NHS England Evidence Review:

Rituximab for prophylactic treatment for Thrombotic Thrombocytopaenic Purpura (TTP)

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Rituximab for prophylactic treatment for Thrombotic Thrombocytopaenic Purpura (TTP)

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of rituximab compared to any treatment regime not using rituximab in people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency.

Rituximab is a monoclonal anti-CD20 antibody. The aim of its use in the context of this review is to prevent relapse of acute immune TTP.

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 go into clinical remission and are eligible to commence prophylactic treatment, and the dose regimens of prophylactic rituximab that were used.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of rituximab compared to any treatment regime not using rituximab in people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, to prevent relapse.

The searches for evidence published since 2005 were conducted on 10th May 2021 and identified 433 references. The titles and abstracts were screened and 17 full text papers were obtained and assessed for relevance.

Four papers were identified for inclusion, one systematic review and meta-analysis (SRMA), one retrospective comparative cohort study, one case series with an additional comparison to an historical group and one retrospective case series, including between 45 and 163 participants. Studies reported outcomes during follow-up ranging from 15 months to 40 months. Two studies were based in France, one in the UK and the SRMA did not specify locations. Two of the included studies were the only studies included in the SRMA, but were also included separately in this review because they reported additional outcomes.

In terms of clinical effectiveness:

- **Relapse (critical).** Four studies (one SRMA, one retrospective comparative cohort study, one case series with an additional comparison to an historical group and one retrospective case series) provided very low certainty evidence that compared to no rituximab treatment, prophylactic rituximab substantially reduces the rate of relapse at up to 38 months follow-up. For example, in the meta-analysis of the only two comparative studies that were identified, the OR for relapse (recurrence of an acute episode of TTP) was 0.09 (95% CI 0.04 to 0.24), p<0.00001 (median follow up 3 years).
- **Disease response (critical).** Three studies (one retrospective comparative cohort study, one case series with an additional comparison to an historical group and one retrospective case series) provided very low certainty evidence that patients may have had a disease response to prophylactic rituximab treatment up to 36 months follow-up. For example, one study reported that 34/92 patients (37%) were considered long-term responders (definition not reported) and another study reported that 20/30 (67.7%) patients had durable ADAMTS13 recovery (ADAMTS13 activity ≥50%) at a median follow-up of 36 months. However, no comparative data were reported for patients who were not treated with rituximab.
- No evidence was available for the critical outcome of hospitalisation or the important outcomes of quality of life and function.

In terms of safety:

- **Adverse events.** Four studies (one SRMA, one retrospective comparative cohort study, one case series with an additional comparison to an historical group and one retrospective case series) provided very low certainty non-comparative evidence relating to adverse events, with rates ranging from 13% for rituximab treatment related events in one study to 30% for any adverse event in another study, and very low certainty evidence that there is no difference in mortality rates when comparing rituximab treatment to no-rituximab treatment.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients that would benefit more from prophylactic treatment with rituximab

Criteria used by the research studies to define eligibility to commence prophylactic treatment:

- Three studies (one retrospective comparative cohort study, one case series with an additional comparison to an historical group and one retrospective case series) provide information on the criteria used to define people who received treatment with prophylactic rituximab and were eligible for their study. Criteria varied and were not always fully defined/reported, but included, where reported, severe ADAMTS13 deficiency at remission or after partial or complete recovery after an acute episode of TTP, and ADAMTS13 levels of under 10% or under 15%.

Dose regimens of prophylactic rituximab:

- Four included studies (one SRMA, one retrospective comparative cohort study, one case series with an additional comparison to an historical group and one retrospective case series) provide information on the doses of rituximab used prophylactically to prevent acute TTP. The doses used varied widely between patients, but the most common dose was 375 mg/m^2, usually once a week for four weeks. One included study, however, reported that lower dose rituximab regimens were used over time in their study based on evidence of its use from other autoimmune disorders.

Limitations:

This review identified four studies only, and participants included in three of these studies overlap. Two studies had small sample sizes and all studies included some participants from retrospective sources with limited details of participants available to compare both within study groups (where appropriate) and between the included studies. Three studies had (non-randomised) comparison groups. The risk of bias was high in these three studies. One study reported non comparative data, and the risk of bias was unclear owing to inadequate reporting. Within the critical outcomes of relapse and disease response, the measures reported were heterogeneous and few were consistently reported between studies. The SRMA statistically pooled data from two included studies for one outcome, number and proportion with relapse, but did not discuss the appropriateness of meta-analysing comparative studies with historical controls. The certainty of the evidence in these studies was very low.

This review did not find any evidence for the critical outcome of hospitalisation or two important outcomes (quality of life (QoL) and functional) and there were no relevant patient subgroup results reported in any included study. This review did not find any evidence for cost-effectiveness of prophylactic rituximab to prevent acute TTP.

Conclusion:

This review included one SRMA, including patients from two comparative studies which were also included separately in this review as they provided additional outcome data, and one retrospective case series. Participants included in three of these studies therefore overlap.

In terms of critical outcomes, studies identified for this review found very low certainty evidence that prophylactic rituximab substantially reduces relapse rate compared with no prophylactic rituximab and very low certainty evidence that patients may have had a disease response to prophylactic rituximab treatment (reported without a comparator group). The studies provided very low certainty evidence that adverse events from rituximab were experienced in 13% to 30% of participants, but no comparative evidence was identified for safety outcomes. No evidence was identified for the critical outcome of hospitalisations or the important outcomes of quality of life and function, or for cost effectiveness.

There are various serious limitations of the studies and a number of important outcomes where there is no evidence available. The key limitation to identifying the effectiveness of prophylactic rituximab for TTP compared to treatment without rituximab is the lack of reliable comparative studies. The included studies generally had small sample sizes and included some participants from retrospective sources with their eligibility for the study, participant characteristics and comparator treatments (where appropriate) being uncertain. Together with heterogeneity of the measures used to assess the critical outcomes, and concerns over outcome measurement and statistical analyses, the risk of bias from these studies was generally high. Consequently, these key areas of uncertainty limit the conclusions that can be drawn about the balance of benefit and harm from prophylactic rituximab, or about the clinical effectiveness and safety of prophylactic rituximab.

3. Methodology

Review questions

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

1. In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the clinical effectiveness of prophylactic rituximab compared with no rituximab?
2. In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the safety of prophylactic rituximab compared with no rituximab?
3. In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the cost effectiveness of prophylactic rituximab compared with no rituximab?
4. From the evidence selected, are there any subgroups of patients that may benefit from prophylactic 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 go into clinical remission following immunosuppression and have ADAMTS13 deficiency who are eligible to commence prophylactic treatment?
6. From the evidence selected, what dose regimens of prophylactic rituximab were used?

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

Four studies were identified for inclusion (Hie et al 2014, Jestin et al 2017, Owattanapanich et al 2018, Westwood et al 2017). 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 2018), one was a retrospective comparative cohort study (Hie et al 2014), one was a case series with an additional comparison to an historical group (Jestin et al 2017) and one was a retrospective case series (Westwood et al 2017). The SRMA (Owattanapanich et al 2018) included two studies: both studies are also included separately in this review (Hie et al 2014, Jestin et al 2017) because the SRMA reported only two of their reported outcomes of relevance.

All four included studies (Hie et al 2014, Jestin et al 2017, Owattanapanich et al 2018, Westwood et al 2017) reported relapse rate and adverse events. Hie et al (2014), Jestin et al (2018) and Westwood et al (2017) also reported disease response. No studies were identified that reported hospitalisations, quality of life (QoL) or functional outcomes. No studies reported patient subgroups although one study reported subgroups by dose of rituximab (Westwood et al 2017).

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
Hie et al 2014 **Cohort study** (retrospective analysis of prospectively collected registry data) **France**	Total Sample size n=48 Idiopathic acquired TTP; severe ADAMTS13 deficiency (< 10%) at remission (n=22) or after an initial, partial, or complete recovery (11 to 29 months) from a previous acute episode (n=26). Pre-emptive rituximab: 30 No pre-emptive rituximab: 18	**Intervention** Pre-emptive rituximab 375 mg/m^2 (physician's discretion, per course; n=11 had 1; n=2 had 2; n=17 had 4 infusions, one each week). Methylprednisolone (30 mg IV) in those not already receiving glucocorticoids (no details dose) **Comparison** No pre-emptive rituximab (no further details)	**Critical outcomes** • Relapse rate • Disease response **Important Outcomes** • Safety/Adverse events
Jestin et al 2018 **Prospective case series (**and comparison to an historical group) **France**	Total Sample size n=115 iTTP, durable remission from a previous acute episode, severe ADAMTS13 deficiency Pre-emptive rituximab: 92 No pre-emptive rituximab: 23	**Intervention** Pre-emptive rituximab 375 mg/m^2 in 79/92 (85.9%) and 500 mg/m^2 in 13/92 (14.1%) Number of infusions was 1 (n=42/92), 2 (n=15/92), 4 (n=33/92), 5 (n=1/92) or 9 (n=1/92) Methylprednisolone (30 mg, IV) was given to those not on glucocorticoid therapy. 85/92 (92%) were on glucocorticoid therapy at baseline, dose not reported) **Comparison** No pre-emptive rituximab (no further details)	**Critical outcomes** • Relapse rate • Disease response **Important Outcomes** • Safety/Adverse events
Owattanapanich et al 2018 **Systematic review and meta-analysis** **Locations not stated**	Total Sample Size n=163 RCTs or cohort studies comparing rituximab and conventional therapy for TTP, reporting relapse rate or mortality This SRMA included 9 studies but only data from the section on prophylactic rituximab (obtained from 2 studies, Hie et al 2014 and Jestin et al 2018) were extracted for this review. Pre-emptive rituximab: 122 Conventional: 41	**Intervention** Pre-emptive rituximab 375 mg/m^2 weekly (1-4 doses/courses) and additional treatments in one study; rituximab 375 mg/m^2 or 500 mg/m^2 weekly (1-9 doses) in one study **Comparison** Conventional treatment (plasma exchange and corticosteroids), no further details	**Critical outcomes** • Relapse rate **Important Outcomes** • Safety/Adverse events
Westwood et al 2017 **Case series** (retrospective analysis of	n=45 (76 episodes) TTP in remission; ≥ 1 previous acute TTP episode; at high risk of relapse.	**Intervention** Pre-emptive rituximab given in four dose groups; the first three dose groups below were used in 60 patient episodes:	**Critical outcomes** • Relapse rate • Disease response

