New Medicine Recommendation

Rituximab Intravenous Infusion

For treatment of Idiopathic Thrombocytopenia Purpura (ITP) in adults

Recommendation: Red (as an alternative 2nd line treatment in adults with ITP following failure of corticosteroid treatment or when corticosteroids and thrombopoietin receptor agonists are contraindicated)

Treatment requires initiation and continuation by specialist haematology services.

Summary of supporting evidence:

- An RCT demonstrated that rituximab plus dexamethasone is more effective in achieving partial or complete response than dexamethasone alone.
- Rituximab is usually given as a single course of treatment and is intended to induce long term remission of ITP.
- Rituximab has been available as a licensed medicine in the UK since 1998 and has an extensive pool of safety data.
- Rituximab may be preferred to alternative treatment options such as invasive splenectomy or the use of cytotoxic medicines.
- The use of rituximab as an alternative treatment for ITP is recognised by the guidance of the British Society for Haematology the American Society of Hematology and the international consensus report on the investigation and management of primary immune thrombocytopenia.
- The continued introduction of biosimilar preparations of rituximab may enable more cost-effective treatment regimens.
- Patients would be required to attend hospital weekly for four weeks to be administered an intravenous infusion of rituximab over several hours.

Details of Review

Name of medicine (generic & brand name)**:** Rituximab (MabThera®, Truxima® and Rixathon®) [1]

Strength(s) and form(s): 100mg and 500 mg concentration for solution for infusion

(also available as 1400mg solution for subcutaneous injection which is not routinely used in ITP) [1]

Dose and administration: Unlicensed indication: Most commonly cited dose in the studies included in this evidence review is:

375mg/m^2 body surface area weekly for four weeks.

(A minority of studies used a lower fixed dose of rituximab 100mg weekly for four weeks). [2]

BNF therapeutic class / mode of action: Antineoplastic drugs, monoclonal antibodies.

Rituximab triggers mediation of B-Cell lysis through complement / antibody dependent cytotoxicity and CD20 induced apoptosis. [1]

Licensed indication(s): Rituximab is indicated in adults for the following indications:

Non-Hodgkin's lymphoma (NHL)

The treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.

Maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

The treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic lymphocytic leukaemia (CLL)

In combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory CLL.

Rheumatoid arthritis

In combination with methotrexate for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Granulomatosis with polyangiitis and microscopic polyangiitis

In combination with glucocorticoids for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).

Proposed use (if different from, or in addition to, licensed indication above): The treatment of idiopathic (immune) thrombocytopenic purpura in adults.

Course and cost: 375mg/m^2 body surface area weekly for four weeks.

For an adult with a body surface area of 1.86 m^2 the total 4-week dose:

= 1.86 x 375 x 4

= 2790mg

Assuming wastage this would require 700mg of rituximab weekly (1 x 500mg vial and 2 x 100mg vial) for 4 weeks.

Cost based on MIMS May 2018 prices (Contract prices may vary within hospital trusts)

MabThera® 1x500mg vial = £873.15

MabThera® 2x100mg vial = £349.25

Total cost of MabThera® = (873.15 + 349.25) x 4 weeks = £4,889.60

Truxima® / Rixathon® 1x500mg vial = £785.84

Truxima® / Rixathon® 2x100mg vial = £314.33

Total cost of Truxima® / Rixathon® = (785.84 + 314.33) x 4 weeks = £4,400.68

(Rituximab is usually given as a single course of treatment to induce long-term remission, however further treatment with rituximab may be given to patients who relapse following initial response. The cost of treatment may therefore be higher than stated). [2]

Current standard of care/comparator therapies:

- Corticosteroids (1st line treatment).
- Thrombopoietin receptor agonists (eltrombopag and romiplostim).
- Intravenous immunoglobulin and intravenous anti-D immunoglobulin.
- Elective splenectomy.
- Azathioprine, ciclosporin, cyclophosphamide, danazol, dapsone, mycophenolate and vinca alkaloids. [2]

Relevant NICE guidance:

NICE evidence summary (ESUOM35): Immune (idiopathic) thrombocytopenic purpura: rituximab.

