NHS England Evidence Review:

Obinutuzumab for prevention of acute immune thrombotic thrombocytopenic purpura

NHS England URN: 2255b

NHS England Evidence Review

Obinutuzumab for prevention of acute immune thrombotic thrombocytopenic purpura

Completed: January 2023

Prepared by NICE on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

Acute immune thrombotic thrombocytopenic purpura (TTP) is a critical medical condition needing urgent treatment, usually with plasma exchange, corticosteroids, caplacizumab and rituximab (a chimeric mouse/human anti-CD20 monoclonal antibody). However, rituximab can occasionally have severe adverse reactions or be ineffective; therefore, other treatments have sometimes been used in clinical practice.

Like rituximab, obinutuzumab targets the CD20 molecule. However, unlike rituximab it is humanised, giving potential advantages in terms of response, tolerance and development of resistance (anti-rituximab antibodies). Obinutuzumab is licensed for chronic lymphocytic leukaemia and follicular lymphoma and use for immune TTP is off label (Summary of product characteristics).

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of obinutuzumab for the prevention of acute immune TTP in people who are intolerant or refractory to rituximab.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with obinutuzumab more than others, as well as the ADAMTS13 levels at which preventative treatment was started, and the dose regimen of obinutuzumab that was used.

A separate evidence review has assessed obinutuzumab as a treatment option in de novo or acute relapse of immune TTP in people who are refractory or intolerant to rituximab.

2. Executive summary of the review

This evidence review aims to assess the clinical effectiveness, safety and cost-effectiveness of obinutuzumab compared with no obinutuzumab for prevention of acute immune thrombotic thrombocytopenic purpura (TTP) relapse in people who are intolerant or refractory to rituximab. The searches for evidence were undertaken on 11 October 2022 and identified 60 references. The titles and abstracts were screened, and 3 full text papers were obtained and assessed for relevance.

One case series of 15 people was included in the evidence review (Doyle et al 2022). Eight participants received obinutuzumab (8 treatment episodes) and 7 received ofatumumab (18 treatment episodes) for acute immune TTP, acute (clinical) relapse or ADAMTS13 relapse of immune TTP. The study had no comparator.

Of the 8 people in the study taking obinutuzumab, the majority (6 people, 75%) had ADAMTS13 relapse and fit the population specified in the PICO. The study has been included because it provides the best available evidence for this review, and only a small proportion of participants taking obinutuzumab were ineligible for inclusion (2/8 people with acute [clinical] relapse, 25%).

In terms of clinical effectiveness:

- Relapse rate: One case series provided very low certainty evidence of the critical outcome of relapse rate after obinutuzumab. The median follow-up time to ADAMTS13 normalisation was 7.7 months, with no relapses reported in this time. Median relapse-free survival was 15.4 months, after which 1 person relapsed.
- Disease response: One case series provided very low certainty evidence relating to the critical outcome of disease response. This outcome was reported for a mixed population treated with ofatumumab or obinutuzumab for an ADAMTS13 relapse, an acute (clinical) relapse or a new acute presentation. All 15 participants taking obinutuzumab or ofatumumab had complete or partial remission after treatment. Of the 26 treatment episodes, 24 resulted in complete remission and 2 resulted in partial remission. The median time to complete remission was 15 days.
- No evidence was identified for the critical outcome of hospitalisation.
- No evidence was identified for the important outcome of quality of life.

In terms of safety:

- One case series provided very low certainty evidence on adverse effects. Four adverse events (2 infections and 2 infusion-related reactions) were reported in 4 people during 26 treatment episodes. No participants had serum sickness, and no deaths were reported in the study. It is not known whether the adverse events were in people taking obinutuzumab or ofatumumab because this outcome was reported for both treatments combined.

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 from obinutuzumab more than the wider population of interest.

In terms of criteria to define ADAMTS13 level when preventative treatment started

- Preventative treatment was started when ADAMTS13 activity levels were less than 20 iu/dl; however, some cases with higher levels were treated if there were concerns about rapid disease relapse.

In terms of dose regimens:

- Six out of 8 people had 100 mg on day 1 and 900 mg on day 2. The other 2 people were treated with 1000 mg on day 1 only.
- Five out of 8 people received 1000 mg weekly for 2 or 3 doses. The other 3 people received a further 1000 mg dose 14 days after day 1.
- Six out of 8 people had a total dose of 2000 mg during their treatment, and 2/8 had a total dose of 3000 mg

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

Limitations

It is difficult to conduct high quality studies in rare diseases such as acute immune TTP because of the small size of the eligible population who are intolerant or refractory to rituximab.

The study by Doyle et al. 2022 has many limitations. For example, there was no comparator and the number of people treated with obinutuzumab was small (n=8). As with many small case series, the study was not powered for statistical hypothesis testing and data were collected retrospectively.

In this case series, most outcomes were reported for a mixed population of 15 people taking obinutuzumab or ofatumumab. The population was also mixed in terms of clinical condition. Most treatment episodes were for ADAMTS13 relapse (21/26, 81%), but some were for acute (clinical) relapse (4/26, 15%) and 1 was for a new acute presentation of immune TTP (1/26, 4%), both of which are outside of the PICO population.

