnosed with acute immune TTP, what is the cost effectiveness of rituximab compared with no rituximab?
4. From the evidence selected, are there any subgroups of patients that may benefit from rituximab more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define those people diagnosed with acute immune TTP who are eligible to commence treatment?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its '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 10th May 2021.

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 of potentially relevant studies 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 (Froissart et al 2012, Kubo et al 2020, Owattanapanich et al 2019, Scully et al 2011, Sun et al 2019, Westwood et al 2013). Table 1 provides a summary of these included studies and full details are given in Appendix E. One was a systematic review and meta-analysis (SRMA) (Owattanapanich et al 2019), two were prospective cohort studies with historical controls (Froissart et al 2012, Scully et al 2011) two were retrospective cohort studies (Kubo et al 2020, Sun et al 2019) and one was a retrospective case series (Westwood et al 2013). The SRMA included six relevant studies and two of these were included separately in this review (Froissart et al 2012, Scully et al 2011).

Five studies reported mortality (Owattanapanich et al 2019, Froissart et al 2012, Kubo et al 2020, Scully et al 2011, Westwood et al 2013), all six studies reported relapse rate, four studies reported disease response (Froissart et al 2012, Scully et al 2011, Sun et al 2019, Westwood et al 2013), three studies reported hospitalisation (Scully et al 2011, Sun et al 2019, Westwood et al 2013), and four studies reported adverse events (Froissart et al 2012, Kubo et al 2020, Scully et al 2011, Westwood et al 2013). No studies were identified that reported quality of life or functional outcomes. One study reported subgroups by early or late administration of rituximab (Westwood et al 2013).

No cost effectiveness studies suitable for inclusion in this evidence review were identified.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Froissart et al 2012 Prospective cohort study with historical controls France	n=79 Idiopathic TTP and either no response or a disease exacerbation during intensive TPE. Rituximab: 22 No rituximab: 57	**Intervention** Rituximab 375 mg/m^2 (4 infusions; 3 in first week; 1 a week after); TPE, glucocorticosteroids if no infection. **Comparison** TPE alone or in combination with vincristine +/- cyclophosphamide; TPE, glucocorticosteroids if no infection.	**Critical outcome** • Mortality • Relapse rate • Disease response **Important Outcomes** • Safety/Adverse events
Kubo et al 2020 Retrospective cohort study Japan	n=156 Refractory or relapsed immune TTP. Rituximab: 58 No rituximab: 98	**Intervention** Rituximab 375 mg/m^2 (4 doses weekly in 80%) TPE 98%, corticosteroids 98%, pulse corticosteroid therapy 78%, other drugs and procedures 26%, cyclophosphamide 18%, vincristine 6%, cyclosporine 8% **Comparison** No rituximab (treatments varied) TPE 89%, corticosteroids 93%, pulse corticosteroid therapy 54%, other drugs and procedures 20%, cyclophosphamide 10%, vincristine 7%, cyclosporine 3%	**Critical outcome** • Mortality • Relapse rate **Important Outcomes** • Safety/Adverse events
Owattanapanich et al 2019 SRMA Study locations not reported	n=365 Acquired TTP Rituximab: 139 Conventional: 226	**Intervention** Rituximab 375 mg/m^2 weekly and conventional treatment (plasma exchange and corticosteroids 'in almost all cases') **Comparison** Conventional treatment (plasma exchange and corticosteroids 'in almost all cases')	**Critical outcome** • Mortality • Relapse rate

Scully et al 2011 Prospective cohort study with historical controls UK	n = 80 De novo or relapsed acute TTP Rituximab: 40 Control: 40	**Intervention** Rituximab (375 mg/m^2 within 3 days of admission, 4 weekly doses; up to 8 infusions if ADAMTS13 levels remained below the normal range or persistently detectable anti-ADAMTS13 IgG antibodies), TPE (twice a day if new/progressive neurologic or cardiac symptoms), steroids. TPE daily from admission until sustained platelet count of >150 x 10^9/L for 2 consecutive days. Steroids per local protocol (typically 1 g of methylprednisolone intravenously daily for the first 3 days from admission. **Comparison** Control (TPE and steroids following standard guidelines as above)	**Critical outcome** • Mortality • Relapse rate • Disease response **Important Outcomes** • Hospitalisation • Safety/Adverse events
Sun et al 2019 Retrospective cohort study, 4 centres USA	n=124 De novo or relapsed acute immune TTP Rituximab: 60 No rituximab: 64	**Intervention** Rituximab (375 mg/m^2 in 97% of patients; 4 weekly doses in 86% of patients). TPE 100% (median procedures 15, range 8 to 23), Steroids 97%, Second-line drug 13% **Comparison** No rituximab: TPE 100% 94% (median procedures 9, 6 to 15), Steroids 88%, Second-line drug 0%	**Critical outcome** • Relapse rate • Disease response **Important Outcomes** • Hospitalisation • Safety/Adverse events
Westwood et al 2013 Single centre retrospective case series UK	n=86 Acute de novo or relapsed TTP	**Intervention** Rituximab 375mg/m^2, median 4 doses (range 1 to 8 doses), weekly (pre-2009) or every 3-4 days (post-2009 in patients at high risk of morbidity/mortality). **Comparison** No comparison	**Critical outcome** • Mortality • Relapse rate • Disease response **Important Outcomes** • Hospitalisation • Safety/Adverse events

Abbreviations

SRMA – systematic review and meta-analysis; TPE – therapeutic plasma exchange; TTP - thrombotic thrombocytopaenic purpura.

5. Results

In people diagnosed with acute immune TTP, what is the clinical effectiveness and safety of rituximab compared with no rituximab?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Mortality **Certainty of evidence:** Very low	Mortality from the acute episode is usually the gold standard for assessing survival benefit of drug treatments. Mortality at 3 months after an acute TTP episode is a critical outcome. This outcome is important to patients because acute TTP is a serious, potentially life-threatening condition. In total five studies (1 SRMA, 3 comparative cohort studies and 1 case series) reported mortality from the acute episode (timepoint not reported). 1 study compared mortality in people with idiopathic TTP and either no response or a disease exacerbation during intensive TPE, 1 study was in people with relapsed or refractory TTP, and 2 studies were in acute de novo or relapsed TTP. • 1 SMRA (Owattanapanich et al 2019) reporting 6 cohort studies (n=362) with follow-up ranging from 1 year to 4 years presented ORs with 95% CIs crossing the line of no effect in all studies, showing no evidence of a difference in mortality (meta-analysis not carried out). **(VERY LOW)** • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) reported mortality in 1/22 (4.5%, day 15) treated with rituximab and in 4/57 (7.0%, mean 8.5 days, SD 1.9) with no rituximab (p value not reported) (median follow-up of survivors: rituximab 33 months (SD 17.4); no rituximab 35.3 months (SD 28.5)). **(VERY LOW)** • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (n=156) showed no statistically significant difference in mortality in people treated with rituximab (3%) compared with no rituximab (8%), p=0.83 (median follow-up rituximab 3.8 years (IQR 2.4 to 7.3); no rituximab 3.9 years (IQR 1.7 to 8.1)). **(VERY LOW)** • 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (n=80) reported mortality in 3/40 (7.5%,11 to 25 days after admission) participants treated with rituximab and in 3/40 (7.5%, 2 during admission, 1 on relapse) participants with no rituximab (during 1 year follow-up) (p value not reported). **(VERY LOW)** • 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) provided non-comparative evidence that of 104 patient episodes (in 86 patients) 6 (5.8%) patients treated with rituximab died, after a median of 12.5 days (range 4 to18) from admission (median follow-up 45 months (range 4 to 100 months)). **(VERY LOW)** **These studies provided very low certainty evidence. They did not provide evidence that there is a difference in mortality from the acute episode after treatment with rituximab compared with no rituximab. Fewer people in rituximab groups died than in no rituximab groups overall across studies, but none of the studies reported that there was a statistically significant difference in mortality.**

Relapse rate **Certainty of evidence:** Very low	Relapse rate is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions. Relapse rate from an acute TTP event is best measured over 2 years, during which time most relapses will occur. In total 6 studies (1 SRMA of 6 cohort studies, 4 cohort studies and 1 case series) provided evidence relating to relapse rate measured at different timepoints. 1 study assessed relapse rate in people with idiopathic TTP and either no response or a disease exacerbation during intensive TPE, 1 study was in relapsed or refractory TTP, and 3 studies were in acute de novo or relapsed TTP. The SRMA did not specify the type of TTP. • 1 SRMA (Owattanapanich et al 2019) of 6 cohort studies (n=365) with follow-up ranging from 1 year to 4 years showed a statistically significant reduction in relapse rate in people with rituximab treatment compared with conventional treatment (OR 0.40, 95% CI 0.19 to 0.85), p=0.02. **(VERY LOW)** At 1 to 2 years: • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) found no difference in the proportion who relapsed within 12 months (rituximab 0% vs no rituximab 9.4%, p=0.34). **(VERY LOW)** • 1 retrospective cohort study in people with de novo or relapsed acute TTP (Sun et al 2019) (n=124) and 20.6 months follow-up found people with rituximab treatment appeared to be protected from relapse at 1 year (Kaplan-Meier analysis, p=0.01). **(VERY LOW)** • 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (n=80) and follow-up of ≥1 year found significantly fewer relapses following rituximab treatment (10%, occurring at median 27 months, range 17 to 31) compared with control (53%, occurring at median of 18 months, range 3 to 60), p=0.0011. **(VERY LOW)** • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (n=156) found relapse-free survival at 2 years was significantly higher with rituximab than no rituximab, p=0.02. In multivariate analysis, rituximab use protected against relapse within 2 years: hazard ratio (HR) 0.18 (95% CI 0.04 to 0.80). • 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) provided non-comparative evidence for relapse rates in patients previously treated with rituximab (n=14, 18 episodes): 5 relapses occurred in 3 patients during 22 months (range 16 to 53) follow-up. **(VERY LOW)** At median follow-up of approximately 3 years: • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) found that at median follow-up of 33 months (SD 17.4) (rituximab) and 35.3 months (SD 28.5) (no rituximab), relapse did not differ between groups (p=0.68). **(VERY LOW)** At median follow-up of approximately 4 years: • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (n=156) found no difference in the proportion of acute episodes that relapsed (rituximab 12.3% vs no

	rituximab 16.4%, p=0.51) during a median follow-up of 3.8 years (IQR 2.4 to 7.3) (rituximab) and 3.9 years (IQR 1.7 to 8.1) (no rituximab). **(VERY LOW)** • 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) provided non-comparative evidence for relapse rates in rituximab naïve patients (n=86) (13.4% of patients who achieved remission, median follow-up 45 months (range 4 to 100). **(VERY LOW)** At 5 years: • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (n=156) found no difference in relapse-free survival at 5 years between those treated with rituximab and no rituximab (Kaplan-Meier analysis, p=0.31). Similarly, multivariate analysis found no significant difference between groups for relapse within 5 years. **(VERY LOW)** • 1 retrospective cohort study in people with de novo or relapsed acute TTP (Sun et al 2019) (n=124) and a median of 20.6 months follow-up found that the effect of rituximab reduced with time, with a HR for time interaction of 1.002 (95% CI 1.0007 to 1.003) per day after administration, and a HR of 1.0 at 2.6 years. At 5 years, people with rituximab treatment did not appear to be protected from relapse (Kaplan-Meier analysis, p=0.45). **These studies provided very low certainty evidence that compared to conventional treatment, rituximab reduces relapse rate in people with acute TTP during the first two years after treatment but no evidence that it does so at longer time points.**
Disease response **Certainty of evidence:** Very low	Disease response is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. In total 4 studies (3 comparative cohort studies, 1 case series) provided evidence relating to disease response following rituximab treatment at different timepoints. Disease response following no rituximab was not reported. All 3 studies reported time to remission or durable remission, 2 studies reported platelet normalisation, 1 study reported normalisation of ADAMTS13 activity, and 1 study reported normalisation of B-cell numbers. 1 study assessed disease response in people with idiopathic TTP and either no response or a disease exacerbation during intensive TPE, and 2 studies in acute de novo or relapsed TTP. Time to remission: • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (rituximab n=22) found the mean time from rituximab initiation to durable remission (complete response with no further thrombocytopenia or clinical worsening ≥30 days following the first day of platelet count recovery) (days from the first TPE to the beginning of remission): was 12 days (SD 6.7) in 21 patients with durable remission. Data were not reported for the control group. **(VERY LOW)** • 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (rituximab n=40) reported median time to remission (sustained platelet count > 150 x 10^9/L for 2

	consecutive days) was 12 days. Data were not reported for the control group. **(VERY LOW)** • 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported median time to remission (sustained platelet count > 150 x 10^9/L for 2 consecutive days, unclear if from admission or first infusion) was 14 days (range 4 to 52) in 82 rituximab naïve patients who achieved remission, and 7 days from admission (range 0 to 25) or 8 days from first infusion (range 4 to 25) in previously treated patients (n=14, remission in 16/18 episodes). **(VERY LOW)** Platelet normalisation • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) found platelet count recovery (Kaplan-Meier estimates up to 160 days) was shorter in the rituximab group compared to the no rituximab group p 0.03). **(VERY LOW)** • 1 retrospective cohort study in people with de novo or relapsed acute TTP (Sun et al 2019) (rituximab n=60) found that for patients receiving rituximab who had not yet achieved a normal platelet count (n not reported), platelet count normalisation occurred a median of 8 days (IQR 5 to 11) after rituximab administration (not stated if this is from first or last infusion). Data were not reported for the control group. **(VERY LOW)** Normalisation of ADAMTS13 activity • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (n=79) found ADAMTS13 activity was higher in the rituximab group than controls at 1 month (p=0.007), 3 months (p=0.01), 6 months (p=0.02) and 9 months (p=0.003). At 12 months there was no significant difference between groups (p=0.12), data in a figure only. **(VERY LOW)** Normalisation of B cell numbers • 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (rituximab n=40) reported CD19 levels (a marker of B-cell levels, normal range 5% to 15%). For the group treated with rituximab, levels were 23% (range 2.6% to 39.90%) on admission, 21% (range 10.7% to 51.1%) before the first infusion, 1.4% (range 0% to 2.78%) at first infusion, 0.97% (range 0% to 5.43%) at second infusion, and 0.5% (range 0% to 2.78%) before fourth infusion. The authors reported that "normalisation of B cell numbers occurred in 75% of patients, with levels above the normal range within 12 months (7.76%; range 0.46 to 32.5). However, this was not associated with further relapse." **(VERY LOW)** **These studies provided very low certainty evidence that median time to remission following rituximab treatment ranges from 8 to 14 days. One study found ADAMTS13 activity was higher with rituximab than no treatment up to 9 months after treatment but not at 12 months. One study reported a substantial reduction in B-cell numbers following rituximab treatment.**
Important outcomes	
Quality of life	Quality of life is an important outcome to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform the patient centred shared decision making and health policy. Quality

Certainty of evidence: Not applicable	of life questionnaires include but are not limited to the EQ-5D & SF 36 which can provide information regarding improvement in symptoms. Disease specific quality of life questionnaires can provide information regarding improvement in symptoms. **No evidence was identified for this outcome.**
Functional **Certainty of evidence:** Not applicable	Functional outcome measures are important to patients as they facilitate enablement, independence and active participation. Functional outcomes may be reflected by measures of end organ damage (eg neurological, cardiac) but also by physical tasks, and emotional, and psycho-social measures (eg PHQ-9). **No evidence was identified for this outcome.**
Hospitalisation **Certainty of evidence:** Very low	Hospitalisation is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. In total 3 studies (2 comparative cohort studies and 1 case series) reported length of hospital stay in people with de novo or relapsed acute TTP. It is assumed that this was for the initial admission, but it is not explicitly stated by the papers. • 1 prospective cohort study with historical controls (Scully et al 2011) (n=80) found no difference in the number of days admitted between rituximab treated patients (16.5 days, range 5 to 49) and controls (20 days, range 5 to 62), p=not significant. **(VERY LOW)** • 1 retrospective cohort study in people with de novo or relapsed acute TTP (Sun et al 2019) (n=124) reported median hospital stay was 18 days (IQR 11 to 27) in the rituximab group and 9 days (IQR 7 to 14) in the no rituximab group (p value not reported). **(VERY LOW)** • 1 case series (Westwood et al 2013) (n=86) reported median hospital stay of 19 days (range 4 to 86) in rituximab naïve patients (n=86) and 10 days (range 4 to 29) in previously treated patients (n=14). **(VERY LOW)** **These studies provided very low certainty evidence, and did not provide evidence of a difference in length of hospital stay for what is assumed to be the acute admission with rituximab treatment compared with no rituximab. Median length of stay ranged from 16.5 days to 19 days with rituximab and 9 days to 20 days with no rituximab.**
Safety	
Adverse events **Certainty of evidence:** Very low	Safety / adverse effects are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. It reflects the tolerability and adverse effects of the treatment. From a service delivery perspective, it reflects the additional demands placed on the health system to manage the adverse consequences of the treatment. In total 4 studies (3 comparative cohort studies and 1 case series) reported safety / adverse events following treatment with rituximab. Adverse events following conventional treatment were not reported by the studies. Up to 1 year follow-up • 1 prospective cohort study with historical controls in people with de novo or relapsed acute TTP (Scully et al 2011) (rituximab n=40) reported 1 chest pain during infusion, 5 chest pain following infusion, 2 chest pain not related to rituximab, and 26 infections following infusion (3 of which

	were related to infusion lines). Neurologic, haematologic, reproductive and other events during admission and up to one year follow-up were also reported, with the following noted as being possibly due to rituximab: 5 joint pain, 3 skin rash, and 2 hair loss/thinning, Median follow-up 3 to 4 years • 1 prospective cohort study with historical controls in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE (Froissart et al 2012) (rituximab n=22) reported narratively that no severe adverse events or clinically significant infections occurred. • 1 retrospective cohort study in people with refractory or relapsed immune TTP (Kubo et al 2020) (rituximab n=58) reported that rituximab led to respiratory distress in one patient. No other severe adverse events occurred. • 1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported no documented increase in infections. Mild joint pains (number not reported), chest pain in six cases (unknown if associated with TTP rituximab), no progressive multifocal leukoencephalopathy. **These studies provided very low certainty non-comparative evidence of adverse events following treatment with rituximab, with one patient experiencing respiratory distress and no other severe adverse events reported.**

Abbreviations

CI - Confidence Interval; HR - Hazard Ratio; IQR - Inter-quartile range; OR - odds ratio; SD – Standard Deviation; SRMA - Systematic review and meta-analysis; TPE – therapeutic plasma exchange; TTP - Thrombotic Thrombocytopaenic Purpura

In people diagnosed with acute immune TTP, what is the cost effectiveness of rituximab compared with no rituximab?

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 rituximab more than the wider population of interest?

Outcome	Evidence statement
Mortality **Certainty of evidence:** Very low	1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported results separately for rituximab naïve patients who received rituximab early (≤3 days from admission, n=54) or late (> 3 days from admission, n=32). Mortality occurred in 2/54 (3.7%) of the early subgroup and 2/32 (6.3%) of the late subgroup (p value not reported). **(VERY LOW)** **One study provided very low certainty evidence that mortality may be lower following early compared with late administration of rituximab, but no statistical analysis was reported**.

Relapse rate **Certainty of evidence:** Very low	1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported results separately for rituximab naïve patients who received rituximab early (≤3 days from admission, n=54) or late (> 3 days from admission, n=32). There was no difference in relapse free survival between early and late subgroups (p=0.77). **(VERY LOW)** **One study provided very low certainty evidence that relapse free survival is not different following early compared with late administration of rituximab**.
Disease response **Certainty of evidence**: Very low	1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported results separately for rituximab naïve patients who received rituximab early (≤3 days from admission, n=54) or late (> 3 days from admission, n=32), and administration weekly or every 3 days. • Median time to remission from admission: early rituximab group 12 days (range 4 to 52); late rituximab group 20 days (range 4 to 42), p<0.001. **(VERY LOW)** • Median time to remission from first infusion: early rituximab group 10 days (range 2 to 50); late rituximab group 9 days (range 0 to 30), p=0.67. **(VERY LOW)** • Early rituximab group: median time to remission from admission: rituximab administration every 3 days group 13 days; weekly group 9 days, p=0.07. **(VERY LOW)** • Late rituximab group: median time to remission from admission: rituximab administration every 3 days group 18 days; weekly group 21 days, p=0.48. **(VERY LOW)** • Early rituximab group: median time to remission from infusion: rituximab administration every 3 days group 11 days; weekly group 7 days, p=ns. **(VERY LOW)** • Late rituximab group: median time to remission from infusion: rituximab administration every 3 days group 8 days; weekly group 9 days, p=ns. **(VERY LOW)** **One study provided very low certainty evidence that time to remission (from the point of admission but not from first infusion) is lower following early compared with late administration of rituximab, but no evidence of a difference was found between administration weekly or every 3 days.**
Hospitalisation Certainty of evidence: Very low	1 case series in people with de novo or relapsed acute TTP (Westwood et al 2013) (n=86) reported results separately for rituximab naïve patients who received rituximab early (≤3 days from admission, n=54) or late (> 3 days from admission, n=32). Median length of admission: early rituximab group 16 days (range 4 to 86); late rituximab group 23 days (range 7 to 52), p=0.01. **One study provided very low certainty evidence that the median length of admission is lower following early compared with late administration of rituximab**.

Abbreviations

NS – not significant; TTP - Thrombotic Thrombocytopaenic Purpura

From the evidence selected, what are the criteria used by the research studies to define those people diagnosed with acute immune TTP who are eligible to commence treatment?

Outcome	Evidence statement
Used by research studies	Five studies (two prospective cohort studies with historical controls, two retrospective cohort studies and one retrospective case series) reported criteria used to identify patients for inclusion in the study, but none reported criteria for eligibility to commence treatment. • 1 prospective cohort study with historical controls (Froissart et al 2012) (n=79) included people with severe, acquired ADAMTS13 deficiency: thrombotic microangiopathy (Coombs negative microangiopathic haemolytic anaemia, acute peripheral thrombocytopenia and absence of an identifiable cause for the thrombocytopenia and microangiopathic haemolytic anaemia); mild renal involvement and ADAMTS13 activity <10%. • 1 retrospective cohort study (Kubo et al 2020) (n=156) included people with severely deficient ADAMTS13 activity (<10% of normal) and detectable ADAMTS13 inhibitor and either refractory TTP, defined as persistent thrombocytopenia despite five treatments with TPE and corticosteroids, or relapsed TTP defined as thrombocytopenia (<150 × 109/l) with or without clinical symptoms > 30 days after TPE for the acute TTP episode was stopped. • 1 prospective cohort study with historical controls (Scully et al 2011) (n=80) included adults with de novo or relapsed acute TTP (thrombocytopenia, microangiopathic haemolytic anaemia, normal clotting screen, increased lactate dehydrogenase to 1.5 times normal upper limit). • 1 retrospective cohort study (Sun et al 2019) (n=124) included people with immune-mediated TTP, thrombocytopenia (<150 x 109 platelets/L), schistocytosis, and one of: ADAMTS13 activity level ≤10% or ADAMTS13 activity level between 10% and 20% with a positive inhibitor titre by Bethesda assay and/or detectable anti-ADAMTS13 immunoglobulin G present in plasma. • 1 case series (Westwood et al 2013) (n=86) included people with acute de novo or relapsed TTP (presence of thrombocytopenia, microangiopathic haemolytic anaemia, normal clotting screen, increased lactate dehydrogenase to ≥ 1 x upper limit of normal). **Five studies reported criteria used to identify patients for inclusion in the study, but none reported criteria for eligibility to commence treatment.**

Abbreviations

TPE – therapeutic plasma exchange; TTP - Thrombotic Thrombocytopaenic Purpura

6. Discussion

This review examined the clinical effectiveness, safety and cost effectiveness of rituximab for acute TTP compared with no rituximab treatment. The critical outcomes of interest were mortality, relapse rate and disease response. The important outcomes of interest were quality of life, functional outcome measures, hospitalisation, adverse events and cost effectiveness.

Evidence was available from six studies: one SRMA (Owattanapanich et al 2019), two prospective cohort studies with historical controls (Froissart et al 2012, Scully et al 2011), two retrospective cohort studies (Kubo et al 2020, Sun et al 2019) and one retrospective case series (Westwood et al 2013). The SRMA included six relevant studies and two of these (Froissart et al 2012, Scully et al 2011) were also included separately in this review as they reported additional outcomes of interest.

Five studies reported mortality (Owattanapanich et al 2019, Froissart et al 2012, Kubo et al 2020, Scully et al 2011, Westwood et al 2013), and all six studies reported relapse rate. Four studies reported disease response following rituximab using different indices including time to remission, platelet normalisation, and normalisation of ADAMTS13 activity (Froissart et al 2012, Scully et al 2011, Sun et al 2019, Westwood et al 2013). Three studies reported length of hospital stay (Scully et al 2011, Sun et al 2019, Westwood et al 2013) and four studies reported adverse events (Froissart et al 2012, Kubo et al 2020, Scully et al 2011, Westwood et al 2013). No studies were identified that reported quality of life, functional outcomes or cost-effectiveness. One study reported subgroups by early or late administration of rituximab and by administration weekly or every 3 days (Westwood et al 2013). Five studies reported criteria used to identify patients for inclusion in the study, but none reported criteria for eligibility to commence treatment.

