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Unusual blood clots with low blood platelets from Covid-19 viral vector vaccines

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Abstract

In providing human immunity from the SARS-CoV-2 virus, AstraZeneca's ChAdOx1 nCov-19 vaccines have been administered in multiple nations around the world. Throughout this literature review, the background behind derivation of this vaccine from chimpanzees to avoid pre-existing human immunity to this adenoviral vector's mechanism of interactions will be discussed prior to clinical issues this vaccine brings. Arranged in sections, this discussion concerns the adenovector vaccine's ability to induce both innate and adaptive immunity, featuring the mucosal route of administration's ability to stimulate tissue-resident memory T cells (TRM), a crucial part of the adaptive immune system. Despite its solid ability to stimulate immunity with high efficiency and efficacy, a surge in female fatalities following administrations of the ChAdOx1 nCov-19 adenovector vaccines have also occurred. Published articles regarding both hypothesised mechanisms as well as recorded incidences of this rare vaccine-induced blood clots, also known as the Thrombosis and Thrombocytopenia Syndrome (TTS), have been discussed. Despite still lacking a causal relationship between AZ administrations in heparin-free patients and TTS incidences, all of these articles have implied the mechanisms inducing this condition arise from an induction of platelet-activating antibodies against PF4. The most plausible arisal of these antibodies is from free DNA molecules within the ChAdOx nCov-19 vaccine. Additionally, TTS draws similarities to autoimmune heparin-induced thrombocytopenia cases, where a platelet count decline also occurs.

Keywords**:** *adenoviral vectors; ChAdOx nCov-19; PF4; vaccine-induced immune thrombotic thrombocytopenia*

1. Introduction

SARS-CoV-2 is a similar coronavirus to the SARS-CoV coronavirus which brought about the SARS (severe acute respiratory syndrome) pandemic back in 2003 (Cherry, 2004; Yang et al., 2020). This novel strain is the causative agent of the COVID-19 (coronavirus disease 2019), which resulted in a pandemic following the spread from its origin in Wuhan, China. First cases were administered in late December 2019 (N. Zhu et al., 2020). Despite the rollout of vaccination schemes in numerous countries, 174 million people worldwide have already been infected with the novel coronavirus, inflicting 3.76 million deaths as of early June 2021 (Baraniuk, 2021; Rosen, Waitzberg, & Israeli, 2021; Watson, 2021). The 29 different protein types are divided into 3 categories, being Structural, Non-structural, and Accessory proteins (Astuti, 2020). Structural Proteins have four different types, making up the novel coronavirus' actual structure (Astuti, 2020). These four types are spike (S) glycoproteins, membrane (M) glycoproteins, small envelope (E) glycoproteins, and nucleocapsid (N) proteins. The spike (S) glycoprotein is located on the outermost surface of the SARS-CoV-2 particle and is a transmembrane protein (Astuti, 2020). It is, however, not exactly identical in structure to the spike glycoprotein in SARS-CoV (Astuti, 2020). Nonetheless, they both are able to bind to the ACE2 receptors expressed in arterial and venous endothelial cells and epithelia of the lower

respiratory tract (Papageorgiou & Mohsin, 2020). However, it is also worth noting that the spike (S) protein of the novel coronavirus consists of a mutation which enables the Proprotein Convertase (PC) enzymes such as furin to do a cut along the S1/S2 cleavage (Jaimes, Millet, & Whittaker, 2020). This interaction with PC enzymes enables the spike protein to be split into 2 subunits namely S1 and S2 (Jaimes et al., 2020). The subunit S1 is responsible for the determination of the virus' spike proteins' compatibility to the ACE2 receptors (host virus range evaluation by S1) (Jaimes et al., 2020; Papageorgiou & Mohsin, 2020). On the other hand, S2 subunits are membrane-anchoring proteins and mediates the coronavirus' fusion into the host cell itself (Jaimes et al., 2020).

