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Clinical Commissioning Policy Proposition
Bortezomib for the treatment in acute immune Thrombotic Thrombocytopaenic Purpura (TTP) and elective therapy to prevent immune TTP relapse in patients who are refractory or intolerant to rituximab (all ages) [2301]

Summary

A final decision as to whether Bortezomib for the treatment in acute immune Thrombotic Thrombocytopenic Purpura (TTP) and elective therapy to prevent immune TTP relapse will be not for routine commissioning will be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

The proposition is: bortezomib is not recommended to be available as a routine commissioning treatment option for acute immune Thrombotic Thrombocytopenic Purpura (TTP) and elective therapy to prevent immune TTP relapse.

Committee discussion

[Text summarising Clinical Panel's discussion to be added here. Must be added prior to stakeholder testing] Please see Clinical Panel reports for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group are asked to consider the evidence and the policy proposition. The Clinical Priorities Advisory Group committee papers can be accessed here:(Link to be added at publication).

What we have decided

NHS England has carefully reviewed the evidence to treat acute immune Thrombotic Thrombocytopaenic Purpura (TTP) and elective therapy to prevent immune TTP relapse with bortezomib. We have concluded that there is not enough evidence to make the treatment available at this time.

The evidence review which informs this commissioning position can be accessed here: [Link to be added at publication].

Links and updates to other policies

This document updates [insert title of existing published policy or policy statement].

Plain language summary

About thrombotic thrombocytopenic purpura

Immune thrombotic thrombocytopenic purpura (TTP) is a rare, potentially life-threatening condition that involves blood clots in the small blood vessels in the body (acute thrombotic microangiopathy (TMA)). Many require ICU admission and without treatment, the mortality in acute TTP is >90%.

Immune TTP happens when platelets (type of blood cell that forms blood clots) stick together too readily. Platelets use a highly adhesive glue called von Willebrand Factor (vWF) to form a clot. The size of the vWF determines how easily platelets stick together and if the vWF becomes too long, platelets stick together even when they're not supposed to.

The size of the vWF is usually regulated by an enzyme (protein in the body) called ADAMTS 13 which keeps the vWF the right length. Less enzymes (ADAMTS 13) leads to vWF not being broken down causing unwanted clotting in small blood vessels. The shortage of ADAMTS 13 can either be caused by a genetic problem that prevents enough enzyme being produced or an overactive immune system that destroys the enzyme.

An increase in blood clots leads to a reduced number of circulating platelets in the blood vessels (thrombocytopaenia) which causes bleeding and can lead to not enough blood flowing to parts of the body (ischaemia). Patients can also develop low levels of red blood cells (anaemia) due to the resulting breaking of these cells.

Damage from the inadequate blood supply can affect almost any organ but generally affects the brain, digestive tract, heart, and/or kidneys. Immune TTP can present with jaundice (yellowing of the skin), purpura (a rash), shortness of breath and fatigue. Other symptoms include headache, confusion, drowsiness, memory problems and occasionally the loss of oxygen to an area of brain resulting in damage (cerebral infarct).

This policy proposition is for patients who, following an acute episode, have either gone into haematological remission and have persistent ADAMTS13 deficiency or patients who achieve full immunological remission and then have immunological relapse.

Current standard treatment

Treatment of acute immune TTP is with urgent plasma exchange (PEX) to replace ADAMTS 13 and immunosuppression to switch off the autoimmune response. Adjunctive therapy with anti VWF nanobody (caplacizumab) is used as a temporising treatment whilst immunosuppression takes effect. Removal of causative antibodies requires high dose steroids initially and anti-CD20 (rituximab). Rituximab is a chimeric IgG1 monoclonal anti-CD20 antibody.

Early use of rituximab (within 3 days of admission for immune TTP) alongside standard care reduces: number of PEX; days on intensive care unit (ICU), relapse rates and mortality. Rituximab should be started within 72 hours of diagnosis. Rituximab is used at a dose of 375mg/m2 in acute immune TTP. Inpatient stay is a median of 14 days and treatment continues as an outpatient, aiming to normalise ADAMTS 13 activity. The majority of patients normalise their ADAMTS 13 activity levels following 4 rituximab infusions of 375mg/m2.

Ideally, PEX should be withheld for at least four hours after a rituximab infusion, as there is evidence that the drug is removed by plasma exchange. Rituximab is given more frequently,

e.g., every 3-4 days, during the acute period whilst a patient is receiving PEX to overcome this, then administered weekly once plasma exchange has stopped.