NICE technology appraisal guidance (TA293): Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura.

NICE technology appraisal guidance (TA221): Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura.

Background and context

Idiopathic thrombocytopenic purpura (ITP) also referred to as immune thrombocytopenic purpura and immune thrombocytopenia is an autoimmune disorder characterised by immunologic destruction of otherwise normal platelets and in many cases, inadequate platelet production. ITP may occur in isolation (primary) or in association with other disorders (secondary). Secondary causes include autoimmune diseases (particularly the antiphospholipid antibody syndrome), viral infections (including hepatitis C and human immunodeficiency virus [HIV]), and certain drugs. [3]

The UK incidence of adult immune thrombocytopenic purpura is estimated to be around 120 per year (equivalent to 0.2 patients per 100,000 population) and 3000–3500 people are affected at any one time in England and Wales. In children, it is estimated that around 4 in every 100,000 develop immune thrombocytopenic purpura each year. People with the condition may be asymptomatic or have symptoms including spontaneous bruising, mucosal bleeding and, in severe cases, gastrointestinal or intracranial bleeding. Diagnosis is based on excluding other possible causes of thrombocytopenia. [2]

The British Society for Haematology guidelines for the management of ITP recommend the use of rituximab for patients who have failed to respond to other treatments and in whom there is a definite requirement to elevate the platelet count. [4] The American Society of Hematology recommendations state that rituximab may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, intravenous immunoglobulins or splenectomy.

For adults that require treatment, corticosteroids are the standard first-line option although intravenous immunoglobulins and intravenous anti-D immunoglobulins are alternative first-line treatments.

Rituximab intravenous infusion may be considered as a second-line treatment option in patients whose condition is refractory to corticosteroid treatment and are unable to use thrombopoietin receptor agonists (eltrombopag and romiplostim).

The effect of rituximab in ITP is thought to be related to B-cell depletion leading to inhibition of B-cell dependent production of platelet autoantibodies. Rituximab has also been shown to up-regulate T cells. [4]

Summary of evidence

Summary of efficacy data in proposed use:

Evidence supporting the efficacy of rituximab in the treatment of ITP consists of a meta-analysis covering all studies undertaken between 2000 and 2011 [4]; as well as 3 randomised controlled trials which have been conducted since the publication of the meta-analysis. [5] [6] [7]

Meta-analysis

Auger et al. produced a meta-analysis of overall response rates (defined as platelet count of ≥ $50x10^9$ per litre) and complete response rates (defined as either a platelet count of greater than $100x10^9$ per litre or $150x10^9$ per litre depending on the individual study) for rituximab in adult patients with ITP before splenectomy. Included data was extracted from 19 studies published between 2000 and 2011 of which four studies were randomised clinical trials. Most studies used rituximab at a dosage of 375 mg/m^2 body surface area weekly for 4 weeks.

The pooled overall response rate for rituximab was 57% (CI95% 48; 65) for 368 non-splenectomised patients and 57% (CI95% 35; 76) at 1 year for 157 patients.

The pooled complete response rate was 41.5% (CI95% 33; 50) for 346 non-splenectomised patients and 40% (CI95% 31; 49) at 1 year for 108 patients. [4]

Randomised controlled trials

For the randomised controlled trials described below, rituximab was administered at a dose of 375mg/m^2 body surface area weekly for four weeks.