prospectively collected registry data) **UK**	n not reported for participants, reports patient episodes only by dose subgroups: Standard dose (375 mg/m^2 x 4) (24 patient episodes) Reduced dose (200 mg x 4) (19 patient episodes) Intermediate dose (500 mg x 4) (17 patient episodes) Other doses (ranged from 100 mg to 500 mg and included 3 patient episodes with mixed doses) (16)	375 mg/m^2 once per week for 4 weeks (standard dose group) 200 mg once per week for 4 weeks (reduced dose group) 500 mg once per week for 4 weeks (intermediate dose group) 100 to 1000 mg rituximab in 1 to 5 doses ('other dose groups', used in 16 episodes) Lamivudine prophylaxis in those at risk of hepatitis B reactivation. No other details of other treatments given. **Comparison** Not applicable	**Important Outcomes** • Safety/Adverse events

Abbreviations

iTTP - idiopathic (immune) thrombotic thrombocytopaenic purpura; IV - intravenous; RCT - randomised controlled trial; TTP - thrombotic thrombocytopaenic purpura

5. Results

In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the clinical effectiveness and safety of prophylactic rituximab compared with no rituximab?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
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, four studies (one SRMA, one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported evidence relating to relapse rates measured at different time points from 15 months to 38 months. Three studies compared results for relapse measures between people treated with rituximab and people not treated with rituximab. Details of the types of comparator treatments were not described in the comparator studies. At median 15 months follow up (pre-emptive rituximab) • 1 case series (Westwood et al 2017) (n=76 patient episodes) provided non-comparative evidence that relapse (readmission with thrombocytopenia with or without new symptoms 30 days after discharge from an acute episode) occurred in 3/76 (3.9%) patient episodes. **(VERY LOW)** Re-treatment with rituximab was given in 38/76 (50%) of patient episodes and the rate of re-treatment episodes per year was 0.25 **(VERY LOW)** At median 36 to 38 months follow up (pre-emptive rituximab) • 1 SRMA (Owattanapanich et al 2018) of 2 cohort studies (Hie et al 2014, Jestin et al 2017) (n=163) showed a statistically significant lower risk of relapse (defined as a recurrence of an acute episode of TTP after remission) in people receiving rituximab prophylaxis (median follow-up 3 years) (OR 0.09 (95% CI 0.04 to 0.24), p<0.00001). **(VERY LOW)** • 1 cohort study (Hie et al 2014) (n=48) found lower rates of relapse over the study period with pre-emptive rituximab (3/30 (10%) than with no pre-emptive rituximab (historical controls 7/18 (38.9%)) (p value not reported) **(VERY LOW)** (these data are included in the SRMA (Owattanapanich et al 2018) pooled estimate of relapse rate). Hie et al (2014) reported a statistically significant lower rate of acute TTP episodes per year (0, IQR 0 to 0.81, median follow-up 36 months) with pre-emptive rituximab than with no pre-emptive rituximab (0.5, IQR 0.12 to 0.5, from historical controls, median follow-up 60 months); p<0.01. **(VERY LOW)** Relapse-free survival in this study (from the first rituximab infusion for pre-emptive rituximab group; from first regular assessment of ADAMTS13 activity after an acute episode for no pre-emptive rituximab group) was not reached in the pre-emptive rituximab group (median follow-up 36 months) and was 9.3 years in the no pre-emptive rituximab group (median follow-up 60 months), p=0.049. **(VERY LOW)** • 1 case series with an additional comparison to an historical group (Jestin et al 2017) (n=115) found lower rates of relapse (reappearance

	of neurological manifestations, renal failure and/or thrombocytopenia with no other identifiable cause after durable remission) over the study period in those given pre-emptive rituximab (14/92 (15%)) than those not given pre-emptive rituximab (historical controls 17/23 (74%)) (p value not reported), **(VERY LOW)** (these data are included in the SRMA (Owattanapanich et al 2018) pooled estimate of relapse rate). Jestin et al (2017) reported that the median cumulative incidence of relapse was lower with pre-emptive rituximab (0 episodes per year, IQR 0 to 1.32) than with no pre-emptive rituximab (0.26 episodes per year, IQR 0.19-0.46); p<0.001. **(VERY LOW)** Jestin et al (2017) also compared data for the pre-emptive rituximab group from a period before pre-emptive rituximab (assumed the same population, median follow-up 54 (IQR, 45 to 82) months) and found 0.33 episodes per year (IQR 0.23 to 0.66), p<0.001 compared to after pre-emptive rituximab**.** The median number of iTTP episodes in the pre-emptive rituximab group (time period not reported, presumed to be over the whole follow-up period of 35.8 (IQR 23.3 to 68) months) was 0 (IQR 0 to 4). This was not reported for the no pre-emptive rituximab historical control group but was compared to a period before pre-emptive rituximab treatment (assumed the same population median follow-up 54 (IQR, 45 to 82) months) and reported that the median number of iTTP relapse episodes prior to pre-emptive rituximab was 3 (IQR 2 to 3), p<0.01 compared to after pre-emptive rituximab. **(VERY LOW)** There were some overlapping participants between the Hie et al (2014) study and Jestin et al (2017) study but the numbers are unclear **These studies provided very low certainty evidence that compared to no rituximab treatment, prophylactic rituximab substantially reduces the rate of relapse at up to 38 months follow-up. For example, in the meta-analysis of the only two comparative studies that were identified, the OR for relapse (recurrence of an acute episode of TTP) was 0.09 (95% CI 0.04 to 0.24), p<0.00001 (median follow up 3 years).**
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 (for example but not limited to a normalisation of platelet number, normalisation of ADAMTS13 activity, and time to remission). In total three studies (one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported evidence relating to disease response measured at different time points from 15 months to 36 months. Two studies compared results for disease response measures between people treated with rituximab and people not treated with rituximab. However, details of the types of comparator treatments were not described in the comparator studies. At median 15 months follow up (pre-emptive rituximab) • 1 case series (Westwood et al 2017) (n=76 patient episodes) provided non-comparative evidence of complete disease response (ADAMTS13 ≥60%): this occurred in 60/76 (78.9%) patient episodes; partial disease response ADAMTS13 30%-59%) in 10/76 (13.2%) patient episodes; and partial response or complete response (ADAMTS13 ≥30%) occurred in 70/76 (92.1%) patient episodes. **(VERY LOW)** Median time to ADAMTS13 recovery was 1 (range <1 to 5) months. **(VERY LOW)** At median 32-36 months follow up (pre-emptive rituximab)

	• 1 cohort study (Hie et al 2014) (n=48) found the median ADAMTS13 activity % was 58.5%[1] (IQR, 30.5% to 86.3%) with pre-emptive rituximab but did not report data for the no pre-emptive rituximab group. **(VERY LOW)** Durable ADAMTS13 recovery (median follow-up 36 (IQR 24 to 65) months) (normal ADAMTS13 activity defined by authors as ≥50%) in the pre-emptive rituximab group was reported in 20/30 (66.7%). The remaining 10/30 had persistent/subsequent ADAMTS13 deficiency. Data were not reported for the no pre-emptive rituximab group. **(VERY LOW).** • 1 case series (Jestin et al 2017) (n=92) provided non comparative evidence of sustained ADAMTS13 recovery following a single course of pre-emptive rituximab and considered 34/92 (37%) to be long-term responders (no definition reported) over the period of follow-up (median follow-up 31.5 (IQR 18 to 65) months). **(VERY LOW)** This was not reported for the no pre-emptive rituximab group. Persistent/severe ADAMTS13 deficiency (undetectable ADAMTS13 activity) 6 months after a single course of pre-emptive rituximab was seen in 13/92 (14.1%) **(VERY LOW)** and at least 1 severe recurrence of ADAMTS13 deficiency (<10% activity) following a single course of pre-emptive rituximab in 45/92 (49%) (period of follow-up not reported). **(VERY LOW)** Neither of these outcomes were reported for the no pre-emptive rituximab groups. There were some overlapping participants between the Hie et al (2014) study and Jestin et al (2017) study. **These studies provided very low certainty evidence that patients may have had a disease response to prophylactic rituximab treatment up to 40 months follow-up. For example, one study reported that 34/92 patients (37%) were considered long-term responders (definition not reported) and another study reported that 20/30 (67.7%) patients had durable ADAMTS13 recovery (ADAMTS13 activity ≥50%) at a median follow-up of 36 months. However, no comparative data were reported for patients who were not treated with rituximab.**
Hospitalisation Certainty of evidence: Not applicable	Hospitalisation due to an acute TTP episode or as a reaction to rituximab (such as acute or delayed serum sickness/anaphylaxis) is important to patients because it indicates that their condition is not adequately controlled. It can increase morbidity and mortality and impacts quality of life from a physical, and psycho-social perspective in the short term with possible implications for the longer term. **No evidence was identified for this outcome**.
Important outcomes	
Quality of Life **Certainty of evidence:** Not applicable	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 **No evidence was identified for this outcome**.
Functional outcomes **Certainty of evidence:**	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 physical tasks, emotional, and psycho-social (eg PHQ-9).

[1] Hie et al (2014) report that ADAMTS13 activity ≥50% was classed as normal.

Not applicable	**No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Very Low	Adverse events are important to patients because they will impact on their treatment choices and recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. In total three studies (one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported evidence relating to adverse events from pre-emptive rituximab treatment groups. Follow-up differed between these studies from 15 months to 36 months; the time of reporting of these adverse events was not reported. No studies compared results between people treated with pre-emptive rituximab and people not treated with pre-emptive rituximab. • 1 case series (Westwood et al 2017) (n=76 patient episodes) reported adverse event rates for those treated with pre-emptive rituximab by patient episodes. 15/76 (19.7%) patient episodes had infusion reactions, 23/76 (30.3%) patient episodes had any adverse event, 8/76 (10.5%) patient episodes had non infusion reactions and there were no Hepatitis B reactivations, significant episodes of abnormal liver function tests or cases of hypogammaglobulinemia. **(VERY LOW)** • 1 cohort study (Hie et al 2014) (n=48) reported treatment related adverse event rates for those in the pre-emptive rituximab group (n=30); no comparative data were reported. 4/30 (13%) of people had rituximab treatment related events, no other details were reported. **(VERY LOW)** • 1 case series with an additional comparison group (Jestin et al 2017) (n=115) reported adverse event rates for those in the pre-emptive rituximab group (n=92) as non-comparative data. 19/92 (20.7%) of people had rituximab treatment related events, no other details were reported except that none of these events led to rituximab interruption, 12/92 (13.0%) had moderate intolerance within 3 days but there were no severe infections, cases of hypogammaglobulinemia, progressive multifocal leukoencephalopathy or Kaposi sarcoma. **(VERY LOW)** There were some overlapping participants between the Hie et al (2014) study and Jestin et al (2017) study. In total three studies (one SRMA, one retrospective cohort study, one case series with an additional comparison to an historical group) reported evidence relating to mortality rates on study. All three studies compared results for mortality between people treated with pre-emptive rituximab and people not treated with pre-emptive rituximab; details of the types of comparator treatments were not described in the comparative studies, and the SRMA reports the same data as the two comparative studies. • Three studies (one SRMA, one retrospective cohort study, one case series with an additional comparison to an historical group) reported evidence relating to deaths. 1 cohort study (Hie et al 2014) (n=48) reported no deaths in the pre-emptive rituximab group and 2 deaths in the no pre-emptive rituximab group (p value not reported). **(VERY LOW)** The SRMA (Owattanapanich et al 2018) calculated the odds ratio for death in the Hie et al (2014) study as 0.11 (95% CI 0.00 to 2.39). **(VERY LOW)** 1 case series with an additional comparison to an historical group (Jestin et al 2017) (n=115) reported 2/92 (2.17%) deaths in the pre-emptive rituximab group and 2/23 (8.69%) deaths in the no pre-emptive rituximab group (p value not reported). **(VERY LOW)** The SRMA (Owattanapanich et al 2018) calculated the odds ratio for death in the Jestin et al (2017) study as 0.12 (95% CI 0.01 to 1.33); however, this

	was based on a different value for deaths in the rituximab group as the SRMA reported 1 participant had died; and Jestin et al (2017 reported that 2 had died. **(VERY LOW)** There were some overlapping participants between the Hie et al (2014) study and Jestin et al (2017) study. **These studies provided very low certainty non-comparative evidence relating to adverse events, with rates ranging from 13% for rituximab treatment related events in one study to 30% for any adverse event in another study, and very low certainty evidence that there is no difference in mortality rates when comparing rituximab treatment to no-rituximab treatment.**
Abbreviations CI - Confidence Interval; EQ-5D - EuroQol 5 dimensions; IQR - Inter-quartile range; iTTP - idiopathic (immune) thrombotic thrombocytopenic purpura; OR - odds ratio; PHQ-9 - Patient Health Questionnaire-9; SF-36 - Short-form 36; SRMA - Systematic review and meta-analysis; TTP - Thrombotic Thrombocytopenic Purpura	

In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the cost effectiveness of prophylactic 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 prophylactic rituximab more than the wider population of interest?

Outcome	Evidence statement
Sub groups	No evidence was identified for patient subgroups

From the evidence selected, what are the criteria used by the research studies to define those people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency who are eligible to commence prophylactic treatment?

Outcome	Evidence statement
Definitions	Three studies (one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported the criteria used to define people with acute immune TTP in clinical remission following immunosuppression and ADAMTS13 deficiency who received prophylactic treatment or not and were eligible for the study. However it is uncertain whether criteria for eligibility for the study were the same as criteria for eligibility to commence treatment (which were not reported) and it is possible that additional participants received prophylactic treatment but did not meet the study criteria. Study eligibility criteria were: • 1 cohort study (Hie et al 2014) (n=48) commenced prophylactic treatment with rituximab in people with idiopathic acquired TTP and

	severe ADAMTS13 deficiency (< 10%) at remission or after an initial, partial, or complete recovery (11 to 29 months) from a previous acute episode. • 1 case series with an additional comparison group (Jestin et al 2017) (n=115) commenced prophylactic treatment with rituximab in people with idiopathic (immune) TTP, durable remission (not defined) from a previous acute episode and severe ADAMTS13 deficiency (level not defined but persistent following clinical remission or following an initial partial or complete enzyme activity recovery). • 1 case series (Westwood et al 2017) (n=45) commenced prophylactic treatment with rituximab in people with TTP in remission, at least 1 previous acute TTP episode and at high risk of relapse (low ADAMTS13 levels on routine monitoring). Low ADAMTS13 level was defined as ≤15% except in 2 cases which had levels of 16% and 17% respectively as they were deemed to be at high risk of relapse on their previous episodes and relapse history. **Three studies provide information on the criteria used to define people who received treatment with prophylactic rituximab and were eligible for their study. Criteria varied and were not always fully defined/reported, but included, where reported, severe ADAMTS13 deficiency at remission or after partial or complete recovery after an acute episode of TTP, and ADAMTS13 levels of under 10% or under 15%.**
Abbreviations TTP - thrombotic thrombocytopaenic purpura	

From the evidence selected, what dose regimens of prophylactic rituximab were used?

Outcome	Evidence statement
Dose regimens	Four studies (one SRMA, one retrospective cohort study, one case series with an additional comparison to an historical group and one case series study) reported the doses of prophylactic rituximab given to participants. 1 cohort study (Hie et al 2014) (n=48) gave pre-emptive rituximab 375 mg/m^2. The number of infusions per course was at the physician's discretion; 11 had 1 infusion; 2 had 2 infusions and 17 had 4 infusions per course (one infusion per week). 1 case series with an additional comparison to an historical group (Jestin et al 2017) (n=115) used either rituximab 375 mg/m^2 (in 79/92 (85.9%)) or 500 mg/m^2 (in 13/92 (14.1%)). The study did not report outcomes by dose subgroup. 1 SRMA reported only the two studies above, with no additional information on doses. 1 case series (Westwood et al 2017) (n=76 patient episodes) reported data by four rituximab dose subgroups (375 mg/m^2 once per week for 4 weeks (standard dose group); 200 mg once per week for 4 weeks (reduced dose group); 500 mg once per week for 4 weeks (intermediate dose group); 100 to 1000 mg rituximab in 1 to 5 doses ('other dose groups)). Westwood et al (2017) reported that standard-dose rituximab was generally used at the beginning of the study but that reduced dose regimens were used over time because of evidence from other autoimmune disorders. The authors also reported that intermediate doses were used more recently in those at risk of hepatitis B reactivation. Results for disease response were reported for the four groups, with different durations of follow-up:

	• Standard dose 375 mg/m^2 once per week for 4 weeks (n=24 patient episodes), median follow up 17.5 (range 1 to 141) months.
	  ○ Complete response (ADAMTS13 ≥60%)[2]: 18/24 (75%) episodes.
	  ○ Partial response (ADAMTS13 30% to 59%): 3/24 (12.5%) episodes
	  ○ Partial response or complete response (ADAMTS13 ≥30%): 21/24 (87.5%) episodes
	  ○ Time to ADAMTS13 recovery median 1 (range <1 to 5) months
	• Reduced dose 200 mg once per week for 4 weeks (n=19 patient episodes), median follow up 25 (range 9 to 43) months:
	  ○ Complete response (ADAMTS13 ≥60%): 16/19 (84.2%) episodes.
	  ○ Partial response (ADAMTS13 30% to 59%): 2/19 (10.5%) episodes
	  ○ Partial response or complete response (ADAMTS13 ≥30%): 18/19 (94.7%) episodes
	  ○ Time to ADAMTS13 recovery median 1 (range <1 to 4) months
	• Intermediate dose 500 mg once per week for 4 weeks (n=17 episodes), median follow up 10 (range 3 to 20) months:
	  ○ Complete response (ADAMTS13 ≥60%): 12/17 (70.6%) episodes.
	  ○ Partial response (ADAMTS13 30% to 59%): 4/17 (23.5%) episodes
	  ○ Partial response or complete response (ADAMTS13 ≥30%): 16/17 (94.1%) episodes
	  ○ Time to ADAMTS13 recovery median 1 (range <1 to 3) months
	• Other doses 100 to 1000 mg (n=16 episodes), median follow up 21 (range 3 to 112) months:
	  ○ Complete response (ADAMTS13 ≥60%): 14/16 (87.5%) episodes.
	  ○ Partial response (ADAMTS13 30% to 59%): 1/16 (6.25%) episodes
	  ○ Partial response or complete response (ADAMTS13 ≥30%): 15/16 (93.4%) episodes
	  ○ Time to ADAMTS13 recovery median 1 (range <1 to 4) months
	Subgroup analyses were undertaken by Westwood et al (2017). There was no statistically significant difference in complete response between standard-dose versus reduced-dose versus intermediate-dose (p=0.61), and no statistically significant differences in time to ADAMTS13 recovery between standard-dose

[2] Westwood et al (2017) reported that the normal range for ADAMTS13 activity is 60% to 123%.

	versus reduced-dose versus intermediate-dose (p=0.69). No other statistical comparisons were reported. **Four included studies provide information on the doses of rituximab used prophylactically to prevent acute TTP. The doses used varied widely between patients, but the most common dose was 375 mg/m^2, usually once a week for four weeks. One included study, however, reported that lower dose rituximab regimens were used over time in their study based on evidence of its use from other autoimmune disorders.**
Abbreviations SRMA - Systematic review and meta-analysis	

6. Discussion

This review examined the clinical effectiveness and safety of rituximab compared to treatment without rituximab in patients to prevent acute immune TTP. The critical outcomes of interest were relapse rate, disease response and hospitalisations. The important outcomes of interest were QoL, functional, adverse events and cost-effectiveness.

Evidence for relapse was available from all four studies. The SRMA (Owattanapanich et al 2018) meta-analysed relapse outcomes from two studies which were also separately included in the review as they reported additional outcomes including additional relapse outcomes (Hie et al 2014; Jestin et al 2017). These two studies which provided comparative data with historical controls, together with one case series study (Westwood et al 2017) reported relapse outcomes using different indices including proportion relapsed, acute relapse episodes per year, median relapse rate and need for re-treatment. Three studies (two comparative cohort studies: Hie et al 2014 and Jestin et al 2017 and one case series: Westwood et al 2017) reported evidence for disease response using measures such as the percentage ADAMTS13 activity, response measured by specified ADAMTS13 thresholds, durable ADAMTS13 recovery and recurrence of ADAMTS13 deficiency. No studies were identified that reported hospitalisations, QoL or functional outcomes. No studies reporting patient subgroups or cost-effectiveness outcomes were identified. Evidence for adverse events was available from all four included studies, however, there were few consistently reported types of adverse events across these studies. Limited data were available on the criteria used to define acute immune TTP following immunosuppression and ADAMTS13 deficiency who are eligible to commence prophylactic treatment from three studies (Hie et al 2014; Jestin et al 2017; Westwood et al 2017). These studies reported the criteria used to define those who received prophylactic treatment or not and were eligible for the study. All four studies reported the dose of prophylactic rituximab given.

The largest sample of the primary studies was 115 participants, and follow-up ranged from 15 months to 40 months for prophylactic rituximab treated participants, varying by outcome in one study (Jestin et al 2017). As the only comparisons were with historical groups, it is possible that the comparator participants were from a time when rituximab was not an available treatment, which should be considered when interpreting the results, for example, outcomes may be poorer, there may have been other differences in care at that time. Although the characteristics of the populations at baseline appeared to be comparable, this was based on a small number of baseline characteristics reported in the comparative studies. The included studies with comparison groups also did not report details of comparator treatments. It is therefore unclear whether all participants included in their respective comparison groups received the same types of treatments or whether the control groups are a fair comparison, because the reasons they did not receive rituximab were not reported. Two of the studies (Hie et al 2014; Jestin et al 2017) had overlapping participants, but it is not clear how many participants were included in both studies. The studies were undertaken in France and the UK and included participants from 2000 to the present day suggesting their generalisability to NHS settings in the present day is reasonably likely. However, at paper selection it was not clear if all participants in these studies had received immunosuppression for their acute TTP, a criterion for eligibility in this review, and an assumption was made that immunosuppression was likely to have been given as this was standard treatment practice, but this remains an additional uncertainty in the evidence.

By the retrospective nature of these studies, the additional review question of the criteria used by the research studies to define those people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency who are eligible to commence prophylactic treatment is only partially answered.

The studies reported the criteria used to define those who received prophylactic treatment or not and were eligible for the study, however, none reported criteria for eligibility to commence treatment and it is uncertain if these would be criteria used in clinical practice, or whether there were additional participants who received prophylactic treatment that did not meet the study criteria. Different doses or number of infusions of rituximab were administered to participants within each study and between studies, and it is unclear if this heterogeneity will impact on the clinical effectiveness and safety results seen for rituximab in this prophylactic setting.

Overall quality of the four included studies was very low. The SRMA (Owattanapanich et al 2018) was at high risk of bias from a number of concerns with the methods of the review. 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.

Hie et al (2014) is a small comparative study with 48 participants. The follow-up was around 3.5 years and varied by study group. The study has a high risk of bias from a number of concerns about the methods. Participants were identified retrospectively and had different disease histories including treatment histories. The treatments given were not standardised within the groups and the assessments and definitions of some of the reported outcomes were unclear. Prior rituximab treatment and number of previous acute TTP episodes may be confounding factors, but these were not taken into account.

Jestin et al (2017) had a larger sample (n=115) and a long period of follow-up which varied for different outcomes and by study group, and also has a high risk of bias. The study was primarily a prospective case series but also reported a small amount of comparative data for an historical control group and, as such, was assessed for risk of bias as a comparative study as this is the most relevant to the present evidence review. Areas of concern in terms of risk of bias include that the rituximab doses varied between participants and it was unclear what treatments were given in the control arm. The assessment of the outcomes was unclear, the analyses did not consider confounding factors, and five participants were excluded because of missing data. Some outcomes were compared to a period of time for the same patients prior to their rituximab treatment, but not with the historical controls, and no details were reported confirming whether this comparison was to all of the same participants or only some.

Westwood et al (2017) is a small case series including 45 participants, however, outcomes were reported by patient episode (n=76), including many of the baseline characteristics. The study has shorter follow up than the other studies, around 15 months. The risk of bias was unclear as the risk of bias for a number of questions could not be ascertained owing to inadequate reporting. The study reported information for small subgroups of participants based on the doses of rituximab given and compared these statistically. However, it is unclear if these analyses were powered for subgroups, and multiplicity was not accounted for in the analyses. The study stated that standard-dose rituximab was generally used at the beginning of the study and, after time, reduced rituximab-dose regimens were used because of evidence from other autoimmune disorders. The study also reported that intermediate doses were used more recently in those at risk of hepatitis B reactivation. Therefore there may be differences within the participant group that have not been accounted for in the analyses. The study also reported outcomes by patient episode as the unit of allocation.

7. Conclusion

This review included one SRMA, including patients from two comparative studies which were also included separately in this review as they provided additional outcome data, and one retrospective case series. Participants included in three of these studies therefore overlap.

In terms of critical outcomes, studies identified for this review found very low certainty evidence that prophylactic rituximab substantially reduces relapse rate compared with no prophylactic rituximab and very low certainty evidence that patients may have had a disease response to prophylactic rituximab treatment (reported without a comparator group). The studies provided very low certainty evidence that adverse events from rituximab were experienced in 13% to 30% of participants, but no comparative evidence was identified for safety outcomes. No evidence was identified for the critical outcome of hospitalisations or the important outcomes of quality of life and function, or for cost effectiveness.

There are various serious limitations of the studies and a number of important outcomes where there is no evidence available. The key limitation to identifying the effectiveness of prophylactic rituximab for TTP compared to treatment without rituximab is the lack of reliable comparative studies. The included studies generally had small sample sizes and included some participants from retrospective sources with their eligibility for the study, participant characteristics and comparator treatments (where appropriate) being uncertain. Together with heterogeneity of the measures used to assess the critical outcomes, and concerns over outcome measurement and statistical analyses, the risk of bias from these studies was generally high. Consequently, these key areas of uncertainty limit the conclusions that can be drawn about the balance of benefit and harm from prophylactic rituximab, or about the clinical effectiveness and safety of prophylactic rituximab.

Appendix A PICO document

The review questions for this evidence review are:

1. In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the clinical effectiveness of prophylactic rituximab compared with no rituximab?
2. In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the safety of prophylactic rituximab compared with no rituximab?
3. In people diagnosed with acute immune TTP who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the cost effectiveness of prophylactic rituximab compared with no rituximab?
4. From the evidence selected, are there any subgroups of patients that may benefit from prophylactic 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 go into clinical remission following immunosuppression and have ADAMTS13 deficiency who are eligible to commence prophylactic treatment?
6. From the evidence selected, what dose regimens of prophylactic rituximab were used?