Participants with ADAMTS13 or acute (clinical) relapse had full (24/26) or partial remission (2/26) after receiving obinutuzumab. From the two people who had partial remission, one received ofatumumab, but it is not possible to determine which treatment the other person received.

The median follow-up was 8.1 months in people taking obinutuzumab and long-term data are not available. This is important when outcomes such as relapse rate (typically measured over 5 years) are considered.

No outcomes were reported for hospitalisation, quality of life, or cost effectiveness and no evidence was identified regarding any subgroups of patients that would benefit more from treatment with obinutuzumab.

Conclusion

This evidence review found very low certainty evidence for the efficacy and safety of obinutuzumab to prevent acute immune TTP relapse in people who are intolerant or refractory to rituximab

One case series Doyle et al. (2022) was included in the evidence review. In the study, acute (clinical) immune TTP relapses were defined as episodes of thrombocytopenia with platelet counts less than 15 $x10^9$ /L and ADAMTS13 relapses were defined as ADAMTS13 activity levels of less than 20 iu/dl, however some cases were treated with higher levels if there were clinical concerns about rapid diseases relapse.

The study was retrospective, had no comparator and the sample size was small (15 people, 26 treatment episodes). Most outcomes were reported for a mixed population taking either obinutuzumab or ofatumumab for ADAMTS13 relapse, acute (clinical) immune TTP relapse or acute immune TTP. Results of subgroups for treatment and clinical condition were not reported separately, meaning that the evidence for preventing acute relapse is indirect. As with all case series, unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating.

Relapse rate was reported for the 8 people in the study taking obinutuzumab only, most of whom had ADAMTS13 relapse and fit the population specified in the PICO. The study found very low certainty evidence that ADAMTS13 normalises after a median time of 7.7 months in people with relapsed immune TTP treated with obinutuzumab. No relapses were reported in this time in the study, but 1 person relapsed after a median 15.4 months, suggesting any benefits seen with obinutuzumab might not be maintained longer-term.

The study also provided very low certainty evidence suggesting that treatment with obinutuzumab or ofatumumab can result in complete or partial remission in people with ADAMTS13 relapses. The median time to complete remission was around 15 days.

The study reported little information on adverse effects, and it provides only very low certainty evidence on the safety of obinutuzumab. Four adverse events were reported during 26 treatments episodes, and it is not known whether these were in people taking obinutuzumab or ofatumumab.

No evidence was identified for quality of life, hospitalisation, or cost effectiveness, and no evidence was identified regarding any subgroups of patients that would benefit more from treatment with obinutuzumab.

Regarding the dose of obinutuzumab used in the study, 6 people received a smaller ‘test’ dose (100 mg on day 1) to ensure they could tolerate the treatment, before they were given a ‘standard’ dose (900 mg on day 2 then 1000 mg weekly). Two people were treated with 1000 mg weekly from the first dose. Six out of 8 people had a total dose of 2000 mg during their treatment, and 2/8 people had a total dose of 3000 mg.

Although no firm conclusions can be drawn from the study results, the findings of this evidence review are important for people with acute immune TTP who are intolerant or refractory to rituximab because they have limited treatment options. Alternative treatments are needed to prevent multi-organ damage and death.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In people diagnosed with immune TTP who are refractory or intolerant to rituximab what is the clinical effectiveness of obinutuzumab treatment to prevent acute relapse compared with no obinutuzumab?
2. In people diagnosed with immune TTP who are refractory or intolerant to rituximab what is the safety of obinutuzumab treatment to prevent acute relapse compared with no obinutuzumab?
3. In people diagnosed with immune TTP who are refractory or intolerant to rituximab, what is the cost effectiveness of obinutuzumab treatment to prevent acute relapse compared with no obinutuzumab?
4. From the evidence selected, are there any subgroups of patients that may benefit from obinutuzumab treatment to prevent acute relapse more than the wider population of interest?
5. From the evidence selected, at what ADAMTS13 level was preventative treatment started?
6. From the evidence selected, what dose regimens of obinutuzumab treatment to prevent acute relapse 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 11 October 2022.

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 texts 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

One paper was identified for inclusion (Doyle et al 2022). Table 1 provides a summary of the included study and full details are given in Appendix E. The included study was a case series of 15 people treated with ofatumumab (7 people, 18 treatment episodes) or obinutuzumab (8 people, 8 treatment episodes) for acute immune TTP, acute (clinical) relapse or ADAMTS13 relapse of immune TTP. Of the 8 people in the study taking obinutuzumab, the majority (6 people, 75%) had ADAMTS13 relapse and fit the population specified in the PICO. The study has been included because it provides the best available evidence for this review, and only a small proportion of participants taking obinutuzumab were ineligible for inclusion (2/8 people with acute [clinical] relapse, 25%).

Table 1: Summary of included study

Study	Population	Intervention and comparison	Outcomes reported
Doyle et al 2022 Case series UK	People diagnosed with immune TTP on the UK TTP registry, treated with ofatumumab or obinutuzumab for either de novo acute immune TTP, acute (clinical) relapse or ADAMTS 13 relapse Total n=15 (ofatumumab and obinutuzumab, 26 treatment episodes) Obinutuzumab n=8 (8 treatment episodes) All participants had previously received rituximab and steroids. Indications for alternative anti-CD20 treatment were severe infusion-related reactions, acute RISS and a short duration of disease remission Acute (clinical) immune TTP relapses were defined as episodes of thrombocytopenia with platelet counts less than 150 × 109/l ADAMTS 13 relapses were defined as ADAMTS 13 activity levels of less than 20 iu/dl; however, some cases with higher levels were treated if concerns about rapid disease relapse No comparator group Of the 8 people treated with obinutuzumab, 6 (75%) had ADAMTS13 relapses and 2 (25%) had acute (clinical) relapses In the total population, 21/26 (81%) treatment episodes were for ADAMTS 13 relapse, 4/26 (15%) were for acute (clinical) relapse and 1/26 (4%) was for an acute de novo presentation of immune TTP	**Intervention** Obinutuzumab monotherapy 6/8 people had an initial dosing of 100 mg on day 1 and 900 mg on day 2, and 2/8 were commenced on 1000 mg on day 1 only 5/8 people subsequently received 1000 mg weekly for 2 or 3 doses The other 3 people had one further 1000 mg dose 14 days after day 1 6/8 people had a total dose of 2000 mg during their treatment and 2/8 had a total of 3000 mg Median total follow up was 8.1 months **Comparison** No comparator	**Critical outcome** • Relapse rate • Disease response **Important Outcomes** • Adverse events

Abbreviations

TTP, Thrombotic thrombocytopenic purpura; RISS, rituximab -induced serum sickness

5. Results

In people diagnosed with immune TTP who are refractory or intolerant to rituximab what is the clinical effectiveness and safety of obinutuzumab treatment to prevent acute relapse compared with no obinutuzumab?

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. In total, 1 case series (Doyle et al 2022) of 15 people, provided very low certainty evidence relating to relapse rate. The study had no comparator treatment and 8 people received obinutuzumab. Of the 8 people treated with obinutuzumab, 2 people were treated for acute (clinical) relapse (outside the PICO population) and 6 people were treated for ADAMTS13 relapses. The median follow-up time until ADAMTS13 normalised was 7.7 months in the 8 people taking obinutuzumab. No relapses were reported in this time. The median relapse-free survival was 15.4 months. One participant was reported to have had a relapse after obinutuzumab treatment. **(VERY LOW)** **This study provided very low certainty evidence that ADAMTS13 normalises after a median time of 7.7 months in people with relapsed immune TTP treated with obinutuzumab. No relapses were reported in this time in the study, but 1 person relapsed after a median 15.4 months, suggesting any benefits seen with obinutuzumab might not be maintained longer-term. However, no firm conclusions can be drawn from an open-label, retrospective study with no comparator.**
Disease response **Certainty of evidence:** Very low	Disease response is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. In total, 1 case series (Doyle et al 2022) of 15 people provided non-comparative evidence relating to disease response. This outcome was reported for a mixed population treated with either ofatumumab or obinutuzumab. The majority of treatment episodes were for ADAMTS13 relapse (21/26, 81%). The rest were for acute (clinical) relapse (4/26, 15%) and de novo acute immune TPP (1/26, 4%), which are outside of the PICO population. Of 26 treatment episodes with obinutuzumab or ofatumumab, 24 (92%) resulted in complete remission (ADAMTS13 activity levels at least 60 iu/dl) and the other 2 (8%) resulted in partial remission (ADAMTS13 activity 20–59 iu/dl). **(VERY LOW)** The median time to complete remission was 15 days (IQR 11.5–32.5 days). **(VERY LOW)** **This study provided very low certainty evidence suggesting that treatment with obinutuzumab or ofatumumab can result in complete or partial remission in people with ADAMTS13 relapses. The median time to complete remission was around 15 days. There was no comparator and outcomes were not reported separately for each intervention, so no conclusions can be drawn.**
Hospitalisation **Certainty of evidence:**	This outcome is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their treatment has been

Not applicable	successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. **No evidence was identified for this outcome.**
Important outcomes	
Quality of life **Certainty of evidence:** Not applicable	This 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 patient centred shared decision making and health policy. **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, 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, it reflects the additional demands placed on the health system to manage the adverse consequences of the treatment. One case series (n=15) provided evidence relating to adverse events. The study had no comparator treatment and the participants received either ofatumumab or obinutuzumab. The majority of treatment episodes were for ADAMTS13 relapse (21/26, 81%). The rest were for acute (clinical) relapse (4/26, 15%) and de novo acute immune TPP (1/26, 4%), which are outside of the PICO population. Two participants had infections needing treatment (COVID-19 and UTI) and 2 participants had infusion-related reactions. No participants died or had serum sickness. **(VERY LOW)** **Four of 15 participants had 4 adverse events during 26 treatment episodes. Two participants had infections needing treatment (COVID-19 and UTI) and 2 participants had infusion-related reactions. No participants died or had serum sickness. This case series reported little information on adverse effects, and it provides very low certainty evidence on the safety of obinutuzumab. Four adverse events were reported during 26 treatments episodes, and it is not known whether these were in people taking obinutuzumab of ofatumumab. Therefore, no conclusions can be drawn about the safety of obinutuzumab.**
Abbreviations TTP, Thrombotic thrombocytopenic purpura; IQR, Interquartile range; UTI urinary tract infection	

In people diagnosed with immune TTP who are refractory or intolerant to rituximab, what is the cost effectiveness of obinutuzumab treatment to prevent acute relapse compared with no obinutuzumab?

Outcome	Evidence statement
Cost- effectiveness	**No evidence was identified for this outcome**

From the evidence selected, are there any subgroups of patients that may benefit from obinutuzumab treatment to prevent acute relapse more than the wider population of interest?

Outcome	Evidence statement

Sub-groups	**No evidence was identified for this outcome**

From the evidence selected, at what ADAMTS13 level was preventative treatment started?

Outcome	Evidence statement
ADAMTS13 level to start preventative treatment	ADAMTS13 relapses were defined as ADAMTS13 activity levels of less than 20 iu/dl; however, some cases with higher levels were treated if there were clinical concerns.

From the evidence selected, what dose regimens of obinutuzumab treatment to prevent acute relapse were used?

Outcome	Evidence statement
Dose regimens	Six out of 8 people had 100 mg on day 1 and 900 mg on day 2. The other 2 people were treated with 1000 mg on day 1 only. Five out of 8 people received 1000 mg weekly for 2 or 3 doses. The other 3 people received a further 1000 mg dose 14 days after day 1. Six out of 8 people had a total dose of 2000 mg during their treatment, and 2/8 had a total dose of 3000 mg.

6. Discussion

It is difficult to conduct high quality studies in rare diseases such as acute immune TTP because it is rare. In addition, only a small proportion of people with acute immune TTP are intolerant or refractory to rituximab.

The study by Doyle et al. 2022 has many limitations. For example, there was no comparator and the number of people treated with obinutuzumab was small (n=8). As with many small case series, the study was not powered for statistical hypothesis testing and data were collected retrospectively. Case series are subject to bias and confounding and cannot prove that an intervention (such as obinutuzumab) caused a particular outcome, only that it is associated with that outcome. Therefore, results of the study should be considered hypothesis generating only.

In this case series, most outcomes were reported for a mixed population of 15 people taking obinutuzumab or ofatumumab. These treatments are both humanised anti-CD20 monoclonal antibodies, which may have advantages over rituximab in terms of response, tolerance and development of resistance.

The population was also mixed in terms of clinical condition. Most treatment episodes were for ADAMTS13 relapse (21/26, 81%), but some were for acute (clinical) relapse (4/26, 15%) and 1 was for a new acute presentation of immune TTP (1/26, 4%), both of which are outside of the PICO population.

Of the 8 people in the study taking obinutuzumab, the majority (6 people, 75%) had ADAMTS13 relapse and fit the population specified in the PICO. Results for the subgroups were not reported separately, meaning that the evidence is indirect.

Despite the mixed population, everyone with ADAMTS13 or acute (clinical) relapse had full or partial remission after receiving obinutuzumab. The median time until ADAMTS13 returned to normal was 7.7 months, and no relapses were reported in this time. Median relapse-free survival was 15.4 months after which 1 person relapsed. Median follow-up was only 8.1 months in people taking obinutuzumab. This may be insufficient to reliably measure longer term outcomes such as relapse rate.

Although all 15 people in the study achieved remission, it is not possible to determine how many had full remission or partial remission with obinutuzumab as opposed to ofatumumab. Similarly, 4 people had 4 (27%) adverse events but it is not known whether they were related to obinutuzumab or ofatumumab because the population was mixed.

The population of interest is people who are refractory to or intolerant to rituximab. All people in the study (treated with obinutuzumab or ofatumumab) had a history of a response to rituximab. The reason for changing to an alternative treatment was acute rituximab-induced serum sickness in 8/15 people, severe infusion-related reactions in 4/15 people and short duration of response to rituximab (less than 3 months) in 3/15 people. Data are not reported for obinutuzumab alone.

The study summarised data from the UK TPP registry and is, therefore, relevant to UK clinical practice. The study did not report participants age, ethnicity, or gender; therefore, it is unclear how the results of the study apply to people of different ages, ethnic backgrounds, or genders.

No outcomes were reported for hospitalisation, quality of life, or cost effectiveness and no evidence was identified regarding any subgroups of patients that would benefit more from treatment with obinutuzumab.

7. Conclusion

This evidence review found very low certainty evidence for the efficacy and safety of obinutuzumab to prevent acute immune TTP relapse in people who are intolerant or refractory to rituximab.

One case series (Doyle et al 2022) was included in the evidence review. In the study, acute (clinical) relapses were defined as episodes of thrombocytopenia with platelet counts less than 15 x10^9/i and ADAMTS13 relapses were defined as ADAMTS13 activity levels of less than 20 iu/dl; however, some cases were treated with higher levels if there were clinical concerns about rapid diseases relapse.

The study was retrospective, had no comparator and the sample size was small (15 people, 26 treatment episodes). Most outcomes were reported for a mixed population taking either obinutuzumab (n=8) or ofatumumab (n=7) for ADAMTS13 relapse (21/26, 81%). However, (4/26, 15%) were treated for acute (clinical) relapse and 1 person (1/26, 4%) was treated for a new acute presentation, both of which are outside of the PICO population. Results of subgroups for treatment and clinical condition were not reported separately, meaning that the evidence is indirect. As with all case series, unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating.

Relapse rate was reported for the 8 people in the study taking obinutuzumab only, most of whom had ADAMTS13 relapse (6/8, 75%) and fit the population specified in the PICO. The study found very low certainty evidence that, after obinutuzumab, the median time until ADAMTS13 became normal was 7.7 months, with no relapses reported in this time. Median relapse-free survival was 15.4 months, during which 1 person relapsed. Median follow-up was only 8.1 months in people taking obinutuzumab and long-term data is not available. This is important when outcomes such as relapse rate (typically measured over 5 years) are considered.

The study also provided very low certainty evidence that, all 15 people treated with obinutuzumab or ofatumumab achieved full (ADAMTS13 activity at least 60 iu/dl) or partial remission (ADAMTS13 activity 20-59 iu/dl). The median time to complete remission was around 15 days. No data are available for obinutuzumab alone.

The study provided very low certainty evidence on adverse effects. Four people experienced adverse events (2/4 had infections and 2/4 had infusion related reactions); however, it is not known if they were receiving obinutuzumab of ofatumumab. No participants had serum sickness, and no deaths were reported in the study.

Regarding the dose of obinutuzumab used in the study, 6 people received a smaller ‘test’ dose (100 mg on day 1) to ensure they could tolerate the treatment, before they were given a ‘standard’ dose (900 mg on day 2 then 1000 mg weekly). Two people were treated with 1000 mg weekly from the first dose. Six out of 8 people had a total dose of 2000 mg during their treatment, and 2/8 people had a total dose of 3000 mg.

No evidence was identified for quality of life, hospitalisation, or cost effectiveness, and no evidence was identified regarding any subgroups of patients that would benefit more from treatment with obinutuzumab.

Appendix A PICO document

The review questions for this evidence review are:

1. In people diagnosed with immune TTP who are refractory or intolerant to rituximab what is the clinical effectiveness of obinutuzumab treatment to prevent acute relapse compared with no obinutuzumab?
2. In people diagnosed with immune TTP who are refractory or intolerant to rituximab what is the safety of obinutuzumab treatment to prevent acute relapse compared with no obinutuzumab?
3. In people diagnosed with immune TTP who are refractory or intolerant to rituximab, what is the cost effectiveness of obinutuzumab treatment to prevent acute relapse compared with no obinutuzumab?
4. From the evidence selected, are there any subgroups of patients that may benefit from obinutuzumab treatment to prevent acute relapse more than the wider population of interest?
5. From the evidence selected, at what ADAMTS13 level was preventative treatment started?
6. From the evidence selected, what dose regimens of obinutuzumab treatment to prevent acute relapse were used?

P –Population and Indication	All people diagnosed with immune TTP who are intolerant or refractory to rituximab who either go into haematological remission and have ADAMTS13 deficiency or achieve full immunological remission and then have immunological relapse. [Immunological relapse is commonly defined as ADAMTS13 levels <20iu/dl] [Intolerance will commonly be described as allergy or hypersensitivity.]
I – Intervention	Obinutuzumab (anti-CD20 antibody) to prevent acute haematological relapse.
C – Comparators	Any immunosuppressant treatment regimen that doesn't include obinutuzumab [for example mycophenolate mofetil or ciclosporin A or azathioprine or bortezomib].
O – Outcomes	**<u>Clinical effectiveness</u>** 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 immune TTP event is best measured over 5 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 normalisation of ADAMTS13 activity or time to immunological remission.] • **Hospitalisation** *This outcome is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention.* **Important to decision making** • **Quality of life** *This 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 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.] **Safety/ adverse events** • *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**
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	2012-2022
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials
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 in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search date: 11 October 2022

Medline

1 purpura, thrombocytopenic/ or purpura, thrombotic thrombocytopenic/ (11008)
2 (thrombo* adj5 (immune or autoimmune or purpura)).tw. (22105)
3 ((familial or congenital or genetic or hereditary) adj5 (thrombo* or microangio*)).tw. (4934)
4 (itp or aitp or ttp or attp or ittp or aittp).tw. (17828)
5 (moschkowitz or schulman or upshaw).tw. (227)
6 or/1-5 (39005)
7 limit 6 to (english language and yr="2012 -Current") (13856)
8 limit 7 to (comment or editorial or letter) (897)
9 7 not 8 (12959)
10 obinutuzumab.tw. (685)
11 gazyvaro.tw. (5)
12 afutuzumab.tw. (2)
13 ga 101.tw. (20)
14 ga101.tw. (93)
15 gazyva.tw. (13)
16 r 7159.tw. (0)
17 r7159.tw. (0)
18 rg 7159.tw. (0)
19 rg7159.tw. (0)
20 ro 5072759.tw. (0)
21 ro5072759.tw. (2)
22 or/10-21 (720)
23 9 and 22 (7)