Two of the studies were conducted in the UK and there is some overlap of participants between these studies (Scully et al 2011, Westwood et al 2013). The other studies were based in France, Japan and the USA, and the SRMA did not report study location. Generalisability to the NHS setting is therefore unclear. There were differences between the target population included in the studies: one study included patients with either no response or a disease exacerbation during intensive TPE (Froissart et al 2012), one study included people with refractory or relapsed immune TTP (Kubo et al 2020), and three studies included de novo or relapsed acute TTP (Scully et al 2011, Sun et al 2019, Westwood et al 2013); subgroup analysis of these were not reported. The SRMA did not describe the target population. History of prior treatments was generally not reported by the studies and may differ. The dose of rituximab was standard across the studies, but there were differences in the timing and number of infusions given and in concomitant treatments. There were also differences in the comparator treatments, which were typically not standardised. The heterogeneity of participants across studies limits reliable comparisons.

Overall, the risk of bias of the included studies was high. The SRMA (Owattanapanich et al 2019) included studies of rituximab for acute TTP and of prophylactic rituximab. A total of six studies of rituximab for acute TTP with 365 participants were included in the meta-analysis for relapse rate, and six studies with 362 participants were reported for mortality. Follow-up ranged from one to four years. There were several concerns with the methods of the SRMA, which was judged to have a high risk of bias. It was unclear whether methods were established prior to the conduct of the review, the selection of study designs and meta-analysing studies with these designs was not justified, and there was no discussion or account for risk of bias of the studies. Additionally, the SRMA did not report duplicate data extraction, provide a list of excluded studies or report sources of funding of the studies, and

the search strategy was only partially comprehensive. Separate meta-analyses of acute TTP studies and prophylactic rituximab studies were undertaken for relapse rate, but not for mortality. Uncertainty of the results was further increased due to the analysis including comparator groups that were not directly appropriate (historical controls), and the presence of statistical heterogeneity and wide confidence intervals in the meta-analysis of relapse rate.

Additional comparative evidence on outcomes of interest was provided by four primary studies. Sample sizes ranged from 79 to 156 and follow-up ranged from around one to four years. All four studies were judged to have a high risk of bias and the certainty of results was very low. Two of the studies (Froissart et al 2012 and Scully et al 2011) had historical control groups and two (Kubo et al 2020, Sun et al 2019) identified both rituximab and no rituximab groups retrospectively. In all four studies it is therefore likely that there are differences in unknown factors between the groups, as well as the reported significant differences in baseline characteristics in some of the studies. It is unclear whether the control groups are a fair comparison or whether some patients did not receive rituximab due to important confounding factors such as disease severity.

Froissart et al (2012) was a small comparative study (only 22 patients with rituximab) using historical controls, where the exposures do not appear to have been standard, participants were excluded from the baseline tables and results if they did not survive, and the assessment of the outcomes was unclear. There were limited data beyond 12 months and much of the data were in figures only. The historical control group in Scully et al (2011) was recruited from a similar population as their rituximab group and matched ‘as far as possible’ by sex, ethnicity, and number of relapses. However, the recruitment period of the historical controls was not reported and duration of follow-up of some outcomes was unclear. These studies did not fully account for potential confounding factors, outcome assessment for the historical controls was unclear, and loss to follow-up was not reported. Length of follow-up appears to be unequal in Scully et al (2011) and not all outcomes were compared statistically.

There were some significant differences between groups at baseline in the two retrospective cohort studies (Kubo et al 2020, Sun et al 2019). Kubo et al (2020) was a large comparative study with long follow-up, but outcomes were assessed by physician questionnaire. There was no standardisation of treatments in either group. People with first rituximab administration less than five days from the start of TPE were excluded to avoid cases where rituximab was used as initial treatment. There were differences between groups for several baseline characteristics and people with incomplete outcome data were excluded from the study. The validity and reliability of exposure assignment and measurement, and outcome measurement, were unclear. Sun et al (2019) was also a large comparative study; however, the rituximab group required a greater number of TPE procedures to achieve remission and therefore may have had more severe disease. The authors noted that the use of rituximab on initial presentation increased during the 14-year recruitment period. Measurement of outcomes was unclear and loss to follow-up was not reported.

One case series (Westwood et al 2013, n=86) provided non-comparative evidence on mortality, relapse rate, disease response and hospitalisation over a median follow-up of 45 months (range 1 to 100) in rituximab naïve patients and 22 months (range 16 to 53) in previously treated patients. It is likely that the previously treated patients were also in the naïve group at an earlier stage, although this is not explicitly stated. The risk of bias was unclear in this study and the certainty of results was very low. Limited eligibility criteria were reported, but authors stated that consecutive patients were included. Limited details were reported on adverse events. There was no reporting of demographic information relating to

the presenting hospital site. Data were reported separately for rituximab naïve and previously treated patients; rituximab naïve and either early or late rituximab and rituximab administration every 3 days or weekly. It is not clear whether the subgroups were pre-specified, and there does not appear to have been any adjustment made for multiple analyses. Thirty-one of the participants are also included in the Scully et al (2011) study included in this review; these patients all had early rituximab (≤3 days from hospital admission).

7. Conclusion

This review included one SRMA including patients from six cohort studies, two cohort studies with historical controls, two retrospective cohort studies and one retrospective case series. The included studies provide very low certainty evidence on critical and important outcomes following treatment with rituximab for patients with acute immune TTP (relapsed or de novo). No evidence was available for two important outcomes (quality of life and functional outcomes). No cost effectiveness studies were identified. One study provided low certainty evidence for subgroups of patients with early or late administration of rituximab. Five studies reported criteria used to identify patients for inclusion in the study, but none reported criteria for eligibility to commence treatment.

The studies identified for this review provided very low certainty evidence relating to the effect of rituximab compared to no rituximab for the treatment of acute TTP. The studies reported fewer deaths in the rituximab groups than in the no rituximab groups overall across the studies, but none of the studies reported a statistically significant difference in mortality. The studies did not provide evidence of a difference in length of hospital stay for what is assumed to be the acute admission with rituximab treatment compared with no rituximab. The studies provided very low certainty evidence that rituximab reduces relapse rate in people with acute TTP during the first two years after treatment but not at longer time points. The studies provided very low certainty evidence that median time to remission following rituximab treatment ranges from 8 to 14 days and that no serious adverse events occurred, but no comparative evidence was identified for these outcomes. In addition, one study compared early and later administration of rituximab and provided very low certainty evidence that time to remission (from the point of admission but not from first infusion) is lower following early compared with later administration of rituximab, as was the median length of admission. Key areas of uncertainty, including the absence of reliable comparative studies and evidence gaps for critical and important outcomes of interest, limit the conclusions that can be drawn about the balance of benefit and harm of rituximab for acute TTP, and about the clinical effectiveness and safety of rituximab.

Appendix A PICO document

The review questions for this evidence review are:

1. In people diagnosed with acute immune TTP, what is the clinical effectiveness of rituximab compared with no rituximab?
2. In people diagnosed with acute immune TTP, what is the safety of rituximab compared with no rituximab?
3. In people diagnosed with acute immune TTP, what is the cost effectiveness of rituximab compared with no rituximab?
4. From the evidence selected, are there any subgroups of patients that may benefit from rituximab more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define those people diagnosed with acute immune TTP who are eligible to commence treatment?

P-Population and Indication	All people diagnosed with acute immune TTP (relapsed or de novo)
I-Intervention	Rituximab [Rituximab is used at a dose of 375mg/m^2 in acute TTP.] [The majority of patients normalise their ADAMTS13 activity levels following 4 rituximab infusions of 375mg/m^2.] [Rituximab may be given with or without additional treatments]
C-Comparator	Any treatment regimen that doesn't include rituximab
O-Outcomes	Clinical Effectiveness Unless stated for the outcome, the minimum clinically important difference (MCID) is unknown. Outcomes of two years or more are of particular interest, unless otherwise specified. Critical to decision making • **Mortality** from the acute episode is usually the gold standard for assessing survival benefit of drug treatments. Mortality at 3 months after an acute TTP episode is a critical outcome. This outcome is important to patients because acute TTP is a serious, potentially life-threatening condition. • **Relapse rate** This outcome is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions. Relapse rate from an acute TTP event is best measured over 2 years, during which time most relapses will occur. • **Disease response** This outcome is important to patients because it can reflect the benefits the

	treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised (for example but not limited to a normalisation of platelet number, normalisation of ADAMTS13 activity, and time to remission). Important to decision making • **Quality of life** is an important outcome to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform the patient centred shared decision making and health policy. Quality of life questionnaires include but are not limited to the EQ-5D & SF 36 which can provide information regarding improvement in symptoms. Disease specific quality of life questionnaires can provide information regarding improvement in symptoms. • **Functional** outcome measures are important to patients as they facilitate enablement, independence and active participation. Functional outcomes (which may be reflected by measures of end organ damage (eg neurological, cardiac) but also physical tasks, emotional, and psycho-social (eg PHQ-9). • **Hospitalisation** This outcome is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. Safety / Adverse Effects • 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. It reflects the tolerability and adverse effects of the treatment. From a service delivery perspective, it reflects the additional demands placed on the health system to manage the adverse consequences of the treatment. Cost effectiveness • Cost effectiveness models consider direct and indirect costs, effects, and quality of life.
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	2005-2021
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines.
Study design	Case reports, resource utilisation studies.

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language from January 2005 onwards. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: January 2005 to 10th May 2021

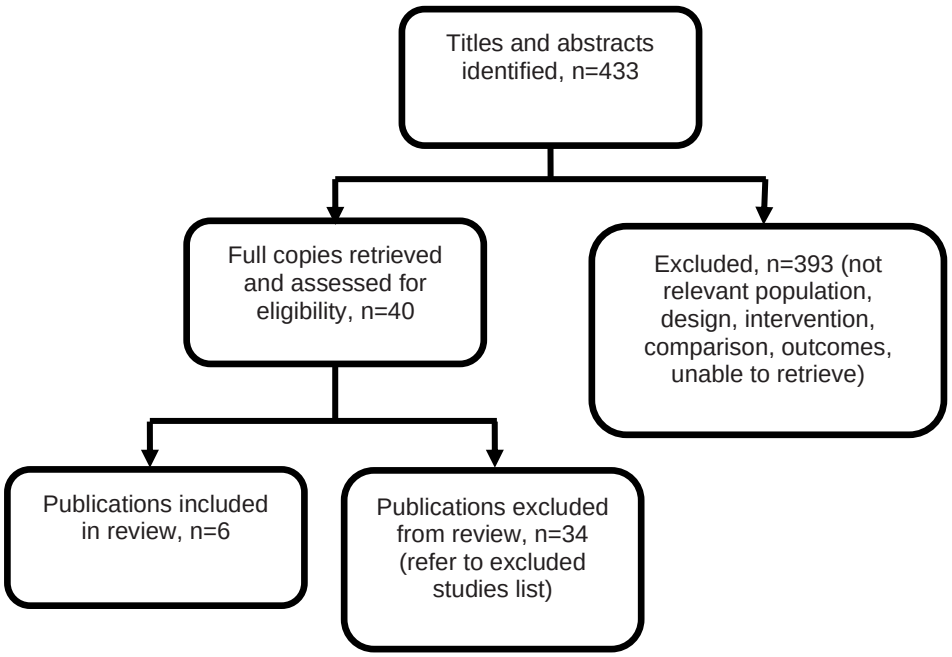
Medline

# ▲	Searches
1	Purpura, Thrombotic Thrombocytopenic/
2	(thrombotic thrombocytop* purpura or ttp).ti,ab,kw.
3	1 or 2
4	Rituximab/
5	(rituximab or mabthera).ti,ab,kw.
6	4 or 5
7	3 and 6
8	limit 7 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
9	(comment or editorial or letter or review).pt. or case report.ti,ab,kw.
10	7 not 9
11	8 or 10
12	exp animals/ not humans/
13	11 not 12
14	limit 13 to (english language and yr="2005 -Current")