Arnold et al

Arnold et al. conducted a double-blind, placebo controlled randomised trial of 60 adult patients with newly diagnosed or relapsed idiopathic thrombocytopenic purpura. To be eligible for inclusion in the study, patients were required to have a platelet count of less than $30x10^9$ per litre and have not undergone a splenectomy. All patients received standard treatment that included 1 or more of: corticosteroids, intravenous immune globulin, rhesus immune globulin, romiplostim, or platelet transfusions. Patients were excluded from the study if they had received any other treatments for ITP within 30 days of starting standard treatments (described above); had significant cardiac, pulmonary or hepatic disease; uncontrolled hypertension or venous/arterial thrombosis in the previous 12 months; acute infection (including HIV, hepatitis B); used anticoagulants or antiplatelet medicines; were pregnant or breastfeeding.

For the primary outcome of treatment failure (defined as the composite of any of: platelet count below 50×10^9 per litre; significant bleeding or administration of rescue treatment because of severe thrombocytopenia; bleeding; or a planned invasive procedure) there was no statistically significant difference between the rituximab and placebo groups (treatment failure: 65.6% in the rituximab group compared with 80.8% in the placebo group; relative risk 0.81, [CI95% 0.59; 1.11]). [5]

Gudbrandsdottir et al

This was a randomised open-label study of 137 newly diagnosed adult ITP patients who had not had a splenectomy and whose platelet count was ≤ $25x10^9$ per litre or ≤ $50x10^9$ per litre with concomitant bleeding symptoms. Study participants received a combination of rituximab 375 mg/m^2 once weekly for 4 weeks plus dexamethasone 40 mg daily for 4 days, or the same dosage of dexamethasone alone. Exclusion criteria were low performance status (>2 using the WHO score system), previous therapy with rituximab or therapy with other immunomodulating agents within 1 month of enrolment, serious comorbidities, pregnancy or lactation, contraindications for rituximab or seropositive tests for HIV, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, anticardiolipid antibodies, or antinuclear antibodies.

The primary outcome of sustained partial response (defined as a platelet count of at least 50×10^9 per litre) or complete response (defined as a platelet count of at least 100×10^9 per litre) at 6 months' follow-up was achieved in 57% of people in the rituximab plus dexamethasone group, compared with 35% of people in the dexamethasone monotherapy group (p=0.01). [6]

Other efficacy data:

Miyakawa et al

Miyakawa at al. performed an open-labelled clinical trial of 26 adult Japanese patients with chronic refractory ITP for at least 12 months prior to the enrolment of the study (defined as platelet count of $30x10^9$ per litre where steroids, splenectomy or thrombopoietin receptor agonists treatments inappropriate / intolerant / ineffective).

The percentage of patients who had achieved the primary outcome of reaching a platelet count ≥50×10^9 per litre at week 24 was 30.8 % (8/26 patients). The 95 % confidence interval of the response rate was 14.3–51.8 %, and the lower limit of the confidence interval did not exceed the prespecified threshold of 20 % defined by the study authors. [7]

Summary of safety data:

In the RCT reported by **Arnold et al**., 2 serious adverse events (serum sickness and accidental fall) were reported in the rituximab group, and 1 serious adverse event (adrenal haemorrhage) was reported in the placebo group. Infusion reactions were more common with rituximab than with placebo (20 reactions reported in the rituximab group, compared with 10 in the placebo group). [2]

In the RCT reported by **Gudbrandsdottir et al.**, the most common adverse events reported in either group were fatigue, dizziness, headache, epigastritis and anxiety. Muscle or joint pain, and fever were statistically significantly more common in the rituximab plus dexamethasone group, whereas anxiety was more common in the dexamethasone monotherapy group (all comparisons $p<0.05$). There were statistically significantly more serious adverse events in the rituximab plus dexamethasone group, compared with the dexamethasone monotherapy group (16 events [including 1 death], compared with 9 events [including 3 deaths] respectively, $p=0.04$). One person in the rituximab plus dexamethasone group and 2 people in the dexamethasone monotherapy group withdrew from the study because of adverse events. [2]

In the study performed by **Miyakawa at al.** three serious adverse events in three patients required inpatient hospitalisation: two patients with viral infections and one with hypermenorrhoea. The causal relationship of all the serious adverse events with rituximab was not completely ruled out. The other adverse drug reactions (ADRs) that occurred in two or more patients were upper respiratory tract infection and headache in three patients each, and diarrhoea, abdominal pain, malaise, and cough in two patients each. Infusion related reactions were observed in eight patients and those that occurred in two or more patients were fever, oropharyngeal pain, headache, pruritus, urticaria, and hypersensitivity. None of the patients had adverse events leading to discontinuation of the study drug, and no deaths were reported in this study.

