Primary immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100x10^9/L, and the absence of any obvious initiating and/or underlying cause of the thrombocytopenia.

Clinical management must 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.

- Consider treatment if patient is symptomatic, has a platelet count <30x10^9/L or requires a procedure that may induce blood loss
- For patients unresponsive to first-line treatment options or with persistent (symptoms lasting between 3 and 12 months) or chronic ITP (symptoms lasting > 12 months) consider second-line pharmacological option or splenectomy
- 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

First-line treatment

1. **Oral prednisolone 1 to 2mg/kg per day, given as single or divided doses**
   Aim to use for 10-28 days and taper quickly to avoid steroid related complications.
   
   **AND/OR**
   2. **IVIG 1g/kg per day for 2 days** *(if critical bleeding, unresponsive to corticosteroids, contraindication to corticosteroid)* **RED INDICATION** as per DOH Immunoglobulin guidelines

Second-line treatment

1. **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 111In-labelled platelets. Patients may also refuse to consent to this procedure.

   **OR**

2. **Rituximab 375mg/m² weekly for 4 weeks**. Rituximab is not licensed for treating ITP and so use for this indication is off-label. Prior funding approval is required from the CCG using Blueteq. The best value product should be used.

   **OR The following agents may be considered if unresponsive or contraindications to above treatments**

3. **Other non-steroid immunosuppressive agents**
   - 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.
Third-line treatment

1. Eltrombopag (as per NICE TA293) – initial dose 50mg daily (25mg daily for patients of East Asian ancestry), titrate to desired response to a maximum of 75mg daily (see SPC). Prior funding approval is required from the CCG using Blueteq.

OR

2. Romiplostim (as per NICE TA22) - initial dose 1microgram/kg SC once weekly, titrate to desired response (see SPC). Prior funding approval is required from the CCG using Blueteq.

OR

3. Repeat course of rituximab if response to initial treatment lasted > 1 year. Funding via CCG Blueteq IFR required prior to use.

References:


Rational for use of rituximab earlier in pathway

1. Clinical Effectiveness

The ASH 2011 (Neunart et al) evidence-based practice guideline for immune thrombocytopenia recommended that rituximab may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy. This decision was based on the systematic review by Arnold et al. The pooled estimate of overall platelet count response in 313 patients from 19 eligible reports was 62.5% (95% CI 52.6-72.5%). Rituximab responses can be enduring, although the rate of durable response at 1 year may be as low as 30%. The rate of long-term responses, in excess of 1 year, has been reported to be between 18% and 35%, but not all of those who relapse require treatment. Arnold et al (2007) evaluated safety outcomes in 306 patients, of whom 10 (3.3%) had severe or life-threatening complications after rituximab treatment. Nine patients (2.9%) died.

The international consensus report (Provan et al. 2010) suggested that available treatment for ITP can be broadly categorized into those that are given only once (or for only one course) and are intended to induce long-term remission (splenectomy, rituximab), and those that need continued or chronic administration (corticosteroids, immunosuppressive agents, thrombopoietin receptor agonists). Several publications have reported the use of rituximab in ITP patients and suggest that about 60% of patients respond, with approximately 40% achieving complete response. Responses generally occur after 1 to 2 weeks to 6 to 8 weeks and last from 2 months in partial responders to 5 years or longer in 15% to 20% of initially treated patients. Most patients with a durable (> 1 year) complete response will respond to repeat treatment if they relapse.

NICE have published an evidence summary in October 2014: Immune (idiopathic) thrombocytopenic purpura: rituximab. A systematic review, Auger et al. (2012), of mainly observational studies (n=368) suggests that rituximab can increase platelet levels in adults with immune thrombocytopenic

Agreed at Central and Eastern Cheshire Area Prescribing Group Date 12th March 2019
purpura; although response rates varied significantly between individual studies. No comparisons with other treatments were made. The ORR was 57% (95% confidence interval [CI]: 48–65), for 368 non-splenectomized patients after rituximab; CR was 41% (95% CI: 0.33–0.51) for 346 patients. The two doses used in the studies by Auger et al. (2012) were 375mg/m2 or 100mg weekly for 4 weeks.

2. Patient preference/tolerability

The availability of rituximab represents a relatively low cost option for treatment that has shown to be of benefit in approximately 60% patients. It is has the advantage of being relatively straightforward to deliver in an outpatient setting and for a one-off course of 4 weeks with a lasting response, although relapse may occurs after a few years. Splenectomy has an approximate 50-80% chance of long term success.

3. Overall Cost

NICE state in their evidence summary (2014) that comparing the cost of rituximab with other second-line drug treatments is difficult because rituximab is usually given as only 1 course of treatment and is intended to induce long-term remission. Other second-line drug treatments usually need to be given continuously. Specialist opinion suggests that further treatment with rituximab may be given to people whose immune thrombocytopenic purpura initially responds to treatment with rituximab, but then relapses. Rescue treatment may also be needed in people whose condition relapses after receiving rituximab.

If generic rituximab is used (e.g. Truxima) costs of a course of rituximab would less than the price to the NICE quoted cost of splenectomy of £3252 to £4548, depending on the complexity of the procedure. Splenectomy has an approximate 50-80% chance of long term success. Current calculated cost of 4 weeks of average dose of 700mg (375mg/m2) of Truxima = £2347.

For further information on evidence base surrounding use of rituximab in ITP see NICE evidence summary.

Additional references:
