Treatment pathway for patients with ITP

Immune thrombocytopenia (ITP) is defined by a low platelet count and an increased risk of bleeding. Fatal bleeding is rare and occurs more frequent in elderly patients and in those with severe thrombocytopenia. Although treatment for ITP is strictly individualized, specific therapy for ITP may not be necessary unless the platelet count is <20x10^9/L or there is extensive bleeding. Another important consideration is that for some patients the morbidity from side effects of therapy may exceed any problems caused by the thrombocytopenia. Clinical management of this condition must therefore take into account patient’s age, the severity of the illness, and the anticipated natural history. Current guidelines consider treatment for ITP appropriate for symptomatic patients and for those at significant risk of bleeding.

Initial treatment

If the clinical presentation is not that of a life-threatening bleeding, corticosteroids are considered the standard initial treatment. Intravenous immunoglobulins (IVIG) are generally recommended for patients with critical bleeding and for those unresponsive to corticosteroids or for whom corticosteroids are contraindicated.

1st line treatment

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

(Approx two thirds of patients respond with 10-20% showing long term response. Aim to use for 10-28 days and taper quickly to avoid steroid related complications)

OR

**IVIG** (Privigen®) 1 g/kg per day for two days

(Approx two thirds of patients respond but response is quicker, often within 24 hours, and transient, 3-4 weeks)
Management of severe or life-threatening bleeding

Emergency treatment is indicated for internal or profound mucocutaneous bleeding. Hospitalization is required, and general measures should be instituted to reduce the risk of bleeding, including avoidance of drugs that inhibit platelet function, control of blood pressure, and other factors.

**Emergency treatment**

- Platelet transfusions (two platelet pools every 4-6 hours or platelet pool/h);
  
  with/without
  
  - IVIG (Privigen® 1 g/kg, repeated the following day if the platelet count remains <50x10^9/L. Concurrent use of IVIG increases platelet life span);
  
  with/without
  
  - Intravenous methylprednisolone, 1 g/d for 3 days.

**Alternative options:** IV anti-D or emergency splenectomy

Management of patients with persistent or chronic ITP

The main aim is to achieve an increase in platelet count that is sustained and haemostatic for the individual patient, and not to ‘normalise’ the platelet count. The options are those that potentially induce a long-term remission (splenectomy, rituximab) and those that need chronic administration (immunosuppressants, steroids, TPO receptor agonists).

**Splenectomy**

For decades splenectomy has been considered the second-line treatment in adults with ITP unresponsive to initial corticosteroid therapy. Recently, however, the availability of effective pharmacological agents has challenged the position of splenectomy in the treatment algorithm.

Two thirds of patients achieve normal platelet counts post-splenectomy with no additional therapy (time to response 1-24 days). Many of the remainder have an improvement in counts.

Generally accepted criteria for splenectomy include a severe thrombocytopenia (<10-20 x 10^9/L), a high risk of bleeding for platelet counts less than 30 x 10^9/L, or the
requirement of continuous glucocorticoid therapy to maintain safe platelet counts. Consider carrying out indium labelled autologous platelet scanning in patients who are candidates to splenectomy as it has been found in studies to be a reliable predictive test.

Absolute contraindications to splenectomy include a high risk for surgery (medical comorbidities) and patient’s refusal. Splenectomy is also not advised in frail elderly patients and in those patients who undergo an indium labelled autologous platelet scanning and are found to have hepatic or mixed hepatic/splenic sequestration of $^{111}$In-labelled platelets.

Current guidelines suggest to defer splenectomy to at least 1 year from the time of ITP diagnosis, since there is still a significant proportion of patients who will enter remission during that time.

A platelet count of $>30\times10^9$/L is suggested pre-operatively. Pneumovax II, Harmophilus influenza B and Meningococcal C vaccine should be given 4 weeks prior to operation (preferably) or 2 weeks post (note if patient has received rituximab in the preceding 6 months vaccination may be unsuccessful – consider repeating once B cell function recovered). 5 year pneumovax booster, annual influenza vaccine and lifelong penicillin V 250mg bd (or erythromycin if penicillin allergic) should be given with education about risk of infection.

**Immunosuppressive drugs**

Several agents can be used in patients who have not responded to first line treatments. Responses with these agents are variable and for some of them, such as azathioprine or danazol, they may only be apparent after several weeks or months. The choice of one agent or the other is eventually based on the assessment of the side effect profile and on the personal experience of the haematologist. The International Consensus Report does not prioritise any agent.

**Rituximab**

The NICE technology appraisal guidance 221, April 2011, reports expert opinion that clinicians increasingly prescribe rituximab as the first choice of active treatment (for approximately 50–60% of patients who need active treatment), and this leads to remission in approximately 50% of people treated. However, the clinical specialists noted that these people will, in general, eventually relapse and need further treatment. If remission $>1$ year patients will usually re-respond to repeat treatment.
Current standard dose is not clear from the literature (375mg/m² vs 100mg/m² weekly for 4 weeks) but the general consensus locally is to use 100mg/m² weekly for 4 weeks.

### 2nd line treatment options
- Rituximab
OR ANY OF THE FOLLOWING
- Mycophenolate mofetil
- Danazol
- Dapsone
- Vinca alkaloids
- Cyclosporin A
OR
- Splenectomy (noting Current guidelines suggest to defer splenectomy to at least 1 year from the time of ITP diagnosis)

### 3rd line treatment
- Splenectomy
OR
- Romiplostim (in those with contraindications to splenectomy or where splenectomy is not advised – see above)
OR
- Eltrombopag (in elderly patients and in those with contraindications to splenectomy or where splenectomy is not advised – see above)
Treatment of ITP patients refractory to splenectomy

The results of phase III clinical trials clearly support the use of either romiplostim or eltrombopag (thrombopoietin receptor agonists - TRAs) as the agents of choice for the treatment of patients who have not responded to splenectomy or who have relapsed after splenectomy. TRAs stimulate platelet production to a sufficient degree to cause an increase in platelet count, outweighing the peripheral destruction of platelets. Long-term therapy is required as most patients relapse on cessation of treatment.

**Treatment of refractory ITP**

- Romiplostim
  - OR
  - Eltrombopag

Romiplostim and eltrombopag are drugs that should be prescribed only by Haematologists who are familiar with ITP and its treatment. NICE’s advice on romiplostim and eltrombopag is that they are recommended for the treatment of adults with chronic idiopathic (immune) thrombocytopenia purpura who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated, only if:

- Their condition is refractory to standard active treatments and rescue therapies OR
- They have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies
  **AND**
- The manufacturer provides the drug with the discount agreed in the patient access scheme

**Romiplostim**

The standard initial dose of romiplostim is 1 mcg/Kg once weekly, as a subcutaneous injection. The dose is based on actual body weight. For patients with severe, life-threatening thrombocytopenia, a higher starting dose of 3 mcg/Kg once weekly may be used. The romiplostim dose has to be modulated according to the platelet
response. The aim of treatment is to achieve a haemostatically safe platelet count, which in most cases is between $50 \times 10^9/L$ and $100 \times 10^9/L$. The dose should be increased by 1 mcg/kg/week until the patient achieves a platelet count $\geq 50 \times 10^9/L$. Some patients can actually decrease the romiplostim dose or frequency of administration, as their platelet count consistently exceeds $100 \times 10^9/L$. The summary of product characteristics reports dose reductions only if platelet counts exceed $200 \times 10^9/L$, as that was the way the drug has been systematically investigated in clinical trials. However, we generally don’t need platelet counts that high and we can reduce to a lower maintenance dose to minimise possible thromboembolic risks and development of reticulin fibrosis in the bone marrow.

A scheme of dose adjustments, which has been modified from the Summary of Product Characteristics, is reported below. There are obviously exceptions to these rules, and each case has to be assessed individually with regards to benefits and risks of achieving a certain platelet count.

<table>
<thead>
<tr>
<th>Platelet count (x $10^9/L$)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 50$</td>
<td>Increase once weekly dose by 1 μg/kg</td>
</tr>
<tr>
<td>$50 – 100$</td>
<td>Do not change the weekly dose</td>
</tr>
<tr>
<td>$100 – 200$ for four consecutive weeks</td>
<td>Consider decreasing once weekly dose by 1 μg/kg</td>
</tr>
<tr>
<td>$&gt; 200$ for two consecutive weeks</td>
<td>Decrease once weekly dose by 1 μg/kg</td>
</tr>
<tr>
<td>$&gt; 400$</td>
<td>Do not administer, continue to assess the platelet count weekly After the platelet count has fallen to $&lt; 200 \times 10^9/L$, resume dosing with once weekly dose reduced by 1 μg/kg</td>
</tr>
</tbody>
</table>
**Eltrombopag**

With regard to eltrombopag, the recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily.

Initiation of eltrombopag at a reduced dose of 25 mg once daily may be considered for patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese or Korean) (see section 5.2). Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

**Method of administration**

The tablets should be administered orally. Eltrombopag should be taken at least four hours before or after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) (see sections 4.5 and 5.2).

After starting treatment the dose should be adjusted to achieve and maintain a platelet count between 50 x 10^9/L and 100 x 10^9/L as necessary to reduce the risk for bleeding. Fluctuations of the platelet counts are obviously accepted and in individual patients counts up to 200 x 10^9/L may be acceptable based on risk assessment. Do not exceed a dose of 75 mg daily.

Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in the Table on the next page.

During therapy with eltrombopag full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥50 x 10^9/L or the count that is believed clinically safe for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated. The standard eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily. However, in a few patients a combination of different film-coated tablet strengths on different days may be required.
### Dose adjustments of eltrombopag

<table>
<thead>
<tr>
<th>Platelet count (x $10^9/l$)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 following at least 2 weeks of therapy</td>
<td>Increase daily dose by 25 mg to a maximum of 75 mg/day</td>
</tr>
<tr>
<td>50 – 150</td>
<td>Do not change the daily dose</td>
</tr>
<tr>
<td>150 – 250 for four consecutive weeks</td>
<td>Consider decreasing the dose by 25 mg/day or by 25 mg/every other day. If the patient was already on 25 mg/day reduce to 25 mg/every other day.</td>
</tr>
<tr>
<td>&gt; 250</td>
<td>Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. After the platelet count has fallen to &lt; 100 x $10^9/l$, resume dosing at a daily dose reduced by 25 mg. If the patient was already on 25 mg/day administer 25 mg/every other day.</td>
</tr>
</tbody>
</table>

Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily.

**REFERENCE**