Embase

1 thrombocytopenic purpura/ (2060)
2 exp thrombotic thrombocytopenic purpura/ (17161)
3 exp autoimmune thrombocytopenia/ (23980)
4 (thrombo* adj5 (immune or autoimmune or purpura)).tw. (25582)
5 ((familial or congenital or genetic or hereditary) adj5 (thrombo* or microangio*)).tw. (7156)
6 (itp or aitp or ttp or attp or ittp or aittp).tw. (28089)
7 (moschkowitz or schulman or upshaw).tw. (361)
8 or/1-7 (67867)
9 limit 8 to (english language and yr="2012 -Current") (40200)
10 limit 9 to (editorial or letter or "preprint (unpublished, non-peer reviewed)") (2109)
11 9 not 10 (38091)
12 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5074443)
13 11 not 12 (20985)
14 obinutuzumab/ (3645)

15 obinutuzumab.tw. (1930)
16 gazyvaro.tw. (67)
17 afutuzumab.tw. (6)
18 ga 101.tw. (312)
19 ga101.tw. (372)
20 gazyva.tw. (200)
21 r 7159.tw. (3)
22 r7159.tw. (0)
23 rg 7159.tw. (4)
24 rg7159.tw. (1)
25 ro 5072759.tw. (32)
26 ro5072759.tw. (12)
27 or/14-26 (3863)
28 13 and 27 (45)

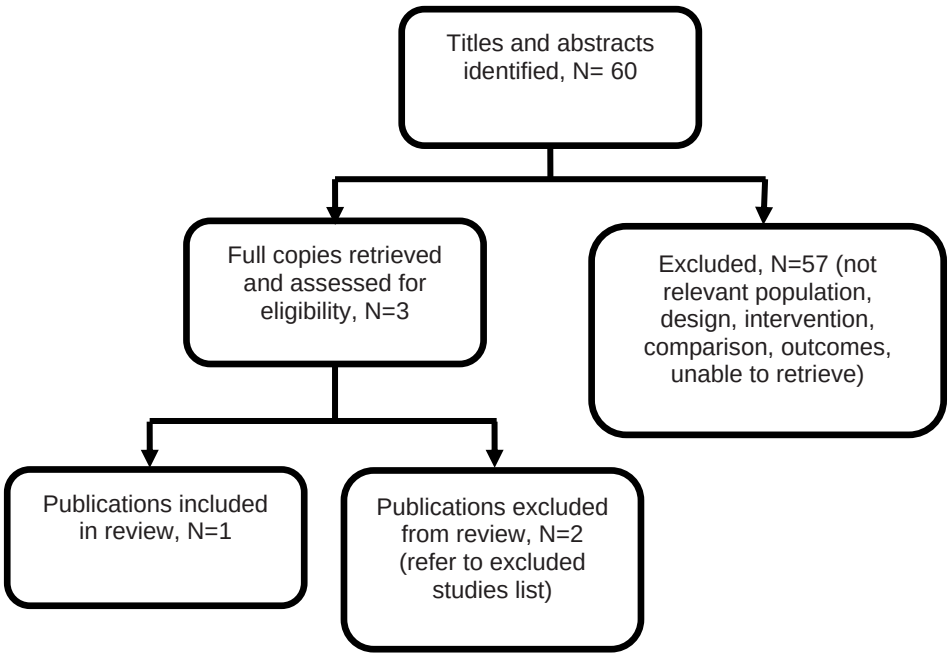
Cochrane Library

ID Search
#1 [mh ^"Purpura, Thrombocytopenic"]
#2 [mh ^"purpura, thrombotic thrombocytopenic"]
#3 (thrombo* NEAR/5 (immune or autoimmune or purpura)):ti,ab,kw
#4 ((familial or congenital or genetic or hereditary) NEAR/5 (thrombo* or microangio*)):ti,ab,kw
#5 (itp OR aitp OR ttp OR attp OR ittp OR aittp):ti,ab,kw
#6 (moschkowitz or schulman or upshaw):ti,ab,kw
#7 {OR #1-#6}
#8 obinutuzumab:ti,ab,kw
#9 gazyvaro:ti,ab,kw
#10 afutuzumab:ti,ab,kw
#11 "ga 101":ti,ab,kw
#12 ga101:ti,ab,kw
#13 gazyva:ti,ab,kw
#14 "r 7159":ti,ab,kw
#15 r7159:ti,ab,kw
#16 "rg 7159":ti,ab,kw
#17 rg7159:ti,ab,kw
#18 "ro 5072759":ti,ab,kw
#19 ro5072759:ti,ab,kw
#20 {OR #8-#19}
#21 #7 AND #20
#22 conference:pt
#23 (clinicaltrials or trialsearch):so
#24 #21 NOT (#22 OR #23)

