Kent and Medway Policy Recommendation and Guidance Committee

PR 2015-13: Rituximab for the treatment of immune (idiopathic) thrombocytopenic purpura (ITP)

Recommendation

The EKPG approved the PRGC recommendation that Rituximab is funded as a second-line option for the treatment of immune (idiopathic) thrombocytopenic purpura (ITP), according to the Kent and Medway ITP treatment pathway.

Approved by: East Kent Prescribing Group *(Representing Ashford CCG, Canterbury and Coastal CCG, South Kent Coast CCG and Thanet CCG)*
Date: Dec 2015
Address: c/o *Canterbury and Coastal CCG, Ground Floor, Council Offices, Military Road, Canterbury, Kent,CT1 1YW*
Contact: T: 01227 791267 | E: accg.eastkentprescribing@nhs.net

Kent and Medway Policy Recommendation and Guidance Committee

Policy Recommendation

Policy:	**PR 2015-13: Rituximab for the treatment of immune (idiopathic) thrombocytopenic purpura (ITP)**
Issue date:	**August 2015**
Review date:	**August 2017**

The Kent and Medway Policy Recommendation and Guidance Committee (PRGC) considered evidence of clinical effectiveness, the baseline position, the views and opinions of local experts and the cost impact. All decisions were made with reference to the Ethical Framework. Taking these into account the PRGC recommends that:

- Rituximab[1] is funded as a second-line option for the treatment of immune (idiopathic) thrombocytopenic purpura (ITP), according to the Kent and Medway ITP treatment pathway
- Clinical audit is undertaken across Kent and Medway[2]
- This policy recommendation is reconsidered in two years, in light of the findings of the clinical audit and any new information

See overleaf for details of supporting evidence and rationale.

This policy recommendation will be reviewed in light of new evidence or guidance from NICE.

Clinical Commissioning Groups in Kent and Medway will always consider appropriate individual funding requests (IFRs) through their IFR process.

[1]Rituximab is listed as a National Tariff Excluded High Cost Drug

[2]Clinical audit will be managed via the Blueteq high cost drug system for requesting treatment, by South East CSU

Supporting documents

Health Care Intervention Appraisal and Guidance (HCiAG) team (2015) *Rituximab for the treatment of immune (idiopathic) thrombocytopenic purpura (ITP) – Scoping report*

Equality Analysis Screening Tool – Rituximab for the treatment of immune (idiopathic) thrombocytopenic purpura (ITP) (2015)

Kent and Medway treatment pathway for adults with immune (idiopathic) thrombocytopenic purpura (ITP)

Key points and rationale

What is immune (idiopathic) thrombocytopenic purpura (ITP)?
ITP is an autoimmune condition characterised by increased platelet destruction and, in many cases, inadequate platelet production. People with the condition may be asymptomatic or have symptoms including spontaneous bruising, mucosal bleeding and, in severe cases, gastrointestinal or intracranial bleeding. ITP is diagnosed by excluding other possible causes of thrombocytopenia.

How is ITP currently managed?
Management of ITP depends on individual circumstances; there is no single treatment pathway regarded as routine practice. The major goal of treatment is to provide a safe platelet count that prevents major bleeding rather than correcting the platelet count to normal levels. For adults who need treatment, first-line options include corticosteroids and intravenous (IV) immunoglobulin. Second-line options include azathioprine, ciclosporin, mycophenolate mofetil, rituximab, and splenectomy. There does not appear to be consensus on whether rituximab should be used before or after splenectomy. Thrombopoietin (TPO) receptor agonists (i.e. eltrombopag and romiplostim) are licensed for adult ITP splenectomised patients refractory to other treatments (e.g. corticosteroids, immunoglobulins) and as second-line treatment for adult non-splenectomised patients where surgery is contraindicated. According to NICE guidance on eltrombopag (TA293), clinical specialists are likely to offer rituximab to patients before TPO receptor agonists.

What is rituximab?
Rituximab is a monoclonal antibody that targets the CD20 surface antigen, which is expressed on normal and malignant B cells. The effect of rituximab in ITP is thought to be related to B-cell depletion leading to inhibition of B-cell activities such as production of platelet autoantibodies.

Rituximab is not licensed for treating ITP; use for this indication is off-label. For the treatment of ITP, rituximab is given in short courses, repeated if necessary.

What national guidance is available?
There is no national guidance on rituximab for ITP; NICE have published an Evidence summary: unlicensed or off-label medicine on this topic (ESUOM35; October 2014), but this does not constitute formal NICE guidance. Eltrombopag (TA293) and romiplostim (TA221) are both recommended by NICE within their marketing authorisations if specific criteria are met.

What is the evidence base for rituximab?
In the only randomised controlled trial (N = 112) to assess the long-term efficacy of rituximab as second-line treatment in ITP (versus placebo), response rates, duration of responses, platelet counts and number of bleeding events were all in favour of rituximab. The benefit of rituximab was most pronounced during the first 30–40 weeks. Long-term response appears modest; rituximab did not significantly reduce the rate of treatment failure within 78 weeks versus placebo. The study authors suggest a ~10% net difference in long-term (>78 weeks) response rate. There was a non-significant increase in infection in the rituximab group. Limitations include the small study size (though comparatively large for this rare disease), which might not have been adequately powered to detect small differences between placebo and rituximab, and the lack of patient-oriented outcomes such as health-related quality of life and fatigue. The lack of prospective studies comparing rituximab with splenectomy makes it difficult to establish their relative positions in the overall care pathway for ITP, while most of the evidence for using alternative second-line agents is from non-randomised or descriptive studies.

