**Guidance from the UK ITP Forum Working Party on ITP/ITP relapse following Covid-19 vaccination.**

Guidance version 1.0 13/08/2021

This is a live document and will be updated as further information comes to light.

**Background**

In February 2021, 20 cases (1 fatal) of new onset ITP occurring within 1-2 weeks of Covid-19 vaccine (Pfizer, Moderna) were reported in the United States (US) as possible post-vaccine secondary ITP (Lee et al, AJH 2021). Establishing causality can be difficult, especially without case-control data. The authors observed that in the 2 month reporting period, the number of cases were not obviously higher than the anticipated background rate. A Scottish case-control study of 2.53 million people receiving first dose Covid-19 vaccination found a small increased risk of ITP with an estimated incidence of 1.13 cases per 100,000 first doses of AstraZeneca, but no increase after the Pfizer vaccine (Simpson et al, Nat Med 2021). This appeared similar to the risk associated with other vaccines such as Hepatitis B, MMR and influenza.

An important clinical question for patients with existing ITP is whether there is a risk of ITP exacerbation/relapse following vaccination. In one small series of 52 patients, following the COVID-19 vaccine (predominantly Pfizer/Moderna) platelets fell significantly in 6/52 patients (12%) by to a level of 1-17 x 109/L, by day 2-5; 5 of the 6 patients responded to prednisolone ± IVIg (Kuter et al, BJH 2021).

**Reporting outcomes to Public Health England (PHE)**

Cases of ITP and relapse of ITP following vaccination should be reported to PHE on the following link: <https://snapsurvey.phe.org.uk/snapwebhost/s.asp?k=162574113593>

Note that this is different from the VITT reporting form (<https://cutt.ly/haem_AE>) (but any ITP information already reported using the VITT link will be captured).

By reporting the outcomes of this serious post-vaccine complication, we will learn more about this condition including natural history, differences by vaccine type and dose, treatment response and importantly, relapse risk with subsequent Covid-19 revaccination. These findings will directly inform future updates of the guidance below.

In order to focus on clinically important cases of ITP/ITP relapse, the inclusion criteria are:

* Adults age 18 or more
* Diagnosis of ITP made by a clinical haematologist, based on history, examination, full blood count and blood film examination consistent with international consensus definition (Provan et al Blood Adv 2019). Cases may be primary or secondary
* Patients who developed a significant new\* episode of ITP within 30 days of COVID-19 vaccination, or developed a significant relapse\*\* of existing ITP

\* significant new episode defined as platelets **<30**

\*\* significant relapse defined as platelets **<30** and a fall from baseline pre-vaccine platelet count of 50% or more

* Minimum follow-up of 12 weeks but also, if ITP is after first dose, give adequate duration of follow-up to determine impact of 2nd vaccine on ITP: either decision to defer, or received 2nd dose and at least 4 weeks FU post 2nd Vaccine with FBC checks

**Guidance on ITP/ITP relapse post following Covid-19 vaccination**

Diagnosis

The diagnosis of ITP can be made using standard criteria described in the international consensus guideline (Provan et al Blood Adv 2019).

A diagnosis of post Covid-19 vaccine associated ITP may be considered with presentation or the onset of relevant symptoms within 30 days of vaccination. However, alternative secondary causes should also be considered e.g. infection (including Covid-19), immunodeficiency, and systemic autoimmune or lymphoproliferative disorders.

Another important post-vaccine complication that can occur during this time is Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT). Updated guidance on VITT is linked from the following webpage: <https://b-s-h.org.uk/about-us/news/guidance-produced-by-the-expert-haematology-panel-ehp-focussed-on-vaccine-induced-thrombosis-and-thrombocytopenia-vitt/>. In cases of suspected post-Covid-19 vaccine ITP, patients should have a clotting screen including Clauss Fibrinogen and D-Dimer. Symptoms or signs of arterial or venous thrombosis should be appropriately investigated.

Treatment

There is currently insufficient published evidence to justify adjustments to previous advice on when to start treatment or the choice of treatment, for ITP (Provan et al Blood Adv 2019) and ITP during the pandemic (Pavord et al BJH 2021). Clinical experience suggests that many cases can either be observed for resolution or respond to typical first line treatments. In contrast, some patients have a more chronic course and require further treatment.

Difficult cases can be discussed with the working group via Teams on Wednesday PM 14.00-15.00.

Link to the meeting:

<https://teams.microsoft.com/l/meetup-join/19%3ameeting_MjYyOWQ5OGMtYjE5YS00MTQ2LTk3YjItNzVjNTFlMGZhMTQy%40thread.v2/0?context=%7b%22Tid%22%3a%2237c354b2-85b0-47f5-b222-07b48d774ee3%22%2c%22Oid%22%3a%22ead49e4b-21d0-4ce2-942a-7df928dc069b%22%7d>

ITP patients receiving the Covid-19 vaccine

Given the effectiveness of vaccination and the morbidities and mortality from Covid-19 infection, including the risk of Covid-19 associated ITP; ITP is not a contra-indication to vaccination.

ITP has not been identified as a risk factor for VITT and does not influence the decision on vaccine type.

Some patients with ITP will be receiving immunosuppression. Those on immunosuppression are considered an at risk group for COVID-19. Although these individuals may not make a full immunological response to vaccination, it is still recommended (<https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a>).

In patients with significant thrombocytopenia, a fine needle (23 or 25 gauge) should be used, with sustained pressure at the injection site (without rubbing) for at least 2 minutes to avoid muscle haematoma. Ideally a platelet count of >30 x109/L is required but a lower platelet count should not preclude it.

The potential for a fall in platelet count post vaccine should be discussed with patients, including the need to check their platelet count if bleeding symptoms develop, particularly in the first 1-2 weeks post vaccine.

With respect to timing of vaccination in patients under consideration for immunosuppression, some useful guidance issued for patients with rheumatological conditions can be accessed here: <http://arma.uk.net/covid-19-vaccination-and-msk/>

Should patients with ITP or ITP relapse after Covid-19 vaccine receive further vaccinations?

There is limited data on the evolution of ITP after vaccine, and whether a second dose would precipitate a further exacerbation. The data so far suggests that ITP remains treatment responsive (Lee et al AJH 2021). ITP following first MMR vaccine has not been considered a contra-indication to second vaccination in US (Miller et al Arch Dis Child 2001) and UK (BSH BJH 2003) guidelines. The current experience encountered by clinicians from the ITP Forum has been that re-vaccination has resulted in either a stable platelet count, or a fall that is treatment responsive.

On the contrary, the benefit of the second vaccine for COVID-19 protection is clear. Furthermore, in the United Kingdom, there has been a rapid rise in the B.1.617.2 (delta) variant. Recent evidence suggests that effectiveness of one Pfizer vaccine was notably lower among persons with the delta variant (30.7%) than among those with the alpha variant (48.7%). The effectiveness of two doses was 93.7% among persons with the alpha variant and 88.0% among those with the delta variant. With the AstraZeneca vaccine, the effectiveness of two doses was 74.5% among persons with the alpha variant and 67.0% among those with the delta variant (Lopez-Bernal et al NEJM 2021).

Furthermore, evidence published in pre-print found that in immunosuppressed patients, reduced vaccine effectiveness against clinical disease was noted after one dose (4%), however, after a second dose of either vaccine, high levels of effectiveness were seen (Pfizer: 73.0%, AstraZeneca 74.6%) (<https://khub.net/documents/135939561/430986542/RCGP+VE+riskgroups+paper.pdf/a6b54cd9-419d-9b63-e2bf-5dc796f5a91f>).

It is unknown whether switching between Covid-19 vaccines would increase or reduce the risk of ITP recurrence. Another related area of uncertainty is whether switching vaccines would confer the same clinical effectiveness against Covid-19, as compared to receiving two vaccinations of the same type. Spanish data in pre-print from the CombivacS trial found that of 441 recipients of a first AstraZeneca vaccine who received a second vaccination with Pfizer, 100% exhibited neutralizing antibodies 14 days later, in comparison to 34.1% at enrolment (<https://ssrn.com/abstract=3854768>). In the UK, initial data from the Com-COV study found greater reactogenicity (e.g. fever) with heterogeneous Pfizer & AstraZeneca vaccine schedules (Shaw et al Lancet 2021).

Current evidence therefore suggests that the risk/benefit balance would favour receiving further Covid-19 vaccination in most cases. However the risk/benefit balance should be considered on an individual bases, taking the patients views into consideration and deferral may be considered appropriate in severe and poorly controlled cases of ITP/ITP relapse.

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