The summary of product characteristics (SPC) for rituximab (MabThera) lists the following adverse events [1]:

System Organ Class	Very Common (>1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to < 1/1000)	Very Rare (<1/10,000)	Not known
Infections and infestations	bacterial infections, viral infections, bronchitis	sepsis, pneumonia, febrile infection, herpes zoster, respiratory tract infection, fungal infections, infections of unknown aetiology, acute bronchitis, sinusitis, hepatitis B		serious viral infection Pneumocystis jirovecii	PML	
Blood and lymphatic system disorders	neutropenia, leucopenia, febrile neutropenia, thrombo-cytopenia	anaemia, pancytopenia, granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels	late neutropenia
Immune system disorders	infusion related reactions, angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome, serum sickness	infusion-related acute reversible thrombocyto-penia
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness,			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	Dysgeusia		peripheral neuropathy, facial nerve palsy	cranial neuropathy, loss of other senses
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss	

Ear and labyrinth disorders		tinnitus, ear pain				hearing loss
Cardiac disorders		myocardial infarction, arrhythmia, atrial fibrillation, tachycardia, cardiac disorder	left ventricular failure, supra-ventricular tachycardia, ventricular tachycardia, angina, myocardial ischaemia, bradycardia	severe cardiac disorders	heart failure	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease	respiratory failure	lung infiltration,
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation	
Skin and subcutaneous tissue disorders	pruritus, rash, alopecia	urticaria, sweating, night sweats, skin disorder			severe bullous skin reactions, Stevens-Johnson syndrome toxic epidermal necrolysis (Lyell's syndrome)	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, fatigue, shivering, multi-organ failure	infusion site pain			
Investigations	decreased IgG levels					

Rituximab is contraindicated for patients with hypersensitivity to the active substance or any product excipients, in active/severe infections and patients who are severely immunocompromised.

The SPC contains special warnings relating to infusion related reactions (listed as a very common adverse event); infections including potentially fatal progressive multifocal leukoencephalopathy, hepatitis B reactivation and the risk of concomitant use of live vaccines; severe and potentially fatal skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson syndrome; cardiac disorders (myocardial infarction, angina pectoris, atrial fibrillation and heart failure); and haematological toxicities (late neutropenia).

According to the SPC there are limited data on possible drug interactions with rituximab. [1]

Strengths and limitations of the evidence:

Strengths

- An RCT conducted by **Gudbrandsdottir et al.** demonstrated that rituximab plus dexamethasone is more effective at achieving partial or complete response than dexamethasone alone in ITP. [6]
- Rituximab has been available as a licensed medicine in the UK since 1998 and has an extensive pool of safety data.
- Adverse events associated with rituximab are generally mild to moderate in severity; with infusion-related reactions and infections the most frequently reported.
- The use of rituximab as an alternative treatment for ITP is recognised by the guidance of the British Society for Haematology the American Society of Hematology and the

international consensus report on the investigation and management of primary immune thrombocytopenia. [3] [8] [9]

- The continued introduction of biosimilar preparations of rituximab may enable more cost-effective treatment regimens.
- Rituximab provides an alternative therapeutic option to splenectomy and cytotoxic drugs in patients unresponsive or contraindicated to steroids and thrombopoietin receptor agonists.
- Rituximab is usually given as a single course of treatment and is intended to induce long term remission of ITP.

