Treatment pathway for adult patients with immune (idiopathic) thrombocytopenic purpura (ITP)

Immune thrombocytopenic purpura (ITP) is defined by a low platelet count and an increased risk of bleeding. Fatal bleeding is rare and occurs more frequently in elderly patients and in those with severe thrombocytopenia. Although treatment for ITP is strictly individualised, specific therapy for ITP may not be necessary unless the platelet count is < 10x10^9/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 the patient’s age, the severity of the illness, and the anticipated natural history. Treatment for ITP is considered appropriate for symptomatic patients and for those at significant risk of bleeding.

**International Working Group (IWG) Standardisation of Terminology, Definitions and Outcome Criteria**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Persistence of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed ITP</td>
<td>Diagnosis to 3 months</td>
</tr>
<tr>
<td>Persistent ITP</td>
<td>3 – 12 months from diagnosis</td>
</tr>
<tr>
<td>Chronic ITP</td>
<td>lasting for more than 12 months</td>
</tr>
</tbody>
</table>

**Definition of response to treatment of ITP**

| Complete response             | Platelet levels > 100 x 10^9/L and absence of bleeding | Measured on 2 occasions over 7 days apart |
| Response                      | Platelet levels ≥ 30 x 10^9/L and greater than 2-fold increase in platelet count from baseline and absence of bleeding | Measured on 2 occasions over 7 days apart |
| No response                   | Platelet levels < 30 x 10^9/L or less than 2-fold increase in platelet count from baseline or presence of bleeding | Measured on 2 occasions over 1 day apart |
| Loss of complete response     | Platelet levels < 100 x 10^9/L or less than 2-fold increase in platelet count from baseline and/or presence of bleeding | Measured on 2 occasions over 1 day apart |
| Loss of response              | Platelet levels < 30 x 10^9/L or less than 2-fold increase in platelet count from baseline or presence of bleeding | Measured on 2 occasions over 1 day apart |

**Expected time to initial response:**

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>Expected time to response</th>
<th>Peak response</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVlg</td>
<td>1–3 days</td>
<td>2 – 7 days</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4 – 14 days</td>
<td>7 – 28 days</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>1 – 56 days</td>
<td>7 – 56 days</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>30 – 90 days</td>
<td>30 – 180 days</td>
</tr>
<tr>
<td>Danazol</td>
<td>14 – 90 days</td>
<td>28 – 180 days</td>
</tr>
<tr>
<td>Vincristine/Vinblastine</td>
<td>7 – 14 days</td>
<td>7 – 42 days</td>
</tr>
<tr>
<td>Rituximab</td>
<td>7 – 56 days</td>
<td>14 – 180 days</td>
</tr>
<tr>
<td>Eltrombopag</td>
<td>7 – 28 days</td>
<td>14 – 90 days</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>5 – 14 days</td>
<td>14 – 60 days</td>
</tr>
</tbody>
</table>

Original written by: Roberto Stasi, Consultant Haematologist, St. George’s Hospital
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Review date: April 2023 (or earlier if indicated)
Acute Emergency Treatment

Management of severe or life-threatening bleeding – Acute Emergency Treatment
Hospitalisation is required. General measures should be instigated to reduce the risk of bleeding, including avoidance of drugs that may exacerbate bleeding (such as anticoagulants, anti-platelets, NSAIDs), control of blood pressure and maintenance of urine output.

Emergency Treatment
- Platelet transfusions (e.g. two platelet units every 4-6 hours)
  with/without
  - Intravenous Immunoglobulin (IVIg)* (1g/kg, repeated the following day if the platelet count remains 50x10^9/L or as RED INDICATION as per DH)
  with/without
  - Intravenous methylprednisolone (1g per day for 3 days)

* IVIg - Refer to local policy for IVIg prescribing
  - RED indication as per DH Clinical Guidelines for Immunoglobulin Use 2nd edition, 2011
  - Registration on National IVIg database required

General Management

1st line treatment - ‘Rescue’ treatment
Consider if patient is symptomatic, has a platelet count < 30x10^9/L or requires a procedure that may induce blood loss.

- Oral prednisolone 1 to 2mg/kg per day, given as single or divided doses
OR
if critical bleeding, unresponsive to corticosteroids, contraindication to corticosteroid, prior to procedure likely to induce bleeding (e.g. pregnancy/pre-delivery), prior to surgery to achieve a safe platelet count; or in children (<16 years) for emergency or more rapid response required;

- IVIG* 1g/kg per day for 2 days – RED INDICATION*

2nd line treatment - ‘Active’ treatment for
• persistent ITP (symptoms lasting between 3 and 12 months) and
• chronic ITP (symptoms lasting > 12 months)

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

- Rituximab 375mg/m^2 weekly for 4 weeks
AND/OR
- 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.