If the patient is in early haematological remission (based on normalisation of haematological lab parameters), to prevent relapse, the patient is followed up 1-2 x /week as an outpatient. If necessary, further rituximab is given or, if the patient is refractory or intolerant, additional off-label therapies e.g., mycophenolate mofetil (MMF), ciclosporin A (CSA), or azathioprine, or bortezomib (velcade®) can be used, although none of these are associated with a sustained immunological response. For patients with no immunological response but in clinical remission, watch and wait is an option however they are at risk of relapse until there is recovery of ADAMTS13 levels.

Follow up on achieving complete immunological remission (i.e., normal haematological results and ADAMTS 13 activity level) is 3 monthly for 1 year, then 3-6 monthly if the ADAMTS 13 activity level remains normal. If and when a reduction in ADAMTS 13 level is identified, patients attend more frequently.

Elective therapy for relapse, requiring day care admission is organised when ADAMTS 13 levels are approaching 20 iu/dl or below.

A routine commissioning policy for the use of rituximab in immune TTP for acute and elective treatment has now been published under Specialised Commissioning [insert publication link].

About bortezomib

Bortezomib is a proteasome inhibitor that is currently licenced for the treatment of multiple myeloma and mantle cell lymphoma. (Bortezomib | Drugs | BNF content published by NICE, 2022). Bortezomib acts to eliminate CD20-expressing B-cells and plasma cells (which produce the autoantibodies) via apoptosis, thus resulting in improved circulating levels of ADAMTS 13. (Patriquin et al., 2016) In the acute setting bortezomib is given alongside plasma exchange therapy, corticosteroids, caplacizumab, and best supportive care.

Epidemiology and needs assessment

The incidence of new immune TTP is between 1-3 per million per year. Immune TTP can affect all ages, although it is exceedingly rare in children. The median age at presentation is 30-40 years. It tends to affect women more than men in a 2:1 ratio. (Joly, Coppo and Veyradier, 2017)

The current national protocol is to use anti-CD20 therapy (rituximab) in all those with immune mediated disease. Exclusions to this include patients diagnosed with congenital TTP (incidence <1/million of the population), untreated HIV patients and other rare cases (e.g., pancreatitis associated TTP). Accounting for these exclusions; at least 90% of acute cases will require anti-CD20 therapy.

There is a further cohort of patients requiring anti-CD20 therapy. This includes patients who are in haematological remission following an acute episode but have failed to achieve immunological remission, and a further group who have achieved full immunological remission, are in active follow up and whose ADAMTS 13 activity levels then decrease. In both cases there is a risk of acute haematological relapse. The median time following an acute episode is 2-2.5 years, but there is a second 'peak' 7-9 years after initial therapy. This occurs in approximately 10% of the total immune TTP cohort per year. Of those patients

requiring further anti-CD20 therapy, anecdotal evidence suggests that 10% are refractory or intolerant to rituximab. This would equate to roughly ten patients a year in England.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

Acute immune TTP	Can also be referred to as haematological relapse. This occurs when platelet levels are < 150 × 10^9/l.
ADAMTS13	A disintegrin and metalloproteinase with thrombospondin type-1 motif, 13.
Haematological remission	This is defined as a normalisation of platelet levels, usually >150 × 10^9/l.
Immune TTP	Also known as immune-mediated TTP is TTP caused by an overactive immune system that destroys ADAMTS13 enzymes, rather than a genetic problem that prevents enough enzyme being produced.
Immunological relapse	This occurs when ADAMTS13 levels <20 iu/dl. When this occurs, there is high risk of haematological relapse.
Immunological remission	This is defined as having ADAMTS13 levels ≥ 20 iu/dl.

Monoclonal antibody	This is an antibody that has been designed to recognise and attach to a specific structure called an antigen that is found in the body. Rituximab has been designed to attach to the cell surface marker called CD-20. This is involved in causing inflammation. By preventing CD-20 attaching to its receptors, rituximab reduces inflammation.
Relapsed disease	Describes when a condition has recurred following response to previous treatment, this may occur at any time following completion of treatment.
Rituximab	A monoclonal antibody that targets CD-20, which is a cell surface marker that is widely expressed on B-cells, leading to B cell depletion.
Rituximab-induced serum sickness (RISS)	An adverse effect characterised by fever, rash, and arthralgias.

References

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