Appendix C Evidence selection

The literature searches identified 60 references. These were screened using their titles and abstracts and 3 references were obtained in full text and assessed for relevance. Of these, 1 is included in the evidence summary. The 2 references that 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
Doyle, A., Stubbs, M., Lester, W., Thomas, W., Westwood, J., Thomas, M., Percy, C., Prasannan, N. and Scully, M., 2022. The use of obinutuzumab and ofatumumab in the treatment of immune thrombotic thrombocytopenic purpura. British Journal of Haematology, 198(2), pp.391-396	Included
Patriquin, C., Thomas, M., Dutt, T., McGuckin, S., Blombery, P., Cranfield, T., Westwood, J. and Scully, M., 2016. Bortezomib in the treatment of refractory thrombotic thrombocytopenic purpura. British Journal of Haematology, 173(5), pp.779-785	Incorrect intervention
Jana van den Berg, Johanna A. Kremer Hovinga, Claudia Pfleger, Inga Hegemann, GregorStehle, Andreas Holbro, Jan-Dirk Studt; Daratumumab for immune thrombotic thrombocytopenicpurpura. Blood Adv 2022; 6 (3): 993–997	Incorrect intervention

Appendix D Excluded studies table

Study reference	Reason for exclusion
Robertz, Judith, Andres, Martin, Taleghani, Behrouz Mansouri et al. Obinutuzumab in two patients suffering from immune-mediated thrombotic thrombocytopenic purpura intolerant to rituximab. American journal of hematology 94(10): e259-e261	Incorrect publication type
Subhan, M. and Scully, M. (2022) Advances in the management of TTP. Blood Reviews 55: 100945	Incorrect publication type

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Doyle AJ, Stubbs MJ, Lester W et al. (2022) The use of obinutuzumab and ofatumumab in the treatment of immune thrombotic thrombocytopenic purpura. British Journal of Haematology 198 (2); 391-6 **Study location** United Kingdom **Study type** Case series **Study aim** The study aimed 'to evaluate the use of ofatumumab and obinutuzumab for immune TTP in the UK to assess their clinical efficacy and safety profile in those who have not tolerated rituximab previously or shown poor responses.' **Study dates** Not reported	**Inclusion criteria** People diagnosed with immune TTP on the UK TTP registry, treated with ofatumumab or obinutuzumab for either de novo acute immune TTP, acute (clinical) relapse or ADAMTS 13 relapse. All had previously received rituximab and steroids. Indications for alternative anti-CD20 treatment were severe infusion-related reactions, acute RISS and a short duration of disease remission Acute (clinical) immune TTP relapses were defined as episodes of thrombocytopenia with platelet counts less than 150×10^9/l ADAMTS13 relapses were defined as ADAMTS13 activity levels of less than 20 iu/dl; however, some cases with higher levels were treated if there were clinical concerns **Exclusion Criteria** None reported **Total sample size** 15 people were included in the study **No. of participants in each treatment group** 8 people were treated with obinutuzumab with 8 episodes of immune TTP relapse	**Interventions** Open label treatment with ofatumumab or obinutuzumab monotherapy. As a general approach, a smaller 'test' dose was given to the patients to ensure tolerability of the drug prior to giving a 'standard' dose Concurrent steroids were used at clinicians' discretion for preventing or treating infusion reactions, depending on history of previous reaction with rituximab Of 8 people treated with obinutuzumab, 6 had 100 mg on day 1 and 900 mg on day 2. The other 2 people were treated with 1000 mg on day 1 only 5/8 people received 1000 mg weekly for 2 or 3 doses. The other 3 people received a further 1000 mg dose 14 days after day 1 6/8 people had a total dose of 2000 mg during their treatment, and 2/8 had a total dose of 3000 mg Median total follow up was 8.1 months in people taking obinutuzumab **Comparators** There was no comparator	**Critical outcomes** **Relapse rate** The median follow-up time until ADAMTS13 normalised was 7.7 months in the 8 people taking obinutuzumab. During this period, there were no relapses The median relapse-free survival time in the 8 participants was 15.4 months. 1 person had a relapse after obinutuzumab treatment **Disease response** The primary outcome of the study was ADAMTS13 activity response after treatment with either ofatumumab or obinutuzumab. Results are reported only for both treatments combined All 15 participants taking obinutuzumab or ofatumumab had complete or partial remission after treatment Of the 26 treatment episodes, 24 (92%) resulted in complete remission (ADAMTS13 activity levels at least 60 iu/dl) and the other 2 (8%) resulted in partial remission (ADAMTS13 activity 20–59 iu/dl) The median time to complete remission was 15 days (IQR 11.532.5 days) **Important outcomes** None reported **Safety: adverse events** Adverse events were not reported for obinutuzumab alone In the mixed population taking, ofatumumab or obinutuzumab, 4/15 people (27%) had adverse events (4/26 treatment episodes [15%])	This study was appraised using the Joanna Briggs Institute checklist for case series 1.Yes 2.Yes 3.Yes 4.Yes 5.Yes 6.No 7.Yes 8.Yes 9.No 10.Yes Other comments: The study is a case series and, as such, is rated as poor in the hierarchy of study designs. However, there are few eligible participants for studies using new treatments in rare diseases (such as immune TPP), meaning it is difficult to conduct high quality studies. Key limitations are that treatment with obinutuzumab was open label, there was no comparator, and the sample size was small (n=8). As with many case series, the study was not powered for statistical hypothesis testing and the data should be regarded as descriptive only. Case series have no comparators, and unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating. Source of funding: Not reported

