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 frequent 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

Terminology	**Persistence of symptoms**
Newly diagnosed ITP	Diagnosis to 3 months
Persistent ITP	3 – 12 months from diagnosis
Chronic ITP	lasting for more than 12 months

Definition of response to treatment by ITP

Complete response	$\geq$ 100 x 10^9/L and absence of bleeding	Measured on 2 occasions over 7 days apart
Response	$\geq$ 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	< 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	< 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	< 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:

Treatment type	**Expected time to response**	**Peak response**
IVIg	1-3 days	2 – 7 days
Prednisone	4 – 14 days	7 – 28 days
Splenectomy	1 – 56 days	7 – 56 days
Azathioprine	30 – 90 days	30 – 180 days
Danazol	14 – 90 days	28 – 180 days
Vincristine/Vinblastine	7 – 14 days	7 – 42 days
Rituximab	7 – 56 days	14 – 180 days
Eltrombopag	7 – 28 days	14 – 90 days
Romiplostim	5 – 14 days	14 – 60 days

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, antiplatelets, 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 - 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)

- 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.
- [Splenectomy may not be appropriate following shared decision making with patient]

- 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.

- Rituximab is excluded from tariff and requires prior approval from the CCG/CSU. Funding applications for 'Rituximab for Persistent or Chronic Immune Thrombocytopenic Purpura' should be submitted online via Blueteq prior to starting treatment.

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, not tolerated or declined.

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)

OR (if patient is not suitable for eltrombopag (see below for contraindications and other reasons such as intolerance or treatment failure)

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

Patients not suitable for eltrombopag	Patients not suitable for romiplostim
• 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 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

- Funding for eltrombopag and romiplostim is subject to NICE TA 221/293 and require prior approval from the CCG/CSU. Funding applications for 'Eltrombopag/Romiplostim for chronic immune thrombocytopenic purpura' should be submitted online via Blueteq prior to starting treatment.

References

1. SPC for Eltrombopag [Revolade]. GlaxoSmithKline UK. Last updated: 18 March 2019. Available online via: https://www.medicines.org.uk/emc/product/7819/smpc
2. SPC for Romiplostim [Nplate with Reconstitution Pack]. Amgen Ltd. Last updated: 09 Aug 2018. Available online via: https://www.medicines.org.uk/emc/product/567/smpc
3. NICE technology appraisal guidance 293. Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (review of technology appraisal 205). July 2013 (update October 2018)
4. NICE technology appraisal guidance 221. Romiplostim for treating chronic immune (idiopathic) thrombocytopenic purpura. May 2011 (update October 2018)
5. Provan D et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* (2010) 115; 2: 168-186
6. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. *British Journal of Haematology* (2003) 120:574-596. Available online via: http://www.bcshguidelines.com/documents/ITP_bjh_2003.pdf [ARCHIVED - not longer updated]
7. Neunert et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* (2011) 117:4190-4207 (update expected 2019)
8. Cheng et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *The Lancet* (2011) 337;9763: 393-402
9. Khellaf et al. A retrospective pilot evaluation of switching thrombopoietic receptor-agonists in immune thrombocytopenia. *Haematologica* (2013);98(6):881-887

Version number	Amendments made	Date of approval
v1	Original written by: Roberto Stasi, Consultant Haematologist, St George's Hospital Adapted for use by: Leonie Woodfinden, Senior Pharmacist Anticoagulation (SGH) Reviewed by: Dr Steve Austin, Dr James Uprichard - Consultant Haematologist (SGH) Approved by: St George's Drug and Therapeutics Committee (SGH) – April 2014	17/07/2014
v2	Development of funding application forms and algorithm	17/03/2016
v3	Removal of requirement for splenectomy for eltrombopag and romiplostim in line with NICE TA 221/293 update (October 2018)	18/07/2019
Date of next review: April 2019 (or earlier if indicated)		

ADDENDUM 1

(Approved by SWL Integrated Medicines Optimisation Committee on 21st December 2022)

NICE published TA835 (Oct 2022) – Fostamatinib for treating refractory chronic immune thrombocytopenia.
This addendum aims to inform clinicians that fostamatinib is available as a treatment option in line with NICE recommendations and local agreements. Fostamatinib is commissioned as follows

4th line treatment option after thrombopoietin receptor agonist or 3rd line when thrombopoietin receptor agonist are unsuitable

ADDENDUM 2

(Approved by SWL Integrated Medicines Optimisation Committee on 15th February 2023)

NICE published TA853 (Jan 2023) – Avatrombopag for treating primary chronic immune thrombocytopenia.

This addendum aims to inform clinicians that avatrombopag is available as a treatment option in line with NICE recommendations and local agreements as follows:

3rd line active treatment for chronic ITP (> 12 months) with ongoing complications where 1st and 2nd line treatment failed, are contraindicated or not tolerated.

Appendix 1 SWL ITP treatment algorithm