P-Population and Indication	People diagnosed with acute immune TTP who go into clinical remission following immunosuppression, and have either a reduction in ADAMTS13 activity or have a persistent ADAMTS13 deficiency
I-Intervention	Prophylactic rituximab to prevent relapse [Standard dose is 375mg/m^2 weekly for a minimum of four doses (up to 8 doses may be required). Alternate regimens are: 1. Standard 375mg/m^2-current prophylactic dose given electively 2. A flat 500mg weekly (1 vial) 3. Low dose rituximab weekly (100-200mg)] [Rituximab may be given with or without additional treatments]
C-Comparator	Any treatment regime not using 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 **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). **Hospitalisation** due to an acute TTP episode or as a reaction to rituximab (such as acute or delayed serum sickness/anaphylaxis) is important to patients because it indicates that their condition is not adequately controlled. It can increase morbidity and mortality and impacts quality of life from a physical, and psycho-social perspective in the short term with possible implications for the longer term. 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). 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 2005 onwards. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: January 2005 to 10th May 2021

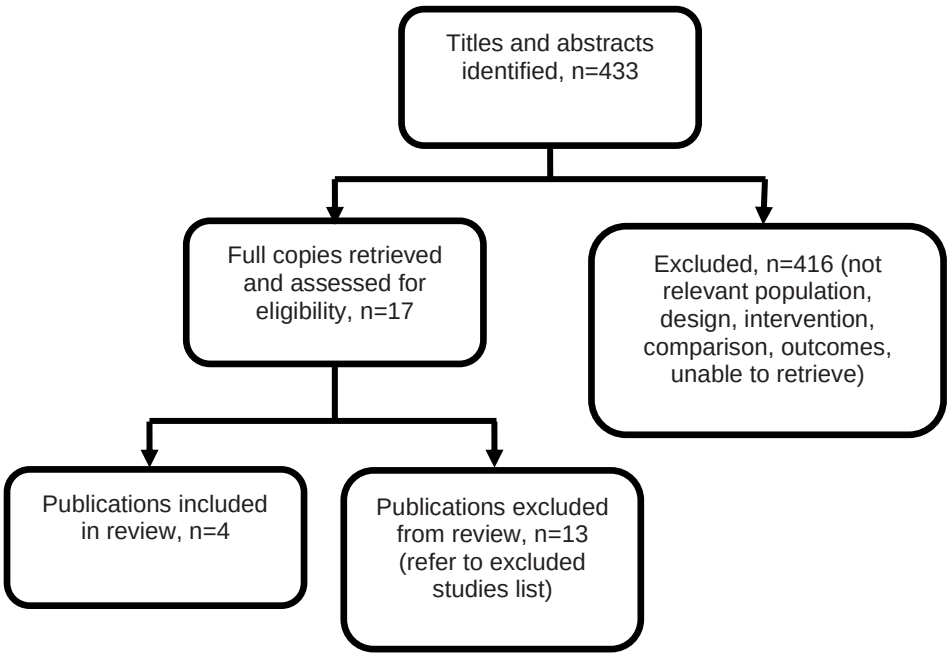
Medline

# ▲	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 17 references were obtained in full text and assessed for relevance. Of these, 4 references are included in the evidence summary. The remaining 13 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**
Jestin M, Benhamou Y, Schelpe AS, Roose E, Provot F, Galicier L, Hie M, Presne C, Poullin P, Wynckel A, Saheb S, Deligny C, Servais A, Girault S, Delmas Y, Kanouni T, Lautrette A, Chauveau D, Mousson C, Perez P, Halimi JM, Charvet-Rumpler A, Hamidou M, Cathebras P, Vanhoorelbeke K, Veyradier A, Coppo P. & French. Thrombotic microangiopathies reference, C. 2018. Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. Blood,132,2143-2153.	Included
Westwood JP, Thomas M, Alwan F, McDonald V, Benjamin S, Lester WA, Lowe GC, Dutt T, Hill QA, Scully M. Rituximab prophylaxis to prevent thrombotic thrombocytopenic purpura relapse: outcome and evaluation of dosing regimens. Blood Adv. 2017 Jun 26;1(15):1159-1166	Included
Hie M, Gay J, Galicier L, Provôt F, Presne C, Poullin P, Bonmarchand G, Wynckel A, Benhamou Y, Vanhille P, Servais A, Bordessoule D, Coindre JP, Hamidou M, Vernant JP, Veyradier A, Coppo P; Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. French Thrombotic Microangiopathies Reference Centre. Blood. 2014 Jul 10;124(2):204-10	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.	Patients who received prophylactic rituximab were excluded
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	Does not include prophylactic use of rituximab
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.	Does not include prophylactic use of rituximab
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.	Does not include prophylactic use of rituximab
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.	Essentially a case series for our purposes. Not included because larger studies available for the outcomes reported by this study.
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.	Does not include prophylactic use of rituximab
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.	Appendix provides information about the 7 cases who received pre-emptive rituximab, however, no outcome data reported.
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.	Case series 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.	Case series 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.	Case series not included because larger studies available for the outcomes reported by this study

Arcudi S, Ferrari B, Pontiggia S, Tufano A, Artoni A, Mancini I, et al. Prevention of relapse in patients with acquired thrombotic thrombocytopenic purpura undergoing elective surgery: a case series. Journal of Thrombosis & Haemostasis. 2019;17(3):492-8.	Single case received prophylactic rituximab; single cases excluded in the PICO for this review.
Bresin E, Gastoldi S, Daina E, Belotti D, Pogliani E, Perseghin P, et al. Rituximab as pre-emptive treatment in patients with thrombotic thrombocytopenic purpura and evidence of anti-ADAMTS13 autoantibodies. Thrombosis & Haemostasis. 2009;101(2):233-8.	Case series 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.	Case series not included because larger studies available for the outcomes reported by this study

1.

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Hie M, Gay J, Galicier L, Provôt F, Presne C, Poullin P, et al. Preemptive rituximab infusions after remission efficiently prevent relapses in acquired thrombotic thrombocytopenic purpura. Blood. 2014;124(2):204-10. **Study location** France **Study type** Cohort study (retrospective analysis of prospectively collected registry data) **Study aim** To 'report our experience on the use of rituximab in patients with persistent acquired ADAMTS13 deficiency during remission' **Study dates** October 2000 to January 2012	**Inclusion criteria** Idiopathic acquired TTP; severe ADAMTS13 deficiency (< 10%) at remission (n=22) or after an initial, partial, or complete recovery (11 to 29 months) from a previous acute episode (n=26); at least 1 year of follow-up **Exclusion Criteria** Other thrombotic microangiopathies; those with detectable ADAMTS13 activity **Total sample size** n=48 **No. of participants in each treatment group** Pre-emptive rituximab n=30 No pre-emptive rituximab n=18 **Baseline characteristics** Clinical characteristics were 'comparable' but no data were shown for the no pre-emptive rituximab group.	**Interventions** Pre-emptive rituximab 375 mg/m^2 (physicians discretion per course; n=11 had 1; n=2 had 2; n=17 had 4 infusions per course, one each week); methylprednisolone (30 mg IV) in those not already receiving glucocorticoids (no details dose) **Comparator** No pre-emptive rituximab (no further details)	**Clinical outcomes** **Relapse rate** (acute episodes per year) Pre-emptive rituximab (median follow-up 36 (IQR 24 to 65) months) 0 (IQR, 0 to 0.81 episodes per year); no pre-emptive rituximab (median follow-up 60 (IQR, 30 to 72) months) 0.5 (IQR, 0.12 to 0.5), p<0.01 Relapse rate % (median follow-up 36 (IQR 24 to 65) months) Pre-emptive rituximab: 3/30 (10%); no pre-emptive rituximab: 7/18 (38.9%), p value not reported Relapse-free survival (from the first rituximab infusion for pre-emptive rituximab group; from first regular assessment of ADAMTS13 activity after an acute episode for no pre-emptive rituximab group): Pre-emptive rituximab (median follow-up 36 months): median relapse-free survival not reached; no pre-emptive rituximab (median follow-up 60 months): median relapse-free survival 9.3 years, p=0.049 (log-rank test). **Disease response** Pre-emptive rituximab (median follow-up 36 months) median ADAMTS13 activity %: 58.5% (IQR, 30.5% to	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Cohort Studies. 1. Unclear 2. No 3. Unclear 4. No 5. No 6. Yes 7. Unclear 8. Yes 9. Yes 10. No 11. Unclear Risk of bias: High **Other comments:** This is a small comparative study with a long follow-up. Patients were identified retrospectively and had different disease histories including treatment histories. The treatments given were not standardised within the groups and the assessments and definitions of outcomes were unclear. Data were not presented to qualify the authors' statements that groups were comparable at baseline. Prior rituximab and number of previous acute TTP episodes may be confounding factors but these were not taken into account. The study also reports disease response in terms of recovery of B cell lymphocytes up to

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Pre-emptive rituximab: Female: 63% Median (range) age: 38 (30-44) years >1 acute episodes: 53% Prior rituximab: pre-emptive rituximab group 10/30 (33%); no pre-emptive rituximab group 5/18 (28%)		86.3%)[3]. Not reported for no pre-emptive rituximab group. Durable ADAMTS13 recovery (median follow-up 36 (IQR 24 to 65) months) (normal ADAMTS13 activity defined by authors as ≥50%): Pre-emptive rituximab: 20/30 (66.7%) (remaining 10/30 had persistent/subsequent ADAMTS13 deficiency); no pre-emptive rituximab not reported. **Hospitalisation** No data **Important outcomes** **Quality of life** No data **Functional** No data **Safety/Adverse events** Pre-emptive rituximab treatment related adverse events (median follow-up 36 (IQR 24 to 65) months): 4/30 (13%) Death (median follow-up 36 (IQR 24 to 65) months): pre-emptive rituximab n=0; no pre-emptive rituximab n=2 (p=0.13) Cost effectiveness No data	24 months follow-up but in a figure only. This study was included in the SR (Owattanapanich et al 2019) for relapse rate as a dichotomous outcome (not an outcome reported by the study, but generated by the SR meta-analysis). Some study participants were also included in Jestin et al (2017) but it is unclear which participants were included in both studies. **Source of funding**: grant funding from Etablissement Français du Sang (CS/2002/009) and the Groupement d'Int´erˆet Scientifique-Institut des Maladies Rares (GIS MR0428).

