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COMMISSION ON HUMAN MEDICINES

VACCINE BENEFIT RISK EXPERT WORKING GROUP

Title of paper: Updated review of COVID-19 Vaccines and the potential risk of thrombocytopenia events

Type of paper: For advice

Active(s) rINN	Pfizer/BioNTech COVID-19 vaccine BNT162b2 AstraZeneca COVID-19 vaccine Moderna COVID-19 vaccine BNT162b2
Product name(s)	
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Legal status	Prescription only medicines
Therapeutic classification (ATC code)	VBR EWG 25 February 2021 COVID-19 Vaccines and the potential risk of immune thrombocytopenia
Previous assessments	
Assessor(s)	Name: [redacted] Email: [redacted] Name: [redacted] Email: [redacted]

1. Introduction

The Pfizer/BioNTech COVID-19 vaccine was authorised for use under Regulation 174 by the MHRA on 2 December 2020. It is estimated that over 11.2 million first doses and 6.2 million second doses have been administered in the UK as of 14 April 2021. The AstraZeneca COVID-19 vaccine was authorised for use under Regulation 174 by the MHRA on 30 December 2020, and over 21.2 million first doses and 2.3 million second doses have been administered in the UK as of 14 April 2021. The Moderna vaccine has also been authorised under Regulation 174 and initial usage in the UK has started, and as of 20th April 2021, just under 60,000 first doses of the Moderna vaccine have been administered in England.

Immune thrombocytopenia is an adverse event of special interest with the COVID-19 vaccines and has been kept under close review by the MHRA since the start of the UK vaccination programme. Immune thrombocytopenia (ITP) has been known to be associated with COVID-19 infection, as has thrombocytopenia. ITP has also been associated with the live MMR vaccine, with a typical onset time of 15-28 days post vaccination[1]. ITP has also been reported to occur after vaccination against pneumococcus, *Haemophilus influenzae B*, varicella zoster virus, and hepatitis B. The biological mechanism may be similar to that of infection, with molecular mimicry causing immune complex formations on the platelet surface leading to clearance of the platelets[4].

The EWG has had data previous presented to it on 25 February 2021 on the potential risk of immune thrombocytopenia, as well as other thrombocytopenia events, with the COVID-19 vaccines and it was concluded that no safety concerns were raised based on the data available at the time.

The MHRA has received several reports of immune thrombocytopenia and thrombocytopenia following administration of both the Pfizer/BioNTech and AstraZeneca COVID-19 vaccines, with an increase in reporting in the past month due to increased awareness around the signal of thromboses and thrombocytopenia with the AstraZeneca vaccine. There have also been international reports of immune thrombocytopenia with the Pfizer/BioNTech COVID-19 vaccine, including a fatal case in the USA[2]. The EMA has recently proposed to include thrombocytopenia as a side effect in the EU product information for the AstraZeneca vaccine based on post-authorisation reporting, and a submission for this update in the UK product information has been made to the MHRA as part of the conditional marketing authorisation submission.

This paper provides an updated summary of the data available to date regarding the potential risk of immune thrombocytopenia and other thrombocytopenia events with the COVID-19 vaccines. The EWGs advice is sought on the proposed inclusion of thrombocytopenia in the AstraZeneca UK product information, and whether any further action is required for other thrombocytopenia events with AstraZeneca, or for the Pfizer and Moderna vaccines, based on this data.

2. Pfizer/BioNTech COVID-19 vaccine

A search was conducted on the MHRA database of UK spontaneous cases for the Pfizer/BioNTech COVID-19 vaccine up to and including 20th April 2021 reporting the Preferred Terms: Ecchymosis, Immune thrombocytopenia, Oral purpura, Petechiae, Platelet count decreased, Platelet disorder, Purpura, Severe fever with thrombocytopenia syndrome, Thrombocytopenia, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura.

[1] https://adc.bmj.com/content/84/3/227
[2] https://www.nytimes.com/2021/01/12/health/covid-vaccine-death.html

The search identified a total of 161 reports, with the following PTs reported: Immune thrombocytopenia (n=36), Oral purpura (n=1), Petechiae (n=50), Platelet count decreased (n=24), Purpura (n=17), Thrombocytopenia (n=50), and Thrombotic thrombocytopenic purpura (n=5). Often more than one PT is reported per case.

Yellow Card Data

Immune Thrombocytopenia

Up to and including the 20 April 2021 there have been 36 reports of immune thrombocytopenia reported with the Pfizer/BioNTech vaccine (incidence of 2.1 cases per million doses). Age was reported in 34 of these cases, with a range of 20-91 years and an average age of 55.9 years. Twenty-two cases were in females and 13 in males, with unknown reported in one case.

The dose was specified in 30 of these cases, of which 22 occurred after the first dose and 8 after the second dose. Of the 22 cases reported after the first dose, 5 cases reported time to onset as 3 days or less, 2 cases reported onset of 4-14 days, 8 reported an onset time of 15-28 days, and 5 report onset of >28 days after vaccination. Two of the first dose cases did not specify time to onset. Of the 8 cases reported after the second dose, two did not provide onset times for the reactions, two provided administration dates for the first dose too and the onsets were 83 and 85 days after the first dose, and of the remaining 4 cases, 3 reported onset times of 1-3 days post dose 2, and 1 reported an onset time of 7 days post-dose 2.

None of the cases were fatal, however, hospitalization was reported in 13 of these cases. One of the hospitalization cases is a duplicate and so is only included once in this analysis. Additionally, 5 of the hospitalization cases had an onset time of 1-3 days after the first dose, and so are unlikely to be associated with the vaccine. These cases were typically older patients (age range 20-91 years, average 73.4 years). Where platelet counts were reported in the hospitalization cases, they were very low (range 0-12).

Regarding other events reported in these hospitalization cases, one case reported a rectal bleed following diagnosis of ITP, in [redacted]. Other events reported included petechiae, epistaxis (n=3), traumatic bruising, subdural hematoma, mucosal bleed, bleeding from mouth and black eyes and hemorrhage (CVST case). One case of a [redacted] reported severe bruising after the first dose which "increased dramatically" after the second dose, possibly indicating a rechallenge, where platelets were recorded to be 4 on hospitalization.

Regarding the 23 cases which did not report hospitalization, other events of note reported alongside ITP included contusion, petechiae (n=2), thrombocytopenia (n=3), COVID-19, oral purpura, purpura (n=2), embolism, and vaginal hemorrhage. ITP is known to be associated with infection and therefore concurrent COVID-19 infection may be a confounding factor in one of the cases.

Six cases report pre-existing ITP:

1. [redacted] (age unknown) [redacted] experienced bruising and mild headache 3 days after the second dose, and platelets of 22 which normalized without treatment. Previous platelet count in this case was 138 in September 2018.
2. [redacted], experienced lowering of platelets three days after the vaccine, along with vaccination site bleeding and purpura, along with hot sweats and skin pricking reported to be typical of ITP flare. Platelets prior to vaccination were 52 and post

vaccination were 32. No treatment was given and the patient was recovering at the time of reporting.

3. [redacted] the patient reported alopecia after the vaccine but did not specify the impact on their ITP
4. [redacted] who reported typical reactogenicity but then followed bruising on finger joints and had platelets tested which were 22; no previous platelet count was provided.
5. [redacted] 7 days post vaccination the platelets were 10, and the patient was treated with romiplostim and was responding to treatment
6. [redacted] reporting an elevation in platelets post vaccination

This sixth case reporting elevation of platelets in an ITP patient may highlight the frequent monitoring of ITP patients which may pick up incidental changes in platelet counts.

Most other medical histories reported in these cases reflect the older ages and vulnerable groups previously prioritized for vaccination including chronic kidney disease, hypertension, type 2 diabetes, inclusion body myositis, immunodeficiency (unspecified), osteoarthritis, cardiac disorders, hepatic cirrhosis and coeliac disease. However, it is noted that one case reports cytomegalovirus infection reactivation and stem cell transplant, and another reports chronic lymphocytic leukemia, both of which may explain the events reported.

Treatment provided in the ITP cases consisted of prednisolone, dexamethasone, unspecified steroids, romiplostim, intravenous immunoglobulin.

Thrombotic thrombocytopenic purpura

Up to an including the 20 April, there have been 5 reports of thrombotic thrombocytopenia purpura (TTP) following vaccination with Pfizer/BioNTech COVID-19 vaccine (0.28 cases per million doses). None of these cases were fatal, however hospitalization was reported in 4 of the cases. Three of the cases are reported post dose two, with onset of 81 and 52 post dose 1 and one reporting 4 days post dose 2. For the two first dose cases the onset times were 29 and 28 days.

One of the cases also reports thrombotic microangiopathy, platelet counts decreased and another also reports hemorrhage, activated partial thromboplastin time prolonged and immune-mediated hepatic disorder (unspecified). Raised d-dimer >4000 was reported in three of the cases, none report positive anti-PF4 antibodies although it is not clear if these testes were carried out, and platelets reported in two cases and were 6 and 9. Treatment was reported in two of these cases, one reporting plasma exchange and another reporting methylprednisolone, plasma exchange, rituximab and caplacizumab.

Past histories reported in the cases were one of cholelithiasis, obesity, fibromyalgia and multiple sclerosis and another patient reported labyrinthitis and head injury only. Past medical histories were not reported in the remaining three cases; none of the cases reported prior thrombocytopenia.

Thrombocytopenia

There are 45 cases of thrombocytopenia reported (2.6 cases per million doses), excluding the 5 reports which have already been included under the ITP case analysis. Ages in these cases range from 23-100

years old (average 58.9 years), and 25 of the cases were in females and 18 males, with sex unknown in two cases.

There were 26 cases reported after the first dose of the vaccine, and with 4 cases occurring 1-3 days post vaccine, 8 cases occurring in a 4-14 day window, 6 occurring in a 15-28 day window and 3 occurring >28 days after the first dose. There were 10 cases reported after the second dose; only 6 of which report an onset time. None of the second dose cases have recorded the date of the first vaccination so onset times are post second dose, of which two are 1-day post-vaccine and the remaining four are 5, 10, 13 and 26 days after second dose.

There were two fatal cases reported under thrombocytopenia:

- [redacted], reporting nosebleed 28 days after the first dose, the next day headache started and nosebleed continued. The patient was assessed for blood pressure, pulse and oxygen and was confirmed as OK. The next night the patient retched at dinner and was hospitalized where he was diagnosed with brain bleeds, bleeding elsewhere, bruising of skin and mouth and thrombocytopenia (platelets zero). The patient was on an unspecified anti-coagulant [redacted]
- [redacted] who had recently undergone [redacted] or a large colonic adenoma. Two hours post-surgery the patient deteriorated with abdominal pain, hypotension and tachycardia and was revealed to have global ischemia of the bowel and thrombocytopenia (platelets 35). The patient died 4 days later and a post-mortem revealed thrombosis and small bowel draining via dilated inferior mesenteric vein into portal vein.

The fatal case of the [redacted] has been reviewed as part of the ongoing topic of thromboses and thrombocytopenia, and the events were considered unlikely to be related to the vaccine due to the recent surgery and colonic adenoma.

There were 12 cases of thrombocytopenia where the patient has reported hospitalization. The other events reported in these cases include hemorrhage intracranial with upper gastrointestinal hemorrhage and posterior reversible encephalopathy, contusion and increased tendency to bruise, epistaxis and mucosal hemorrhage, pulmonary embolism with respiratory failure and neutrophilia, encephalitis and ataxia, autoimmune neutropenia, and deep vein thrombosis and disseminated intravascular coagulation. The cases reporting thromboembolic events have also been considered in the ongoing review of thromboembolisms with thrombocytopenia. Hospitalized patients were generally older in age, with an average age of 70.5 years, and 5 of the cases reported relevant medical histories associated with the events including campylobacter infection, autoimmune neutropenia, prior deep vein thrombosis, and rheumatoid arthritis. One of the patients also reports pre-existing immune thrombocytopenia alongside autoimmune neutropenia and autoimmune hemolytic anemia and immunodeficiency. One case also reported a positive SAR-CoV2 test two months prior to vaccination and another reported COVID-29 infection two months prior to vaccination.

Of the remaining 31 non-fatal cases not reporting hospitalization, other events reported included bruising (n=4), petechiae (n=3), epistaxis (n=2), neutropenic sepsis with intravascular hemolysis and pancytopenia, embolism and hemorrhage, anemia and mouth hemorrhage. Six of these cases reported relevant past medical histories: hemodialysis, renal transplant, breast cancer, gastrointestinal carcinoma, colorectal cancer and neoplasm.