Several technologies of vaccines for immunity from COVID-19 have been developed and produced, with all achieving the end process of producing antibodies and memory immune cells that will respond to SARS-CoV-2 virus in the bloodstream (Ahluwalia et al., 2021). In addition, mRNA-based vaccines (Pfizer, Moderna) involve injecting mRNA molecules, a molecule resulting from transcription in the nucleus (Goel et al., 2021). This mRNA will be coding for a similar protein to the SARS-CoV-2 virus' spike (S) protein, thus enabling the body cell to display a corresponding protein on its surface (Goel et al., 2021). The body's immune system will produce corresponding specific antibodies which will remain in the bloodstream in the case of a real infection (Jeyanathan et al., 2020; Rubin, 2021). Adenovirus vector vaccines (AstraZeneca, Johnson & Johnson, Sputnik V) utilises the a different serotype of the SARS-CoV-2 known as an adenovirus to use as a vector to enable body cells to self-produce a spike protein with complete similarity to the ones found on the SARS-CoV-2 virus (De Soto & DSSc, 2020; Jones & Roy, 2021). In AstraZeneca, the ChAdOx1 nCov-19 adenovirus used is extracted from primates (De Soto & DSSc, 2020; Knoll & Wonodi, 2021). Displaying this spike protein on the cell's surface membranes, this prompts the immune system to create immune response cells such as antibodies as well. Inactivated vaccines (Sinovac, Sinopharm) instead opts for harmless SARS-CoV-2 virus particles which have been treated with formaldehyde, thus disabling its ability to create an antigenicity in the body whilst triggering an immune response (Gao et al., 2020; Tao et al., 2021; Wang et al., 2020; Xia et al., 2021). Throughout this literature review, the origins of the chimpanzee-derived adenoviral vector vaccines will be discussed, along with both the innate and adaptive immunity it brings. The advantages of this vaccine will be initially investigated, including the vital activation of Tissue-resident memory cells (TRM) in forming adaptive immunity. However, this vaccine platform's drawbacks will also be discussed, involving its previous incidences of stimulating rare vaccine-induced blood clots, also known as the Thrombosis and Thrombocytopenia Syndrome (TTS). The mechanisms stemming from administration of the ChAdOx1 nCov-19 to the induction of this condition will be further reviewed, and whether a causal connection can be produced between the two. Lastly, the clinical methodology in diagnosis of TTS would also be reviewed, along with viable treatments to this life-threatening condition.

This literature review addresses the current public concerns regarding lethal blood clots associated with adenoviral vector technology vaccines such as the AZ vaccine. These potential reactions are one of the major reasons for the ongoing existence of vaccine hesitancy as seen around the world. Despite the actual mechanism of TTS still yet to be officially recognised, recorded observations by several research teams and their final conclusions discussed in this literature review will serve as a stepping stone towards fully understanding this complex side-effect of the AZ vaccine. Further research would need to be undertaken to pinpoint the mechanisms and establishment of effective treatments. Additionally, this review will also address speculations of higher female vaccine-induced TTS incidences, as published reports will prove otherwise so. Finally, the justification of why it is still highly recommended to receive adenoviral vector vaccines will also be discussed in this paper.

2. Current adenovirus based-COVID-19 vaccines

The evolution and progress of the adenovirus vector technology in vaccine usage has one lengthy background. Ad26.ZEBOV was the first adenovirus-based vaccine approved to create immunity from EBOLA in humans (Sadoff et al., 2021). Due to high fatality rates of up to 90% in some Ebola patient groups, urgent demands for an effective vaccine caused the intense conduction of research on adenovirus vector technology to occur (Capelle et al., 2018; Goldstein et al., 2020; Marzi & Mire, 2019). In 2020, the EU-approved Ebola vaccine which consisted of two total components utilised Ad26.ZEBOV in its first dose (Herder, Graham, & Gold, 2020). Other adenovirus vector vaccines undergoing research include the Influenza, HIV, and most notably the COVID-19 vaccine (Arunkumar et al., 2019; Chan et al., 2021; Gary et al., 2020; Herder et al., 2020; Lundstrom, 2021).

Regarding COVID-19 vaccines, each pharmaceutical company's vaccine has been

developed and undergone several extensive clinical trials of great scales. Quite a considerable portion of approved vaccines including AstraZeneca and Johnson & Johnson utilises recombinant adenoviral vector technology platforms (Jeyanathan et al., 2020). HAd5, HAd26, and ChAdOx-1 (all non-replicating) are all examples of recombinant adenovirus vectors which are either in development phases with extensive clinical trials or approved for usage as of this date (McDonald, Murray, Reynolds, Altmann, & Boyton, 2021; Rice et al., 2021).

As a majority, these vaccines aim to express SARS-CoV-2 particle's external protein molecules onto the host cells (Matchett et al., 2021). This includes both the spike protein and receptor binding domain (RBD) (Xie, Yi, & Li, 2021). Adenovirus technology vaccines have the capabilities of inducing a strong cellular and humoral immunity (Custers et al., 2021; Kim et al., 2021). Furthermore, it is known that the adenovirus' natural tropism is the respiratory mucosa, thus making this a highly advantageous feature for adenoviral vector-based COVID-19 vaccines due to the disease's association with respiratory infections (Kim et al., 2021). However, this vaccine technology's efficacy is not airways guaranteed. In the case of a presence of the host's prior existing immunities towards the adenoviral vector's polynucleotide backbone, the vaccine may not retain the same high efficacy levels with people without the immunities. For instance, any pre-existing immunity to HAd5 will cause a reduction in HAd5-based vaccine efficacy (Singh, Pandey, Jayashankar, & Mittal, 2008). Nonetheless, the vaccine will be able to induce responses from antibodies (Ab) and T cells as a vaccine should (Swanson et al., 2021; Zhu, 2020a; Zhu, et al., 2020b). In overcoming these limitations, the adenovirus have also been procured from non-humans, most notably being chimpanzees' ChAdOx-1 (Fischer et al., 2021). The vaccine AstraZeneca is one which uses ChAdOx-1 recombinant vectors. According to reports of the second phase of this vaccine's trial, it demonstrates its safety and ability to stimulate immunity (Fischer et al., 2021). This occurred in both injecting routes of single parenteral and homologous booster vaccinations, where responses from Ab and T cells was evident (Ramasamy et al., 2021; Swanson et al., 2021). Same concept but for primate use, the human-derived adenovirus Ad26.COV2.S is used in COVID-19 vaccines (Custers et al., 2021). With one intramuscular administration, it is able to offer immunity from infection for non-human primates (Xu et al., 2021).

3. Rare immune response may cause clots after Covid-19 viral vector vaccine

The adenoviral vector definitely fulfills the criteria of stimulating appropriate immune responses. However, its mechanism of action is also responsible for health issues involved with the vaccine. Although infrequent, reports of blood clots linked to decreased blood platelet counts have been made subsequently to administration of the COVID-19 vaccines of AstraZeneca (AZ) or Johnson & Johnson (J&J) (Aladdin, Algahtani, & Shirah, 2021; Marcucci & Marietta, 2021). This condition is identified as basis with Thrombocytopenia Syndrome, or TTS for short. According to earlier media reports, indications that ageing females suffered increased risks of developing this condition were not proven true yet, and that there are currently no indications of any risk elements which heightens a person's susceptibility to TTS (Tsilingiris, Vallianou, Karampela, & Dalamaga, 2021). The TTS condition is defined by these three symptoms (De Cristofaro & Sanguinetti, 2021; Lavin et al., 2021). Firstly, it is venous or arterial thrombosis (De Cristofaro & Sanguinetti, 2021; Lavin et al., 2021). It is more probable to conclude for TTS if it occurs at unexpected sites such as with cerebral sinus venous thrombosis (CSVT) (De Cristofaro & Sanguinetti, 2021). These are unusual manifestations of the more common venous thromboembolism (Abou-Ismail, Moser, Smock, & Lim, 2021). Secondly, symptoms of TTS include mild to severe thrombocytopenia (Marcucci & Marietta, 2021).

Thirdly is the testing for Platelet Factor 4 (PF4) heparin-induced thrombocytopenia (HIT) enzyme-linked immunoabsorbent assay (ELISA) positivity, or PF4 HIT ELISA for short (Marcucci & Marietta, 2021; Reilly-Stitt et al., 2021). This positivity was first observed in TTS patients who had received the ChAdOx1 nCov-19 AZ vaccine five to sixteen days prior (Reilly-Stitt et al., 2021). This vaccine is currently being offered in parts of the world, such as Europe, UK, and Canada (Reilly-Stitt et al., 2021). According to reports from Europe and the United Kingdom, most TTS patients were under the age of 50, with the eldest being 77 years of age (Reilly-Stitt et al., 2021). More than 65% of patients positively-tested for PF4 HIT ELISA patients were female (Reilly-Stitt et al., 2021). Only a tiny proportion of the positively-tested patients had a record of pre-existing thrombotic risk factors, with none having recently been administered heparin prior to condition development. A considerable portion of patients featured severe symptoms at the moment of thrombosis or thrombocytopenia discovery. Additionally, more than 30% of this group of TTS patients have died (Reilly-Stitt et al., 2021). More

recently, the TTS condition has been discovered in individuals being administered the Johnson & Johnson (J&J)'s Ad26.COV2.S vaccine as well (Valsecchi et al., 2021). Patterns in clinical manifestations, duration following vaccine jab, as well as age and gender correlations were strikingly identical to those observed in TTS occurrences after vaccination of AZ. These two vaccines are based on recombinant adenoviral vectors, which encodes for the immunogen of SARS-CoV-2's S protein, with AZ being chimpanzee-derived and human-based for J&J (Marcucci & Marietta, 2021). There were no reports about patients who were vaccinated with Moderna or Pfizer-BioNTech's mRNA technology were reported to be diagnosed with TTS. Remarkable clinical parallelism of TTS to heparin-induced thrombocytopenia or HIT, and PF4-heparin ELISAs involved in these indicative cases resulted in the eventual recognition of circulating PF4-reactive antibodies. These PF4-reactive antibodies have platelet-activation capabilities without requiring presence of heparins. However, *in vitro*, IVIGs (intravenous immune globulins) or monoclonal antibodies which block Fc receptors can succeed in preventing the PF4-reactive antibodies from activating platelets. These clinical and laboratory characteristics are comparable to those seen in a few uncommon conditions of autoimmune thrombosis, which is related to thrombocytopenia and displays HIT-like symptoms (De Cristofaro & Sanguinetti, 2021; Warkentin & Greinacher, 2021). A few individuals have complained of headaches four days after receiving the vaccine. According to the case reports, patients experienced a generalised epileptic seizure on day 7, hemianopia to the right, and mild aphasia 13 days following the vaccination (Wolf et al., 2021).

4. Mechanism of thrombosis with thrombocytopenia syndrome (TTS)

TTS is a condition in which blood clots occur in the presence of low platelet counts following vaccination (Tsilingiris et al., 2021). The most plausible mechanism is the antibodies cause the activation of platelets on a large scale, resulting in decreased platelet numbers and thus thrombosis, even though the exact mechanism remains unknown (Aladdin et al., 2021). TTS is thus said to resemble HIT but not heparin-induced (Arepally & Ortel, 2021; Long, Bridwell, & Gottlieb, 2021). VITT is induced by antibodies that bind to platelet factor 4 (PF4, also known as CXCL4). These antibodies are immunoglobulin G (IgG) molecules that stimulate platelet FcIIa receptors with a modest affinity (receptors on the platelet surface that bind the Fc portion of IgG) (Greinacher et al., 2021). VITT antibodies attach to platelets via an eight amino acid region on the platelet surface called PF4 positioned within the heparin-binding site. Heparin inhibits VITT antibody binding (Greinacher et al., 2021; Huynh, Kelton, Arnold, Daka, & Nazy, 2021; Schultz et al., 2021). VITT antibodies recognise amino acids that overlap but diverge from those recognised by HIT antibodies, and VITT antibody binding to platelets is greater than HIT antibody binding. The understanding of the mechanisms by which the vaccines in question induce the production of new antibodies (and immune stimulation of preexisting antibodies) are unknown. According to preliminary theories, vaccine components (which include virus proteins and free DNA) could bind to PF4 and produce a neoantigen. It is unspecified which of the vaccine's >1000 protein components could contribute to platelet activation (Huynh et al., 2021). PF4 is a positively-charged tetrameric protein; the positive charge of PF4 molecules causes them typically to repel one another; however, in the presence of negatively charged (polyanionic) molecules such as heparin or endogenous polyphosphates, PF4 may form higher-order structures that function as neoantigens, causing the immune system to respond. DNA and RNA have polyanionic characteristics, and when attached to PF4, they may produce a neoantigen that can cause disease (Huynh et al., 2021). Anti-PF4 antibodies induce "pancellular" activation, which means that they activate monocytes (resulting in tissue factor expression), neutrophils (resulting in NETosis), and endothelial cells in addition to platelets and coagulation reactions (leading to tissue factor expression). The activation of these additional cell types results in an increased risk of thrombosis (Greinacher et al., 2021; Huynh et al., 2021).