Limitations

- There is a lack of high quality double-blinded RCT data relating to the use of rituximab in ITP, most of the evidence for using rituximab in adults with ITP comes from observational studies.
- The RCTs performed to date were conducted in a limited number of patients and have inconsistent efficacy findings.
- The overall quality of reported studies is poor with varied study populations and outcome measures.
- Although data from a meta-analysis demonstrates relatively high overall and complete response rates to rituximab, the data is mainly derived from observational studies and lacks comparison with placebo.
- Rituximab is **NOT licensed for use in ITP** and has limited safety data for this indication.
- Patients would be required to attend hospital weekly for four weeks to be administered an intravenous infusion of rituximab over several hours.

Summary of evidence on cost effectiveness:

There is no cost-effectiveness data for the use of 375mg of rituximab/m^2 body surface area weekly for four weeks. One study demonstrated the cost-effectiveness of using low-dose (100mg/m^2 body surface area) within the Indian health economy [10], although data cannot be translated to the use of higher doses in the UK health economy.

Prescribing and risk management issues:

Rituximab should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available. Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine should be given before each dose of rituximab. Patients should be given information relating to potential increased infection risk including progressive multifocal leukoencephalopathy. [1]

Commissioning considerations:

Comparative unit costs:

The comparative costs in the table, below, represent options for treatment when corticosteroids/ thrombopoietin receptor agonists are contraindicated or in cases of treatment failure.

Drug	Example regimen	Pack cost	Cost per patient per course/ year
Rituximab (MabThera®)	***For average adult body surface area of 1.86 m^2 the total 4-week dose = 2790mg***	***2x10ml (100mg) vial = £349.25 1x50ml (500mg) vial = £873.15***	***£4,889.60 per course***

Drug	Example regimen	Pack cost	Cost per patient per course/ year
Rituximab (Truxima®/ Rixathon®)	***For average adult body surface area of 1.86 m^2 the total 4-week dose = 2790mg***	***2x10ml (100mg) vial = £314.33 1x50ml (500mg) vial = £785.84***	***£4,400.68 per course***
Elective splenectomy	One-off treatment	N/A	**£3,252 to £4,548** [2]
Azathioprine	150mg daily for 18 months [9]	56x50mg tabs = £2.20	**£59.40 per course**
Ciclosporin	Adult dose is 2.5 to 3mg/kg, for 63kg patient = 157.5mg to 189mg daily [9]	30x100mg caps = £68.28 30x50mg caps = £35.97	**Approx. £1,267 to £1,661 per year**
Cyclophosphamide	Average adult (63kg) dose = 63mg to 126mg daily for 16 weeks [9]	100x50mg tabs = £139	**£156 to £389 per course**
Danazol	200mg two to four times daily [9]	56x200mg = £66.20	**£863 to £1,726 per year**
Dapsone	75mg to 100mg daily [9]	28x50mg tabs = £38.04 28x100mg tabs = £95.15	**£744 to £1,240 per year**
Mycophenolate mofetil	250mg up to 1000mg twice a week for three weeks [9]	100x250mg caps = £82.26 50x500mg tabs = £5.66	**Less than £5 per course**
Vincristine	For average adult body surface area of 1.86m^2 the total dose for 3-6 weeks treatment = 7.8mg to 15.6mg [11]	£13.47 per ml (mg) (regardless of size and quantity)	**£105 to £210 per course**
Costs based on June 2018 MIMS list prices, excluding VAT. Provider contract prices may vary. This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

The cost of rescue treatments following relapse and hospital admissions related to the different interventions may lead to additional costs however the level of additional cost for each intervention cannot be accurately estimated.

Provider trusts may be able to obtain rituximab at a discounted contract price (these prices are confidential).

Productivity, service delivery, implementation:

Adult ITP is a rare condition with an incidence of approximately 120 new cases per year and 3000-3500 adults are affected at any one time in England and Wales. Patients would be required to attend specialist haematology services weekly for four weeks to be administered an intravenous infusion of rituximab over several hours.