Appendix C Evidence selection

The literature searches identified 433 references. These were screened using their titles and abstracts and 40 references were obtained in full text and assessed for relevance. Of these, 6 references are included in the evidence summary. The remaining 34 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Scully M, McDonald V, Cavenagh J, Hunt BJ, Longair I, Cohen H. & Machin SJ. 2011. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood,118,1746-53.	Included.
Scully M, Cohen H, Cavenagh J, Benjamin S, Starke R, Killick S, Mackie I. & Machin SJ. 2007. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. British Journal of Haematology,136,451-61.	Excluded. Case series n=25. Not prioritised as SR reporting relapse rate and larger studies reporting disease response and adverse events have been included.
Westwood JP, Webster H, McGuckin S, McDonald V, Machin SJ. & Scully M. 2013. Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse.Journal of thrombosis and haemostasis : JTH,11,481-90	Included.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Tun NM, Villani GM. Efficacy of rituximab in acute refractory or chronic relapsing non-familial idiopathic thrombotic thrombocytopenic purpura: a systematic review with pooled data analysis. Journal of Thrombosis & Thrombolysis. 2012;34(3):347-59.	Not included because larger studies available for the outcomes reported by this study.
Elliott MA, Heit JA, Pruthi RK, Gastineau DA, Winters JL, Hook CC. Rituximab for refractory and or relapsing thrombotic thrombocytopenic purpura related to immune-mediated severe ADAMTS13-deficiency: a report of four cases and a systematic review of the literature. European Journal of Haematology. 2009;83(4):365-72.	Not included because more recent systematic reviews available for these outcomes.
Jasti S, Coyle T, Gentile T, Rosales L, Poiesz B. Rituximab as an adjunct to plasma exchange in TTP: A report of 12 cases and review of literature. Journal of Clinical Apheresis. 2008;23(5):151-6.	Not included because larger studies available for the outcomes reported by this study.
George JN, Woodson RD, Kiss JE, Kojouri K, Vesely SK. Rituximab therapy for thrombotic thrombocytopenic purpura: a proposed study of the Transfusion Medicine/Hemostasis Clinical Trials Network with a systematic review of rituximab therapy for immune-mediated disorders. Journal of Clinical Apheresis. 2006;21(1):49-56.	Not included because more recent and larger case series included for these outcomes.
Sun RX, Xu J, Zhu HD, Yu XZ, Yang J. Clinical presentation and management of acquired thrombotic thrombocytopenic purpura: A case series of 55 patients. Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. 2021;25(1):118-23.	Rituximab was one of several possible therapies; number of patients and outcomes for rituximab not reported separately.
Goshua G, Gokhale A, Hendrickson JE, Tormey C, Lee AI. Cost savings to hospital of rituximab use in severe autoimmune acquired thrombotic thrombocytopenic purpura. Blood Advances. 2020;4(3):539-45.	Not included because larger studies available for the outcomes reported by this study
Stubbs MJ, Low R, McGuckin S, Newton R, Thomas M, Westwood JP, et al. Comparison of Rituximab originator (MabThera) to biosimilar (Truxima) in patients with immune-mediated thrombotic thrombocytopenic purpura. British Journal of Haematology. 2019;185(5):912-7.	Not included because comparative studies available for the outcomes reported by this study
Sadeghi A, Ashrafi F, Sourani A. Efficacy of rituximab in the treatment of plasma exchange refractoy thrombotic thrombocytopenic purpura. Iranian Journal of Blood and Cancer. 2018;10(3):87-91.	Not included because larger studies available for the outcomes reported by this study.
Page EE, Kremer Hovinga JA, Terrell DR, Vesely SK, George JN. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. Blood Advances. 2017;1(10):590-600.	Number of patients receiving rituximab unclear, and no subgroup results for those receiving rituximab.
Vazquez-Mellado A, Pequeno-Luevano M, Cantu-Rodriguez OG, Villarreal-Martinez L, Jaime-Perez JC, Gomez-De-Leon A, et al. More about low-dose rituximab and plasma exchange as front-line therapy for patients with thrombotic thrombocytopenic purpura. Hematology. 2016;21(5):311-6.	Not included because larger studies available for the outcomes reported by this study.
Soucemarianadin M, Benhamou Y, Delmas Y, Pichereau C, Maury E, Pene F, et al. Twice-daily therapeutical plasma exchange-based salvage therapy in severe autoimmune thrombotic thrombocytopenic purpura: the French TMA Reference Center experience. European Journal of Haematology. 2016;97(2):183-91.	Not included because larger studies available for the outcomes reported by this study.

Miyakawa Y, Imada K, Ichinohe T, Nishio K, Abe T, Murata M, et al. Efficacy and safety of rituximab in Japanese patients with acquired thrombotic thrombocytopenic purpura refractory to conventional therapy. International Journal of Hematology. 2016;104(2):228-35.	Not included because larger studies available for the outcomes reported by this study
Joly BS, Stepanian A, Leblanc T, Hajage D, Chambost H, Harambat J, et al. Child-onset and adolescent-onset acquired thrombotic thrombocytopenic purpura with severe ADAMTS13 deficiency: a cohort study of the French national registry for thrombotic microangiopathy. The Lancet Haematology. 2016;3(11):e537-e46.	Not included because no relevant outcomes reported.
Iqbal S, Zaidi SZ, Motabi IH, Alshehry NF, AlGhamdi MS, Tailor IK. Thrombotic thrombocytopenic purpura - analysis of clinical features, laboratory characteristics and therapeutic outcome of 24 patients treated at a Tertiary Care Center in Saudi Arabia. Pakistan Journal of Medical Sciences. 2016;32(6):1494-9.	Not included because larger studies available for the outcomes reported by this study
Benhamou Y, Paintaud G, Azoulay E, Poullin P, Galicier L, Desvignes C, et al. Efficacy of a rituximab regimen based on B cell depletion in thrombotic thrombocytopenic purpura with suboptimal response to standard treatment: Results of a phase II, multicenter noncomparative study. American Journal of Hematology. 2016;91(12):1246-51.	Not included because larger comparative studies available for the outcomes reported by this study
Wieland I, Kentouche K, Jentzsch M, Lothschutz D, Graf N, Sykora KW. Long-term remission of recurrent thrombotic thrombocytopenic purpura (TTP) after Rituximab in children and young adults. Pediatric Blood & Cancer. 2015;62(5):823-9.	Not included because larger studies available for the outcomes reported by this study.
Rinott N, Mashiach T, Horowitz NA, Schliamser L, Sarig G, Keren-Politansky A, et al. A 14-Year Experience in the Management of Patients with Acquired Immune Thrombotic Thrombocytopenic Purpura in Northern Israel. Acta Haematologica. 2015;134(3):170-6.	Not included because larger studies available for the outcomes reported by this study.
Omri HE, Taha RY, Gamil A, Ibrahim F, Sabah HA, Mahmoud ZO, et al. Efficacy and Safety of Rituximab for Refractory and Relapsing Thrombotic Thrombocytopenic Purpura: A Cohort of 10 Cases. Clinical Medicine Insights Blood Disorders. 2015;8:1-7.	Not included because larger studies available for the outcomes reported by this study.
Clark WF, Rock G, Barth D, Arnold DM, Webert KE, Yenson PR, et al. A phase-II sequential case-series study of all patients presenting to four plasma exchange centres with presumed relapsed/refractory thrombotic thrombocytopenic purpura treated with rituximab. British Journal of Haematology. 2015;170(2):208-17.	Not included because larger studies available for the outcomes reported by this study.
Goyal J, Adamski J, Lima JL, Marques MB. Relapses of thrombotic thrombocytopenic purpura after treatment with rituximab. Journal of Clinical Apheresis. 2013;28(6):390-4.	Not included because larger studies available for the outcomes reported by this study.
Abdel Karim N, Haider S, Siegrist C, Ahmad N, Zarzour A, Ying J, et al. Approach to management of thrombotic thrombocytopenic purpura at university of cincinnati. Advances in Hematology. 2013;2013:195746.	Not included because larger studies available for the outcomes reported by this study.
McDonald V, Liesner R, Grainger J, Gattens M, Machin SJ, Scully M. Acquired, noncongenital thrombotic thrombocytopenic purpura in children and adolescents: clinical management and the use of ADAMTS 13 assays. Blood Coagulation & Fibrinolysis. 2010;21(3):245-50.	Not included because larger studies available for the outcomes reported by this study.
Chemnitz JM, Uener J, Hallek M, Scheid C. Long-term follow-up of idiopathic thrombotic thrombocytopenic purpura treated with rituximab. Annals of Hematology. 2010;89(10):1029-33.	Not included because larger studies available for the outcomes reported by this study.

Ling HT, Field JJ, Blinder MA. Sustained response with rituximab in patients with thrombotic thrombocytopenic purpura: A report of 13 cases and review of the literature. American Journal of Hematology. 2009;84(7):418-21.	Not included because larger studies available for the outcomes reported by this study.
Heidel F, Lipka DB, von Auer C, Huber C, Scharrer I, Hess G. Addition of rituximab to standard therapy improves response rate and progression-free survival in relapsed or refractory thrombotic thrombocytopenic purpura and autoimmune haemolytic anaemia. Thrombosis & Haemostasis. 2007;97(2):228-33.	Not included because larger studies available for the outcomes reported by this study.
Schieppati F, Russo L, Marchetti M, Barcella L, Cefis M, Gomez-Rosas P, et al. Low levels of ADAMTS-13 with high anti-ADAMTS-13 antibodies during remission of immune-mediated thrombotic thrombocytopenic purpura highly predict for disease relapse: A multi-institutional study. American Journal of Hematology. 2020;95(8):953-9.	Case series of 74; subgroup of 13 had rituximab but no separate data reported for these.
Mancini I, Pontiggia S, Palla R, Artoni A, Valsecchi C, Ferrari B, et al. Clinical and Laboratory Features of Patients with Acquired Thrombotic Thrombocytopenic Purpura: Fourteen Years of the Milan TTP Registry. Thrombosis & Haemostasis. 2019;119(5):695-704.	No outcomes reported relating to rituximab.
Falter T, Herold S, Weyer-Elberich V, Scheiner C, Schmitt V, von Auer C, et al. Relapse Rate in Survivors of Acute Autoimmune Thrombotic Thrombocytopenic Purpura Treated with or without Rituximab. Thrombosis & Haemostasis. 2018;118(10):1743-51.	Not included because larger studies available for the outcomes reported by this study.
Chen H, Fu A, Wang J, Wu T, Li Z, Tang J, et al. Rituximab as first-line treatment for acquired thrombotic thrombocytopenic purpura. Journal of International Medical Research. 2017;45(3):1253-60.	Not included because larger studies available for the outcomes reported by this study.
Rubia J, Moscardo F, Gomez MJ, Guardia R, Rodriguez P, Sebrango A, et al. Efficacy and safety of rituximab in adult patients with idiopathic relapsing or refractory thrombotic thrombocytopenic purpura: results of a Spanish multicenter study. Transfusion & Apheresis Science. 2010;43(3):299-303.	Not included because larger studies available for the outcomes reported by this study.
McDonald V, Manns K, Mackie IJ, Machin SJ, Scully MA. Rituximab pharmacokinetics during the management of acute idiopathic thrombotic thrombocytopenic purpura. Journal of Thrombosis & Haemostasis. 2010;8(6):1201-8.	Not included because larger studies available for the outcomes reported by this study.
Scully M, Cohen H, Cavenagh J, Benjamin S, Starke R, Killick S, et al. Remission in acute refractory and relapsing thrombotic thrombocytopenic purpura following rituximab is associated with a reduction in IgG antibodies to ADAMTS-13. Br J Haematol. 2007;136(3):451-61.	Not included because larger studies available for the outcomes reported by this study.
Reddy MS, Hofmann S, Shen YM, Nagalla S, Rambally S, Usmani A, et al. Comparison of low fixed dose versus standard-dose rituximab to treat thrombotic thrombocytopenic purpura in the acute phase and preemptively during remission. Transfusion & Apheresis Science. 2020;59(6):102885.	Not included because larger studies available for the outcomes reported by this study.
Fakhouri F, Vernant JP, Veyradier A, Wolf M, Kaplanski G, Binaut R, et al. Efficiency of curative and prophylactic treatment with rituximab in ADAMTS13-deficient thrombotic thrombocytopenic purpura: a study of 11 cases. Blood. 2005;106(6):1932-7.	Not included because larger studies available for the outcomes reported by this study.

