Clinical Commissioning Policy:

Obinutuzumab elective therapy to prevent immune Thrombotic Thrombocytopenic Purpura (TTP) relapse in patients who are refractory or intolerant to rituximab (adults) [2255]

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Summary

Obinutuzumab is recommended to be available off-label as a routine commissioning treatment option as elective therapy to prevent immune TTP relapse in patients who are intolerant or refractory to rituximab within the criteria set out in this document.

The policy is restricted to adults as there is insufficient evidence to confirm safety in children and therefore obinutuzumab is not recommended to be used in those age groups not included in the policy. Obinutuzumab may be used in post-pubescent children via NHS England's Policy 170001/P Commissioning Medicines for Children in Specialised Services (commissioning medicines children). Note that obinutuzumab is not licenced in adults for immune TTP and therefore this is an off-label use.

Committee discussion

Clinical Panel considered the evidence base and the decision was made to progress the policy as for routine commissioning. Please see the Clinical Panel report for full details of Clinical Panel's discussion.

The Clinical Priorities Advisory Group committee papers can be accessed on the NHS England website.

What we have decided

NHS England has carefully reviewed the evidence to electively prevent immune TTP relapse in those intolerant or refractory to rituximab with obinutuzumab. We have concluded that there is enough evidence to make the treatment available for this indication at this time.

The evidence review which informs this commissioning position can be accessed on the NHS England website.

Links and updates to other policies

This document relates to the following other policies:

- NHS England » Rituximab treatment for acute TTP: Clinical Commissioning Policy

Plain language summary

About immune 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 immune 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 are not supposed to.

The size of the vWF is usually regulated by an enzyme (protein in the body) called ADAMTS13 which keeps the vWF the right length. Less enzymes (ADAMTS13) leads to vWF not being broken down causing unwanted clotting in small blood vessels. The shortage of ADAMTS13 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 tends to affect 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 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 ADAMTS13 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/m^2 in acute immune TTP. Inpatient stay is a median of 14 days and treatment continues as an outpatient, aiming to normalise ADAMTS13 activity. The majority of patients normalise their ADAMTS13 activity levels following 4 rituximab infusions of 375mg/m^2.

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 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 ADAMTS13 activity level) is 3 monthly for 1 year, then 3-6 monthly if the ADAMTS13 activity level remains normal. If and when a reduction in ADAMTS13 level is identified, patients attend more frequently. Approximately 30% of patients will have immunological relapse over 10 years with some patients having multiple episodes. Immunological relapse is when the ADAMTS13 levels drop, and this precedes clinical relapse. Therefore, prompt treatment of immunological relapse can prevent the risk of death and morbidity associated with clinical relapse.

Elective therapy for relapse, requiring day care admission is organised when ADAMTS13 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: NHS England » Rituximab treatment for acute TTP: Clinical Commissioning Policy.

Intervention

The intervention is obinutuzumab, a humanised type II monoclonal antibody, currently licenced for the treatment of chronic lymphocytic leukaemia and follicular lymphoma in adults. (Obinutuzumab | BNF, 2022). Like rituximab, obinutuzumab targets the CD20 molecule, improving circulating levels of ADAMTS13. However, unlike rituximab obinutuzumab is humanised, giving potential advantages in terms of response, tolerance, and development of reactions (anti-rituximab antibodies).

For those patients who are intolerant or refractory to rituximab, obinutuzumab would be a treatment option in those with immune TTP who have not achieved immunological remission or who achieved immunological remission, but their ADAMTS13 levels start to fall.

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 ADAMTS13 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. Historical data from the TTP registry shows that 30% of rituximab treated patients will relapse over 10 years, with a proportion relapsing on multiple occasions. The NHS England commissioning policy for rituximab for immune TTP estimated that 100 patients per year would require elective treatment with rituximab. It is therefore estimated that between 8-10 patients will require treatment with Obinutuzumab per year, with estimated growth of 2 patients per year. The NHS England commissioning policy for rituximab for immune TTP estimated that 100 patients per year would require elective treatment with rituximab. It is therefore estimated that between 8-10 patients will require treatment with Obinutuzumab per year, with estimated growth of 2 patients per year.