Anticipated patient numbers and net budget impact:

Given that 3,000-3,500 adults are affected by ITP at any one time in England and Wales, the extrapolated number of patients who may have a diagnosis of ITP in the Lancashire and South Cumbria health economy is 94-109. Not all patients with ITP require treatment and many will be managed with treatments other than rituximab.

If 25% (approximation) of ITP patients were treated with rituximab this would equate to 24 to 27 patients from the Lancashire and South Cumbria STP requiring treatment.

Using the MIMS listed price for biosimilar rituximab (Truxima®/Rixathon®) the total annual cost for one course of treatment for the Lancashire and South Cumbria population would be:

24 to 27 x £4,400.68 = **£105,616** to **£118,818**

For the same group of patients an alternative one-off intervention, an elective splenectomy would cost:

24 to 27 x £3,252 (lowest cost estimate)= **£78,048** to **£87,804**

24 to 27 x £4,548 (complex splenectomy) = **£109,152** to **£122,796**

Excluding differences in relapse rates and associated costs, use of rituximab in place of elective splenectomy would therefore represent a maximum cost pressure of approximately **£30,000** and a maximum saving of approximately **£4,000** depending on the cost and complexity of the alternative option of splenectomy.

Innovation, need, equity:

Rituximab intravenous infusion may be considered as a second-line treatment option in those patients whose condition is refractory to corticosteroid treatment in patients unable to use thrombopoietin receptor agonists (eltrombopag and romiplostim).

Patients may need to travel to a specialist haematology service for four weekly infusions of rituximab. This may present accessibility issues particularly for those unable to travel due to age, disability or socioeconomic reasons.

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics for MabThera," Roche Products Limited, 26 April 2018. [Online]. Available: https://www.medicines.org.uk/emc/product/3801/smpc. [Accessed 31 May 2018].

[2] National Institute for Health and Care Excellence, "Immune (Idiopathic) thrombocytopenic purpura: rituximab," 2014 October 2014. [Online]. Available: https://www.nice.org.uk/advice/esuom35/chapter/Key-points-from-the-evidence. [Accessed 31 May 2018].

[3] Neunert C et al, "The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia," *Blood,* vol. 117, no. 16, pp. 4190-4207, 2011.

[4] S Auger et al, "Rituximab before splenectomy in adults with primary thrombocytopenic purpura: a meta-analysis," *British Journal of Haematology,* vol. 158, pp. 386-398, 2012.

[5] D Arnold et al, "A pilot randomized trial of adjuvant rituximab or placebo for nonsplenectomized patients with immune thrombocytopenia," *Blood,* vol. 119, pp. 1356-1362, 2012.

[6] S Gudbrandsdottir et al, "Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia," *Blood,* vol. 121, pp. 1976-1981, 2013.

[7] Y Miyakawa et al, "Efficacy and Safety of rituximab in Japanese patients with relapsed chronic immune thrombocytopenia refractory to conventional therapy," *International Journal of Hematology,* vol. 102, no. 6, pp. 654-661, 2015.

[8] British Committee for Standards in Haematology General Haematology Task Force, "Guidelines for the Investigation and Management of Idiopathic Thrombocytopenic Purpura in Adults, Children and in Pregnancy," *British Journal of Haematology,* vol. 120, pp. 574-596, 2003.

[9] D Provan et al, "International consensus report on the investigation and management of primary immune thrombocytopenia," *Blood,* vol. 115, pp. 168-186, 2010.

[10] R Kapoor et al, "Low Dose Rituximab in Chronic ITP: Still an Option in Resource Limited Settings," *Indian Journal of Hematology and Blood Transfusion,* vol. 33, no. 4, pp. 568-573, 2017.

[11] Electronic Medicines Compendium, "Summary of product characteristics for vincristine sulphate," Hospira UK Ltd, January 2017. [Online]. Available: https://www.medicines.org.uk/emc/product/1501/smpc. [Accessed 6 June 2018].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR