

Practical Guidance for the Management of Adults with Immune Thrombocytopenia During the COVID-19 Pandemic (*)

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In this article the authors aim to provide a practical guidance for the assessment and management of patients with thrombocytopenia, with a particular emphasis on immune thrombocytopenia (ITP) during the COVID -19 pandemic. It is a consensus paper written by clinicians with an interest in ITP or coagulation disorders and reviewed by members of the UK ITP forum.

Introduction :

Thrombocytopenia was described in 36% of patients hospitalised with COVID -19 in one of the early studies (Guan et al. , 2020) , although subsequent researchers have confirmed this is usually mild. The hyper -inflammatory state and cytokine storm induced by the viral infection results in a prothrombotic state and likely endothelial and platelet activation occurs (Violi, 2020) . The authors mention that pathogenesis of thrombocytopenia is more complex than the conventional model of platelet consumption associated with thrombin - mediated platelet activation, and the use of antibiotics, antivirals, heparin and other commonly used agents, as well as haemodialysis and extracorporeal membrane oxygenation (ECMO) may contribute in some cases.

In end stage COVID -19 infection multi -organ failure may exacerbate thrombocytopenia and pooled results of nine studies involving 1779 COVID -19 positive patients revealed that the platelet count was lower in those with very severe disease. Immune causes such as thrombotic thrombocytopenia purpura and atypical haemolytic uraemia syndrome should be considered if there is associated microangiopathic haemolytic anaemia (MAHA) and, in the former, an ADAMTS13 level 50% over 24 -48 hours may indicate an immune aetiology.

The authors also mention that other causes of immune thrombocytopenia, such as HIT, MAHA and drugs, to be considered before a diagnosis of ITP is made. It must be remembered in the management of new/relapsed ITP that COVID -19, like all viral infections, may trigger a new presentation of ITP, as illustrated in a recently published case report (Zulfiqar , 2020), or it may cause relapse in an existing patient. The need to actively treat ITP is unchanged from current consensus guidelines (Provan et al. , 2019).

Treatment decisions may differ depending on whether the patient is COVID -19 negative or positive.

First line therapy for COVID -19 negative patients :

Standard 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). There are few data to inform whether or not steroids pose a higher risk of the development of COVID - 19 infection or worsening symptoms once infected. However, current guidance from the WHO is to avoid steroids if there are alternative treatment options (WHO 2020). In patients who are negative for COVID -19 infection, using thrombopoietin receptor agonists (TPO -RAs) as first line therapy may be the preferred option. This use is off -label and local funding may need to be sought through the COVID -19 Interim Measures scheme. One should be mindful that TPO -RAs can take 7 -14 days before an effect is seen and if urgent platelet elevation is needed, intravenous immunoglobulin may be required.

First line therapy for COVID -19 positive patients :

The treatment dilemma is even more pronounced. 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).

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, 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 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 standard treatment with steroids may be the preferred option for initial treatment. There is concern about potential higher risks of mortality and secondary infection , which were seen in a systematic review of observational studies of corticosteroids in patients with influenza; however, most of the included studies reported on patients receiving high steroid doses (>40mg methylprednisolone per day) and the evidence was judged as very low to low quality, owing to confounding by indication (Lansbury et al., 2019).

Thus, whilst further evidence is awaited, steroids may be the better option for COVID -19 positive patients presenting with new or relapsed ITP; however the dose and duration of treatment should be kept to the minimum necessary. Starting doses of 20mg daily (regardless of patient's weight) may be considered in non-bleeding patients, and increasing after 3 - 5 days if no response. Long courses of steroids should be avoided, and the usual recommendation of tapering after 2 weeks should be adhered to.

Intravenous Immunoglobulin

The authors state that intravenous immunoglobulin (IvIg) may be necessary if immediate elevation of the platelet count is required to control bleeding, although this cannot be relied upon as indicated in a recent case report of ITP occurring in the context of COVID -19 infection (Zulfiqar, 2020). IvIg may also be used as second line treatment if there is failure to respond to steroids. However, administration requires hospital attendance, supply is short and whilst clinical complications are rare, they can be significant (Stiehm, 2013). The role IvIg may play in the management of patients with severe COVID -19 infection is unknown. In the absence of adequate titres of neutralizing antibodies, standard IvIg is unlikely to have a biologic effect on COVID -19.

The authors stated that in a bleeding patient with COVID -19 disease, judgement should be made regarding the balance of risks associated with bleeding and thrombosis. If tranexamic acid is used, the duration of treatment should be kept to the minimum necessary. For oral bleeding, tranexamic acid mouthwashes can be given to rinse and spit out. Interestingly, a recent report in *Physiological Reviews* proposed that the endogenous protease plasmin acts on COVID -19 virus by cleaving a newly inserted furin site in the S protein portion of the virus resulting in increased infectivity and virulence (Ji et al., 2020).

Immunosuppressant drugs :

There is concern that patients on immunosuppressant drugs may be at high risk of developing COVID -19 and/or the disease becoming more severe. However, unlike common viral agents such as adenovirus, rhinovirus, norovirus, influenza, and respiratory syncytial virus, coronaviruses have not been shown to cause a more severe disease in immunosuppressed patients (D'Antiga, 2020) . Preliminary experience with patients on disease modifying agents for chronic arthritis and other immune-mediated inflammatory disease, is that they do not seem to be at increased risk of respiratory or life -threatening complications from COVID -19 than the general population (Monti, 2020, Haberman, 2020). Perhaps this is not unsurprising as the severe complications caused by this family of viruses are driven by the aberrant inflammatory and cytokine response perpetuated by the host immune system. Rituximab is responsible for long -lasting B -cell depletion and potentially severe infectious events and the impact of the drug on infection risk of COVID -19 is not clear. Furthermore it can decrease formation of de novo antibodies. Until further information becomes available, the authors advise to avoid immunosuppressant agents and rituximab in new or relapsed patients during the COVID -19 pandemic, if possible.

Platelet transfusions :

Platelet transfusions are not usually necessary and should not be routinely used in thrombocytopenic COVID-19 patients with no bleeding. They may exacerbate a prothrombotic state in COVID-19 positive patients with coagulopathy and in patients with immune thrombocytopenia and they are likely to be consumed too quickly. Platelet transfusions should only be given if it is considered that haemorrhage is life -threatening or in a critical site such as the eyes.

Recommendation :

There is little evidence to inform the optimal management of a patient presenting with new or relapsed acute ITP. In patients who are negative for COVID -19, TPO -RAs may be preferred

as first line treatment, to avoid corticosteroids which may increase risk of COVID -19 infection during the pandemic. In patients who are positive for COVID -19, TPO -RAs may potentially increase the thrombotic complications and identifying eltrombopag hepatotoxicity may be difficult. If steroids are used as first line therapy, the dose and duration should be kept to the minimum necessary. A starting dose of 20mg daily may be considered in non -bleeding patients, with increase to 1mg/kg after 3 -5 days if there has been no response. Steroid doses should be tapered after 2 weeks – slowly if there has been good response, rapidly if there is no response . Intravenous immunoglobulin (1g/kg) may be necessary if immediate elevation of the platelet count is required to control bleeding. It may also be used as second line treatment if there is failure to respond to steroids. Tranexamic acid in COVID -19 infected patients should be used as required for the management of bleeding in ITP patients, but avoided in those with frank DIC. Platelet transfusions should only be given if bleeding is thought to be life threatening, or at a critical site. Management of patients with chronic stable ITP should not alter because of the pandemic; patients should remain on their current medication, even if this includes steroids and immunosuppressants. However attention to isolation procedures is crucial.

Patients with splenectomy are probably not at increased risk of COVID -19 infection but are susceptible to bacterial infections and must be vigilant with their prophylactic antibiotics during this time and up to date with their pneumococcal, haemophilus influenza and meningitis vaccinations. ITP patients not requiring treatment in the last 12 months, or on non -immunosuppressive agents such as TPO -RAs, are not considered to be at increased risk of COVID -19 infection and should comply with self-isolation measures as for all individuals in the UK. Recommendation Patients with chronic ITP should remain on their usual treatment.

They should be vigilant with self-isolation and shielding measures as appropriate. Splenectomised patients should be stringent with their antibiotic prophylaxis and up to date with vaccinations. Regular patient contact should be maintained and appointments conducted by telephone or online platforms. There is a mild elevation in the thrombotic risk associated with ITP, with a cumulative incidence of 3.2% for arterial (95% CI, 2.0 –5.0) and 1.4% (95% CI, 0.8 –2.5) for venous thrombosis at 5 years (Ruggeri et al., 2014). Risk may be slightly heightened by treatment-related factors such as splenectomy and TPO RAs and is higher where there are associated antiphospholipid antibodies. It is unknown how this combines with the hypercoagulable state associated with COVID -19 and whether the increment in thrombotic risk is negligible or synergistic. Venous and arterial thromboembolic complications have been identified in 31% of 182 patients with COVID -19 pneumonia in ITU (Klok et al., 2020).

Predominantly these were pulmonary emboli (81%), with at least two thirds involving more than just subsegmental arteries. Deep vein thrombosis was less frequent in this study, although has been shown to increase with duration of hospitalisation and be significantly higher in ITU patients compared with those not on ITU (Middledorp et al, 2020). Low molecular weight heparin (LMWH) has been shown to reduce mortality in patients with COVID-19 associated coagulopathy (Tang et al, 2020), however in both of the above studies, the patients had been taking prophylactic LMWH, raising the question whether doses should be increased in patients with more severe disease.

LMWH also has anti -inflammatory and anti -platelet properties which may be of benefit in these patients but use and dose of LMWH needs to be balanced against the bleeding risk which is seen in some patients with severe COVID -19 infection, even without

thrombocytopenia (Wang et al., 2020). LMWH may need to be avoided if platelets are $\leq 30 \times 10^9/l$ and there are no haemorrhagic features.

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