Implementation

NHS England will routinely commission obinutuzumab in accordance with the patient pathway for patients meeting all of the following inclusion criteria, and none of the exclusion criteria.

Inclusion criteria

Adults who:

- have a diagnosis of immune TTP and are in haematological remission defined as platelets >150 × 10^9/l

  AND

- have previously been treated with rituximab and either:
  - developed severe allergy or infusion-related reactions **OR**
  - developed acute rituximab-induced serum sickness (RISS) **OR**
  - had a duration of disease remission with rituximab of under 12 months

  AND

- have either:
  - a persistent ADAMTS13 deficiency defined as ADAMTS13 <20 iu/dl **OR**
  - achieved immunological remission and are immunologically relapsing[1]**.** The threshold for treatment will take clinical symptoms into account.

Exclusion criteria

Individuals with contraindications to obinutuzumab, as outlined in the summary of product characteristics (SmPC) **OR**

Individuals who meet any of the following criteria:

- Malignancy driven thrombotic microangiopathy (TMA)
- Organ or stem cell transplant associated TMA
- Congenital TTP

[1] This is typically defined as ADAMTS13 <20 iu/dl

Starting criteria

Obinutuzumab should be initiated and managed by physicians with experience in the treatment of immune TTP. Confirmation of the diagnosis and initiation of obinutuzumab should be agreed at a specialist TTP multi-disciplinary team (MDT) meeting.

Stopping criteria

Treatment with obinutuzumab will be stopped when ADAMTS13 activity levels are ≥ 50 iu/dl. Patients will usually complete one course (or cycle) of up to three doses of obinutuzumab regardless, as this is sufficient for most patients.

Treatment with obinutuzumab should be stopped in any of the following circumstances:

- Serious adverse events e.g., anaphylaxis, severe allergic reaction, or serum sickness **OR**
- no evidence of immunological remission following one course **OR**
- disease progression despite treatment.

Monitoring

Following initial treatment with obinutuzumab, ADAMTS13 activity levels should be regularly monitored as an outpatient every three to six months to assess the need for further treatment with obinutuzumab.