Appendix E Evidence table

Study details	Population	Intervention	Study outcomes	Appraisal and funding
Full citation Froissart A, Buffet M, Veyradier A, Poullin P, Provot F, Malot S, et al. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. Experience of the French Thrombotic Microangiopathies Reference Center. Critical Care Medicine. 2012;40(1):104-11. **Study location** France **Study type** Prospective cohort study with historical controls **Study aim** To evaluate rituximab as a first-line salvage treatment in adults with idiopathic TTP and either no response or a disease exacerbation during intensive TPE. **Study dates** 2005 to 2008 (prospective data collection)	**Inclusion criteria** Severe, acquired ADAMTS13 deficiency: thrombotic microangiopathy (Coombs negative microangiopathic haemolytic anaemia, acute peripheral thrombocytopenia and absence of an identifiable cause for the thrombocytopenia and microangiopathic haemolytic anaemia); mild renal involvement and ADAMTS13 activity <10%.[1] **Exclusion Criteria** Features of haemolytic uremic syndrome; detectable ADAMTS13 activity after rituximab performed (it is possible that this is a misprint and should have said TPE); prior rituximab for a previous TTP episode. **Total sample size** n=79	**Interventions** Rituximab 375 mg/m^2 (4 infusions; 3 in first week; 1 a week after); TPE, glucocorticosteroids if no infection. **Comparators** TPE alone or in combination with vincristine +/- cyclophosphamide; glucocorticosteroids if no infection.	**Critical outcomes** **Mortality** Median follow-up of survivors: rituximab 33 (SD 17.4) months, no rituximab 35.3 (SD 28.5). Rituximab 1/22 (4.5%, day 15); no rituximab 4/57 (7.0%, mean 8.5 days, SD 1.9), unclear if timing is from start of treatment or from start of illness (p value not reported) **Relapse rate** Reappearance of neurologic manifestations and/or thrombocytopenia for at least 2 days with no other identifiable cause after achieving a durable remission. Relapse (median follow-up of survivors 33 (SD 17.4) months and 35.3 (SD 28.5) months for the two groups respectively) did not differ between both groups (data in a Kaplan Meier figure only, log rank test: p = 0.68) Relapse within 12 months among survivors: rituximab n=0/21; no rituximab n=5/53 (9.4%), p=0.34 **Disease response** Durable remission (complete response with no	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Cohort Studies. 1. Yes 2. Unclear 3. Unclear 4. No 5. No 6. Yes 7. Unclear 8. No 9. No 10. No 11. Unclear Risk of bias: High Other comments: This is a small comparative study using historical controls where the exposures do not appear to have been standard, participants were excluded from the baseline tables and results if they did not survive, and the assessment of the outcomes was unclear. There was limited data beyond 12 months and much of the data was in figures only. It is not clear whether the day of death is from start of treatment or illness.

[1] Normal range of ADAMTS13 activity was not reported in any of the included studies.

Study details	Population	Intervention	Study outcomes	Appraisal and funding
2000 to 2005 (historical controls)	**No. of participants in each treatment group** Rituximab: 22 No rituximab: 57 **Baseline characteristics** Baseline characteristics reported for the surviving patients (rituximab n=21; no rituximab n=53) and the two groups were comparable at baseline for the characteristics reported. Mean age: rituximab 36.8 years (SD 11); no rituximab 41.7 years (SD 16). Female: rituximab 66.7%; no rituximab 69.8%. ADAMTS13 activity: rituximab <10%; no rituximab <10%. Proportion with anti-ADAMTS13 inhibitor: rituximab 85%; no rituximab 71%. Mean anti-ADAMTS13 antibodies: rituximab 100.4 U/mL (SD 38.4); no rituximab 111.1 U/mL (SD 77.9).		further thrombocytopenia or clinical worsening ≥30 days following the first day of platelet count recovery) among survivors, unclear time frame: rituximab n=21/21; no-rituximab: not reported. Mean time from rituximab initiation to durable remission (days from the first TPE to the beginning of remission): rituximab 12 days (SD 6.7), no rituximab, not reported. Platelet count recovery (Kaplan-Meier estimates up to 160 days) was shorter in the rituximab group compared to the no rituximab group (data in a Kaplan Meier figure only, log-rank test: p = 0.03). ADAMTS13 activity higher in the rituximab group than controls at 1 month (p=0.007), 3 months (p=0.01), 6 months (p=0.02) and 9 months (p=0.003). At 12 months there was no significant difference between groups (p=0.12), data in a figure only. **Important outcomes** **Quality of life** No data **Functional** No data **Hospitalisation** No data	Source of funding: part funded by grants from the Etablissement Franc¸ais du Sang (CS/2002/009) and the GISInstitut des Maladies Rares (GIS MR0428).

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	Mean platelet count (x10^9/L): rituximab 13.4 (SD 8.3); no rituximab 14.4 (SD 6.4). The number with refractory TTP and with exacerbations of TTP were n=6 and n=16 (of the 22 included) in the rituximab group and n=8 and n=47 in the no rituximab group (of the 53 survivors, n=2 were refractory, responded and then had an exacerbation).		**Safety/Adverse events** Narrative report that there were no severe adverse events or clinically significant infections.	
Full citation Kubo M, Sakai K, Yoshii Y, Hayakawa M, Matsumoto M. Rituximab prolongs the time to relapse in patients with immune thrombotic thrombocytopenic purpura: analysis of off-label use in Japan. International Journal of Hematology. 2020;112(6):764-72. **Study location** Japan **Study type** Retrospective cohort study **Study aim**	**Inclusion criteria** Severely deficient ADAMTS13 activity (<10% of normal) and detectable ADAMTS13 inhibitor; and refractory TTP defined as persistent thrombocytopenia despite five treatments with TPE and corticosteroids, or relapse defined as thrombocytopenia (<150 × 10^9/l) with or without clinical symptoms > 30 days after TPE for the acute TTP episode was stopped. **Exclusion Criteria**	**Interventions** Rituximab 375 mg/m^2 (4 doses weekly in 80%) TPE 98% Corticosteroids 98% Pulse corticosteroid therapy 78% Other drugs and procedures 26% Cyclophosphamide 18% Vincristine 6% Cyclosporine 8% **Comparators** No rituximab (treatments varied) TPE 89% Corticosteroids 93% Pulse corticosteroid therapy 54%	**Critical outcomes** Median follow-up (IQR): rituximab 3.8 years (2.4–7.3) vs no rituximab 3.9 years (1.7–8.1), p=0.83. **Mortality** Rituximab 3% vs no rituximab 8%, p=0.83 **Relapse rate** Relapse defined as thrombocytopenia (< 150 × 109/L) with or without clinical symptoms > 30 days after TPE for the acute TTP episode was stopped. Proportion of episodes: rituximab 8/65 (12.3%) vs no rituximab 17/104 (16.4%), p=0.51 Relapse-free survival at 2 years significantly higher with rituximab than no rituximab, p=0.02, but not at 5	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Cohort Studies. 1. No 2. Unclear 3. Unclear 4. Yes 5. Yes 6. Yes 7. Unclear 8. Yes 9. No 10. No 11. Yes Risk of bias: High Other comments: This is a large comparative study with long follow-up, but patients were identified retrospectively and outcomes were

Study details	Population	Intervention	Study outcomes	Appraisal and funding
To evaluate the efficacy of off-label rituximab for refractory or relapsed immune TTP. **Study dates** January 2006 to December 2018	Secondary TTP associated with medications or underlying conditions, age <12 years, missing outcome or treatment data, <30 days follow-up, first rituximab administration less than 5 days from the start of TPE. **Total sample size** n=156 **No. of participants in each treatment group** Rituximab: 58 (65 episodes) No rituximab: 98 (104 episodes) **Baseline characteristics** Median age: rituximab 49 years (IQR 37 to 65); no rituximab: 59 years (IQR 40 to 71), p=0.04. Median ADAMTS13 inhibitor: rituximab 4.4 BU/ml (IQR 2.9 to 6.5); no rituximab 2.1 BU/ml (IQR 1.5 to 3.6), p<0.01. Median maximum value of ADAMTS13 inhibitor: rituximab 7.0 BU/ml (IQR 4.2 to 13.1); no rituximab 2.5 BU/ml (IQR 0.6 to 4.1), p<0.01.	Other drugs and procedures 20% Cyclophosphamide 10% Vincristine 7% Cyclosporine 3%	years, p=0.31 (Kaplan-Meier analysis, data in figure). Relapse within 2 years, multivariate analysis, rituximab vs no rituximab: HR 0.18 (95% CI 0.04–0.80). Relapse within 5 years, multivariate analysis, rituximab vs no rituximab: no difference between groups. **Disease response** No data **Important outcomes** **Quality of life** No data **Functional** No data **Hospitalisation** No data **Safety/Adverse events** Rituximab led to respiratory distress in one patient. No other severe adverse events occurred.	assessed by physician questionnaire. There was no standardisation of treatments in either group. People with first rituximab administration less than 5 days from the start of TPE were excluded to avoid cases where rituximab was used as initial treatment. There were differences between groups for several baseline characteristics and people with incomplete outcome data were excluded from the study. The validity and reliability of exposure assignment and measurement, and outcome measurement, were unclear. Source of funding: Research grants from the Ministry of Health, Labour and Welfare of Japan. ‘MM is an inventor of the ELISA used to assess ADAMTS13 activity. MM received research funds from Chugai Pharmaceutical. The other authors have no conflicts of interest.’

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	Proportion of episodes treated with TPE: rituximab 98%; no rituximab 89%, p=0.03; or pulse corticosteroid therapy: rituximab 78%; no rituximab 54%, p<0.01. Other treatments, symptoms, laboratory findings and characteristics were similar, including the proportion of episodes occurring in women (rituximab: 60%; no rituximab 53%, p<0.43) and the proportion of episodes that were relapses (rituximab: 11%; no rituximab 8%, p<0.58).			
Full citation Owattanapanich W, Wongprasert C, Rotchanapanya W, Owattanapanich N, Ruchutrakool T. Comparison of the Long-Term Remission of Rituximab and Conventional Treatment for Acquired Thrombotic Thrombocytopenic Purpura: A Systematic Review and Meta-Analysis. Clinical & Applied Thrombosis/Hemostasis. 2019;25:1076029618825309. **Study location**	**Inclusion criteria** RCTs or cohort studies comparing rituximab and conventional therapy for TTP, reporting relapse rate or mortality. **Exclusion Criteria** Reviews, meta-analyses, commentaries, reports irrelevant to TTP or to comparisons between rituximab and conventional treatments, no primary endpoints. **Total sample size**	**Interventions** Rituximab 375 mg/m^2 weekly and conventional treatment (plasma exchange and corticosteroids 'in almost all cases') **Comparators** Conventional treatment (plasma exchange and corticosteroids 'in almost all cases')	**Critical outcomes** **Mortality** Follow-up 1 year to 4 years Study 1: rituximab 3/40, control 3/40, OR 1.00 (95% CI 0.19 to 5.28) Study 2: rituximab 1/22, control 4/57, OR 0.63 (95% CI 0.07 to 5.98) Study 3: rituximab 0/9, control 6/13, OR 0.06 (95% CI to 0.00 1.26) Study 4: rituximab 2/14, control 6/31, OR 0.69 (95% CI 0.12 to 3.96)	This study was appraised using the AMSTAR 2 tool for systematic reviews. 1. Yes 2. No 3. No 4. Partial yes 5. Yes 6. No 7. No 8. Partial yes 9. Partial yes 10. No 11. No 12. No 13. No 14. No

Study details	Population	Intervention	Study outcomes	Appraisal and funding
Locations not stated **Study type** Systematic review and meta-analysis. **Study aim** To 'summarize the results of all available studies to compare the efficacies of rituximab and conventional treatment for acquired thrombotic thrombocytopenic purpura'. **Study dates** December 2018	n=365 for studies of relapse rate, n=362 for mortality (whole review n=570) **No. of participants in each treatment group** Rituximab: 139 for relapse rate, 141 for mortality (whole review n=280) Conventional: 226 for relapse rate, 221 for mortality (whole review n=290) **Baseline characteristics** The age range was 18 to 79 years for rituximab and 16 to 88 years for conventional treatment. About three-quarters of each group were female. Studies included both de novo and relapsed or refractory TTP. Less than 10% of participants in most studies had ADAMTS13 activity.		Study 5: rituximab 0/16, control 2/21, OR 0.24 (95% CI 0.01 to 5.28) Study 6: rituximab 1/40, control 3/59, OR 0.48 (95% CI 0.05 to 4.77) (meta-analysis not reported) **Relapse rate** Follow-up 1 year to 4 years Rituximab vs conventional treatment: OR 0.40 (95% CI 0.19 to 0.85), p=0.02 **Disease response** No data **Important outcomes** **Quality of life** No data **Functional** No data **Hospitalisation** No data **Safety/Adverse events** No data	15. Yes 16. Yes Risk of bias: high Other comments: This is a systematic review and meta-analysis of nine retrospective or prospective cohort studies, six of which provided data for relapse rate in acute TTP and were combined in a meta-analysis. Mortality data for the acute TTP studies were not pooled separately from prophylactic studies, six studies provided data for mortality (five of those that also provided relapse rate data and one additional study). There were several concerns with the methods of the review, where the authors did not state that methods were established prior to the conduct of the review, explain their selection of study designs, report duplicate data extraction, provide a list of excluded studies, report sources of funding of the studies, justify combining data, assess the potential impact of or account for risk of bias, discuss heterogeneity; and the search strategy was only partially comprehensive. Statistical heterogeneity of the included studies was moderate (I^2 43%) for relapse rate. Source of funding: none
Full citation	**Inclusion criteria**	**Interventions**	**Critical outcomes**	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Cohort Studies.
Scully M, McDonald V, Cavenagh J, Hunt BJ, Longair I, Cohen H, et al. A phase 2	Rituximab: age > 18 years, de novo or relapsed acute TTP	Rituximab (375 mg/m^2 within 3 days of admission, 4 weekly doses; up to 8 infusions if	**Mortality**	

Study details	Population	Intervention	Study outcomes	Appraisal and funding
study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood. 2011;118(7):1746-53. **Study location** UK **Study type** Prospective cohort study with historical controls **Study aim** 'To determine the safety, efficacy, and tolerability of rituximab in combination with plasma exchange in patients with acute idiopathic TTP.' **Study dates** Rituximab: 2006 to 2009 Control: not reported	(thrombocytopenia, microangiopathic haemolytic anaemia, normal clotting screen, increased lactate dehydrogenase to 1.5 times normal upper limit). Control: identified from registry from hospitals involved in trial, matched 'as far as possible' by sex, ethnicity, and number of relapses. **Exclusion Criteria** Died within 24 hrs of admission, other thrombotic microangiopathy, pregnancy or breastfeeding, HIV positive, childhood TTP (< 18 years), haemolytic uremic syndrome, 'diarrhoea positively or negatively associated with acute renal failure' (no further detail), transplant-associated thrombotic microangiopathy, concurrent malignancies. **Total sample size** n=80 **No. of participants in each treatment group**	ADAMTS13 levels remained below the normal range or persistently detectable anti-ADAMTS13 IgG antibodies), TPE (twice a day if new/progressive neurologic or cardiac symptoms), steroids. TPE daily from admission until sustained platelet count of >150 x 10^9/L for 2 consecutive days. Steroids per local protocol (typically 1 g of methylprednisolone intravenously daily for the first 3 days from admission. **Comparators** Control (TPE and steroids following standard guidelines as above)	Rituximab 3/40 (7.5%,11 to 25 days after admission); control: 3/40 (7.5%, 2 during admission, 1 on relapse) (p value not reported) **Relapse rate** Relapse defined as readmission with thrombocytopenia (> 150 x 10^9/L) with or without new symptoms 30 days after discharge from acute episode. Length of follow-up ≥1 year (median not reported). Rituximab: 4/40 (10%) at median 27 months (range 17 to 31); control: 21/40 (53%, states 57% in publication) at median of 18 months (range 3 to 60), p=0.0011. **Disease response** Remission defined as sustained platelet count > 150 x 10^9/L for 2 consecutive days. Median time to remission: rituximab 12 days; control not reported. CD19 (a marker of B-cell levels, normal range 5% to 15%): rituximab 23% (range 2.6% to 39.90%) on admission, 21% (range 10.7% to 51.1%) before first infusion, 1.4% (range 0% to 2.78%) at first infusion, 0.97% (range 0% to 5.43%) at second infusion, 0.5% (range 0% to 2.78%) before fourth infusion, "normalisation of B cell numbers occurred in 75% of patients, with levels above the normal range within 12 months (7.76%; range 0.46 to 32.5). However, this was not	1. No 2. No 3. Unclear 4. Yes 5. Unclear 6. Yes 7. Unclear 8. Yes 9. No 10. No 11. No Risk of bias: High Other comments: This was a prospective study with historical controls from a similar population who were matched 'as far as possible' by sex, ethnicity, and number of relapses. Duration of follow-up was unclear. Although the groups were similar in reported baseline characteristics, the recruitment period of the historical controls was not reported. The study did not fully account for potential confounding factors, outcome assessment for the historical controls was unclear, loss to follow-up was not reported and length of follow-up appears to be unequal, and not all outcomes were compared statistically. Source of funding: Roche Pharmaceuticals (UK) supplied rituximab for all patients entering the trial. One author is funded by Baxter (UK).

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	Rituximab: 40 Control: 40 **Baseline characteristics** There were no significant differences between groups. Median age: rituximab 42 years (range 21 to 76); control 42 years (range 18 to 78). Female: rituximab 26/40; control 33/40. Relapsed: rituximab 6/40; control 9/40. Median ADAMTS13 activity: rituximab < 5% (range <5 to 32); control <5% (range <5 to 40). Median anti-ADAMTS13 IgG[1]: rituximab 40% (range 6 to 62); control: 78% (range 8 to 140) Median platelets (x 10^9/L): rituximab 13 (range 5 to 60); control 14 (range 4 to 84).		associated with further relapse"; control not reported. **Important outcomes** **Quality of life** No data **Functional** No data **Hospitalisation** Median number of days admitted (assumed for initial admission but not stated in paper): rituximab 16.5 days (range 5 to 49); control 20 days (range 5 to 62), p=not significant. **Safety/Adverse events** Number of events in rituximab group (during admission and up to 1- year follow-up): Acute anuric/oliguric renal failure: 0 Total deaths 3 (1 cerebral infarction and heart involvement, 2 cardiac TTP) Chest pain: during infusion 1; following infusion 5 (1 associated with troponin T > 0.05); not related to rituximab 2 Infections following rituximab infusion (up to 1 year follow-up) 26 Viral infections 10 Bacterial infections 1 (*Clostridium difficile*)	

Study details	Population	Intervention	Study outcomes	Appraisal and funding
			Skin infections 4 (2 *Staphylococcus aureus*; 1 fungal) Cellulitis 2 Urinary tract infections 6 (3 *E coli*, twice in same patient; 1 *Enterococcus*) Infections due to infusion lines 3 Infections prior to rituximab infusion/unrelated to rituximab 10 (1 *E coli*; *S aureus*) Transient ischaemic attack 4 (3 sequentially in same patient) Numbness in limb 4 (2 in same patient) Depression after discharge 3 Sensory/motor abnormalities not related to rituximab 5 Headaches 4 Reduced neutrophil count 3 (transitory, incidental, no infections) Reduced platelet count 1 Deep vein thrombosis 1 Increased blood pressure 2 Hypotensive 2 Other vascular 2 Joint pain possibly related to rituximab 5	

Study details	Population	Intervention	Study outcomes	Appraisal and funding
			Skin rash (in remission) possibly related to rituximab 3 Hair loss/thinning possibly related to rituximab 2 Temperature 38°C 3	
Full citation Sun L, Mack J, Li A, Ryu J, Upadhyay VA, Uhl L, et al. Predictors of relapse and efficacy of rituximab in immune thrombotic thrombocytopenic purpura. Blood Advances. 2019;3(9):1512-8. **Study location** USA **Study type** Retrospective cohort study, 4 centres **Study aim** To compare relapse rates between people with and without rituximab during their index presentation (de novo or relapse) with acute immune TTP. **Study dates** 2004 to 2017	**Inclusion criteria** Immune-mediated TTP, consecutive patients age ≥18 years, thrombocytopenia (<150 x 10^9 platelets/L), schistocytosis, and one of: ADAMTS13 activity level ≤10% or ADAMTS13 activity level between 10% and 20% with a positive inhibitor titre by Bethesda assay and/or detectable anti-ADAMTS13 immunoglobulin G present in plasma. **Exclusion Criteria** ADAMTS13 assay sent as an outpatient, known source of interference with the ADAMTS13 assay, secondary cause of thrombotic microangiopathy. **Total sample size** n=124	**Interventions** Rituximab (375 mg/m^2 in 97%; 4 weekly does in 86%). TPE 100% (median procedures 15, range 8 to 23) Steroids 97% Second-line drug 13% **Comparators** No rituximab: TPE 94% (median procedures 9, range 6 to 15) Steroids 88% Second-line drug 0%	**Critical outcomes** **Mortality** No data **Relapse rate** Defined as recurrence of iTTP after 30 consecutive days without TPE, median follow-up 20.6 months, Rituximab group appeared to be protected from relapse at 1 year (p=0.01) but not at 5 years (p=0.45, Kaplan-Meier analysis). Rituximab vs no rituximab risk of subsequent relapse: HR on day of administration 0.16 (95% CI 0.04 to 0.70); effect of rituximab reduced with time, HR for time interaction 1.002 (95% CI 1.0007 to 1.003) per day after administration, HR 1.0 at 2.6 years. **Disease response** For patients receiving rituximab who had not yet achieved a normal platelet count (n not reported), platelet count normalisation occurred a median of 8 days (IQR 5 to 11) after administration (not stated if this is from first or last infusion). **Important outcomes**	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Cohort Studies. 1. No 2. Yes 3. Unclear 4. Yes 5. Yes 6. Yes 7. Unclear 8. Yes 9. Unclear 10. Yes 11. Yes Risk of bias: High Other comments: This is a large comparative study; however, patients were identified retrospectively and it is unclear whether the control group is a fair comparison or whether they did not receive rituximab due to factors such as disease severity or usual practice at the time of presentation; the authors noted that the use of rituximab on initial presentation increased during the study period. The index presentation was defined as the patient's first episode of TTP captured within the consortium,

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	No. of participants in each treatment group Rituximab: 60 No rituximab: 64 **Baseline characteristics** Age, sex, ethnicity, proportion with a first episode or relapsed and presenting laboratory features were similar between groups. The rituximab group were more likely to have a higher reticulocyte count (p<0.01), lower platelet count on day 4 (p<0.001), and more TPE procedures required to achieve remission (p<0.0001). Median (IQR) age: rituximab 41 years (31 to 52), no rituximab 43 years (31 to 53). Female: rituximab 70%, no rituximab 69%. Presenting in relapse: rituximab 17%, no rituximab 16%. Prior rituximab: rituximab 4/60, no rituximab 0/60. Median ADAMTS13 activity: rituximab 0%		**Quality of life** No data **Functional** No data **Hospitalisation** Median (IQR) hospital stay (assumed for initial admission but not stated in paper): rituximab 18 days (11 to 27); no rituximab 9 days (7 to 14) (p value not reported). **Safety/Adverse events** No data	regardless of previous episodes that may have occurred at other institutions. The index presentation could be de novo TTP or a relapse. Source of funding: Luick Family Fund of the Massachusetts General Hospital. Two authors supported by grants from National Institutes of Health, National Heart, Lung, and Blood Institute.

