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# A United Kingdom Immune Thrombocytopenia (ITP) Forum review of practice: thrombopoietin receptor agonists

[1]Jecko Thachil, [2]Catherine Bagot, [3]Charlotte Bradbury, [4]Nichola Cooper, [5]Will Lester, [6]John D Grainger, [5]Gillian Lowe, [7]Gillian Evans, [8]Kate Talks, [9]Keith Sibson, [10]Mamta Garg, [11,12]Michael F Murphy, [13]Henry G Watson, [14]Paula HB Bolton-Maggs, [15]Shirley Watson, [16]Marie Scully, [17]Drew Provan, [17]Adrian Newland, [18]Quentin A Hill.

**Affiliations**:

[1]Department of Haematology, Manchester Royal Infirmary, Manchester, United Kingdom.
[2]Department of Haematology, Glasgow Royal Infirmary, Glasgow, United Kingdom
[3]Department of Haematology, Bristol Royal Infirmary, Bristol, United Kingdom
[4]Department of Haematology, Hammersmith Hospital, London, United Kingdom
[5]Department of Haematology, Queen Elizabeth Hospital, Birmingham, United Kingdom
[6]Royal Manchester Children's Hospital, Manchester, United Kingdom
[7]Department of Haematology, Kent and Canterbury Hospital, Canterbury, United Kingdom
[8]Department of Haematology, Royal Victoria Infirmary, Newcastle, United Kingdom
[9]Department of Haematology, Great Ormond Street Hospital, London, United Kingdom
[10]Department of Haematology, Leicester Royal Infirmary, Leicester, United Kingdom
[11]National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, Oxford University Hospitals and the University of Oxford, United Kingdom
[12]NHS Blood & Transplant
[13]Department of Haematology, Aberdeen Royal Infirmary, Aberdeen, United Kingdom
[14]Serious Hazards of Transfusion Office, Manchester Blood Centre, Manchester, United Kingdom
[15]ITP Support Association, The Platelet Mission, Bolnhurst, United Kingdom
[16]Department of Haematology, University College London Hospitals, London, United Kingdom
[17]Department of Haematology, The Royal London Hospital, London, United Kingdom
[18]Department of Haematology, St James's University Hospital, Leeds, United Kingdom

**Corresponding author**: Dr Quentin A Hill MB ChB, Level 3, Bexley Wing, St James's University Hospital, Leeds, LS9 7TF, United Kingdom

Tel +44 113 2068465, Fax +44 113 2068177 Email: quentinhill@nhs.net

**Short title:** A UK ITP forum review: thrombopoietin receptor agonists

The United Kingdom (UK) immune thrombocytopenia (ITP) forum is a working group of health professionals with an interest in the care of patients with ITP (http://itpsupport.org.uk/itpforum/about.htm). We were aware of differences in when and how thrombopoietin receptor agonists (TPO-RAs) are used throughout the UK and a 12 question survey was designed to assess several aspects of prescribing practice. In April 2015, it was circulated to all 16 paediatric and all 20 adult UK haematology consultants providing an ITP clinical centre service. All responses were received by November 2015. 14/20 (70%) adult clinical centres responded. Their responses are in table 1 and relevant published evidence is reviewed in supplementary appendix 1. Only 2/16 (12.5%) paediatric haematologists responded, probably reflecting the absence of a paediatric TPO-RA licence at that time. Because of the low overall response rate, and the influence of an active trial protocol, these two are not included.

We found that most respondents positioned TPO-RAs ahead of splenectomy, but usually after at least one alternative second line agent. Many cited that individual patient factors (including preference) or local funding arrangements influenced this decision. Current National Institute for Health and Care Excellence (NICE) recommendations are for TPO-RA use in a) patients with refractory chronic ITP post-splenectomy or b) when splenectomy is contra-indicated, in those refractory to standard and rescue therapies or with severe disease needing frequent rescue therapies. This position reflected the European Medicines Agency (EMA) marketing authorisation for TPO-RA at the time. However TPO-RAs remain the only licensed, best studied and most efficacious second line medical therapy and the EMA authorization was revised in December 2015 to “adult chronic immune (idiopathic) ITP patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)” and for eltrombopag in January 2016 to “patients age 1 year and above who are refractory to other treatments e.g. corticosteroids, immunoglobulins”.

Some clinicians started romiplostim at 2-3 µg/kg rather than the 1 µg/kg recommended in the summary of product characteristics (SPC) (Amgen Ltd, 2016), or increased the dose at greater than the recommended 1 µg/kg per week under some circumstances. The average effective dose in most studies was 4-5 µg/kg and higher starting doses or faster titration, depending on clinical urgency, has been

used in clinical trials (Kuter *et al*, 2008;Kuter *et al*, 2010) and supported by expert opinion (Mitchell & Bussel, 2015).

The efficacy and side effect profiles of romiplostim and eltrombopag are sufficiently similar that most respondents offered patients the choice between a daily tablet with dietary restrictions and a weekly injection. Respondents were divided on whether to routinely carry out a bone marrow biopsy prior to starting TPO-RA but all would do so to exclude myelodysplasia if any diagnostic uncertainty existed. Clinicians did not consider biopsy during treatment unless there were changes on the full blood count (FBC) or film suggesting fibrosis. Marrow fibrosis occurs in a subset of patients on TPO-RA. This resolves on stopping TPO-RA in the majority of cases (Kuter *et al*, 2009). So far, this fibrosis has not appeared to result in adverse clinical outcomes but this remains a potential concern, particularly if collagen fibrosis proves to increase with treatment duration (Ghanima *et al*, 2014) and this will only be established through longer follow up.

All respondents waited no more than 3-6 weeks at maximum dose of TPO-RA before determining a treatment failure. All conducted laboratory monitoring with FBC/film, and liver function tests in patients on eltrombopag. Monitoring was initially weekly but some respondents extended the interval up to 8 weeks in stable patients.

In patients on TPO-RA, the SPCs recommend dose interruption when platelets are >250 x $10^9$/l. However for approximately 10% of patients, dose interruption results in rebound below the pre-treatment baseline within days (Cuker, 2010) and frequent dose changes can lead to wide platelet count fluctuations. Respondents would initially manage wide fluctuations with small and infrequent dose changes. Some would switch from romiplostim to eltrombopag if wide swings persisted.

Respondents would also consider switching either TPO-RA to the other after treatment failure. This strategy proved effective in 44-80% of patients in one study, despite the first TPO-RA having been titrated to maximum dose (Khellaf *et al*, 2013). In patients refractory to TPO-RAs, 12/14 respondents would consider adding an agent such as mycophenolate, low dose steroid or intravenous immunoglobulins. Combining treatments with different mechanisms of action appears to be beneficial

in refractory patients. TPO-RA combined with immunosuppression was effective in 7/10 severe chronic ITP patients who had not responded to rituximab, splenectomy, romiplostim and eltrombopag (Mahevas *et al*, 2016).

An unexpected finding has been that up to a third of patients responding to TPO-RA can be weaned off treatment and still maintain their response (Newland *et al*, 2016). All respondents would taper TPO-RA after a period with stable normal platelet counts.

Based on available evidence, we draw the following conclusions:

- Although decisions must still be individualised, TPO-RAs should be considered in patients who have failed first line therapy.
- For romiplostim, both the starting dose and speed of titration can be higher than is recommended in the SPC and this should be based on the patient's clinical circumstances.
- The choice of TPO-RA can usually be patient led, based on preferred route of administration.
- Bone marrow biopsy should be considered prior to TPO-RAs where diagnostic uncertainty exists. Biopsy is also required during treatment where FBC/film changes suggest fibrosis. Clinicians should also be vigilant for emerging data on fibrosis risk in patients receiving long term TPO-RAs.
- In patients with wide platelet fluctuation on romiplostim, make small and infrequent dose changes. If control remains poor, switching to eltrombopag can be effective.
- In patients failing to respond to the maximum dose of either TPO-RA, switching TPO-RA is a reasonable option but treatment decisions should be individualised.
- In patients refractory to TPO-RAs, adding an immunosuppressant such as mycophenolate to TPO-RA may also be useful.
- In patients with a stable platelet count of 50-150 x $10^9$/l on TPO-RA, a taper should be considered periodically to ensure that remission is not missed.

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JT conceived and designed the study, analysed the data and wrote the paper

CB, ChB, NC, WL, JDG, GL, GE, KT, KS, MG, MFM, HGW, PHBB-M, SW, MS,DP and AN designed the study

QAH designed the study, analysed the data and wrote the paper

All authors critically revised the paper and approved the final version

**Conflict of interest**

JT has received speaker honoraria from Amgen and Novartis

CB has received speaker honoraria from GSK and Novartis, chaired an Amgen advisory board and received a travel grant from Amgen.

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KT has received a travel grant from Novartis

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PBM has received hospitality from Novartis and honoraria from Grifols for chairing and speaking at an educational meeting.

SW has sat on GSK and Novartis advisory boards as patient representative.

MS has received speaker honoraria from Novartis

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**Supporting Information**

Additional supporting information can be found in the online version of this article:

**Supplementary appendix 1.** Evidence to support clinical practice in the use of thrombopoietin receptor agonists

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| Question | Responses |
|---|---|
| 1) When would you start TPO-RAs? | In addition to NICE indications, all 14 respondents would consider TPO-RAs before splenectomy in some situations. The majority (8/14) would use TPO-RAs after failure of one steroid sparing agent (mycophenolate or rituximab). Two after failure of two steroid sparing agents (oral immunosuppression then rituximab). Three presented TPO-RAs as a second line option to patients (vs. mycophenolate, rituximab or splenectomy). One respondent would follow NICE guidance but consider second line use in bleeding patients failing steroids and intravenous immunoglobulins. |
| 2) What starting dose of TPO-RA would you use? | All respondents would use eltrombopag as recommended in the SPC. One exclusively used eltrombopag because of wide platelet count fluctuation with romiplostim. Three started romiplostim at 1 μg/kg, three more started at 1 μg/kg but 3 μg/kg in bleeding patients or if steroid refractory. One started at 2 μg/kg and two more at 2-3 μg/kg, usually rounding to the nearest vial size*. Two started at 250 μg and two at 3 μg/kg. Reasons provided for starting at 1 μg/kg were compliance with SPC guidance and experience that some patients required ≤1 μg/kg maintenance. Those starting at 2-3 μg/kg or 250 μg cited cost effectiveness and achieving therapeutic platelet counts faster. One respondent had changed practice when local audit showed only 1 in 20 patients responded to a starting dose of 1 μg/kg. Two reported increasing at >1 μg/kg per week in symptomatic unresponsive patients. |
| 3) On what do you base the choice of TPO-RA? | Of the 13 clinicians who used both drugs, all would offer the patient a choice. Two commented that they found eltrombopag easiest for short term treatment e.g. for surgery, since fewer dose adjustments are required. |
| 4) How long do you wait for a TPO-RA response? | When determining the effectiveness of treatment, all clinicians would wait for no more than 3-6 weeks at the maximum dose of TPO-RA. Within that range, duration was usually shorter when no reduction in haemorrhagic symptoms was observed. |
| 5 & 6) Do you perform a bone marrow prior to starting TPO-RA and at regular intervals during treatment? | Seven respondents did and seven usually did not carry out a pre-treatment bone marrow biopsy. However all qualified this by stating that biopsy was more likely to be done if there was any diagnostic uncertainty. No clinician carried out regular biopsies during treatment. Instead, the FBC/film was monitored and biopsy taken if there were changes suggestive of fibrosis. |
| 7) How do you manage wide fluctuations in platelet counts? | There was consensus that the first step was to make smaller and less frequent dose changes. This was achieved through less frequent FBC checks in asymptomatic patients or reacting to out of range counts only if persistent on several occasions. Five cited bleeding symptoms as an indication to increase dose and one would interrupt therapy if the platelet count was above the normal range, especially in those with risk factors for cardiovascular disease. One respondent would manage wide fluctuation by reducing TPO-RA dose and introducing a second agent. Three reported that they would switch to eltrombopag if wide swings were persistent and one only used eltrombopag for this reason. |
| 8) Would you add in a second agent to facilitate responses? | Ten would consider adding mycophenolate, eight would consider a low dose of steroid and one IVIg. Two respondents had no experience of adding a second agent to TPO-RAs. |
| 9) How often do you monitor the patient? | All respondents started monitoring weekly. However for stable patients, the maximum interval between reviews varied. Six monitored monthly, three 4-6 weekly and five 8 weekly. |
| 10) What blood tests are done during | All would monitor with blood films and LFTs (two only monitored LFTs with eltrombopag). Seven also monitored renal function. |

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|---|---|
| follow up in addition to the FBC? | |
| 11) Is there any role for switching between the two TPO-RA? | All thirteen respondents using both TPO-RAs, would consider switching agents. Respondents switched for lack of response, wide platelet fluctuation or other adverse events. Two commented that they switched when next TPO-RA dose was due, to avoid treatment overlap. |
| 12) Do you ever discontinue TPO-RA? | All respondents would discontinue TPO-RA for adverse effects or lack of response. Respondents would also taper down TPO-RA in patients with stable platelet counts in order to assess for a possible remission. Of those defining a platelet threshold, three would taper drug for a stable platelet count in the normal range, two for stable platelets >100 x $10^9$/l and one tapered to the minimum dose required to keep platelets >50 x $10^9$/l. Two specified they would consider a taper in stable patients after one year. |

**Table 1. Thrombopoietin receptor antagonist questionnaire**

TPO-RA; thrombopoietin receptor agonist, NICE; national institute for health and care excellence, SPC; summary of product characteristics, FBC; full blood count, LFTs; liver function tests, IVIg; intravenous immunoglobulins.

*smallest vial is 250 µg