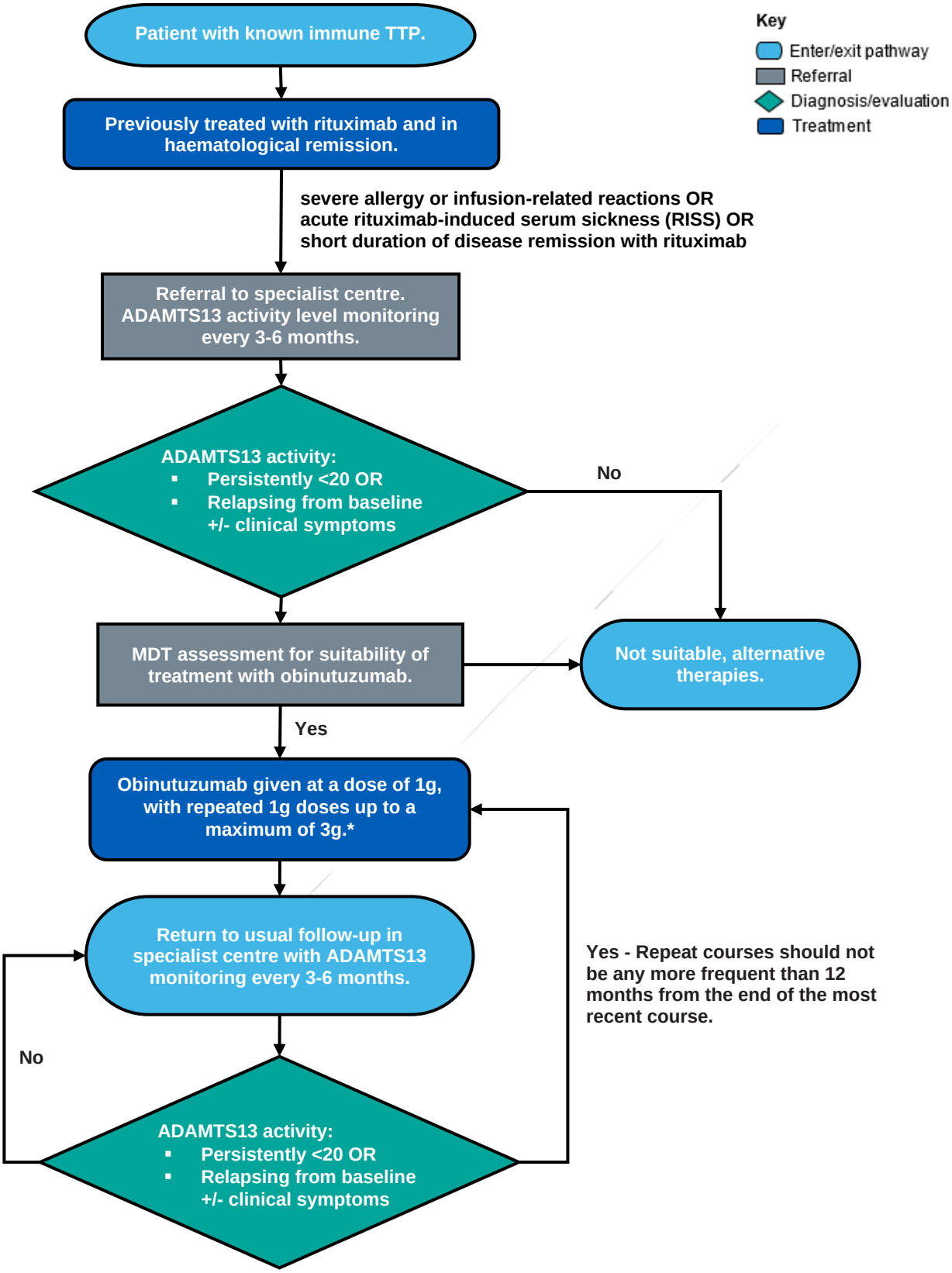
Dose

Obinutuzumab is usually given as an outpatient. The dose is 1g (a smaller test dose of 100mg may be given initially, followed by the rest of the dose). Patients then receive repeat doses of 1g up to a maximum of 3g (one course).

The target is normalisation of ADAMTS13 activity (see stopping criteria).

The interval for repeated courses of obinutuzumab in chronic immune TTP is highly variable between patients and guided primarily by ADAMTS13 levels with the threshold for intervention taking symptoms into account. Repeat courses should not be any more frequent than 12 months from the end of the most recent course. Many patients have prolonged intervals of 12 months or more.

Patient pathway



*See dose section above for alternative dosing.

Governance arrangements

This policy should be used in conjunction with the Thrombotic Thrombocytopenic Purpura (TTP) Service Specification 1668.

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Please note that this is an off-label use of obinutuzumab, therefore Trust policy regarding unlicensed medicines should apply.

Mechanism for funding

Obinutuzumab elective treatment to prevent immune TTP relapse will be commissioned and funded by NHS England Specialised Commissioning under existing arrangement for the provision of Specialised blood disorders.

Audit requirements

An intervention specific audit dataset will be agreed nationally and collected locally. This will contribute to the United Kingdom TTP Registry.

The outcome measures will be collated from the national database and reported back to the National Clinical Reference Group (CRG) annually by the subcommittee. The annual assessment will allow a demonstration of the outcomes of the policy and also allow potential recommendations for policy revision (through the policy revision pathway).

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	This occurs when ADAMTS13 levels are reduced and 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 are reduced (typically <20 iu/dl). When this occurs, there is high risk of haematological relapse.
Immunological remission	This is defined as having ADAMTS13 levels in the normal range, typically defined as ≥ 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.
Refractory disease	This is failure to normalise ADAMTS13 after an episode of acute TTP (typically the ADAMTS13 level remains <10 iu/dl)
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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