There were 9 cases which reported a history of immune thrombocytopenia or thrombocytopenia. Ages in these cases range form 26-70 years (average age 42 years). Six cases are reported after the

first dose, with dose unspecified in the remaining 3 cases, and onset times range from 2-41 days, although all but one are 7 days or less from vaccination which lessens the likelihood of being associated with vaccine as the immune response is still developing. However, the potential mechanism for ITP flares is unclear. Four cases reported the outcome for thrombocytopenia as recovering and 3 were recovered with the remaining 2 not recovered.

Platelet count decreased

There were also 18 reports with the event platelet count decreased which are not included in the above analysis for ITP, TTP or thrombocytopenia. These are in patients aged 39-91 (average age 64.2 years) with 9 reports in females and 9 in males. Five of these cases were post-dose 2, ranging from 5 minutes to 91 days post dose 2, and 10 cases were after the first dose, one with an onset of 1 day and the remaining onset time ranging from 18-51 days after dose one (average 29.6 days).

One of these cases was fatal, in a [redacted] with an unknown onset time. The patient was non-responsive to intravenous immunoglobulin and steroids were stopped due to delirium. The patient experienced an intracranial bleed which was treated with platelets, but the patient deteriorated and passed away. The patient has previous suspected COVID-19 infection on an unknown date.

Other events reported in these cases include hemorrhage, contusion and epistaxis, pancreatitis and embolism, and nasopharyngitis. Pancreatitis and nasopharyngitis may be alternative explanations for the low platelets reported. Three of the cases report relevant past histories of “gastroma tumor” assumed to be gastrinoma, hepatitis and rheumatoid arthritis, and prostate cancer.

There was one case reported in a patient with pre-existing immune thrombocytopenia, in a [redacted] whose platelet count fell from 75 prior to vaccination to 19 post-vaccination, with an onset of [redacted] days post-first dose. The patient was treated with dexamethasone without effect and was started on intravenous immunoglobulins. The patient notes they have had two ITP relapses following the flu vaccination.

Purpura and petechia

There are 15 reports of purpura which do not include a thrombocytopenia term or decreased platelet count. None of these are fatal and none report hospitalization. Four of the reports are male and 11 are female. Ages range from 25-94 years, with an average age of 55.4 years. Six cases are reported after the first dose and two post second dose, with 7 cases not specifying the dose. Onset times for the first dose or where dose wasn’t specified range from 1-16 days, with an average onset time of 5.5 days. Onset times in the two second dose cases were 1 and 47 days post dose 2.

None of these cases report prior ITP or thrombocytopenia. Other events reported in these cases include oral blister, hemorrhage subcutaneous, oral blood blister and vasculitis.

There are an additional 42 reports of petechia; 12 of are reported to occur after the second dose and 14 after the first dose, with dose not specified in the remaining 16 cases. Onset times in the first dose cases or those where dose isn’t specified range from 1-28 days, with an average onset time of 6.7 days. None of these cases are fatal. Four cases report hospitalization, two with an onset of 1 day post dose 1 and so the events are unlikely associated with the vaccine, and the third case reporting seizure with dyspnea and skin exfoliation in [redacted] at an unknown time after vaccination. The fourth case is one day post second dose, and also reports myalgia, pyrexia and rash.

Three of the petechia cases reports suspected infections (gastroenteritis with hematemesis and normal blood test results, nasopharyngitis and lower respiratory tract infection) and another reports

a likely allergic reaction with rash. Other events of note reported in these vases include vasculitis rash, hemorrhage and contusion.

Of note, one of these cases is in [redacted] who also reports more bruising than normal, with events starting 28 days post vaccination.

Clinical Trial Data

As previously reported to the EWG, there were no reports of ITP in the clinical trials. There were three reports of thrombocytopenia in the unblinded data review, all serious and all assessed as non-related: one event was associated with cirrhosis, one with cellulitis and one had a four-month history of rectal bleeding. Two events of thrombocytopenia were reported in the placebo arm, both considered serious.

Pfizer/BioNTech Summary Monthly Safety Report

In the most recent Summary Monthly Safety Report for Pfizer, an updated observed expected analysis for ITP has been provided, which does not show an increased number of cases compared to the expected background rate with an O/E ratio of 0.503 for a 21 day risk window. The company has received 53 reports of ITP, 75 reports of thrombocytopenia and 2 reports of TTP up to the data lock point of 31 March 2021.

Summary

Overall, in the UK data there is a relatively low incidence of UK reports of ITP, TTP and thrombocytopenia events reported with the Pfizer/BioNTech vaccine considering the usage of the vaccine. Amongst these cases, there is a low number fatal cases and also infrequent reporting of serious bleeding events associated with the thrombocytopenia. There are a number of cases with a reasonable time to onset of more than 7 days which could indicate an association with the vaccine, however there is not strong pattern in the onset times in these cases. There are also a number of cases reported after the second dose, although again without a particular patten in the onset time. There are a number of cases in patients with pre-existing ITP or prior thrombocytopenia. There is no strong pattern of onset times in these cases, and infrequent reporting of hemorrhage associated with the ITP flares. . It is also of note that one patient with pre-existing ITP had an increase in platelet count after vaccination and indicates the changes in platelet counts may be coincidental but more likely to be identified in patients who are frequently monitored.

The most recent company report with post-authorization data also does not indicate a high amount of reporting of thrombocytopenia events with the Pfizer vaccine, and the company observed vs expected analysis does not indicate increased reporting rates above the expected background.

3. Moderna

There have been no UK reports of thrombocytopenia or related events for Moderna, up to the data lock point of 20 April 2021.

In the most recent Summary Monthly Safety Report there had been a total of 95 cases of thrombocytopenia reported with Moderna vaccine, with a reporting rate 0.66 per 100,000 person years. The company estimates an expected reporting rate of 913.4 cases (rate ratio 0.01, 95% CI 0.08-0.13) based on estimates from CPRD from 2019. The company has also received a total of 30 reports of ITP up to the data lock point of 31 March 2021. As of 31 March 2021, a total of 78,494,588 doses of the vaccine have been administered based on information retrieved through the CDC.

From Phase 3 clinical trials, no reports of autoimmune/ immune thrombocytopenia were noted. In the safety set, there were 2 reports of thrombocytopenia occurring in the vaccine arm (N=15185), compared to no reports from the placebo arm (N=15166).

Summary

There is limited exposure to the Moderna vaccine in the UK; however international data provided by the company does not suggest that reporting levels are above the expected background rate and remains low in the context of global usage.

4. AstraZeneca

Yellow Card data

A search was conducted on the MHRA database of UK spontaneous cases for the AstraZeneca COVID-19 vaccine up to and including 20th April 2021 reporting the Preferred Terms: Ecchymosis, Immune thrombocytopenia, Oral purpura, Petechiae, Platelet count decreased, Platelet disorder, Purpura, Severe fever with thrombocytopenia syndrome, Thrombocytopenia, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura. The search identified a total of 755 cases.

Up to and including 20 April 2021, the MHRA has received 121 reports of immune thrombocytopenia (estimated incidence of 5.1 cases per million doses) and 379 reports of thrombocytopenia (estimated incidence of 16.1 per million doses). There are also 145 reported events of platelet count decreased (of which 17 cases also report thrombocytopenia and 8 cases report immune thrombocytopenia).

140 reports of petechiae have been received co-reported with platelet count decreased (5 cases), immune thrombocytopenia (15 cases) and thrombocytopenia (20 cases).

61 reports of purpura have been received co-reported with petechiae (3 cases), platelet count decreased (5 cases), immune thrombocytopenia (7 cases) and thrombocytopenia (13 cases).

The remaining reports were distributed as follows: Ecchymosis (2 cases), Oral purpura (2 cases), Platelet disorder (3), Severe fever with thrombocytopenia syndrome (5), Thrombocytopenic purpura (6), Thrombotic thrombocytopenic purpura (1). The cases of Severe fever with thrombocytopenia syndrome are considered misclassifications in patient reports.

60 fatal cases have been received of which one case is a duplicate. From the relevant reaction terms of interest 50 fatal cases report thrombocytopenia, 8 report immune thrombocytopenia, 5 report platelet count decreased and 4 report purpura.

Immune thrombocytopenia

Of the 121 reports of immune thrombocytopenia, 66 were female (55%), 52 male (43%) and 3 unknown (2%). Age where reported covers the range of 17 years to 98 years old (median = 55 years). 334 reports were submitted following the 1st dose, 5 reports following the 2nd dose and 11 cases where dose 1 or 2 was not specified.

73 cases report an onset time of 7 days or more (which is more plausible for a vaccine associated ITP). 15 out of the 121 cases fall within a time to onset window between 15-28 days. 12 cases have a

recorded time to onset beyond 28 days.

Out of 73 cases reporting an onset time of 7 days or more, 36 cases specifically note that a review by a haematologist supported a diagnosis of immune thrombocytopenia. Several of these cases have submitted additional information (no other confounders, platelets only cell line affected, responding to treatment with IVIg/ steroids) with summaries provided in Annex 1.

Of the 8 fatal cases reporting immune thrombocytopenia, 6 have an onset of more than 7 days. There is no cluster in the reported fatal terms (1 case each) [Brain death, Cerebral Haemorrhage, Cerebral venous sinus thrombosis, Death, Haemorrhage, Haemorrhagic Stroke, Immune thrombocytopenia and Respiratory Failure]. On review of these cases it is noted that 4 of them specifically relate to intracerebral bleeds which would be anticipated in the context of severe thrombocytopenia. One patient had a past medical history of immune thrombocytopenia which was steroid responsive. [redacted] was discharged from haematology care in 2016 with her routine platelet counts in the range of 250-400 in blood samples taken during 2020. [redacted] passed away due to pulmonary haemorrhage approximately 1-2 days after her first dose of the AstraZeneca covid vaccine. Short summaries for each of these fatal cases are presented in Annex 2.6 cases report immune thrombocytopenia occurring in patients with previously diagnosed immune thrombocytopenia. 1 of these cases was fatal, as mentioned above, in [redacted] with previously controlled ITP who died 1-2 days post vaccination. The onset times vary from 1-22 days. 3 cases state that the patient's condition and platelet counts had been stable prior to receiving the vaccine. 1 case was managed on fortnightly IVIg to maintain platelet count >20. While some cases exhibit relatively short onset times for a causal association with the vaccine, it could be possible that the pre-existing condition allows a more rapid reaction in these patients.

Thrombocytopenia

Of the 379 reports of thrombocytopenia, 203 were female (54%), 168 male (44%) and 8 unknown (2%). Age where reported covers the range of 18 years to 93 years old (median = 55 years). 106 reports were submitted following the 1st dose, 19 reports following the 2nd dose and 24 cases where dose 1 or 2 was not specified.

259 cases report an onset time of 7 days or more. 242 are from healthcare professionals whilst the remaining 17 are from patients/carers. 17 cases co-report immune thrombocytopenia as a reaction term alongside thrombocytopenia. 76 out of the 379 cases fall within a reported time to onset window between 15-28 days. 50 cases have a recorded time to onset beyond 28 days.

There are 50 fatal cases reporting thrombocytopenia as a reaction term. The most frequent fatal terms are: cerebral haemorrhage (8 cases), cerebral venous sinus thrombosis (8 cases), pulmonary embolism (4 cases), portal vein thrombosis (3 cases), haemorrhagic intracranial (3 cases), cerebrovascular accident (3 cases), thrombocytopenia (3 cases), cerebrovascular accident (3 cases), cerebral venous thrombosis (2 cases), superior sagittal sinus thrombosis (2 cases) and 1 case each for the remaining fatal terms [arterial thrombosis, brain oedema, brain stem infarction, Budd-Chiari syndrome, cerebral haematoma, coronary artery thrombosis, haemorrhagic cerebral infarction, ischaemic stroke, purpura, respiratory failure, respiratory distress, sepsis, thrombosis, visceral venous thrombosis).

12 cases report thrombocytopenia occurring in patients with previously diagnosed thrombocytopenia. The onset times for the majority of these cases falls within a 1-15 day time period. 1 of these cases was fatal and is reported by a GP for a [redacted] with a pre-existing

thrombocytopenia due to [redacted] 13 days after [redacted] 1st vaccine dose the patient was admitted to hospital for a stroke (infarct) despite a low platelet count and passed away. Past medical history includes [redacted] cancer which was not currently active.

Platelet count decreased

Of the 145 reports of platelet count decreased, 84 were female (58%), 57 were male (40%) and 4 unknown (2%). Age where reported covers the range of 20 years to 98 years old (median = 55 years). 123 reports were submitted following the 1st dose, 4 reports following the 2nd dose and 18 cases where dose 1 or 2 was not specified. Time to onset varies from 1 day up to 3 months. Cases reporting longer time to onset are usually in the context of low platelets identified on routine/annual blood tests. 95 cases (66%) reported platelet count decreased within 14 days of receiving the vaccination.

As noted above amongst the 145 reported events of platelet count decreased, 17 co-report thrombocytopenia and 8 cases co-report immune thrombocytopenia.

Platelet count decreased is reported as a reaction term in the following 5 fatal cases (1 case per fatal reaction term) – Brain stem infarction, Death, Haemorrhage Intracranial, Myocardial Infarction, Thrombosis. Short summaries for each of these fatal cases are presented in Annex 3.

Petechiae

Of the 140 reports of petechiae, 103 were female (74%), 31 male (22%) and 6 unknown (4%). Age where reported covers the range of 19 years to 87 years old (median = 55yrs). 117 reports were submitted following the 1st dose, 6 reports following the 2nd dose and 17 cases where dose 1 or 2 was not specified. Time to onset varies from 1 day to 30 days. 57 reports are from health care professionals whilst the remaining 83 cases are from patients/carers.

As noted above co-reported terms included platelet count decreased (5 cases), immune thrombocytopenia (15 cases) and thrombocytopenia (20 cases). There are no fatal cases amongst the 140 cases citing petechiae as a reaction term.

One solicited case reporting petechiae has been received via the Yellow Card Vaccine Monitor route. The reporter is a patient who [redacted] describes the development of petechiae on [redacted] forehead 2 weeks after her 1st dose. [redacted] experienced no side effects after her 2nd dose. There are no other reported reaction terms for this case. [redacted] medical history notes hypertension as well as IgM-MGUS identified in [redacted] Current concurrent medications include [redacted]

Purpura

Of the 61 reports of purpura, 40 were female (66%), 20 male (33%) and 1 unknown (1%). Age where reported covers the range of 19 years to 85 years old (median = 55 years). 53 reports were submitted following the 1st dose, 5 reports following the 2nd dose and 3 cases where dose 1 or 2 was not specified. Time to onset varies from 1 day to 77 days. 48 cases (79%) reported petechiae within 14 days of receiving the vaccination. 24 reports are from health care professionals whilst the remaining 37 cases are from patients/carers.

As noted above 61 reports of purpura have been received co-reported with petechiae (3 cases), platelet count decreased (5 cases), immune thrombocytopenia (7 cases) and thrombocytopenia (13 cases).

Purpura is reported as a reaction term in the following 4 fatal cases (1 case per fatal reaction term) – Diffuse vasculitis, Death, Purpura, Pulmonary embolism. Short summaries for each of these fatal cases are presented in Annex 4.

Clinical trial data

There were no cases of ITP, thrombocytopenia or purpura reported in either arm of AZ clinical trials. There was one case of petechiae reported in the control arm.

Proposed Updates to the Product Information

The MHRA is currently assessing the updated safety data submitted as part of the AstraZeneca conditional marketing authorisation application. Within this, there is a variation to include thrombocytopenia in the UK product information in line with a similar update in the EU product information. It is proposed that thrombocytopenia is included in section 4.8 as a side effect, with a frequency designation common.

This inclusion has been made in the EU product information based on post-marketing data and also an observed vs expected analysis which indicated a higher reporting rate than the expected background incidence rate. An observed/expected analysis from the company identified 141 post-authorisation cases of thrombocytopenia with the AstraZeneca vaccine, as of 21 March 2021. The expected number of cases in the risk window of 42 days was 104.85, and therefore there was a significantly higher number of observed cases compared to the expected incidence.

The frequency of “common” for thrombocytopenia has been proposed based on analysis of the haematology laboratory results, rather than adverse events reported. The haematology results showed a total of 997 patients with platelets decreased after the first dose compared to 694 in the control, and 294 in the active arm post dose 2 compared to 95 in the control arm.

However, this laboratory data was only collected from a subset of subjects in several of the clinical trials and these results were pooled. It is unclear how these subjects were chosen and there are more subjects with data in the AZD1222 group than for the control group with limited data after second dose . There were also some subjects that had a decreased platelet count at baseline, particularly in the AZD1222 group, which should be taken into consideration with any frequency calculation. Therefore, the validity of the numerical difference observed in the pooled clinical trial data is uncertain. Furthermore, there were no adverse events reported with the active in the pooled clinical trial data for ‘Thrombocytopenia’, ‘Platelets decreased’ or ‘Immune thrombocytopenia’.

Discussion

In comparison to the spontaneous data previously presented on this topic (EWG paper – 25/02/2021) there is an increasing number of spontaneous reports for the reaction terms of interest. This increase is likely secondary to continued roll out of the vaccine as well as improved awareness amongst health care professionals and patients of the need to be vigilant for thrombotic +/- thrombocytopenic events. With receipt of follow up information, the quality of information is improving to provide additional evidence for a causal relationship on top of the temporality of events to vaccine administration. This includes follow up reports confirming no other confounders/diagnoses identified, platelets only cell

line affected, response to treatment with IVIg/ steroids and haematologist opinion that the diagnosis is immune thrombocytopenia/vaccine induced immune thrombocytopenia. Given the known limitations of Yellow Card data reports, the decision to attribute causality should also take into account other data sources including epidemiological analysis as well as clinical trial data.

The proposal to include thrombocytopenia in section 4.8 of the UK conditional marketing authorisation is based EU analysis of post-authorisation data and observed/expected analysis. There is also a significant number of reports in the UK database, with the majority reporting an onset time of more than 7 days, although the onset times within these cases are variable. Epidemiological analysis based on CPRD data has also indicated a higher than expected incidence rate of ITP, however, separate analysis for thrombocytopenia has not been conducted.

5. Epidemiological analysis

As part of the safety surveillance strategy for COVID-19 vaccines, MHRA are undertaking enhanced passive surveillance, which compares the observed number of case reports with the expected given the underlying age-specific background risk and size of the vaccinated population. We are also conducting rapid cycle analyses, which rely on primary care data available through the Clinical Practice Research Datalink and compare the incidence rate of cases within a risk window post vaccination to historical background rates.

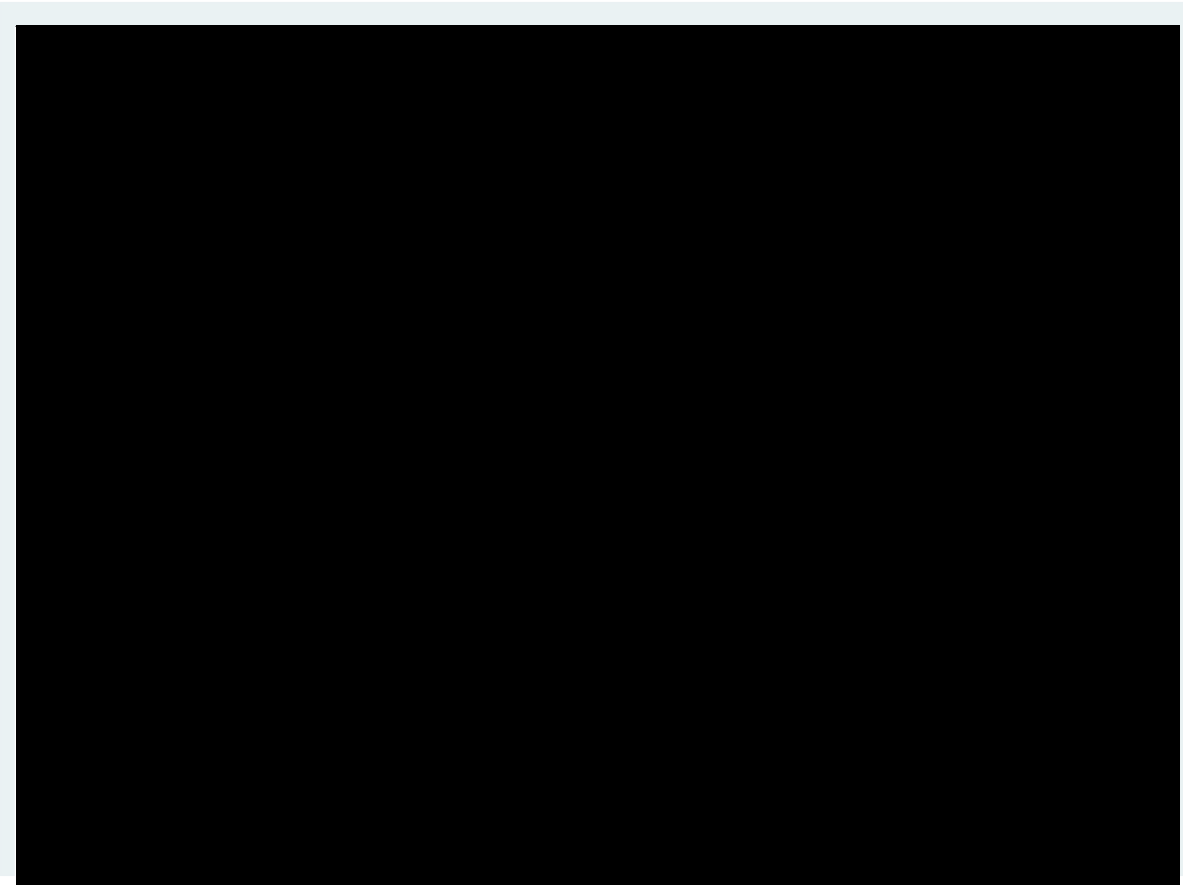
For the Observed vs Expected analyses, expected rates are based on background risks calculated prior to the pandemic using linked Hospital Episode Statistic and primary care data captured in the Clinical Practice Research Datalink (CPRD) for the period 2015-2019. The analyses presented here are based on UK cases reported up to 21st April 2021 i.e. 35 cases of immune thrombocytopenia and 1 case of reported fatal thrombocytopenia where ITP was a likely diagnosis for the Pfizer/BioNTech vaccine and 116 cases of immune thrombocytopenia and 2 cases of thrombocytopenic purpura where ITP was a likely diagnosis for the AstraZeneca vaccine. For the Pfizer vaccine, the log likelihood of the Observed vs Expected ratio (LLR) crossed the signal threshold at the 10% reporting level in patients aged under 50 for ITP within 42 days of the first dose of the Pfizer vaccine. There were no signals of increased risk are seen in the other age groups at any level of under-reporting. For the AstraZeneca vaccine, the LLR has crossed the signal threshold in patients aged <50 years, assuming 100% reporting, and in patients aged 50-64 years assuming 75% reporting, and in patients aged over 65 assuming 10% reporting level.

Rapid cycle analyses are based on data in the CPRD up to 11th April 2021. For the Pfizer vaccine, rapid cycle analyses show the observed number of recorded cases of ITP within 42 days of the first dose (11) to be consistent with the expected (13.2) based on over 185,000 patient years of follow up adjusting for delays in recording of cases in primary care records. For the AstraZeneca vaccine, 31 cases of ITP have been recorded within 42 days of a first dose. This compares to an expected 15.8 cases based on approximately 250,000 patient years of follow up adjusting for delays in recording of cases in primary care records. This had crossed the threshold within the overall analyses for signalling an increased rate of ITP compared to the background rate at the last review. This signal was previously only seen when we allow the null hypothesis to be excluded based on small numbers of cases, however the signal has strengthened over time. When looking at this risk across different age groups a signal is only raised in the youngest age group, those aged 18-49, in whom 7 cases have been observed compared to an expected 1.5. However, it is not clear if the case identified are seen in conjunction with a thrombosis or not.

However, it should also be noted that Hospital Episode Statistics data show a considerable impact of the pandemic on the number of admissions with a diagnosis of ITP. Figure 1 below shows the number of admissions in England in the period 2015-2020 and a clear and sudden decline is seen in March/April

2020. The number of admissions has increased since then but has not yet reached pre-pandemic levels. Both the observed vs expected, and rapid cycle analyses need to be interpreted in this context. This strengthens further the signal for the AstraZeneca vaccine. However, further analyses are required to assess if there is any potential increase in reporting or recording of ITP following a first dose of the Pfizer vaccine.

Figure 1: data, Number of admissions in England with ICD10: D69.3; 2015-2020 (HES data as analysed by PHE)



6. Discussion

Regarding the Pfizer/BioNTech vaccine, there is a relatively low level of reporting of ITP, TTP and thrombocytopenia, and related PTs. While there is a significant proportion reporting plausible time to onsets in association with the vaccine, there is no strong pattern in the onset times and no particular clustering around the 15-28 time window associated with ITP cases with the MMR vaccine. There is also a low number of fatalities or serious haemorrhagic events reported in these cases. There are a number of cases reported in those with pre-existing IPT or prior thrombocytopenia, however, there is no indication of particularly severe outcomes in these patients, nor any pattern in the onset times. Similarly, the company and clinical trial data does not suggest a high number of these events being identified with the Pfizer/BioNTech vaccine. The MHRA epidemiological analysis also does not provide string evidence of a signal for ITP with the vaccine although further analyses are planned. Therefore, there is limited data indicating an association between thrombocytopenia events and the Pfizer/BioNTech vaccine at present.

There is currently limited experience with the Moderna vaccine in the UK, however, no reports of thrombocytopenia and related events had been reported up to and including 20 April 2021. There is also a low level of reporting of these events in the company data available up to 31 March 2021, and the overserved expected analysis from the company did not indicate reporting rates above the expected background incidence. Overall, there is no data indicating a potential safety concern with the Moderna vaccine.

There is higher reporting of ITP, TTP and thrombocytopenia with the AstraZeneca vaccine, even when taking into account the higher usage in the UK, although these events remain rarely reported in association with the vaccine. It also needs to be taken into account that reporting biases may be present for the AstraZeneca vaccine, considering the extensive interest and awareness around the topic of thromboses and thrombocytopenia with the vaccine. There are also reports of ITP and thrombocytopenia in those with pre-existing ITP, mostly occurring within 15 days of vaccination. The potential mechanism for COVID-19 vaccines triggering ITP flares is unclear.

The UK observed vs expected analysis for ITP with AstraZeneca indicates that the reported number of cases is above that expected in the background incidence across the age groups, assuming 100% reporting in <50 age group, under reporting of 75% in the 50-64 years and 10% reporting in the 65+ age group. The rapid cycle analysis also indicates a signal for ITP with the AstraZeneca vaccine, although this is only in the 18-49 age group when broken down by age. However, given the decreased levels of ITP during the cause of the pandemic, and uncertainty on the current background rates, the signal is stronger than these estimates suggest.

The proposal to include thrombocytopenia as a common side effect in section 4.8 of the AstraZeneca conditional marketing authorisation product information is based on a similar inclusion in the EU product information for the vaccine. The EMA included thrombocytopenia based on observed expected analysis which indicated a higher reporting rate for the event than expected, and an imbalance in haematological laboratory results from clinical trial data suggesting a higher incidence of platelet count decreases in the active arm vs the comparator. However, these laboratory investigations were not carried out uniformly across the study and so the validity of these results are unknown, and there were no adverse events of 'Thrombocytopenia', 'Platelets decreased' or 'Immune thrombocytopenia' reported in the study. Therefore, it is questionable whether the clinical trial data contributes to this inclusion, and whether a frequency of common is supported by this or if "frequency unknown" would be more appropriate, given the available data.

7. Advice sought from the EWG

- Does the EWG consider there is sufficient evidence to support inclusion of thrombocytopenia as a side effect of the AstraZeneca vaccine in the UK product information?
    - If so, should this be assigned the frequency of "not known"?
    - If not, what, if any, further analysis required to make this decision?
- Does the EWG consider that any further action is required regarding reports of ITP or TTP with the AstraZeneca vaccine? If so, what further action is proposed?

- Does the EWG consider any further action is required for the Moderna or Pfizer vaccines regarding:
    - Immune thrombocytopenia?
    - Thrombotic thrombocytopenic purpura?
    - Thrombocytopenia?

If so, what further action is proposed?

Annex 1

Summary of key ITP Cases with TTO > 7 days and additional information (AZ Vaccine)

1. [redacted] Dose – Not specified; TTO = 9 days; Presentation = Bruising/Rash. [redacted]

[redacted]

2. [redacted] Dose – 1st dose; TTO = 14-21 days; Presentation = Haematemesis. [redacted]

3. [redacted] Dose – 1st dose; TTO = 13 days; Presentation = Incidental finding on routine blood test. [redacted]

4. . [redacted] Dose – 1st dose; TTO = 8 days; Presentation = Not detailed. [redacted] Platelets were the only cell lineage affected. [redacted]

5. [redacted] Dose – 1st dose; TTO = 14 days; Presentation = Dural venous sinus thrombosis in the superior longitudinal, right transverse and right sigmoid sinuses. [redacted]

6. [redacted] Dose – 1st dose; TTO = 8 days; Presentation = headache and neck ache progressing to left facial weakness, hemisensory and visual neglect. Diagnosed as cerebral venous sinus thrombosis with associated venous haemorrhage/Vaccine associated thrombocytopenia. [redacted]

7. [redacted] Dose – 1st dose; TTO = 9 days; Presentation = Headache, eye swelling, back pain. Diagnosed with inferior ophthalmic vein thrombus left. [redacted]

8. [redacted] Dose – 1st dose; TTO = 26 days; Presentation = purpuric rash. [redacted]

9. [redacted] Dose – 1st dose; TTO = 15 days; Presentation = contusion, haemorrhage. Acute ITP (platelets [redacted]

10. [redacted] Dose – 1st dose; TTO = 7 days; Presentation = Spontaneous bruising. A&E admission with platelets of [redacted]

11. [redacted] Dose – 1st dose; TTO = 12 days; Presentation = petechial rash on right arm – Platelets found to be [redacted]

12. [redacted] Dose – 1st dose; TTO = 49 days; Presentation = Background of DVT/PE on warfarin. Presents with right leg swelling. Platelets [redacted] confirmed genuine thrombocytopenia [redacted]

13. [redacted] Dose – 1st dose; TTO = 15 days; Presentation = bruising, petechiae, epistaxis, mouth blood blisters - platelet count [redacted]

Annex 2

Summary of Fatal Immune Thrombocytopenia Cases (AZ Vaccine)

1. **Fatal Reaction = Cerebral haemorrhage [HCP report]**
[redacted] Dose – Not specified; TTO = 7 days; Presentation = Headache with platelets noted at [redacted] Platelets dropped further to [redacted]

2. **Fatal Reaction = Brain death [HCP report]**
[redacted] Dose – 1st dose; TTO = 7 days; [redacted] severe headaches - low platelets (19) - [redacted] diagnosis of likely ITP. CT Head showed small subdural haematoma. [redacted] extensive intracranial haemorrhage and venous sinus thrombosis. [redacted].

3. **Fatal Reaction = Death [HCP report]**
[redacted] Dose – Not specified; TTO = 10 days; [redacted] headache, backpain, nausea and vomiting, photophobia and urinary frequency. [redacted] Platelet count noted to [redacted] Suspected new onset immune thrombocytopenic purpura possibly secondary to COVID-19 vaccine. [redacted]

4. **Fatal Reaction = Haemorrhage [Consumer report]**
[redacted] **Dose – Dose 1; TTO = 8 days; Received vaccination on** [redacted] diagnosed anterior uveitis [redacted] suspected stroke; [redacted]

[redacted] **Fatal Reaction = Respiratory failure [HCP report]**
[redacted] Dose – Dose 1; TTO = 14 days; Presented with swollen arm and short of breath. [redacted] ow platelets [redacted] and extensive bilateral pulmonary emboli [redacted]
1a) Respiratory failure 1b) Motor Neurone Disease, Pulmonary Embolism 1c) Right iliac vein thrombosis 2 Immune thrombocytopenia; [redacted]

6. **Fatal Reaction = Cerebral venous sinus thrombosis [HCP report]**
[redacted] Dose – Dose 1; TTO = 10 days; [redacted]; [redacted] acute severe headache; [redacted] seizure, [redacted] cerebral venous sinus thrombosis, [redacted] [redacted] idiopathic thrombocytopenic purpura (platelets = [redacted] [redacted]

7. **Fatal Reaction = Haemorrhagic Stroke [HCP report]**
[redacted] Dose – Dose 1; TTO = 6 days; [redacted] severe headache, vomiting, left-sided hemiplegia, and slurring words. [redacted] [redacted] large right-sided haemorrhagic stroke. [redacted]

8. **Fatal Reaction = Immune Thrombocytopenia [HCP report]**
[redacted] Dose – Dose 1; TTO = 1-2 days; [redacted] short of breath, hypoxia, epistaxis & platelets of [redacted] pulmonary haemorrhage, [redacted] rapid onset multi organ failure and death. Diagnosis of ITP [redacted]

Annex 3

Summary of Fatal Platelet Count Decreased Cases (AZ Vaccine)

1. **Fatal Reaction = Brain stem infarction [HCP report]**
[redacted] Dose – 1st dose; TTO = 8 days; Presentation = Fever/Body aches [redacted] developed headache. [redacted] neurological disturbance with left arm. [redacted] intracerebral haemorrhage [redacted] venous sinus thrombosis. [redacted] thrombocytopaenia (platelet counts between [redacted]
Cause of death: 1a) Brainstem infarction 1b) Spontaneous intracranial haemorrhage 1c) Sagittal venous sinus thrombosis. No post mortem undertaken.

2. **Fatal Reaction = Myocardial Infarction [Family member report]**
[redacted] Dose – 1st dose; TTO = 6 days; Presentation = Developed severe headache [redacted] Experienced myocardial infarction a[redacted] patient died from stroke (clot on brain), another myocardial infarction and haemopericardium. [redacted] very low platelet count during admission - platelet count down to [redacted] dropping.

3. **Fatal Reaction = Haemorrhage Intracranial [Carer report]**
[redacted] Dose – 1st dose; TTO = 2 days; Presentation = Developed headache [redacted] thrombocytopaenia [redacted] and slightly raised prothrombin [redacted] Ongoing headache [redacted] intracranial haemorrhage [redacted]

4. **Fatal Reaction = Death [Carer report]**
[redacted] Dose – Not specified.; TTO = 9 days; Presentation = severe headache. [redacted] blood spot rash on ankle and abdominal pain. [redacted] low platelets. [redacted] appendicitis. [redacted]

5. **Fatal Reaction = Thrombosis [HCP report]**

[redacted] Dose – 1st dose; TTO = 14 days; Presentation = [redacted] abdominal pain. [redacted] low platelets [redacted] acute abdomen and [redacted] Small bowel Ischaemia following thrombosis of mesenteric vessels. [redacted] DIC and multi organ failure. [redacted]

Annex 4

Summary of Fatal Purpura Cases (AZ Vaccine)

1. **Fatal Reaction = Diffuse Vasculitis [HCP report]**
[redacted] Dose – 1st dose; TTO = 3 days; Presentation = Developed a purpuric skin rash 3[redacted] episodes of coffee ground vomiting. [redacted] respiratory problems. [redacted] aspiration pneumonia. [redacted] 1a. aspiration pneumonia due to vomiting 1b. small bowel enteritis and stasis 1c. systemic small vessel vasculitis 2. ¿

2. **Fatal Reaction = Death [Family member report]**
[redacted] Dose – Not specified.; TTO = 9 days; Presentation = severe headache. [redacted] blood spot rash on ankle and abdominal pain. [redacted] low platelets. [redacted] appendicitis. [redacted]

3. **Fatal Reaction = Purpura [Carer report]**
[redacted] Dose – 1st dose.; TTO = 3 days; Presentation = Spontaneous bruising [redacted] abnormal blood results identified (low platelet count between [redacted] elevated white cell count). [redacted] haematemesis, aspirated and suffered cardio-respiratory arrest.

4. **Fatal Reaction = Purpura [HCP report]**
[redacted] Dose – 1st dose.; TTO = 16 days; Presentation = Feeling feverish, headaches and two episodes of diarrhoea on day of admission. [redacted] drop in platelet count (44). [redacted] bilateral PE. [redacted] abdo pain [redacted] Long segment thrombus involving the superior mesenteric vein, splenic vein with extension to portal vein as described. [redacted]
Reported cause of death for this patient was multi organ failure / pulmonary embolism / ischaemic bowel; confirmed by a post-mortem.