[3] Hie et al (2014) reports ADAMTS13 ≥50% was classed as normal

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Jestin M, Benhamou Y, Schelpe AS, Roose E, Provôt F, Galicier L, et al. Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura. Blood. 2018;132(20):2143-53. **Study location** France **Study type** Prospective case series (before and after) and comparison to an historical group **Study aim** To report long-term outcomes in patients with iTTP who received pre-emptive rituximab while in clinical remission but with severe ADAMTS13 deficiency. Study dates 2012 to 2017	**Inclusion criteria** iTTP, durable remission (not defined) from a previous acute episode, severe ADAMTS13 deficiency (level not defined but persistent following clinical remission or following an initial partial or complete enzyme activity recovery), at least 1 year follow-up **Exclusion Criteria** iTTP secondary to cancer, pregnancy, chemotherapy, or transplantation **Total sample size** n=115 No. of participants in each treatment group Pre-emptive rituximab group n=92 No pre-emptive rituximab group n=23 **Baseline characteristics** Groups were comparable. Median age:	**Interventions** Pre-emptive rituximab 375 mg/m^2 in 79/92 (85.9%) and 500 mg/m^2 in 13/92 (14.1%) Number of infusions was 1 (n=42/92), 2 (n=15/92), 4 (n=33/92), 5 (n=1/92) or 9 (n=1/92) Methylprednisolone (30 mg, IV) was given to those not on glucocorticoid therapy. n=85/92 (92%) were on glucocorticoid therapy at baseline, (dose not reported) **Comparators** No pre-emptive rituximab, no further details	**Clinical outcomes** **Relapse rate** iTTP relapse (reappearance of neurological manifestations, renal failure and/or thrombocytopenia with no other identifiable cause after durable remission): Pre-emptive rituximab group (follow-up 35.8 (IQR 23.3 to 68) months): median number of iTTP episodes: 0 (IQR 0 to 4) (time period not reported, presumed to be over the whole follow-up period). Not reported for the no pre-emptive rituximab group. Compared to a period of time prior to pre-emptive rituximab treatment (median follow-up 54 (IQR, 45 to 82 months)): median number of iTTP episodes: 3 (IQR, 2-3), p<0.01 vs rituximab Proportion with clinical relapse: Pre-emptive rituximab group (median follow-up 37.8 (IQR 20 to 57) months): 14/92 (15%) (leading to death in 2); Historical controls (median follow-up of 7 (IQR, 5-11) years: 17/23 (74%), including multiple relapses in n=11, p value not reported Median cumulative incidence of annual relapses (episodes per year): Rituximab group, (median follow-up 35.8 (IQR, 23.3 to 68) months): 0 (IQR 0 to 1.32). Historical controls, (median	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Cohort Studies. 1. Unclear 2. No 3. Unclear 4. No 5. No 6. Yes 7. Unclear 8. Yes 9. Unclear 10. No 11. Unclear Risk of bias: High **Other comments:** Study had a long period of follow-up, but was primarily a before and after study with a small amount of comparative data to an historical control group. The groups appeared similar, however, the period of the historical control was unclear but likely during a time when rituximab use was not standard practice. The rituximab doses varied between participants and it was unclear what treatments were given in the control arm. The analyses did not consider confounding factors and how the outcomes were assessed was unclear. The study updates outcomes of some of the participants in Hie et al (2014) study but it is unclear which participants were included in both studies. Five participants were excluded because of missing data. Some outcomes were compared to a

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Pre-emptive rituximab group 42 (25th-75th percentile 33.3-51) years; no pre-emptive rituximab group 38 (25th-75th percentile 31-50) years Women: Pre-emptive rituximab group: 73%; no pre-emptive rituximab group: 82% Rituximab for the acute episode: Pre-emptive rituximab group: 50/92 (54.3%); no pre-emptive rituximab group 9/23 (39%) Pre-emptive rituximab group only: Previous iTTP episodes: 37/92 (40.2%) Refractory: 25/92 (27%) (of whom 8 received rituximab in the acute TTP episode) Clinical remission with severe ADAMTS13 deficiency: 67/92 (73%) (of whom 40 received rituximab in the acute TTP episode)		follow-up of 7 (IQR 5 to 11) years): 0.26 (IQR 0.19 to 0.46); log-rank test p<0.001 Also compared to a period of time prior to pre-emptive rituximab treatment (median follow-up 54 (IQR, 45 to 82 months)): 0.33 episodes per year (IQR 0.23 to 0.66), p<0.001 vs pre-emptive rituximab. **Disease response** Sustained ADAMTS13 recovery following single course of pre-emptive rituximab: 34/92 (37%), considered long-term responders over the period of follow-up (no definition reported) (median follow-up of 31.5 (IQR 18 to 65) months. Not reported for the no pre-emptive rituximab group. Persistent/severe ADAMTS13 deficiency (undetectable ADAMTS13 activity) 6 months after single course of pre-emptive rituximab: 13/92 (14.1%). Not reported for the no pre-emptive rituximab group. At least 1 severe recurrence of ADAMTS13 deficiency (<10% activity) following single course of pre-emptive rituximab 45/92 (49%) (period of follow-up not reported) Not reported for the no pre-emptive rituximab group. **Hospitalisation** No data	period of time prior to pre-emptive rituximab treatment, details of the participants for this comparison were not given but assumed to be the same participants. Disease response outcomes assumed to be after a single course of pre-emptive rituximab. **Source of funding**: grant funding from the French Ministry of Health, the National Plan for Rare Diseases of the French Ministry of Health and by a Horizon 2020 Marie Skłodowska-Curie Innovative Training Network grant. One author was supported by a PhD grant from the Agency for Innovation and Entrepreneurship, Flanders, Belgium.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Important outcomes **Quality of life** No data **Functional** No data **Safety/Adverse events** Rituximab related adverse events (median follow-up 37.8 (IQR 20 to 57) months): 19/92 (20.7%), none led to rituximab interruption Severe infections: 0 Moderate intolerance within 3 days: 12/92 (13.0%) Hypogammaglobulinemia: 0 Progressive multifocal leukoencephalopathy: 0 Kaposi sarcoma: 0 Deaths: Rituximab group, (median follow-up 37.8 (IQR 20 to 57) months): 2/92 (2.17%) (differs from SR) Historical controls (median follow-up 7 (IQR 5 to 11 years): 2/23 (8.69%), p value not reported	
Full citation Owattanapanich W, Wongprasert C, Rotchanapanya W, Owattanapanich N, Ruchutrakool T. Comparison of the Long-Term Remission	**Inclusion criteria** RCTs or cohort studies comparing rituximab and conventional therapy for TTP, reporting relapse rate or mortality.	**Interventions** Rituximab 375 mg/m^2 weekly (1 to 4 doses/courses) and additional treatments in one study; Rituximab 375 mg/m^2 or 500 mg/m^2 weekly (1 to 9 doses) in one study	**Clinical outcomes** **Relapse rate** (defined as the recurrence of an acute episode of TTP after remission) (median follow-up 3 years)	This study was appraised using the AMSTAR 2 tool for systematic reviews. 1. Yes 2. No 3. No 4. Partial yes