	The other 7 people were treated with ofatumumab (18 treatment episodes) **Baseline characteristics of disease** In the total population, 21/26 (81%) treatment episodes were for ADAMTS 13 relapse, 4/26 (15%) were for acute (clinical) relapse and 1/26 (4%) was for an acute de novo presentation of immune TTP Of the 8 people treated with obinutuzumab, 6 (75%) had ADAMTS13 relapses and 2 (25%) had acute (clinical) relapses All people in the study (treated with obinutuzumab or ofatumumab) had a history of a response to rituximab. 12/15 had a complete response and 3/15 had a partial response. The reason for changing to an alternative treatment was acute RISS in 8/15 people, severe infusion-related reactions in 4/15 people and short duration of response to rituximab (less than 3 months) in 3/15 people. Data are not reported for obinutuzumab alone		2 people had infections (COVID-19 and UTI) needing treatment and 2 people had infusion-related reactions. No participants had serum sickness, and no deaths were reported in the study	

Abbreviations

TTP, Thrombotic thrombocytopenic purpura; IQR, interquartile range; RISS, rituximab -induced serum sickness; UTI, urinary tract infection

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

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

Appendix G GRADE profiles

Table 2: Question: In people diagnosed with immune TTP who are refractory or intolerant to rituximab what is the clinical effectiveness of obinutuzumab treatment to prevent acute relapse compared with no obinutuzumab?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Obinutuzumab	Comparator	Result		
Relapse rate (1 retrospective case series)									
Median follow-up time without relapse (A longer time to relapse indicates a positive outcome)									
Retrospective case series Doyle et al (2021)	No serious	Serious[1]	Not applicable	Not calculable	n=8	N/A	During the median 7.7 months until ADAMTS13 normalised, there were no relapses The median follow-up time without relapse was 15.4 months. 1 person had a relapse after obinutuzumab treatment	Critical	Very low
Disease response (1 retrospective case series)									
Remission in terms of normalisation or improvement in ADAMTS13 activity (Higher levels indicate a good response to the treatment)									
Retrospective case series Doyle et al (2021)	No serious	Very serious[2]	Not applicable	Not calculable	Obinutuzumab n=8 (Total n=15)	N/A	Results were not reported for obinutuzumab alone, but for people taking obinutuzumab or ofatumumab. All 15 people had complete or partial remission after treatment Of the 26 treatment episodes, 24 (92%) resulted in complete remission (ADAMTS13 activity levels at least 60 iu/dl) and the other 2 (8%) resulted in partial remission (ADAMTS13 activity 20–59 iu/dl) The median (time to complete remission was 15 (IQR 11.5–32.5) days	Critical	Very low
Safety (1 retrospective case series)									
Adverse events									
Retrospective case series Doyle et al (2021)	No serious	Very serious[2]	Not applicable	Not calculable	Obinutuzumab n=8 (Total n=15)	N/A	Adverse events were not reported for obinutuzumab alone In the mixed population taking, ofatumumab or obinutuzumab,	Safety	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Obinutuzumab	Comparator	Result		
							4/15 people (27%) had adverse events (4/26 treatment episodes [15%]) 2 people had infections (COVID-19 and UTI) needing treatment and 2 people had infusion-related reactions. No participants had serum sickness, and no deaths were reported in the study		

Abbreviations

TTP, Thrombotic thrombocytopenic purpura; IQR, Interquartile range; UTI, urinary tract infection

[1] Mixed population: 6/8 people (75%) taking obinutuzumab had ADAMTS13 relapse and are within the PICO, but 2/8 people (25%) had acute (clinical) relapse and are outside of the PICO.
[2] Mixed population: results are for obinutuzumab and ofatumumab combined and included 21/26 (81%) treatment episodes for ADAMTS 13 relapse, 4/26 (15%) for acute (clinical) relapse and 1/26 (4%) an acute de novo presentation of immune TTP.

Glossary

ADAMTS13	A disintegrin and metalloproteinase with thrombospondin type-1 motif, 13.
Rituximab-induced serum sickness (RISS)	An adverse effect characterised by fever, rash, and arthralgias
Thrombotic thrombocytopenic purpura (TTP)	TTP is a critical medical condition requiring intensive care unit admission and, without treatment, mortality is >90%. Immune TTP results from a deficiency of the enzyme ADAMTS13.

References

Included studies

- Doyle AJ, Stubbs MJ, Lester W et al (2022) The use of obinutuzumab and ofatumumab in the treatment of immune thrombotic thrombocytopenic purpura. British journal of Haematology. 198 (no. 2); 391-396

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