NHS England Evidence Review:

Bortezomib for acute immune thrombotic thrombocytopenic purpura

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NHS England Evidence Review

Bortezomib for acute immune thrombotic thrombocytopenic purpura

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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.

Bortezomib is a proteasome inhibitor that acts to eliminate CD20-expressing B-cells and plasma cells. Bortezomib is licenced for the treatment of multiple myeloma and mantle cell lymphoma and use for acute immune TTP is off label (Summary of product characteristics).

This evidence review examines the clinical effectiveness, safety and cost effectiveness of bortezomib in people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with bortezomib more than others, as well as the criteria used by the included studies to define haematological remission, and the dose regimen of bortezomib that was used.

A separate evidence review has assessed bortezomib to prevent relapse in people with immune TTP 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 bortezomib compared with no bortezomib in people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab. The searches for evidence published since October 2012 were conducted on 11 October 2022 and identified 292 references. The titles and abstracts were screened and 7 full text papers were obtained and assessed for relevance.

One case series of 6 people was included in the evidence review (Patriquin et al. 2016). The included study has no comparator.

In terms of clinical effectiveness:

- Mortality. One case series provided very low certainty evidence for the critical outcome of mortality. One of 6 people died during admission.
- No evidence was identified for the critical outcome of relapse rate.
- Disease response. One case series provided very low certainty evidence on the critical outcome of disease response (ADAMTS13 activity and platelet normalisation) after bortezomib. All people who survived had an ADAMTS13 activity greater than 10% at discharge and follow up and all had platelet normalisation within 29 days. However, because there was no comparator and rituximab was given concomitantly in 5/6 people, no conclusions can be drawn.
- Functional measures. One case series provided very low certainty evidence on the important outcome of functional measures. Two of 6 people had neurological resolution, 1/6 people had transient atrial fibrillation with normal echo, 1/6 people had partial blindness and hearing loss, and the person who died had confusion, new acute aphasia, biventricular congestive heart failure, and cardiac arrest. However, because there was no comparator and rituximab was given concomitantly in 5/6 people, no conclusions can be drawn.
- No evidence was identified for the important outcomes of quality of life and hospitalisation.

In terms of safety:

- One case series provided very low certainty evidence that there were no adverse events in the 5/6 people who survived.

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 treatment with bortezomib.

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 TTP because acute TTP is rare and a small proportion of these are intolerant or refractory to rituximab or obinutuzumab. Although the study by Patriquin et al. 2016 was well reported, it has many limitations. For example, there was no comparator, the sample size was small (n=6) and follow up was short (3 to 33 months). The short follow up time meant long term outcome data, such as relapse rate, which is typically measured over 5 years, were not available. In this case series, data were reported for each case separately and no pooling or statistical analyses were undertaken.

The population of interest is people who are refractory to or intolerant to rituximab or obinutuzumab. In the included study, rituximab was given first but there was overlap between rituximab and bortezomib dosing for all except one person. Therefore, it is not possible to say whether any observed effects were because of rituximab, bortezomib, or both treatments in combination.

All of the people included in the study were admitted to hospital with their first episode of acute immune TTP, therefore it is unclear whether the findings apply to people with recurrent episodes of acute immune TTP.

No outcomes were reported for quality of life, hospitalisation, or cost effectiveness.

Conclusion

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

One case series (Patriquin et al. 2016) was included in the evidence review. In the study, refractory disease was defined as persistent thrombocytopenia or lack of sustained platelet count increment, and increasing lactate dehydrogenase despite intensive treatment with therapeutic plasma exchange and corticosteroids. Non-response to rituximab was not clearly defined in the inclusion criteria, however all cases in the study were initiated on rituximab prior to bortezomib and a drop in platelets was reported for most cases after receiving rituximab and before receiving bortezomib.