Study details	Population	Interventions	Study outcomes	Appraisal and funding
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** 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	**Exclusion Criteria** Reviews, meta-analyses, commentaries, reports irrelevant to TTP or to comparisons between rituximab and conventional treatments, no primary endpoints. **Total sample size** n=163 No. of participants in each treatment group Pre-emptive rituximab: n=122 Conventional: n=41 **Baseline characteristics** Minimal data reported, no aggregate information. Ages appear similar, proportion female higher in the Jestin et al study (approximately 73% versus 63% in Hie et al (2014)). ADAMTS13 Activity was <10% in both studies.	**Comparators** Conventional treatment (plasma exchange and corticosteroids), no further details	Rituximab vs conventional treatment: OR 0.09 (95% CI 0.04 to 0.24), p<0.00001 **Disease response** No data **Hospitalisation** No data **Important outcomes** **Quality of life** No data **Functional** No data **Safety/Adverse events** Deaths Hie et al: rituximab n=0; no-rituximab n=2; OR 0.11 (95% CI 0.00 to 2.39) Jestin et al: rituximab n=1; no-rituximab n=2; OR 0.12 (95% CI 0.01 to 1.33); n differs from that reported by Jestin et al (2018)	5. Yes 6. No 7. No 8. Partial yes 9. Partial yes 10. No 11. No 12. No 13. No 14. No 15. Yes 16. Yes Risk of bias: high **Other comments**: This is a systematic review and meta-analysis of two cohort studies with data for the prophylactic use of rituximab in iTTP. 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, and the search strategy was only partially comprehensive. The systematic review includes all of the patients in Hie et al (2014) and Jestin et al (2017) which are also reported separately here, and no other patients. The systematic review was included because it provides a meta-analysis.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				Source of funding: no external funding
Full citation Westwood JP, Thomas M, Alwan F, McDonald V, Benjamin S, Lester WA, et al. Rituximab prophylaxis to prevent thrombotic thrombocytopenic purpura relapse: outcome and evaluation of dosing regimens. Blood Adv. 2017;1(15):1159-66. **Study location** UK **Study type** Case series (retrospective analysis of prospectively collected registry data) **Study aim** To evaluate prophylactic rituximab to prevent TTP relapse and examine the ideal dosage regimen for ADAMTS13 recovery and treatment-free survival **Study dates** 2005 to 2016	**Inclusion criteria** Consecutive patients with TTP in remission; ≥ 1 previous acute TTP episode; at high risk of relapse (low ADAMTS13 levels on routine monitoring) and treated with rituximab prophylaxis. Low ADAMTS13 level defined as ≤15% except in 2 cases which had levels of 16% and 17% respectively as they were deemed to be at high risk of relapse based on their previous episodes and relapse history. **Exclusion Criteria** Not reported **Total sample size** n=45 (76 episodes) No. of participants in each treatment group n not reported for participants; reports patient episodes only by dose subgroup: Standard dose (375 mg/m^2 x 4) (n=24 patient episodes)	**Interventions** Pre-emptive rituximab given in four dose groups; three of the dose groups were used for 60 patient episodes: 375 mg/m^2 once per week for 4 weeks (standard dose group) 200 mg once per week for 4 weeks (reduced dose group) 500 mg once per week for 4 weeks (intermediate dose group) 100 to 1000 mg rituximab in 1 to 5 doses ('other dose groups', used in 16 episodes) Lamivudine prophylaxis in those at risk of hepatitis B reactivation. No other details of other treatments given. **Comparators** Not applicable (rituximab dose comparisons as per above)	**Clinical outcomes** **Relapse rate** Relapse (readmission with thrombocytopenia with or without new symptoms 30 days after discharge from an acute episode; median follow-up period of 15 months (range 1 to 141): 3/76 (3.9%) patient episodes Re-treatment with rituximab (median of 17.5 months (range 9 to 112 months) after the initial prophylactic dose): 38/76 (50%) patient episodes (35/38, 92.1% as a result of a decrease in ADAMTS13 levels to ≤15%; 3/38, 7.9% for relapse). Re-treatment episodes per year 0.25 <u>Dose subgroups:</u> Re-treatment episodes per year Standard-dose group: 0.17 vs Reduced-dose group: 0.38, p=0.039 Median treatment-free survival Standard-dose group: 29 months vs reduced-dose groups 25 months, p=0.25 (log-rank test) **Disease response** Median follow up 15 (range 1 to 141) months	This study was appraised using the Joanna Briggs Institute 2017 Critical Appraisal Checklist for Case series. 1. Unclear 2. Yes 3. Unclear 4. Yes 5. Yes 6. Unclear 7. Unclear 8. Yes 9. Unclear 10. Unclear Risk of bias: Unclear **Other comments:** This is a small study which reports outcomes by patient episode, including many of the baseline characteristics. The study had shorter follow up than other studies, and reported information for small subgroups based on doses of rituximab given, however it is unclear if the analyses were powered for these subgroups and multiplicity was not accounted for in the analyses. The study stated that standard-dose rituximab was generally used at the beginning of the study and after time reduced rituximab-dose regimens were used because of evidence from other autoimmune disorders. Study also says that intermediate doses are used more recently in those at risk of hepatitis B reactivation.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Reduced dose (200 mg x 4) (n=19 patient episodes) Intermediate dose (500 mg x 4) (n=17 patient episodes) Other doses (ranged from 100 mg to 500 mg and included 3 patient episodes with mixed doses) (n=16) **Baseline characteristics** Median age 43.5 (range 18-78) years Female: 75.6% 1 prior acute TTP episode: 14 (31.1%) > 1 prior acute TTP episode: 31 (68.9%) (range 2 to 6 episodes). Median platelets (range), x 10^9/L: 268 (83 to 443) Median ADAMTS13 activity (range), %: 5 (<5 to 17)		Complete response (ADAMTS13 ≥60%)[4]: 60/76, 78.9% episodes. Partial response (ADAMTS13 30% to 59%): 10/76, 13.2% episodes Partial response or complete response (ADAMTS13 ≥30%): 70/76, 92.1% episodes Time to ADAMTS13 recovery: median 1 (range <1 to 5) months <u>Dose subgroups:</u> Standard dose 375 mg/m^2 once per week for 4 weeks (n=24 patient episodes), median follow-up 17.5 (range 1 to 141) months: • Complete response (ADAMTS13 ≥60%): 18/24, 75% episodes. • Partial response (ADAMTS13 30% to 59%): 3/24, 12.5% episodes • Partial response or complete response (ADAMTS13 ≥30%): 21/24, 87.5% episodes • Time to ADAMTS13 recovery median 1 (range <1 to 5) months Reduced dose 200 mg once per week for 4 weeks (n=19 patient episodes), median follow up 25 (range 9 to 43) months: • Complete response (ADAMTS13 ≥60%): 16/19 84.2% episodes.	**Source of funding**: No funding reported

[4] Westwood et al (2017) reports the normal range for ADAMTS13 activity is 60% to 123%.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Partial response (ADAMTS13 30% to 59%): 2/19 10.5% episodes • Partial response or complete response (ADAMTS13 ≥30%): 18/19 94.7% episodes • Time to ADAMTS13 recovery median 1 (range <1 to 4) months Intermediate dose 500 mg once per week for 4 weeks (n=17 episodes), median follow up 10 (range 3 to 20) months: • Complete response (ADAMTS13 ≥60%): 12/17, 70.6% episodes. • Partial response (ADAMTS13 30% to 59%): 4/17, 23.5% episodes • Partial response or complete response (ADAMTS13 ≥30%): 16/17, 94.1% episodes • Time to ADAMTS13 recovery median 1 (range <1 to 3) months Other doses 100 to 1000 mg (n=16 episodes), median follow up 21 (range 3 to 112) months: • Complete response (ADAMTS13 ≥60%): 14/16, 87.5% episodes. • Partial response (ADAMTS13 30% to 59%): 1/16, 6.25% episodes • Partial response or complete response (ADAMTS13 ≥30%): 15/16, 93.4% episodes	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Time to ADAMTS13 recovery median 1 (range <1 to 4) months **Subgroup analysis:** Complete response: standard-dose vs reduced-dose vs intermediate dose groups, p=0.61 Time to ADAMTS13 recovery: standard-dose vs reduced-dose vs intermediate dose groups, p=0.69 **Hospitalisation** No data **Important outcomes** **Quality of life** No data **Functional** No data **Safety/Adverse events** Median follow up 15 (range 1 to 141) months Any AE: 23/76 (30.3%) patient episodes Infusion reactions: 15/76 (19.7%) patient episodes (2 in the same patient given 375mg/m^2 dose rituximab were severe) Non infusion reactions: 8/76 (10.5%) patient episodes (1 given 500 mg rituximab was severe)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Both severe reactions had developed a human antichimeric antibody against rituximab Hepatitis B reactivation: 0 Significant episodes of abnormal liver function tests: 0 Hypogammaglobulinemia: 0	

Abbreviations: AE - Adverse events; CI - Confidence interval; IQR - Inter-quartile range; iTTP - idiopathic (immune) thrombotic thrombocytopaenic purpura; IV - Intravenous; OR - odds ratio; RCT - Randomised controlled trial; TTP - thrombotic thrombocytopaenic purpura

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 who go into clinical remission following immunosuppression and have ADAMTS13 deficiency, what is the clinical effectiveness and safety of prophylactic rituximab compared with 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)		
Relapse rate (1 SRMA, 2 comparative cohort studies, 1 case series)									
Relapse rate (number and proportion relapsed; lower result indicates a greater benefit; follow-up 15 to 38 months for rituximab groups and up to 7 years for controls)									
1 SRMA Owattanapanich et al 2019	Very serious limitations[1]	No serious indirectness	No serious inconsistency	No serious imprecision	122	41	Pre-emptive rituximab vs conventional treatment (median follow-up 3 years): OR 0.09 (95% CI 0.04 to 0.24), p<0.00001	Critical	Very Low
1 Comparative cohort study Hie et al 2014	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	30	18	Relapse rate %, median follow-up 36 (IQR 24 to 65) months Pre-emptive rituximab: 3/30 (10%); no pre-emptive rituximab: 7/18 (38.9%), p value not reported.	Critical	Very Low
1 Case series with additional comparison group Jestin et al 2018	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	92	23	Proportion with clinical relapse: Pre-emptive rituximab group (median follow-up 37.8 (IQR 20 to 57) months): 14/92 (15%) (leading to death in 2); No pre-emptive rituximab (Historical controls) (median follow-up of 7 (IQR 5 to 11) years: 17/23 (74%), including multiple relapses in n=11, p value not reported	Critical	Very Low
1 Case series Westwood et al 2017	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	45 (n=76 patient episodes)	None	Relapse (readmission with thrombocytopenia with or without new symptoms 30 days after discharge from an acute episode; median follow-up period of 15 months (range 1 to 141): 3/76 (3.9%)	Critical	Very Low
Relapse rate (acute episodes per year, lower result indicates a greater benefit; follow-up up to 36 months for rituximab and between 5 to 7 years for controls)									
1 Comparative cohort study	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	30	18	Pre-emptive rituximab (median follow-up 36 months (IQR 24 to 65) 0 (IQR 0 to 0.81 episodes per year);	Critical	Very Low