• Rituximab is used off-label for treatment of persistent and chronic ITP. However, as stated in NICE TA 221 (Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura), clinicians increasingly prescribe Rituximab as the first choice of active treatment and it is therefore considered as an option within the treatment pathway.

• Notification forms must be received via the Bluteq system, by the CCG before the first invoice for that treatment is made to the CCG.

• Treatment should not be withheld, whilst waiting for the CCG to respond to the treatment request on the Bluteq system, if the patient meets all the criteria for funding, treatment should commence without delays for the patient.

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.

**3rd line treatment - Active treatment for chronic ITP (symptoms lasting > 12 months)**

Third line options can be considered for patients with symptoms lasting for longer than 12 months 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.

**Thrombopoetin receptor agonists:**

- **Eltrombopag** – initial dose 50mg daily (for patients of East Asian ancestry start at a reduced dose of 25mg daily), titrate to desired response, max 75mg daily (see local Eltrombopag prescribing policy and/or Summary of Product Characteristics (SPC) for full details)

- **Romiplostim** – initial dose 1mcg/kg SC once weekly, titrate to desired response (see local Romiplostim prescribing policy and/or SPC for full details)

(patients will be allowed to switch between these drugs if clinically indicated see below for contraindications and other reasons such as intolerance or treatment failure)
### Patients not suitable for Eltrombopag
- Patients with liver disease (Child Pugh ≥5)
- Patients with dietary restrictions/GIT pathology
- Patients who are unable to adhere to the dosing requirements of eltrombopag
- Patients who are intolerant of eltrombopag
- Patients who are known to be unresponsive to eltrombopag
- Patients at high risk of non-adherence

### Patients not suitable for Romiplostim
- Patients with liver disease (Child Pugh ≥7)
- Patients who are unable to adhere to the dosing or administration (SC injection) requirements of romiplostim
- Patients who are intolerant of romiplostim
- Patients who are known to be unresponsive to romiplostim
- Patients at high risk of non-adherence or non-attendance to weekly clinic appointments
- Patients who have previously developed increased bone marrow reticulin during treatment with romiplostim

- Use of Eltrombopag and Romiplostim is subject to NICE TA 293/221. Notification forms must be received via the Blueteq system, by the CCG before the first invoice for that treatment is made to the CCG.

- Treatment should not be withheld, whilst waiting for the CCG to respond to the treatment request on the Blueteq system, if the patient meets all the criteria for funding, treatment should commence without delays for the patient.

### References
4. NICE technology appraisal guidance 221. Romiplostim for treating chronic immune (idiopathic) thrombocytopenic purpura. May 2014
Appendix 1 ITP treatment algorithm

Surrey & North-West Sussex Facing Area Prescribing Committee

0-3 months
Newly diagnosed ITP

3-12 months
Persistent ITP

> 12 months
Chronic ITP

0-3 months
Newly diagnosed ITP

3-12 months
Persistent ITP

> 12 months
Chronic ITP

Spleenectomy (after 6 months)
- Platelet count < 10-20x10^9/L
- High risk of bleeding with platelet count < 30x10^9/L
- Continuous glucocorticosteroid therapy

Contraindications:
- Frail elderly
- Hepatic or mixed hepatic/splenic sequestration of 111In-labelled platelets on autologous platelet scan

Rituximab
375mg/m^2 weekly for 4 weeks

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

3rd line treatment - Active treatment for chronic ITP with ongoing complications where 1st and 2nd line treatment failed or are contraindicated

Splenectomy (see above)

Consider TPO-RA (Eltrombopag po OR Romiplostim sc) after splenectomy or if splenectomy is contraindicated

Consider using alternative option if first TPO-RA drug tried is not suitable (contraindicated, adverse drug reactions, treatment failure)

Acute Emergency Treatment
For Severe life-threatening bleeding

Hospitalisation including general measures to reduce bleeding risk
- Contributing medication (NSAIDs, anticoagulants, anti-platelets)
- Blood pressure control
- Maintenance of urine output

Platelet transfusions (e.g. two platelet units every 4-6 hours and/or

Intravenous Immunoglobulin (1 g/kg repeated the following day if the platelet count remains 50x10^9/L and/or

Intravenous Methylprednisolone (1 g per day for 3 days)

DRAFT ITP (Adults) Treatment Pathway June-20.Doc
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