The study had no comparator and the sample size was small (n=6). Whilst follow up was reasonably long with a mean follow up time of 17 months (range 3 to 33 months), it was not sufficient to report long term outcomes such as relapse rate and subsequent hospitalisations. Outcomes were reported separately for each case and no pooling or statistical analyses were reported. 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.

One out of 6 people died following treatment with bortezomib (9th day after admission, very low certainty evidence). The study also provided very low certainty evidence on disease response (ADAMTS13 activity and platelet normalisation) after bortezomib. All participants who survived had resolution of TTP, platelet normalisation and ADAMTS13 activity greater than 10% at discharge and follow up. Two people had neurological resolution, 1/6 people had transient atrial fibrillation with normal echocardiogram, 1/6 people had partial blindness and hearing loss, and

the person who died had confusion, new acute aphasia, biventricular congestive heart failure, and cardiac arrest.

The study provided very low certainty evidence that there were no adverse events in the 5/6 people who survived.

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

3. Methodology

Review questions

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

1. In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the clinical effectiveness of bortezomib compared with no bortezomib?
2. In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the safety of bortezomib compared with no bortezomib?
3. In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the cost effectiveness of bortezomib compared with no bortezomib?
4. From the evidence selected, are there any subgroups of patients that may benefit from bortezomib more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define haematological remission?
6. From the evidence selected, what dose regimens of bortezomib 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 12 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 (Patriquin et al. 2016). 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 6 people, with outcomes reported separately for each case.

Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Patriquin et al. 2016 Case series UK	Severe acquired refractory TTP. TTP was defined as the presence of MAHA, thrombocytopenia and ADAMTS13 activity less than 10%. Refractory disease was defined as persistent thrombocytopenia or lack of sustained platelet count increment, and increasing lactate dehydrogenase (more than 2 times the upper limit of normal) despite intensive treatment with TPE and corticosteroids. N=6 No comparator group.	**Intervention** Bortezomib 1 mg/m^2: • Case 1: 1.8 mg IV, 2 treatments (days 15 and 27) • Case 2: 2.0 mg SC, 1 treatment (day 7) • Case 3: 2.13 mg SC, 1, treatment (day 6) • Case 4: 1.55 mg SC, 3 treatments (days 9, 12, 20) • Case 5: 2.0 mg SC, 3 treatments (days 22,26, 29) • Case 6: 2.0 mg SC, 2 treatments (days 6, 12) Other interventions: All cases had TPE and rituximab prior to bortezomib. Rituximab was given at 375 mg/m^2 IV. Details for each case are given below. • Case 1: TPE, twice daily (37 exchanges); rituximab 670 mg, 6 treatments (days 5, 9, 12, 15, 24, 34); methylprednisolone, mycophenolate mofetil, and N-acetyl-cysteine. • Case 2: TPE, once daily (12 exchanges); 730 mg, 4 treatments (days 3, 6, 10, 18); methylprednisolone. • Case 3: TPE, twice daily (14 exchanges); rituximab 800 mg, 2 treatments (days 3 and 7); methylprednisolone. • Case 4: TPE, twice daily (30 exchanges); rituximab 590 mg, 5 treatments (days 4, 7, 10, 14, 17); methylprednisolone. • Case 5: TPE, twice daily (82 exchanges); rituximab 750 mg, 4 treatments (days 4, 8, 12, 16); methylprednisolone. • Case 6: TPE, twice daily (36 exchanges); rituximab 750 mg, 4 treatments (days 4, 8, 12, 21); methylprednisolone. **Comparison** No comparator.	**Critical outcomes** • Mortality • Disease response **Important outcomes** • Functional measures • Adverse events

Abbreviations

MAHA, microangiopathic haemolytic anaemia; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura

5. Results

In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the clinical effectiveness and safety of bortezomib compared with no bortezomib?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Mortality **Certainty of evidence:** Very low	Mortality is important to patients because acute immune TTP is a serious, potentially life-threatening condition. In total 1 case series (Patriquin et al. 2016) of 6 people, provided evidence relating to mortality. The study had no comparator treatment and all participants received concomitant rituximab. One person died of cardiac arrest on the 9th day after admission, 5/6 people were alive at follow up (mean 17 months, range 3 to 33 months after discharge). **(VERY LOW)** **This study provided very low certainty evidence that 1 person out of 6 died after bortezomib. No conclusions can be drawn.**
Relapse rate **Certainty of evidence:** Not applicable	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. **No evidence was identified for this outcome.**
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 (Patriquin et al. 2016) of 6 people, provided evidence relating to disease response. The study had no comparator treatment and all participants received concomitant rituximab. Resolution of TTP: • TTP resolution was reported in 5/6 people. **(VERY LOW)** ADAMTS13 activity: • at time of discharge ADAMTS13 activity ranged from 75 to 89% (Case 1: 87%; Case 2: 89%; Case 3: died; Case 4: 83%; Case 5: 83%; Case 6: 75%). **(VERY LOW)** • At mean 17 months follow up after discharge (range 3 to 33 months) ADAMTS13 activity had increased in 5/6 cases ranging from 65 to 119% (Case 1: 116%, 33 months; Case 2: 119%, 12 months; Case 3: died; Case 4: 106%, 19 months; Case 5: 65%, 18 months; Case 6: 87%, 3 months). **(VERY LOW)** Time from first bortezomib dose to platelet normalisation (days): • 3 to 29 days (Case 1: 6; Case 2: 3; Case 3: died; Case 4: 12; Case 5: 29; Case 6: 21 days). **(VERY LOW)** **This study provided very low certainty evidence on disease response (ADAMTS13 activity and platelet normalisation) after bortezomib. All people**

	who survived had an ADAMTS13 activity greater than 10% at discharge and follow up and all had platelet normalisation within 29 days.the
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. **No evidence was identified for this outcome.**
Functional measures **Certainty of evidence:** Very low	These outcome measures are important to patients as they facilitate enablement, independence and active participation. In total 1 case series (Patriquin et al. 2016) of 6 people, provided evidence relating to functional measures. The study had no comparator treatment and all participants received concomitant rituximab. Functional measures reported: • Neurological resolution reported in 2/6 people. • Transient atrial fibrillation with normal echo reported in 1/6 people. • Partial blindness and hearing loss in 1/6 people. • Confusion, new acute aphasia, biventricular congestive heart failure, and cardiac arrest in the person who died. **(VERY LOW)** **This case series provides very low certainty evidence on the effect of bortezomib on functional measures. The authors reported a range of descriptive functional measures. However, because there was no comparator and rituximab was given concomitantly in 5/6 people, no conclusions can be drawn.**
Hospitalisation **Certainty of evidence:** Not applicable	Hospitalisation is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Very low	Safety outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. One case series (n=6) provided evidence relating to adverse events. The study had no comparator treatment and all participants received concomitant rituximab. Of the 5/6 people who survived, no adverse events were reported. **(VERY LOW)** **This case series provides very low certainty evidence on the safety of bortezomib. The authors reported that there were no adverse events in the 5/6 people who survived.**

Abbreviations

TTP, thrombotic thrombocytopenic purpura

In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the cost effectiveness of bortezomib compared with no bortezomib?

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 bortezomib more than the wider population of interest?

Outcome	Evidence statement
Subgroups	**No evidence was identified for this outcome.**

From the evidence selected, what are the criteria used by the research studies to define haematological remission?

Outcome	Evidence statement
Criteria	TTP was defined as the presence of MAHA, thrombocytopenia and ADAMTS13 activity less than 10%. Refractory disease was defined as persistent thrombocytopenia or lack of sustained platelet count increment, and increasing lactate dehydrogenase (more than 2 times the upper limit of normal) despite intensive treatment with TPE and corticosteroids.

Abbreviations

MAHA, microangiopathic haemolytic anaemia; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura

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

Outcome	Evidence statement
Dosage	Bortezomib was administered as 1 mg/m^2, either IV or SC (total dose: range 1.55 to 2.13 mg; number of treatments: range 1 to 3). Details of dosing for each case are: • Case 1: 1.8 mg IV, 2 treatments (days 15 and 27) • Case 2: 2.0 mg SC, 1 treatment (day 7) • Case 3: 2.13 mg SC, 1, treatment (day 6) • Case 4: 1.55 mg SC, 3 treatments (days 9, 12, 20) • Case 5: 2.0 mg SC, 3 treatments (days 22, 26, 29) • Case 6: 2.0 mg SC, 2 treatments (days 6, 12)

Abbreviations

IV, intravenous; SC, subcutaneous

6. Discussion

It is difficult to conduct high quality studies in rare diseases such as acute TTP because acute TTP is rare and a small proportion of these are intolerant or refractory to rituximab or obinutuzumab. Although the study by Patriquin et al. 2016 was well reported, it has many limitations. For example, there was no comparator, the sample size was small (n=6) and follow up was short (3 to 33 months). The short follow up time meant long term outcomes, such as relapse rate, which is typically measured over 5 years, were not available. As with many small case series, the study was not powered for statistical hypothesis testing. In this case series, data were reported for each case separately and no pooling or statistical analyses were undertaken. Case series are subject to bias and confounding and cannot prove that an intervention (such as bortezomib) caused a particular outcome, only that it is associated with that outcome. Therefore, results of the study should be considered hypothesis generating only.

The population of interest is people who are refractory to or intolerant to rituximab or obinutuzumab. In the included study, rituximab was given first, but rituximab was continued after the first dose of bortezomib for all except one person. Therefore, it is not possible to say whether any observed effects were because of rituximab, bortezomib, or both treatments.

The study summarised data from UK centres and is, therefore, relevant to UK clinical practice. Ethnicity was not reported therefore it is unclear how the results of the study apply to people with different ethnic origins. Three participants in the study were female and 3 were male and the age range was 27 to 76. No children were included in the study, therefore it is unclear whether the findings apply to children.

All of the people included in the study were admitted to hospital with their first episode of acute immune TTP, therefore it is unclear whether the findings apply to people with recurrent episodes of acute immune TTP. ADAMTS13 activity at baseline was less than 5% for 4/6 people, 8% in one person, and 10% in one person. ADAMTS13 activity of less than 10% indicates an episode of acute immune TTP. The authors reported that the person with an ADAMTS activity of 10% had received plasma and corticosteroids prior to the baseline measurement.

No outcomes were reported for quality of life, hospitalisation, or cost-effectiveness.

7. Conclusion

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

One case series (Patriquin et al. 2016) was included in the evidence review. In the study, refractory disease was defined as persistent thrombocytopenia or lack of sustained platelet count increment, and increasing lactate dehydrogenase despite intensive treatment with therapeutic plasma exchange and corticosteroids. Non-response to rituximab was not clearly defined in the inclusion criteria, however all cases in the study were initiated on rituximab prior to bortezomib and a drop in platelets was reported for most cases after receiving rituximab and before receiving bortezomib.

The study had no comparator and the sample size was small (n=6). Whilst follow up was reasonably long with a mean follow up time of 17 months (range 3 to 33 months), it was not sufficient to report long-term outcomes such as relapse rate and subsequent hospitalisations. Outcomes were reported separately for each case and no pooling or statistical analyses were reported. 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.

The study found very low certainty evidence that, of the 6 people included, one person died during follow up, on the 9th day after admission. The study also provided very low certainty evidence on disease response (ADAMTS13 activity and platelet normalisation) after bortezomib. All participants who survived had resolution of TTP, platelet normalisation and ADAMTS13 activity greater than 10% at discharge and follow up. Two people had neurological resolution, 1/6 people had transient atrial fibrillation with normal echo, 1/6 people had partial blindness and hearing loss, and the person who died had confusion, new acute aphasia, biventricular congestive heart failure, and cardiac arrest.

The study provided very low certainty evidence that there were no adverse events in the 5/6 people who survived.

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

Appendix A PICO document

The review questions for this evidence review are:

1. In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the clinical effectiveness of bortezomib compared with no bortezomib?
2. In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the safety of bortezomib compared with no bortezomib?
3. In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab what is the cost-effectiveness of bortezomib compared with no bortezomib?
4. From the evidence selected, are there any subgroups of patients that may benefit from bortezomib more than the wider population of interest?
5. From the evidence selected, what are the criteria used by the research studies to define haematological remission?
6. From the evidence selected, what dose regimens of bortezomib were used?

P –Population and Indication	People with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab. [These patients may or may not have already received caplacuzimab.] [Intolerance will commonly be described as allergy or hypersensitivity.]
I – Intervention	Bortezomib (proteasome inhibitor). [This is given alongside plasma exchange therapy, corticosteroids, and best supportive care.]
C – Comparators	Any immunosuppressant treatment regimen that doesn't include bortezomib [for example mycophenolate mofetil or ciclosporin A or azathioprine] and plasma exchange therapy, corticosteroids, and best supportive care. Plasma exchange therapy, corticosteroids, and best supportive care alone.
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 Mortality

	This outcome is important to patients because acute immune TTP is a serious, potentially life-threatening condition. [Mortality from the acute episode is usually the gold standard for assessing survival benefit of drug treatments. Mortality at 3 months after an acute immune TTP episode is a critical outcome.] 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, a normalisation of platelet number, normalisation of ADAMTS 13 activity, exacerbation, and time to remission.] 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.] Functional measures *These outcome measures are important to patients as they facilitate enablement, independence and active participation.* [Functional outcomes (which may be reflected by measures of end organ damage (eg neurological, cardiac) but also physical tasks, emotional, and psycho-social (eg PHQ-9).] Hospitalisation

	This outcome is important to patients and their carers because a reduction in number and length of hospitalisations indicates that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. <u>Safety/ adverse events</u> *These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.* <u>Cost effectiveness</u>
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: 11th 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 Bortezomib/ (6656)
11 bortezomib.tw. (9333)
12 velcade.tw. (530)
13 bxcl 101.tw. (0)
14 bxcl101.tw. (0)
15 jnj 26866138.tw. (0)
16 jnj26866138.tw. (0)
17 ldp 341.tw. (5)
18 ldp341.tw. (1)
19 mg 341.tw. (6)
20 mg341.tw. (2)
21 milatib.tw. (0)
22 mln 341.tw. (1)
23 mln341.tw. (3)
24 mylosome.tw. (0)
25 ps 341.tw. (383)
26 ps341.tw. (48)
27 or/10-26 (10516)
28 9 and 27 (70)

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 bortezomib/ (37045)
15 bortezomib.tw. (22019)
16 velcade.tw. (3680)
17 bxcl 101.tw. (0)
18 bxcl101.tw. (0)
19 jnj 26866138.tw. (0)
20 jnj26866138.tw. (0)
21 ldp 341.tw. (37)
22 ldp341.tw. (1)
23 mg 341.tw. (29)
24 mg341.tw. (3)
25 milatib.tw. (0)
26 mln 341.tw. (36)
27 mln341.tw. (4)
28 mylosome.tw. (0)
29 ps 341.tw. (1475)
30 ps341.tw. (73)
31 or/14-30 (38375)
32 13 and 31 (290)

Cochrane Library

#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
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#7 {OR #1-#6}
#8 [mh ^Bortezomib]
#9 bortezomib:ti,ab,kw
#10 velcade:ti,ab,kw
#11 "bxcl 101":ti,ab,kw
#12 bxcl101:ti,ab,kw
#13 "jnj 26866138":ti,ab,kw
#14 jnj26866138:ti,ab,kw
#15 "ldp 341":ti,ab,kw
#16 ldp341:ti,ab,kw
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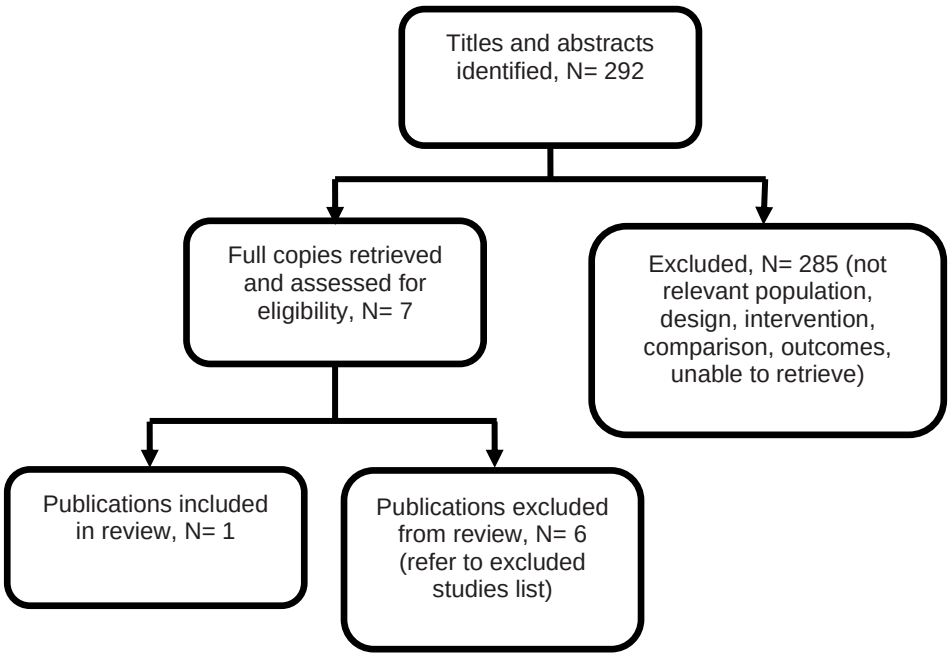
#22 mylosome:ti,ab,kw
#23 "ps 341":ti,ab,kw
#24 ps341:ti,ab,kw
#25 {OR #8-#24}
#26 #7 AND #25
#27 conference:pt

#28 (clinicaltrials or trialsearch):so
#29 #26 NOT (#27 OR #28)

Appendix C Evidence selection

Example text: The literature searches identified 292 references. These were screened using their titles and abstracts and 7 references were obtained in full text and assessed for relevance. Of these, 1 reference is included in the evidence summary. The remaining 6 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
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.	Included
Doyle AJ, Stubbs MJ, Lester W, Thomas W, Westwood JP, Thomas M, Percy C, Prasannan N,Scully M. The use of obinutuzumab and ofatumumab in the treatment of immune thromboticthrombocytopenic purpura. Br J Haematol. 2022 Apr 17. doi: 10.1111/bjh.18192. Epub ahead ofprint. PMID: 35430727	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. doi:https://doi.org/10.1182/bloodadvances.2021005124	Incorrect intervention

Appendix D Excluded studies table

Study reference	Reason for exclusion
Eskazan, Ahmet Emre (2016) Bortezomib therapy in patients with relapsed/refractory acquired thrombotic thrombocytopenic purpura. Annals of hematology 95(11): 1751-6	Incorrect study design
Khandelwal, P., Davies, S.M., Grimley, M.S. et al. (2014) Bortezomib for refractory autoimmunity in pediatrics. Biology of Blood and Marrow Transplantation 20(10): 1641-1665	Incorrect population
Owattanapanich, W., Wongprasert, C., Rotchanapanya, W. et al. (2019) Comparison of the Long-Term Remission of Rituximab and Conventional Treatment for Acquired Thrombotic Thrombocytopenic Purpura: A Systematic Review and Meta-Analysis. Clinical and Applied Thrombosis/Hemostasis 25	Incorrect intervention
Pavenski, K.; Huang, S.-H.S.; Patriquin, C.J. (2021) Predictors of relapse and preventative strategies in immune thrombotic thrombocytopenic purpura. Expert Review of Hematology 14(11): 1027-1040	Incorrect study design
Ratnasingam, Sumita, Walker, Patricia A, Tran, Huy et al. (2016) Bortezomib-based antibody depletion for refractory autoimmune hematological diseases. Blood advances 1(1): 31-35	Incorrect study design
Yap, Yee Yee, Sathar, Jameela, Law, Kian Boon et al. (2018) Clinical characteristics and outcomes of thrombotic microangiopathy in Malaysia. Blood research 53(2): 130-137	Data not reported in an extractable format

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation 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. **Study location** Two UK centres **Study type** Case series **Study aim** To evaluate the effect of bortezomib in a series of primary refractory TTP patients unresponsive to intensive therapy. **Study dates** November 2013 to October 2015	**Inclusion criteria** Severe acquired refractory TTP. TTP was defined as the presence of MAHA, thrombocytopenia and ADAMTS13 activity less than 10%. Refractory disease was defined as persistent thrombocytopenia or lack of sustained platelet count increment, and increasing lactate dehydrogenase (more than 2 times the upper limit of normal) despite intensive treatment with TPE and corticosteroids. **Exclusion Criteria** None **Total sample size** 6 **No. of participants in each treatment group** Bortezomib: 6 No comparator **Baseline characteristics** Age range 27 to 76 years, 3 female, 3 male. ADAMTS13 range at presentation <5% to 10%. Platelets range 5 to 13 x 10^9/litre.	**Interventions** Bortezomib 1 mg/m^2: • Case 1: 1.8 mg IV, 2 treatments (days 15 and 27) • Case 2: 2.0 mg SC, 1 treatment (day 7) • Case 3: 2.13 mg SC, 1, treatment (day 6) • Case 4: 1.55 mg SC, 3 treatments (days 9, 12, 20) • Case 5: 2.0 mg SC, 3 treatments (days 22,26, 29) • Case 6: 2.0 mg SC, 2 treatments (days 6, 12) Other interventions: All cases had TPE and started rituximab prior to bortezomib. Rituximab was given at 375 mg/m^2 IV. Details for each case are given below. • Case 1: TPE, twice daily (37 exchanges); rituximab 670 mg, 6 treatments (days 5, 9, 12, 15, 24, 34) • Case 2: TPE, once daily (12 exchanges); 730 mg, 4 treatments (days 3, 6, 10, 18) • Case 3: TPE, twice daily (14 exchanges); rituximab 800 mg, 2 treatments (days 3 and 7) • Case 4: TPE, twice daily (30 exchanges); rituximab 590 mg, 5 treatments (days 4, 7, 10, 14, 17) • Case 5: TPE, twice daily (82 exchanges); rituximab 750 mg, 4 treatments (days 4, 8, 12, 16)	**Critical outcomes** **Mortality** One person died of cardiac arrest **Disease response** TTP resolved in 5/6 people ADAMTS13 activity at time of discharge for the 5 people who survived: Case 1: 87%; Case 2: 89%; Case 4: 83%; Case 5: 83%; Case 6: 75%. ADAMTS13 activity at follow up for the 5 people who survived: Case 1: 116% (33 months); Case 2: 119% (12 months); Case 4: 106% (19 months); Case 5: 65% (18 months); Case 6: 87% (3 months). Time from first bortezomib dose to platelet normalisation (days): Case 1: 6; Case 2: 3; Case 4: 12; Case 5: 29; Case 6: 21. **Important outcomes** **Functional measures** Neurological resolution reported in 2/6 people. Transient atrial fibrillation with normal echo reported in 1/6 people. Partial blindness and hearing loss in 1/6 people. Confusion, new acute aphasia, biventricular congestive heart failure, and cardiac arrest in the person who died. **Adverse events** No adverse events reported in 5/6 people. One person died and adverse events for bortezomib were not reported.	This study was appraised using the JBI critical appraisal checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. No 10. Not applicable Other comments: The number of cases was small (n=6), outcomes were not pooled and were reported for each case. No statistical analysis was performed. Source of funding: Not reported