Study details	Population	Intervention	Study outcomes	Appraisal and funding
	(IQR 0 to 0); no rituximab 0% (IQR 0 to 0). Median ADAMTS13 inhibitor: rituximab 1.4 BU (IQR 0.8 to 2.0), no rituximab 1.4 BU (IQR 0.6 to 2.0). Platelets (10^9/L): rituximab 15 (IQR 10 to 20); no rituximab 17 (IQR 11 to 24).			
Full citation Westwood JP, Webster H, McGuckin S, McDonald V, Machin SJ, Scully M. Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse. J Thromb Haemost. 2013;11(3):481-90. **Study location** UK **Study type** Single centre retrospective case series **Study aim** To review the response to rituximab in patients with acute de novo or relapsed TTP. (The study also aimed to review patients treated as	**Inclusion criteria** Consecutive patients with acute de novo or relapse TTP (presence of thrombocytopenia, microangiopathic haemolytic anaemia, normal clotting screen, increased lactate dehydrogenase to ≥ 1 x upper limit of normal). **Exclusion Criteria** Not reported. **Total sample size** n=86 (104 episodes) **No. of participants in each treatment group** Rituximab: 86 **Baseline characteristics**	**Interventions** Rituximab 375mg/m^2, median 4 doses (range 1 to 8 doses), weekly (pre-2009) or every 3 to 4 days (post-2009 in patients at high risk of morbidity/mortality). **Comparators** Not applicable	**Critical outcomes** **Mortality** Overall: 6/104 patient episodes (5.8%) (86 patients), median 12.5 days (range 4 to 18) from admission. Rituximab naïve: 4/86 (early rituximab group: 2/54 (3.7%); late rituximab group 2/32 (6.3%), p value not reported) Previously treated: 2/14 **Relapse rate** Relapse defined as readmission with thrombocytopenia (< 150 x 10^9/L) with or without new symptoms 30 days after discharge from acute episode. *Rituximab naïve patients (n=86):* Median follow-up 45 months (range 4 to 100 months): 11 of 82 (13.4%) patients who achieved remission.	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case series. 1. Unclear 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Unclear 9. No 10. Yes Risk of bias: Unclear Other comments: Subgroups included rituximab naive or previously treated (these may be the same patients at different stages); rituximab naïve and either early or late rituximab and rituximab administration every 3 days or weekly. 31 of the participants are included in the Scully 2011 study included in this review; these all had early rituximab (≤3 days from hospital admission). Relapse free survival for

Study details	Population	Intervention	Study outcomes	Appraisal and funding
prophylaxis, not extracted here). **Study dates** January 2004 to December 2011	Mean age: 43 years (range 12 to 78), female: 61/86. Rituximab naive: 86/104 episodes (74 de novo, 12 relapses); previously treated 18/104 episodes (14 patients). Rituximab naïve patients, early rituximab (≤3 days from admission): 54; late rituximab (> 3 days from admission): 32. Median ADAMTS13 activity: < 5% (range < 5 to 39). Median anti-ADAMTS13 IgG: 40% (range 4 to 160).		There was no difference in relapse free survival between early and late rituximab groups (p=0.77). *Previously treated patients (n=14, 18 episodes):* Follow-up 22 months (range 16 to 53): 5 relapses in 3 patients. **Disease response** Remission defined as sustained platelet count of > 150 x 10^9/L for 2 consecutive days. *Rituximab naïve patients (n=86):* Overall: remission in 82/86 (95%), time to remission 14 days (range 4 to 52) (median not stated but assumed; not stated whether time from admission or first infusion). Median time to remission from admission: early rituximab group 12 days (range 4 to 52); late rituximab group 20 days (range 4 to 42), p<0.001. Median time to remission from first infusion: early rituximab group 10 days (range 2 to 50); late rituximab group 9 days (range 0 to 30), p=0.67. Early rituximab group: median time to remission from admission: rituximab administration every 3 days group 13 days; weekly group 9 days, p=0.07. Late rituximab group: median time to remission from admission: rituximab	early and late subgroups presented in figure but numbers not reported. Limited eligibility criteria reported, but states consecutive patients included. Limited details reported on adverse events. No reporting of demographic information of presenting site. Source of funding: grant from the UK Medical Research Council.

Study details	Population	Intervention	Study outcomes	Appraisal and funding
			administration every 3 days group 18 days; weekly group 21 days, p=0.48. Early rituximab group: median time to remission from first infusion: rituximab administration every 3 days group 11 days; weekly group 7 days, p=not significant. Late rituximab group: median time to remission from first infusion: rituximab administration every 3 days group 8 days; weekly group 9 days, p=not significant. *Previously treated patients (n=14, 18 episodes):* Overall: remission in 16/18 episodes. Median time to remission from admission 7 days (range 0 to 25) Median time to remission from infusion 8 days (range 4 to 25) **Important outcomes** **Quality of life** No data **Functional** No data **Hospitalisation** *Rituximab naïve patients (n=86):* Median length of hospital admission (assumed for initial admission but not stated in paper): 19 days (range 4 to 86).	

Study details	Population	Intervention	Study outcomes	Appraisal and funding
			Median length of admission: early rituximab group 16 days (range 4 to 86); late rituximab group 23 days (range 7 to 52), p=0.01. *Previously treated patients (n=14):* Median length of hospital stay (assumed for initial admission but not stated in paper): 10 days (range 4 to 29). **Safety/Adverse events** No documented increase in infections. Mild joint pains (number not reported), chest pain in six cases (unknown if associated with TTP rituximab), no progressive multifocal leukoencephalopathy.	

Abbreviations:
CI - Confidence interval; HR – Hazard Ratio; HIV – Human Immunodeficiency Virus; IQR - Inter-quartile range; iTTP - idiopathic (immune) thrombotic thrombocytopaenic purpura; OR - odds ratio; RCT - Randomised controlled trial; SD – Standard deviation; TTP - thrombotic thrombocytopaenic purpura.

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Appendix F Quality appraisal checklists

AMSTAR 2 Critical Appraisal Tool for Systematic Reviews

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?
17. Reviewer's summary of risk of bias

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people
3. to both exposed and unexposed groups?
4. Was the exposure measured in a valid and reliable way?

5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
8. Were the outcomes measured in a valid and reliable way?
9. Was the follow up time reported and sufficient to be long enough for outcomes to occur?
10. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
11. Were strategies to address incomplete follow up utilized?
12. Was appropriate statistical analysis used?
13. Reviewer's summary of risk of bias

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?
11. Reviewer's summary of risk of bias

Appendix G GRADE profiles

Table 2: In people diagnosed with acute immune TTP, what is the clinical effectiveness and safety of rituximab compared to no rituximab?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Rituximab	No rituximab	Result (95%CI)		
Mortality from the acute episode (3 comparative cohort studies, 1 case series)									
Mortality (number and proportion died, 1 to 4 years follow-up)									
1 SRMA Owattanapanich et al 2019	Very serious limitations[1]	No serious indirectness	Not calculable	Very serious imprecision[2]	141	221	Follow-up 1 year to 4 years Study 1: rituximab 3/40, control 3/40, OR 1.00 (95% CI 0.19 to 5.28) Study 2: rituximab 1/22, control 4/57, OR 0.63 (95% CI 0.07 to 5.98) Study 3: rituximab 0/9, control 6/13, OR 0.06 (95% CI to 0.00 1.26) Study 4: rituximab 2/14, control 6/31, OR 0.69 (95% CI 0.12 to 3.96) Study 5: rituximab 0/16, control 2/21, OR 0.24 (95% CI 0.01 to 5.28) Study 6: rituximab 1/40, control 3/59, OR 0.48 (95% CI 0.05 to 4.77) (meta-analysis not reported)	Critical	Very low
Mortality (number and proportion died, 1 year follow-up)									
1 comparative cohort study Scully et al 2011	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	40	40	1 year follow-up Rituximab 3/40 (7.5%,11 to 25 days after admission); control: 3/40 (7.5%, 2 during admission, 1 on relapse) (p value not reported)	Critical	Very low
Mortality (number and proportion died, median 33 to 35 months follow-up)									
1 comparative cohort study Froissart et al 2012	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	22	57	Median follow-up of survivors: rituximab 33 months (SD 17.4); no rituximab 35.3 months (SD 28.5) Rituximab 1/22 (4.5%, day 15); no rituximab 4/57 (7.0%, mean 8.5 days, SD 1.9), unclear if timing is from start of	Critical	Very low

							treatment or from start of illness (p value not reported)		
Mortality (number and proportion died, approximately 4 years follow-up)									
1 comparative cohort study Kubo et al 2020	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	58	98	Median follow-up: rituximab 3.8 years (IQR 2.4 to 7.3); no rituximab 3.9 years (IQR 1.7 to 8.1) Rituximab 3% vs no rituximab 8%, p=0.83	Critical	Very low
1 case series Westwood et al 2013	Serious limitations[6]	Serious indirectness[7]	Not applicable	Not calculable	86	none	Median follow-up 45 months (range 4 to 100 months) 6/104 patient episodes (5.8%) (86 patients), median 12.5 days (range 4 to 18) from admission	Critical	Very low
Relapse rate (1 meta-analysis, 4 comparative cohort studies, 1 case series)									
Relapse rate (number and proportion relapsed, lower result indicates a greater benefit, follow-up range 1 year to 4 years)									
1 SRMA Owattanapanich et al 2019	Very serious limitations[1]	No serious indirectness	Serious inconsistency[8]	Serious imprecision[9]	139	226	Rituximab vs conventional treatment: OR 0.40 (95% CI 0.19 to 0.85), p=0.02	Critical	Very low
Relapse rate (number and proportion relapsed, lower result indicates a greater benefit, at 1 to 2 years)									
1 comparative cohort study Froissart et al 2012	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	22	57	Median follow-up of survivors: rituximab 33 months (SD17.4); no rituximab 35.3 months (SD 28.5) Relapse within 12 months among survivors: rituximab n=0/21; no rituximab n=5/53 (9.4%), p=0.34	Critical	Very low
1 comparative cohort study Sun et al 2019	Very serious limitations[10]	No serious indirectness	Not applicable	Not calculable	60	64	Defined as recurrence of iTTP after 30 consecutive days without TPE, median follow-up 20.6 months. HR on day of administration 0.16 (95% CI 0.04 to 0.70). Rituximab group appeared to be protected from relapse at 1 year (p=0.01).	Critical	Very low
1 comparative cohort study Scully et al 2011	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	40	40	Relapse defined as readmission with thrombocytopenia (> 150 x 10^9/L) with or without new symptoms 30 days after discharge from acute episode. Rituximab: 4/40 (10%) at median 27 months (range 17 to 31); control: 21/40	Critical	Very low

							(53%, states 57% in publication) at median of 18 months (3 to 60 months), p=0.0011.		
1 comparative cohort study Kubo et al 2020	Very serious limitations[5]	No-serious indirectness	Not applicable	No serious imprecision	58	98	Relapse defined as thrombocytopenia (< 150 × 109/L) with or without clinical symptoms > 30 days after TPE for the acute TTP episode was stopped. Median follow-up: rituximab 3.8 years (IQR 2.4 to 7.3); no rituximab 3.9 years (IQR 1.7 to 8.1) Relapse-free survival at 2 years significantly higher with rituximab than no rituximab (Kaplan-Meier analysis, p=0.02, data in figure). Relapse within 2 years, multivariate analysis, rituximab vs no rituximab: HR 0.18 (95% CI 0.04–0.80).	Critical	Very low
1 case series Westwood et al 2013	Serious limitations[6]	Serious indirectness[7]	Not applicable	Not calculable	86	none	Relapse defined as readmission with thrombocytopenia (< 150 x 10^9/L) with or without new symptoms 30 days after discharge from acute episode. Median follow-up: previously treated patients 22 months (range 16 to 53)) Previously treated patients (n=14, 18 episodes): remission in 16 episodes, 5 relapses in 3 patients.	Critical	Very low
Relapse rate (number and proportion relapsed, lower result indicates a greater benefit, median follow-up approximately 3 years)									
1 comparative cohort study Froissart et al 2012	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	22	57	Reappearance of neurologic manifestations and/or thrombocytopenia for at least 2 days with no other identifiable cause after achieving a durable remission. Median follow-up of survivors: rituximab 33 (SD17.4) months; no rituximab 35.3 (SD 28.5). Relapse did not differ between both groups (data in a Kaplan Meier figure only, log rank test: p=0.68)	Critical	Very low
Relapse rate (number and proportion relapsed, lower result indicates a greater benefit, median follow-up approximately 4 years)									
1 comparative cohort study Kubo et al 2020	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	58	98	Relapse defined as thrombocytopenia (< 150 × 109/L) with or without clinical symptoms > 30 days after TPE for the acute TTP episode was stopped. Median follow-up: rituximab 3.8 years	Critical	Very low

							(IQR 2.4 to 7.3); no rituximab 3.9 years (IQR 1.7 to 8.1) Proportion of episodes: rituximab 8/65 (12.3%) vs no rituximab 17/104 (16.4%), p=0.51		
1 case series Westwood et al 2013	Serious limitations[6]	No serious indirectness	Not applicable	Not calculable	86	none	Relapse defined as readmission with thrombocytopenia (< 150 x 10^9/L) with or without new symptoms 30 days after discharge from acute episode. Median follow-up: rituximab naïve patients 45 months (range 4 to 100). Rituximab naïve patients (n=86): relapse in 11 of 82 (13.4%) patients who achieved remission.	Critical	Very low
Relapse rate (number and proportion relapsed, lower result indicates a greater benefit, follow-up at 5 years)									
1 comparative cohort study Kubo et al 2020	Very serious limitations[5]	No serious indirectness	Not applicable	Not calculable	58	98	Relapse defined as thrombocytopenia (< 150 × 109/L) with or without clinical symptoms > 30 days after TPE for the acute TTP episode was stopped. Median follow-up: rituximab 3.8 years (IQR 2.4 to 7.3); no rituximab 3.9 years (IQR 1.7 to 8.1) No difference in relapse-free survival at 5 years between rituximab and no rituximab, p=0.31 (Kaplan-Meier analysis, data in figure). Relapse within 5 years, multivariate analysis, rituximab vs no rituximab: no difference between groups.	Critical	Very low
1 comparative cohort study Sun et al 2019	Very serious limitations[10]	No serious indirectness	Not applicable	Not calculable	60	64	Defined as recurrence of iTTP after 30 consecutive days without TPE, median follow-up 20.6 months. Effect of rituximab reduced with time, HR for time interaction 1.002 (95% CI 1.0007 to 1.003) per day after administration, with HR 1.0 at 2.6 years. No difference in relapse between groups at 5 years (Kaplan-Meier analysis, p=0.45).	Critical	Very low