Hie et al 2014							No pre-emptive rituximab (median follow-up 5 years (IQR 30 to 72 months) 0.5 (IQR 0.12 to 0.5); p<0.01		
1 Case series with additional comparison group Jestin et al 2018	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	92	23	Median cumulative incidence of relapses, episodes per year: Pre-emptive rituximab group (median follow-up 35.8 (IQR 23.3 to 68) months) 0 (IQR 0 to 1.32). No pre-emptive rituximab (Historical controls) (median follow-up of 7 (IQR 5 to 11) years): 0.26 (IQR 0.19 to 0.46); log-rank test p<0.001 Also compared to a period of time prior to pre-emptive rituximab treatment (median follow-up 54 (IQR, 45 to 82) months): 0.33 episodes per year (IQR 0.23 to 0.66), p<0.001 vs rituximab.	Critical	Very Low
Relapse rate (median iTTP episodes, lower result indicates a greater benefit, median follow-up 36 months rituximab)									
1 Case series with additional comparison group Jestin et al 2018	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	92	23	iTTP relapse (reappearance of neurological manifestations, renal failure and/or thrombocytopenia with no other identifiable cause after durable remission): Pre-emptive rituximab group (follow-up 35.8 (IQR 23.3 to 68) months): median number of iTTP episodes: 0 (IQR 0 to -4) (time period not reported, presumed to be over whole follow-up period). Not reported for the no pre-emptive rituximab group. Compared to a period of time prior to pre-emptive rituximab treatment (median follow-up 54 (IQR 45 to 82) months): median number of iTTP episodes: 3 (IQR, 2-3), p<0.01 vs pre-emptive rituximab	Critical	Very Low
Relapse-free survival (median follow-up rituximab group 36 months; no pre-emptive rituximab group 60 months)									
1 Comparative cohort study	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	30	18	Relapse-free survival (from the first rituximab infusion for pre-emptive rituximab group; from first regular assessment of ADAMTS13 activity	Critical	Very Low

Hie et al 2014							after an acute episode for no pre-emptive rituximab group): Pre-emptive rituximab (median follow-up 36 months): median relapse-free survival not reached; no pre-emptive rituximab (median follow-up 60 months): median relapse-free survival 9.3 years, p=0.049 (log-rank test).		
Relapse rate (need for re-treatment rituximab, lower result indicates a greater benefit, median follow-up 17.5 months)									
1 Case series Westwood et al 2017	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	45 (n=76 patient episodes)	None	Re-treatment with rituximab (median of 17.5 months (range 9 to 112 months) after the initial prophylactic dose): 38/76 (50%) patient episodes (35/38 (92.1%) as a result of a decrease in ADAMTS13 levels to ≤15%; 3/38, 7.9% for relapse). Re-treatment episodes per year 0.25	Critical	Very Low
Disease response (2 comparative cohort studies, 1 case series)									
ADAMTS13 activity %, higher result indicates a greater benefit, median follow-up 36 months)									
1 Comparative cohort study Hie et al 2014	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	30	18	Pre-emptive rituximab (median follow-up 36 months) median ADAMTS13 activity %: 58.5%[a] (IQR 30.5% to 86.3%). Not reported for no pre-emptive rituximab group.	Critical	Very Low
Complete or partial response (ADAMTS13 activity %, higher result indicates a greater benefit, median follow-up 15 months)									
1 Case series Westwood et al 2017	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	45 (n=76 patient episodes)	None	Median follow up 15 (range 1 to 141) months Complete response (ADAMTS13 ≥60%)[b] 60/76 (78.9%) episodes. Partial response (ADAMTS13 30%-59%): 10/76 (13.2%) episodes Partial response or complete response (ADAMTS13 ≥30%): 70/76 (92.1%) episodes	Critical	Very Low
Durable / Sustained ADAMTS13 recovery, higher result indicates a greater benefit, median follow-up 31-36 months)									
1 Comparative cohort study	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	30	18	Durable ADAMTS13 recovery, median follow-up 36, IQR 24 to 65 months (normal ADAMTS13 activity defined by authors as ≥50%):	Critical	Very Low

Hie et al 2014							Pre-emptive rituximab: 20/30 (66.7%); (remaining 10/30 had persistent/subsequent ADAMTS13 deficiency) No pre-emptive rituximab not reported.		
1 Case series with additional comparison group Jestin et al 2018	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	92	23	Sustained ADAMTS13 recovery following single course of pre-emptive rituximab: 34/92 (37%), considered long-term responders over the period of follow-up (no further definition) (median follow-up of 31.5 (IQR 18 to 65) months. Not reported for the no pre-emptive rituximab group.	Critical	Very Low
Persistent / subsequent / recurrence of ADAMTS13 activity deficiency, lower result indicates a greater benefit, median follow up 40 months									
1 Case series with additional comparison group Jestin et al 2018	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	92	23	Persistent/severe ADAMTS13 deficiency (undetectable ADAMTS13 activity) 6 months after single course of pre-emptive rituximab: 13/92 (14.1%). Not reported for the no pre-emptive rituximab group. At least 1 severe recurrence of ADAMTS13 deficiency (<10% activity) following single course of pre-emptive rituximab: 45/92 (49%) (period of follow-up not reported). Not reported for the no pre-emptive rituximab group.	Critical	Very Low
Time to ADAMTS 13 recovery, longer duration indicates a greater benefit, median follow up 15 months									
1 Case series Westwood et al 2017	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	45 (n=76 patient episodes)	None	Median follow up 15 (range 1 to 141) months Time to ADAMTS13 recovery: median 1 (range <1 to 5) months	Critical	Very Low
Safety / Adverse events (1 SRMA, 2 comparative cohort studies)									
Mortality (number and proportion died) during median follow-up 36-38 months									
1 SRMA Owattanapanich et al 2019	Very serious limitations[1]	No serious indirectness	No serious inconsistency	Very serious imprecision[5]	122	41	No pooled estimate. ORs from individual studies: Hie et al: pre-emptive rituximab n=0; no pre-emptive rituximab n=2 (OR 0.11 95% CI 0.00 to 2.39) Jestin et al pre-emptive rituximab n=1; no pre-emptive rituximab n=2	Important	Very Low

							(OR 0.12 95% CI 0.01 to 1.33) N differs from Jestin et al		
1 Comparative cohort study Hie et al 2014	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	30	18	Death (median follow-up 36 (IQR 24 to 65) months): pre-emptive rituximab n=0; no pre-emptive rituximab n=2, p value not reported.	Important	Very Low
1 Case series with additional comparison group Jestin et al 2018	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	92	23	Pre-emptive rituximab group (median follow-up, 37.8 (IQR 20 to 57) months): 2/92 (2.17%) (differs from SR) No pre-emptive rituximab (Historical controls), (median follow-up 7 (IQR 5 to 11) years): 2/23 (8.69%)	Important	Very Low
Adverse events during median follow-up 15 to 38 months									
1 Comparative cohort study Hie et al 2014	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	30	18	Pre-emptive rituximab treatment related adverse events (median follow-up 36 (IQR 24 to 65 months): 4/30 (13%)	Important	Very Low
1 Case series with additional comparison group Jestin et al 2018	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	92	23	Rituximab related adverse events, (median follow-up 37.8 (IQR 20 to 57 months): 19/92 (20.7%), none led to rituximab interruption Severe infections: 0 Moderate intolerance within 3 days: 12/92 (13.0%) Hypogammaglobulinemia: 0 Progressive multifocal leukoencephalopathy: 0 Kaposi sarcoma: 0	Important	Very Low
1 Case series Westwood et al 2017	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	45 (n=76 patient episodes)	None	Median follow up 15 (range 1 to 141) months Any AE, 23/76 (30.3%) patient episodes Infusion reactions: 15/76 (19.7%) patient episodes (2 in the same patient given 375mg/m^2 dose rituximab were severe) Non infusion reactions: 8/76 (10.5%) patient episodes (1 given 500 mg rituximab was severe)		Very Low

							Both severe reactions had developed a human antichimeric antibody against rituximab Hepatitis B reactivation: 0 Significant episodes of abnormal liver function tests: 0 Hypogammaglobulinemia: 0		

Abbreviations

AE - Adverse event; CI - Confidence interval; IQR - Inter-quartile range; iTTP - Idiopathic (immune) thrombotic thrombocytopenic purpura; OR - Odds Ratio; SRMA - Systematic review with meta-analysis

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. Risk of bias: very serious limitations due to differences in exposure measurement to assign people to groups, analyses did not consider confounding factors, unclear participant selection and assessment of the outcomes
3. Risk of bias: very serious limitations due to differences in exposure measurement to assign people to groups, lack of adjustments for confounding variables in the statistical analysis, incomplete follow-up not adequately accounted for, uncertain outcome assessment and statistical analyses.
4. Risk of bias: serious limitations due to unclear reporting of study participants, outcome assessment, details of the included participants and statistical analysis.
5. Very serious imprecision as ORs from each study have very wide 95% CIs which cross both the lower and upper default thresholds for minimally clinically important difference (0.8 and 1.25); meta-analysis not reported

a. Hie et al (2014) reports ADAMTS13 ≥50% was classed as normal
b. Westwood et al (2017) reports the normal range for ADAMTS13 activity is 60% to 123%

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.
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)	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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