What is the cost-impact of prescribing rituximab for ITP?
Rituximab is already used by Kent and Medway acute trusts for patients with ITP; until recently this was funded by NHS England. It has now been confirmed that rituximab for ITP is the commissioning responsibility of CCGs. As a consequence, there will be a new cost pressure to Kent and Medway CCGs, the extent of which will depend on whether CCGs choose to fund rituximab for ITP or not:

- If Kent and Medway CCGs do not fund rituximab for ITP, patients not suitable for splenectomy will move to the more expensive TPO receptor agonists at an estimated cost impact of £216,889 to £253,185 annually
- If Kent and Medway CCGs fund rituximab, the estimated cost impact will be £88,000 annually

- Therefore, by commissioning rituximab for ITP, Kent and Medway CCGs will realise an estimated cost avoidance of £128,876 to £165,172 per year.

Why is rituximab recommended as a second-line treatment option for ITP on the local NHS?
The decision by the Kent and Medway Policy Recommendation and Guidance Committee (PRGC) to recommend rituximab as a second-line option for ITP was informed by the baseline position (rituximab is currently used as a treatment option for ITP by local haematologists) and evidence from a randomised controlled trial suggesting rituximab may be effective (at least in the short-term) and may be associated with a small cost-avoidance (versus TPO receptor agonists). There was no consensus on whether rituximab should be used before or after splenectomy among local experts, but an increasing reluctance amongst physicians and patients regarding splenectomy as a treatment option was noted.

Kent and Medway treatment pathway for adults with ITP

ITP is an autoimmune condition characterised by low platelet count and an increased risk of bleeding. Management depends on individual circumstances. For some patients the morbidity from side effects of therapy may exceed any problems caused by thrombocytopenia. Clinical management must therefore take into account the patient's age, the severity of the condition, and the anticipated natural history. The major goal of treatment is to provide a safe platelet count that prevents major bleeding rather than correcting the platelet count to normal levels (Rodeghiero et al 2009).

- Consider treatment if patient is symptomatic, has a platelet count <30x10^9/L or requires a procedure that may induce blood loss

First-line treatment

- Oral prednisolone 1 to 2mg/kg per day, given as single or divided doses

OR (if critical bleeding, unresponsive to corticosteroids, contraindication to corticosteroid)

- IVIG 1g/kg per day for 2 days

- For patients unresponsive to first-line treatment options or with persistent or chronic ITP consider second-line pharmacological option or splenectomy

Second-line treatment

- Splenectomy. Offer if severe thrombocytopenia (platelet count <10–20x10^9/L), a high risk of bleeding for platelet counts <30x10^9/L, or patients who require continuous glucocorticoid therapy to maintain safe platelet counts. Splenectomy may not be appropriate due to medical co-morbidities. It is not recommended in elderly patients or those who have hepatic or mixed hepatic/splenic sequestration of ^{111}In-labelled platelets. *OR*
- Rituximab 375mg/m^2 weekly for 4 weeks. Rituximab is not licensed for treating ITP and so use for this indication is off-label. The summary of product characteristics (SPC) lists contraindications and adverse events separately for each licensed indication.

- Third-line options can be considered for patients in whom first- AND second-line treatment options have failed and there are ongoing complications from their thrombocytopenia OR for patients in whom second-line treatment options are contraindicated

Third-line treatment

- Eltrombopag – initial dose 50mg daily (25mg daily for patients of East Asian ancestry), titrate to desired response to a maximum of 75mg daily (see local eltrombopag prescribing policy and/or SPC for full details). *OR*
- Romiplostim – initial dose 1mcg/kg SC once weekly, titrate to desired response (see local romiplostim prescribing policy and/or SPC for full details)

The following pharmacological agents offer further alternative treatment options for consideration in unresponsive patients:

- Mycophenolate mofetil (1000mg twice daily)
- Danazol (200mg 2-4 times daily)
- Dapsone (75-100mg daily)
- Vinca alkaloids (vincristine total course dose 6mg, vinblastine total course dose 30mg)
- Ciclosporin A (5mg/kg/day for 6 days then 2.5-3mg/kg/day)
- Azathioprine (1-2mg/kg – max 150mg/day)
- Cyclophosphamide (1-2mg/kg orally daily for a minimum of 16 weeks)

Responses to these agents are variable and for some of them may only be apparent after several weeks or months. The choice of one agent over another is based on the assessment of the side effect profile and the personal experience of the haematologist. International guidelines do not prioritise. Some haematologists advocate trying one or more of these agents prior to splenectomy or using thrombopoietin receptor agonists.

Enrolment in an appropriate clinical trial may also be an option in some cases.

Original written by: Roberto Stasi, Consultant Haematologist, St. George's Hospital

Original adapted for use by: Leonie Woodfinden, Senior Pharmacist, Anticoagulation, St. George's Hospital – March 2014

Original reviewed by: Dr Steve Austin, Consultant Haematologist, Dr James Uprichard, Consultant Haematologist, St. George's Hospital – April 2014

Original approved by St. George's Drug and Therapeutics Committee – 15 April 2014

Original adapted and approved by South West London Medicines Commissioning Group – 17 July 2014

Adapted by South East CSU Health Care Intervention Appraisal and Guidance (HCiAG) team – 29 June 2015

Approved by Kent and Medway Policy Recommendation and Guidance Committee (PRGC) – 1 July 2015