		• Case 6: TPE, twice daily (36 exchanges); rituximab 750 mg, 4 treatments (days 4, 8, 12, 21) **Comparators** No comparator		

Abbreviations

IV, intravenous; MAHA, microangiopathic haemolytic anaemia; SC, subcutaneous; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura

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 1: In people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab, what is the clinical effectiveness and safety of bortezomib compared with no bortezomib?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Bortezomib	No comparator	Result (95%CI)		
Mortality (1 case series)									
Mortality, at follow up after hospital discharge (mean 17 months, range 3 to 33 months)									
1 case series Patriquin 2016	No serious	Very serious[1]	Not applicable	Not applicable	1/6	N/A	1/6 cases died of cardiac arrest[2]	CRITICAL	VERY LOW
Disease response (1 case series)									
Resolution of TTP[A]									
1 case series Patriquin 2016	No serious	Very serious[1]	Not applicable	Not applicable	5/6	N/A	5/6 people had resolution of TTP	CRITICAL	VERY LOW
ADAMTS13 activity at discharge[B]									
1 case series Patriquin 2016	No serious	Very serious[1]	Not applicable	Not applicable	N/A	N/A	75 to 89% (Case 1: 87%, Case 2: 89%, Case 3: died, Case 4: 83%, Case 5: 83%, Case 6: 75%)	CRITICAL	VERY LOW
ADAMTS13 activity, at follow up after hospital discharge (mean 17 months, range 3 to 33 months)[B]									
1 case series Patriquin 2016	No serious	Very serious[1]	Not applicable	Not applicable	N/A	N/A	65 to 119% (Case 1: 116%, Case 2: 119%, Case 3: died, Case 4: 106%, Case 5: 65%, Case 6: 87%)	CRITICAL	VERY LOW
Time from first bortezomib dose to platelet normalisation (days)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Bortezomib**	**No comparator**	**Result (95%CI)**		
1 case series Patriquin 2016	No serious	Very serious[1]	Not applicable	Not applicable	N/A	N/A	3 to 29 days (Case 1: 6 days, Case 2: 3 days, Case 3: died, Case 4: 12 days, Case 5: 29 days, Case 6: 21 days)	CRITICAL	VERY LOW
Functional measures									
1 case series Patriquin 2016	No serious	Very serious[1]	Not applicable	Not applicable	N/A	N/A	Neurological resolution reported in 2/6 people. Transient atrial fibrillation with normal echo reported in 1/6 people. Partial blindness and hearing loss in 1/6 people. Confusion, new acute aphasia, biventricular congestive heart failure, and cardiac arrest in the person who died.	IMPORTANT	VERY LOW
Adverse events, mean follow up after hospital discharge 17 months (range 3 to 33 months)									
1 case series Patriquin 2016	No serious	Very serious[1]	Not applicable	Not applicable	5/6	N/A	No adverse events in 5/6 people. One person died and adverse events for bortezomib were not reported.	IMPORTANT	VERY LOW

Abbreviations

TTP, thrombotic thrombocytopenic purpura

A Where TTP was defined as the presence of microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and ADAMTS13 activity <10%.
B Where the definition of TTP includes ADAMTS13 activity less than 10%.
1 Downgraded for indirectness because 5/6 participants continued to receive rituximab after starting bortezomib.
2 Died on the 9th day after admission to hospital for acute TTP.

Glossary

ADAMTS13	A disintegrin and metalloproteinase with thrombospondin type-1 motif, 13.
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

- 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.

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