Adoption of NHS England's Interim Clinical Commissioning Policy:

Thrombopoietin receptor agonists as first line therapy for new or relapsed immune thrombocytopenia in adults during the COVID-19 pandemic

Paper type: for commissioning policy
For: agreement

Executive summary

In **May 2020**, during the first wave of the COVID-19 pandemic, haematologists in Kent had expressed using the thrombopoietin receptor agonists (TPO-RAs), romiplostim and eltrombopag in patients with immune thrombocytopenia (ITP) earlier than presently commissioned. That is, in patients with symptoms lasting <12 months in order to avoid the use of immunosuppressants (including steroids and rituximab) and IV immunoglobulin (as patients would need to attend the hospital).

This was supported by the consensus 'Practical guidance for the management of adults with Immune Thrombocytopenia during the COVID-19 pandemic' written by clinicians with an interest in ITP or coagulation disorders, reviewed by members of the UK ITP forum and issued by the British Society of Haematologists (BSH).

At the time, NHS England (NHSE) decided not to support / fund the early use of these agents as 'the use of eltrombopag before treatment with rituximab is not based upon published evidence that the panel were able to locate'.

NHSE

On the **22nd February 2021**, NHSE published a rapid policy statement entitled 'Interim Clinical Commissioning Policy: Thrombopoietin receptor agonists as first line therapy for new or relapsed immune thrombocytopenia in adults and children over the age of 1 year during the COVID-19 pandemic' (appendix 1). Three papers were presented for review by NHSE:

Paper 1

A non-inferiority randomised trial of eltrombopag compared to intravenous immunoglobulin (IVIg) in 74 perioperative immune thrombocytopenia (ITP) patients from eight academic hospitals in Canada.

Paper 2

A pooled analysis of subgroup data by ITP duration (ITP ≤1 year and ITP >1 year) taken from nine studies primarily from Europe and North America assessing romiplostim efficacy in patients with newly diagnosed or persistent ITP for up to one year and patients with chronic ITP for more than one year.

Paper 3

A phase 2 uncontrolled trial of 75 romiplostim patients with primary ITP diagnosed in the past six months from 32 sites in Europe, North America and Australia.

After a review of the available evidence, NHSE **now supports** the early use of TPO-RAs through this rapid policy statement.

Please note that the safety reporting section states that:

- 'No evidence is available for the use of TPO RAs in patients with COVID-19, caution is advised. The SmPC should be checked for further information'.

Further clarification from NHSE has provided the following information:

- The interim policy runs for 3 months from the review date of 31st March 2021 until the **30th June 2021** (it is currently under review).
- The policy is not a mandate, but a tool to use if local services wish to avoid the use of high dose steroids during COVID-19.
- NHSE is responsible for paediatric patients (between 1-17 years old).
- **The commissioning responsibility for adults (18 years of age and above) remains with the CCG.**
- **Use of TPO-RAs in both adults and paediatrics is currently part of the NHS standard block contract.**
- Blueteq® forms have been developed for use in both adult and paediatric populations - the forms for paediatric use are currently active and forms for adults may be uploaded with approval from CCGs, if commissioned.
- Patients started on TPO-RAs during this period would not be required to go back to treatments usually used before treatment with TPO-RA, such as rituximab but would continue on TPO-RAs as long as they were gaining benefit.

BSH consensus update:

The BSH has updated the consensus 'Practical guidance for the management of adults with Immune Thrombocytopenia during the COVID-19 pandemic' in January 2021 (appendix 2).

The recommendations for the management of new/relapsed ITP are:

ITP per se does not pose increased risk of COVID-19 infection or worsening disease and indications for treatment of ITP are no different during the pandemic. The need for treatment should be case-based and depend on the severity of thrombocytopenia (platelet count <20 $x10^9$/l), bleeding manifestations, bleeding risk, comorbidities and other medications such as anticoagulants.

Choice of treatment may differ depending whether the patient is COVID-19 negative or positive.

NEGATIVE COVID-19 patients - 1st line drug therapy

Usual first line therapy for the management of new or relapsed acute ITP is prednisolone, given at a dose of 1mg/kg (max 80mg) for 2 weeks and thereafter tapered off, slowly if there is a good response, or rapidly if treatment is ineffective (Provan D et al., 2019). However, during the COVID-19 pandemic, current guidance from the WHO is to avoid steroids if there are alternative treatment options (WHO 2020); there is concern that the immunosuppression will increase risk of COVID-19 infection and lead to more severe disease. Evidence with coronaviruses has shown steroids to delay clearance of the virus from the lower respiratory

tract (Arabi et al., 2018), and the recent RECOVERY trial showed that, whilst patients on ventilation derived significant benefit from dexamethasone, patients with less severe COVID-19 disease who received dexamethasone had a tendency to worse outcomes (Horby et al., 2020).

Therefore, ***during the pandemic, thrombopoietin receptor agonists (TPO-RAs) are preferred as first line therapy for ITP in patients who are negative for COVID-19 infection as they are not immunosuppressive.*** Although this use is off-label there is growing evidence of the benefit of early use of TPO RAs in ITP (Arnold, et al., 2020, Kuter, et al., 2019, Lozano, et al., 2020, Newland, et al., 2016) and increasing experience amongst experts in the field. ***The practice has been endorsed by NHS England (NHSE 2020)***. One should be mindful that TPO-RAs can take 7-14 days before an effect is seen and if the urgent platelet elevation is needed, intravenous immunoglobulin may be required.

POSITIVE COVID-19 patients - 1st line therapy

For patients who are COVID-19 positive, a concern with the use of TPO-RAs for initial treatment is the increased thrombotic potential, which might exacerbate thromboembolic risk in a patient with COVID-19. A recent in vitro study of samples from 26 patients showed that those with ITP (not in the context of COVID-19) had increased microvesicle-associated thrombin generation two weeks after initiation of TPO-RA treatment compared with controls and pre-treatment levels (Garabet et al., 2020).
A systematic review of trials looking at clinical thromboembolic events has found higher rates in patients on TPO-RAs compared with controls (Catala-Lopez et al., 2012) and a long-term clinical study of eltrombopag showed 6% of patients developed arterial or venous thrombosis (Wong et al., 2017). There are similar findings with romiplostim but direct comparison with placebo, showed no increase in thrombotic risk (Cines et al., 2017, Kuter et al., 2019), however, as expected, the risk of thrombosis increases with age (Kuter et al., 2019).

Additionally, hepatobiliary events have been found to occur in 15% of patients on eltrombopag (Wong et al., 2017) and the drug carries a black box warning for risk for hepatotoxicity. Although the clinically significant liver injury has reported to be uncommon in COVID-19 (Bangash et al., 2020), liver enzymes are usually elevated and the required monitoring of liver function tests throughout treatment with eltrombopag (Promacta®, 2018, Revolade, 2018), would be complicated.

Although there are no data on the use of TPO-RAs in COVID-19 positive patients, the risk of hepatotoxicity and potential for increased thrombosis would prompt caution with their use in this setting and, ***whilst further evidence is awaited, intravenous immunoglobulin may be the better first-line option for patients presenting with new or relapsed ITP during hospitalisation with COVID-19.*** The exception is those requiring supplementary oxygen or ventilatory support for COVID-19 infection, where dexamethasone 6mg daily for 10 days has been shown to reduce mortality (Horby, et al., 2020).

Summary:

NHSE supports the use of TPO-RAs as first line therapy for new or relapsed ITP in adults and children over the age of 1 year during the COVID-19 pandemic. A rapid review has resulted in NHSE commissioning this service nationally for the paediatric population.

Based on local demand from our haematologists and national endorsement of the evidence (and implementation of this service for children) by NHSE, the JPC is asked whether the CCG needs to commission a similar service for our adult population.

Commissioning considerations:

- The acute demand for this service may have reduced as COVID-19 infection rates fall.
- This interim service would be for adult patients (aged 18 years of age and above) until June 30th 2021 (in line with the 3 months from the NHSE rapid review). Eligibility criteria being adults with newly diagnosed ITP or acute relapse of ITP, who require treatment for bleeding, profound thrombocytopenia or to cover the surgery.
- Patients initiated during this time period can continue with TPO-RA treatment after June 30th 2021 if they show treatment benefit.
- Although the drug costs are currently within the national block arrangements, at some future point the costs will be the responsibility of the CCG.
- Switching between the TPO-RAs has not been considered.

NHSE Update – 30th June 2021

This policy will be reviewed alongside the other interim Covid-19 policies in June. NHSE are still waiting to hear if the policy recommendation will be extended. NHSE are having a meeting with the national team on Tuesday, 6th July and will provide an update following the meeting.

Appendices:

Appendix 1 – NHSE commissioning policy

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Appendix 2 – BSH guidance on management of ITP during the COVID-19 pandemic (update)

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