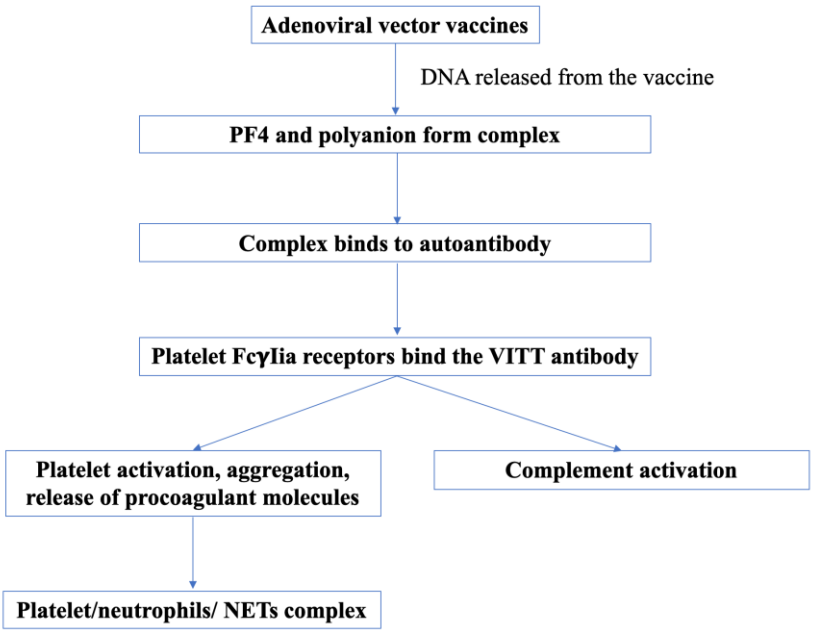

Figure 1. Proposed mechanism of adenoviral vector-based vaccines induced thrombosis with thrombocytopenia syndrome. PF4; Anti-Platelet Factor 4, NETs; Neutrophil Extracellular Traps, VITT; Vaccine-induced Thrombotic Thrombocytopenia

Thrombosis in VITT can eventuate in typical venous thromboembolism sites, including pulmonary embolism (PE) or deep vein thrombosis (DVT) (Gabarin et al., 2021). However, a distinct feature of the syndrome is thrombosis in unusual sites such as the splanchnic (splenic, portal, mesenteric) veins, adrenal veins (risk of adrenal failure), and cerebral and ophthalmic veins. Arterial thrombosis, such as ischemic stroke (often in the middle cerebral artery), and peripheral arterial occlusion have also occurred, frequently in patients with venous thrombosis (Pomara et al., 2021a & 2021b). The pathophysiologic basis for these uncommon thrombosis sites is unknown. The allocation is comparable to other rare thrombophilias, such as paroxysmal nocturnal hemoglobinuria (PNH) and thromboembolic complications associated with a JAK2 mutation. Autopsy studies on VITT victims revealed a catastrophic venous thrombosis involving numerous large and small vessels (Pomara et al., 2021a & 2021b). The majority of cases occurred between 4 and 20 days after receiving the AZ vaccine and in women under 60 years of age. Several cases have also occurred following vaccination with the J&J vaccine (Sharifian-Dorche et al., 2021). As with many other studies, the underlying mechanisms of the rare adverse condition of TTS remains a mystery, although a clinical resemblance to HIT has constantly been recognised (Greinacher et al., 2021). Eichinger and colleagues examined patients featuring clotting disorders which resembled HIT after administration of the AZ ChAdOx1 nCov-19, and not receiving heparin prior to symptom onset either (Eichinger, Warkentin, & Greinacher, 2021). Plasma samples from patients show antibodies' presence which is consistent with an HIT's autoimmune variant, in which platelets become abnormally activated without heparins' presence (Eichinger et al., 2021). These findings are useful as a proposed diagnostic and therapeutic strategy for management based on laboratory and clinical data (Eichinger et al., 2021). Eichinger and colleagues' antibody tests can be used in the clinic to diagnose and inform treatment decisions. Additional research is needed to explain the specific vaccine compositions that may cause this uncommon disorder and further elucidate the mechanisms involved (Eichinger et al., 2021). Additionally, patients with severe thrombocytopenia had low plasma fibrinogen levels and exceedingly high D-dimer levels (Pomara et al., 2021a & 2021b). According to another research led by Pomara's team, they suggested that the anti-PF4 antibodies of the IgG class could have been produced by being exposed to substances of polyanionic nature within the vaccine contents (Pomara et al., 2021a & 2021b). Furthermore, Pomara's team also decided to distinguish HIT from this similar syndrome by utilising the term 'vaccine-induced thrombotic thrombocytopenia' or VITT. Regarding the thrombus formation being linked to a reduction in platelet count, it should also be noted

that this phenomenon also occurs during natural COVID-19 and influenza infections (Pomara et al., 2021a & 2021b). This pattern in platelet decrease is also recorded in humans after being injected with various vaccine types. This includes MPR-mups, polio, and hepatitis vaccines (Pomara et al., 2021a & 2021b). With this information, Pomara and team suggested that the cause of this platelet decrease could be resulted from a 'cross-reaction' with platelets of the new antibody (Pomara et al., 2021a & 2021b). In molecular mimicry, similarities could occur between the antigen of the platelets' surface and those of the pathogens (Pomara et al., 2021a & 2021b). This cross-reaction meant that platelets would eventually go through the process of lysis via T-cell lymphocytes (Pomara et al., 2021a & 2021b)). A hypothesis suggesting the possibility of impurities within the vaccine contents was also raised. However, this notion was dismissed as the two cases used in Pomara's study confirmed that they were administered vaccines of different batches (Pomara et al., 2021a & 2021b).

5. Genders concern about rare blood clot from viral vector Covid-19 vaccine

Not targeting women only in particular, suspected cases of blood clots have emerged in patients of all ages and all genders (Riad et al., 2021). Despite reports from several countries conveying a considerably greater female to male case ratio such as events based on the report given to the UK's MHRA, a distinctive gender divergence has not been observed and thus cannot be established (Makris, Pavord, Lester, Scully, & Hunt, 2021). It is true that the total reported female incidence rates are higher than in males. However, this difference is not only small, but also not seen across all age groups. Furthermore, external factors that may be unprecedented for such as higher female vaccination rates earlier on in the rollout may come into play (Cliff-Patel. Moncrieff, & Ziauddin, 2021; Makris et al., 2021). This may be one of the factors contributing to the slight edge of female cases over their counterparts.

According to the United States' CDC and the Food and Drug Administration (FDA), the recommended usage of Johnson & Johnson's Janssen (J&J/Janssen) COVID-19 Vaccine has resumed in the United States, despite a temporary pause earlier (Oliver & Shimabukuro, 2021). In reports, adverse events documented after usage of J&J/Janssen vaccine indicate a heightened risk of the thrombosis with thrombocytopenia syndrome (Oliver & Shimabukuro, 2021). Virtually all reports of this severe reaction involving thrombosis with low platelet counts are seen occurring within women of 50 years of age or younger (Oliver & Shimabukuro, 2021). Up to current date, a thorough review of all available data shows that the J&J/Janssen COVID-19 Vaccine's established and potential benefits outweigh its established and potential risks. Nonetheless, adult women younger than 50 years of age should still be mindful of a greater occurrence of this rare adverse reaction in their gender and age group (Marcucci & Marietta, 2021; Oliver & Shimabukuro, 2021). The point that this risk of adverse reactions are linked to the adenovirus vector technology, and that there are also other COVID-19 vaccine options available for which no similar risk has been identified.

There was publication for Nicolai and team stated that TTS could cause from platelet distribution, platelet larger cell ratio also known as P-LCR as well as mean platelet volumes are values which did not show any difference in the study (Nicolai et al., 2021). This reduction of platelet count observed was in fact dose-dependent, which showed direct correlation with the quantity of adenovirus-binded platelets present in the blood after one hour of intravenous injection. Mice with AID-/- sIgM-/- and lacking the IgM and IgG antibodies displayed a similar platelet count dynamic. This also indicates that the development of thrombocytopenia within 48 hours following an intravenous injection of ChAdOx1 nCov-19 is not antibody-dependent too. Nevertheless, intravenous injection and not intramuscular injection of ChAdOx1 nCov-19 brought about a great rise in platelet-adenovirus clumps/aggregates (Nicolai et al., 2021). However, these clumps/aggregates formed had a rather limited dwelling time and thus quickly vanished from the blood circulation after not long (Nicolai et al., 2021). Following this disappearance of clumps/aggregates, the value of platelet counts rose up accordingly as well. In this study, Nicolai and his colleagues also did a further investigation on whether the adenovirus binding is responsible for this platelet reduction, they simultaneously administered labeled platelets which were either ChAdOx1 nCov-19 or BNT162b2 (Nicolai et al., 2021). An observation has also been recorded, showing that platelets incubated with the ChAdOx1 nCov-19 adenovirus were particularly removed from the blood circulation (Nicolai et al., 2021). Results show a 2.8 ± 1.1 hours half-life for ChAdOx1 nCov-19 incubated platelets compared to a 10 ± 3.7 hours half-life for BNT162b2 incubated platelets. Additionally, mouse platelets were also recorded to display an activated phenotype, featuring an increased P-Selectin (CD62P) when injected intravascularly ChAdOx nCov-19 24 hours ago

compared with an intramuscular injection (Nicolai et al., 2021). According to a study by Cari and team, it was concluded that CVT, SVT, and thrombocytopenia frequencies show very limited differences between the two genders in younger age groups. However, occurrences of these serious adverse effects (SAEs) are more frequent in middle aged females than males from the same age group. Ever since vaccination took place, it is widely known that the numbers of SAEs and mortality from ChAdOx1 nCov-19 recipients was greater in females compared to males. According to Cari and team, this observation can be stemmed from greater vaccination rates amongst the females than males. This data was obtained from several European countries. Their team has come up with a generalised ratio of females to males in the vaccinated population to be 3:2. It was also found that SAE risks in females remained equally high throughout all age groups whereas males' risk decreased with increased age (Cari et al., 2021).

6. Conclusion

To conclude, the vaccination of AstraZeneca's ChAdOx1 nCov-19 is a direct stimulant for induction of the rare albeit life-threatening immune thrombotic thrombocytopenia syndrome (TTS). Its mechanism involves mediation utilising platelet-activating antibodies against PF4, and as a result, imitating autoimmune heparin-induced thrombocytopenia. However, it must be noted that despite the possibilities of these rare clinical issues, overall benefits of adenoviral vector-induced immunity greatly overweigh its drawbacks. Clinical testing for TTS should involve seeking for CSVT presence, mild to severe Thrombocytopenia, and a positivity for PF4-Heparin Induced Thrombocytopenia (HIT) ELISA

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