Disease response (3 comparative cohort studies, 1 case series)									
Time to remission (days, lower result indicates a greater benefit, median follow-up 33 to 35 days)									
1 comparative cohort study Froissart et al 2012	Very serious limitations[4]	Serious indirectness[7]	Not applicable	Not calculable	22	57	Durable remission (complete response with no further thrombocytopenia or clinical worsening ≥30 days following the first day of platelet count recovery), unclear time frame: rituximab n=21/21 survivors; no-rituximab: not reported. Median follow-up: rituximab 33 (SD17.4) months; no rituximab 35.3 (SD 28.5). Mean time from rituximab initiation to durable remission (days from the first TPE to the beginning of remission): rituximab 12 days (SD 6.7), no rituximab, not reported.	Critical	Very low
Time to remission (days, lower result indicates a greater benefit, ≥1 year follow-up,)									
1 comparative cohort study Scully et al 2011	Very serious limitations[3]	Serious indirectness[7]	Not applicable	Not calculable	40	40	Remission defined as sustained platelet count > 150 x 10^9/L for 2 consecutive days. Median time to remission: rituximab 12 days; control not reported.	Critical	Very low
Time to remission (days, lower result indicates a greater benefit, median follow-up approximately 2 to 4 years)									
1 case series Westwood et al 2013	Serious limitations[6]	Serious indirectness[7]	Not applicable	Not calculable	86	none	Remission defined as sustained platelet count of > 150 x 10^9/L for 2 consecutive days. Median follow-up: rituximab naïve patients 45 months (range 4 to 100); previously treated patients 22 months (range 16 to 53). *Rituximab naïve patients (n=86):* Overall: remission in 82/86 (95%), time to remission 14 days (range 4 to 52) (median not stated but assumed; not stated whether time from admission or first infusion). *Previously treated patients (n=14, 18 episodes):* Overall: remission in 16/18 episodes. Median time to remission from admission 7 days (range 0 to 25)	Critical	Very low

							Median time to remission from infusion 8 days (range 4 to 25)		
Platelet normalisation (days to platelet count recovery, lower result indicates a greater benefit)									
1 comparative cohort study Froissart et al 2012	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	22	57	Platelet count recovery (Kaplan-Meier estimates up to 160 days) was shorter in the rituximab group compared to the no rituximab group (data in a Kaplan Meier figure only, log-rank test: p = 0.03).	Critical	Very low
1 comparative cohort study Sun et al 2019	Very serious limitations[10]	Serious indirectness[7]	Not applicable	Not calculable	60	64	Median follow-up 20.6 months. For patients receiving rituximab who had not yet achieved a normal platelet count (n not reported), platelet count normalisation occurred a median of 8 days (IQR 5 to 11) after administration (not stated if this is from first or last infusion).	Critical	Very low
Normalisation of ADAMTS13 activity (ADAMTS13 activity up to 12 months, higher result indicates a greater benefit)									
1 comparative cohort study Froissart et al 2012	Very serious limitations[4]	No serious indirectness	Not applicable	Not calculable	22	57	ADAMTS13 activity higher in the rituximab group than controls at 1 month (p=0.007), 3 months (p=0.01), 6 months (p=0.02) and 9 months (p=0.003). At 12 months there was no significant difference between groups (p=0.12), data in a figure only.	Critical	Very low
Normalisation of B-cell numbers (higher result indicates a greater benefit, ≥12 months follow-up)									
1 comparative cohort study Scully et al 2011	Very serious limitations[3]	Serious indirectness[7]	Not applicable	Not calculable	40	40	CD19 (a marker of B-cell levels, normal range 5% to 15%): rituximab 23% (range 2.6% to 39.90%) on admission, 21% (range 10.7% to 51.1%) before first infusion, 1.4% (range 0% to 2.78%) at first infusion, 0.97% (range 0% to 5.43%) at second infusion, 0.5% (range 0% to 2.78%) before fourth infusion, “normalisation of B cell numbers occurred in 75% of patients, with levels above the normal range within 12 months (7.76%; range 0.46 to 32.5). However, this was not associated with further relapse”. Control not reported.	Critical	Very low

Hospitalisation (2 comparative cohort studies, 1 case series)									
Length of hospital stay (assumed to be for initial admission but not explicitly stated in publications) (median days, lower result indicates a greater benefit)									
1 comparative cohort study Scully et al 2011	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	40	40	1 year follow-up. Median number of days admitted: rituximab 16.5 days (range 5 to 49); control 20 days (range 5 to 62), p=not significant.	Important	Very low
1 comparative cohort study Sun et al 2019	Very serious limitations[10]	No serious indirectness	Not applicable	Not calculable	60	64	Median follow-up 20.6 months. Median (IQR) hospital stay: rituximab 18 days (11 to 27); no rituximab 9 days (7 to 14) (p value not reported).	Important	Very low
1 case series Westwood et al 2013	Serious limitations[6]	Serious indirectness[7]	Not applicable	Not calculable	86	none	*Rituximab naïve patients (n=86):* Median follow-up 45 months (range 4 to 100 months). Median length of hospital stay: 19 days (range 4 to 86). *Previously treated patients (n=14):* Follow-up 22 months (range 16 to 53). Median length of hospital stay: 10 days (range 4 to 29).	Important	Very low
Safety / Adverse events (3 comparative cohort studies, 1 case series)									
Adverse events (follow-up up to 1 year)									
1 comparative cohort study Scully et al 2011	Very serious limitations[3]	Serious indirectness[7]	Not applicable	Not calculable	40	40	Number of events in rituximab group (during admission and up to 1- year follow-up): Acute anuric/oliguric renal failure: 0 Total deaths 3 (1 cerebral infarction and heart involvement, 2 cardiac TTP) Chest pain: during infusion 1; following infusion 5 (1 associated with troponin T > 0.05); not related to rituximab 2 Infections following rituximab infusion (up to 1 year follow-up) 26 Viral infections 10 Bacterial infections 1 (Clostridium difficile) Skin infections 4 (2 Staphylococcus aureus; 1 fungal)	Important	Very low

							Cellulitis 2 Urinary tract infections 6 (3 E coli, twice in same patient; 1 Enterococcus) Infections due to infusion lines 3 Infections prior to rituximab infusion/unrelated to rituximab 10 (1 E coli; S aureus) Transient ischaemic attack 4 (3 sequentially in same patient) Numbness in limb 4 (2 in same patient) Depression after discharge 3 Sensory/motor abnormalities not related to rituximab 5 Headaches 4 Reduced neutrophil count 3 (transitory, incidental, no infections) Reduced platelet count 1 Deep vein thrombosis 1 Increased blood pressure 2 Hypotensive 2 Other vascular 2 Joint pain possibly related to rituximab 5 Skin rash (in remission) possibly related to rituximab 3 Hair loss/thinning possibly related to rituximab 2 Temperature 38°C 3		
Adverse events (median follow-up up to approximately 3 to 4 years)									
1 comparative cohort study Froissart et al 2012	Very serious limitations[4]	Serious indirectness[7]	Not applicable	Not calculable	22	57	Median follow-up: rituximab 33 months (SD17.4); no rituximab 35.3 months (SD 28.5) States no severe adverse events or clinically significant infections.	Important	Very low

1 comparative cohort study Kubo et al 2020	Very serious limitations[5]	Serious indirectness[7]	Not applicable	Not calculable	58	98	Median follow-up: rituximab 3.8 years (IQR 2.4 to 7.3); no rituximab 3.9 years (IQR 1.7 to 8.1 Rituximab led to respiratory distress in one patient. No other severe adverse events occurred.	Important	Very low
1 case series Westwood et al 2013	Very serious limitations[11]	Serious indirectness[7]	Not applicable	Not calculable	86	none	Median follow-up 45 months (range 4 to 100 months). No documented increase in infections. Mild joint pains (number not reported), chest pain in six cases (unknown if associated with TTP rituximab), no progressive multifocal leukoencephalopathy.	Important	Very low

Abbreviations

CI - Confidence interval; HR – Hazard ratio; IQR - Inter-quartile range; iTTP - idiopathic (immune) thrombotic thrombocytopaenic purpura; OR - odds ratio; SD – Standard deviation; SRMA - Systematic review and meta-analysis; TPE – therapeutic plasma exchange; TTP - thrombotic thrombocytopaenic purpura

1 Risk of bias: very serious limitations due to absence of an explicit statement that the review methods were established prior to the conduct of the review, no explanation of the selection of study designs for inclusion, a partially comprehensive search strategy, method of data extraction not reported, list of excluded studies not provided, description of included studies partially adequate, partially satisfactory technique for assessing risk of bias, sources of funding for the studies included in the review not reported, risk of bias not accounted for, no discussion of heterogeneity in results
2 Very serious imprecision because the 95% CI for the OR crosses 0.8 and 1.25 for all studies.
3 Risk of bias: very serious limitations due to historical controls, differences in methods to assign exposure, unclear methods of measuring exposure, dealing with confounding factors and measuring outcomes, and strategies to address follow-up and statistical analysis not appropriate.
4 Risk of bias: very serious limitations due to use of historical controls, exposures not standard, confounding factors not identified, unclear assessment of outcomes and statistical analysis.
5 Risk of bias: very serious limitations due to retrospective identification of participants, significant difference between groups at baseline, unclear exposure measures to assign people to groups, incomplete follow-up and no strategies to address this.
6 Risk of bias: serious limitations due to unclear reporting of inclusion criteria for the case series, no reporting of presenting site demographic information.
7 Serious indirectness due to no comparison across treatment arms.
8 Serious inconsistency because of level of statistical heterogeneity present in the meta-analysis (I^2 43%).
9 Serious imprecision because wide confidence intervals were present in the meta-analysis (95% CI for the OR includes the lower default MCID threshold of 0.8 but not the higher threshold of 1.25).
10 Risk of bias: very serious limitations due to differences between groups at baseline, unclear methods for assigning exposure, unclear outcome measurement, loss to follow-up not reported.
11 Risk of bias: very serious limitations due to unclear reporting of inclusion criteria for the case series, no reporting of presenting site demographic information, and limited details on adverse events.

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether 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.
Before-and-after study	An approach in which dependent variables are measured before and after an intervention has been delivered. Often called a pre–post study. The people in the pre- and post-intervention stages can either be the same or different.
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.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted because of an association between the population or intervention or outcome and another factor (the 'confounding variable' or 'confounder') that can influence the outcome independently of the intervention under investigation. For example, a study of heart disease may look at a group of people who exercise regularly and a group who do not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Control / Comparator group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to

	check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
Cost-effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve one outcome (for example, cost per life year gained).
EQ-5D	A standardised 5-dimensional instrument used to measure health outcomes. It is completed by the person having a treatment themselves and is quick to use.
Follow up	Observation over a period of time of a person, group or defined population to observe changes in health status, or health- and social care-related variables.
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.
Hazard ratio	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
Heterogeneity	A term used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Inter-quartile range (IQR)	The interquartile range shows the range in values of the central 50% of the data.
Mean	A measure of central tendency calculated by dividing the sum of all the observed values by the number of observations
Median	A measure of central tendency corresponding to the value below which 50% of the observations are found. The median is the midpoint of observations ranked in ascending order. It can provide a better estimate of the mean when extreme values cause asymmetry in the distribution of the observations
Meta-analysis	A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.
Methodology	Describes how research is done, including how information is collected and analysed, and why a particular method has been chosen. The overall approach taken by a research project: for example, the study could be a randomised controlled trial of 200 people over 1 year.
Odds Ratio (OR)	Compares the odds (probability) of something happening in 1 group with the odds of it happening in

	another. An odds ratio of 1 shows that the odds of the event happening (for example, a person developing a disease or a treatment working) is the same for both groups. An odds ratio of greater than 1 means that the event is more likely in the first group than the second. An odds ratio of less than 1 means that the event is less likely in the first group than in the second group.
Outcomes	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Depending on the intervention, outcomes could include changes in knowledge and behaviour related to health or in people's health and wellbeing, the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, symptoms or situation.
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).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
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.
Sample	People in a study recruited from part of the study's target population. If they are recruited in an unbiased

	way, the results from the sample can be generalised to the target population as a whole.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Systematic review	A study which involves systematically searching for evidence using pre-defined criteria. Relevant studies are selected and quality appraised. Evidence from multiple studies is extracted and reported and may be combined in a meta-analysis (see above).

References

Included studies

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