NHS England Evidence Review:

Bortezomib for prevention of acute immune thrombotic thrombocytopenic purpura

NHS England URN: 2301b

NHS England Evidence Review

Bortezomib 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.

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 to prevent acute relapse in people with immune TTP who are refractory or intolerant 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 in people with de novo or relapsed acute immune TTP who are intolerant or refractory to rituximab or obinutuzumab.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety, and cost effectiveness of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant 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. None of these were suitable for inclusion in the evidence review.

In terms of clinical effectiveness:

- No evidence was identified for the critical outcomes of acute relapse rate, hospitalisation and disease response.
- No evidence was identified for the important outcomes of quality of life, functional measures and mortality.

In terms of safety:

- No evidence was identified for adverse events.

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.

In terms of criteria to define haematological remission:

- No evidence was identified for criteria to define haematological remission.

In terms of dose regimens:

- No evidence was identified for dose regimens of obinutuzumab

Limitations

No evidence was identified assessing the clinical effectiveness, safety or cost-effectiveness of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant to rituximab or obinutuzumab.

Conclusion

Because of the lack of evidence, no conclusions can be drawn about the clinical effectiveness, safety or cost-effectiveness of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant to rituximab or obinutuzumab. Well conducted, published studies are needed to determine the place in therapy of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant to rituximab or obinutuzumab.

3. Methodology

Review questions

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

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

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

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

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

5. From the evidence selected, at what ADAMTS 13 level was preventative treatment started?

6. From the evidence selected, what dose regimens of bortezomib 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.

No relevant studies were identified for inclusion. Therefore, the appendices for evidence tables, quality appraisal checklists and GRADE profiles were not completed (See Appendix E, Appendix F and Appendix G).

4. Summary of included studies

No papers assessing the clinical effectiveness, safety or cost-effectiveness of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant to rituximab or obinutuzumab were identified for this evidence review.

5. Results

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

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Hospitalisation **Certainty of evidence:** Not applicable	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. **No evidence was identified for this outcome**
Relapse rate **Certainty of evidence:** Not applicable	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. **No evidence was identified for this outcome.**
Disease response **Certainty of evidence:** Not applicable	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. **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.**
Functional measures **Certainty of evidence:** Not applicable	This outcome measure is important to patients as they facilitate enablement, independence, and active participation. **No evidence was identified for this outcome.**
Mortality **Certainty of evidence:** Not applicable	This is important because acute immune TTP is a serious, potentially life-threatening condition. **No evidence was identified for this outcome.**
Safety	

Adverse events **Certainty of evidence:** Not applicable	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. **No evidence was identified for this outcome.**

In people diagnosed with immune TTP who are refractory or intolerant to rituximab or obinutuzumab what is the cost effectiveness of bortezomib treatment to prevent acute relapse 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 treatment to prevent acute relapse more than the wider population of interest?

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

From the evidence selected, at what ADAMTS 13 level was preventative treatment started?

Outcome	Evidence statement
Criteria to define haematological relapse	**No evidence was identified for this subgroup of patients.**

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

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

6. Discussion

No evidence was identified assessing the clinical effectiveness, safety or cost-effectiveness of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant to rituximab or obinutuzumab.

Searches were undertaken on 3 databases for studies published between 2012 and October 2022. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, case reports and resource utilisation studies were not eligible for inclusion.

7. Conclusion

No evidence was identified that allowed any conclusions to be drawn about the clinical effectiveness, safety or cost-effectiveness of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant to rituximab or obinutuzumab.

Well conducted, published studies are needed to determine the place in therapy of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant to rituximab or 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 or obinutuzumab, what is the clinical effectiveness of bortezomib treatment to prevent acute relapse compared with no bortezomib?
2. In people diagnosed with immune TTP who are refractory or intolerant to rituximab or obinutuzumab what is the safety of bortezomib treatment to prevent acute relapse compared with no bortezomib?
3. In people diagnosed with immune TTP who are refractory or intolerant to rituximab or obinutuzumab what is the cost effectiveness of bortezomib treatment to prevent acute relapse compared with no bortezomib?
4. From the evidence selected, are there any subgroups of patients that may benefit from bortezomib treatment to prevent acute relapse more than the wider population of interest?
5. From the evidence selected, at what ADAMTS 13 level was preventative treatment started?
6. From the evidence selected, what dose regimens of bortezomib treatment to prevent acute relapse were used?

P –Population and Indication	People with immune TTP who are intolerant or refractory to rituximab or obinutuzumab who either go into haematological remission and have ADAMTS 13 deficiency or achieve full immunological remission and then have immunological relapse. [Immunological relapse is commonly defined as ADAMTS 13 levels <20iu/dl] [Intolerance will commonly be described as allergy or hypersensitivity.]
I – Intervention	Bortezomib (proteasome inhibitor) to prevent acute haematological relapse.
C – Comparators	Any immunosuppressant treatment regimen that doesn't include bortezomib [for example mycophenolate mofetil or ciclosporin A or azathioprine].
O – Outcomes	**Clinical effectiveness** Unless stated for the outcome, the minimum clinically important difference (MCID) is unknown. Outcomes of two years or more are of particular interest, unless otherwise specified. **Critical to decision making** • **Relapse rate** *This outcome is important to patients because it can indicate that their condition may not be adequately controlled by their current treatment, impacting on quality of life and patient treatment decisions.*

	[Relapse rate from an acute 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 ADAMTS 13 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.] • **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).] • **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 key outcome.] **<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.*

	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 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

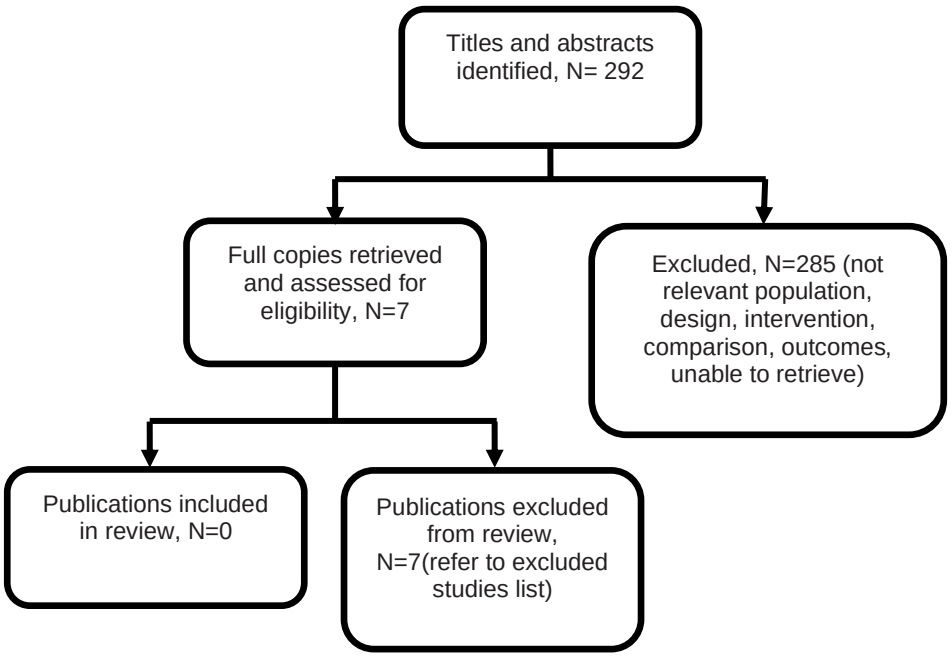
#1 [mh ^"Purpura, Thrombocytopenic"]
#2 [mh ^"purpura, thrombotic thrombocytopenic"]
#3 (thrombo* NEAR/5 (immune or autoimmune or purpura)):ti,ab,kw
#4 ((familial or congenital or genetic or hereditary) NEAR/5 (thrombo* or microangio*)):ti,ab,kw
#5 (itp OR aitp OR ttp OR attp OR ittp OR aittp):ti,ab,kw
#6 (moschkowitz or schulman or upshaw):ti,ab,kw
#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
#17 "mg 341":ti,ab,kw
#18 mg341:ti,ab,kw
#19 milatib:ti,ab,kw
#20 "mln 341":ti,ab,kw
#21 mln341:ti,ab,kw
#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

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, none are included in the evidence summary. The 7 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.	Incorrect population
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
Lemiale, V.; Valade, S.; Mariotte, E. (2021) Unresponsive thrombotic thrombocytopenic purpura (TTP): Challenges and solutions. Therapeutics and Clinical Risk Management 17: 577-587	Incorrect study design
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
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

No papers assessing the clinical effectiveness, safety or cost-effectiveness of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant to rituximab or obinutuzumab were identified in this review.

Appendix F Quality appraisal checklists

No quality appraisal checklists were used for this evidence review.

Appendix G GRADE profiles

No papers assessing the clinical effectiveness, safety or cost-effectiveness of bortezomib to prevent acute relapse in people with immune TTP who are refractory or intolerant to rituximab or obinutuzumab were identified for this evidence review.

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

No studies were included in this evidence review.

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