Vaccine-Induced Thrombotic Thrombocytopenia (VITT) Associated with AstraZeneca Vaccine: A Comprehensive Review

Babar Naeem, Junaid Saleem, Mamoon Akbar Qureshi

Allama Iqbal Medical College/Jinnah Hospital, Lahore; Federal Medical College (FMC), Islamabad

Abstract

Several vaccines have been approved to be used during the COVID-19 pandemic. However, serious concerns have been raised due to vaccine-induced thrombotic thrombocytopenia (VITT) reported with the AstraZeneca vaccine. This study is done to assess the vaccine’s safety and summarize the background, evaluation, and management of a patient with VITT. Employing a meticulous literature search on PubMed and Google Scholar using keywords such as "AstraZeneca," "COVID-19 vaccine," "Clot," "Clots," "Thrombosis," and "Thrombus formation" in various combinations, 34 resources were identified, with 11 containing primary data on 28 documented VITT cases. The analysis revealed a gender distribution of 28.6% male and 71.4% female, spanning ages 22 to 74 years (median: 36 years). VITT symptoms manifested within 1 to 17 days post-vaccination. The predominant thrombotic sites were Central Venous Thrombosis, Splenic Vein Thrombosis, and Pulmonary Embolism. Notably, 46.4% of cases showed improvement, while 53.6% resulted in fatalities. This research underscores the rare but serious risk of vaccine-induced thrombotic thrombocytopenia associated with AstraZeneca vaccination, highlighting the importance of continued vigilance and monitoring in the ongoing global vaccination campaigns.

Corresponding Author | Dr. Babar Naeem, Allama Iqbal Medical College/Jinnah Hospital, Lahore
Email: babar_naeem@hotmail.com
Keywords | Vaccine, Thrombotic, Thrombocytopenia, AstraZeneca
Africa indicated a 62% efficacy with two standard doses and 90% with a low dose followed by a standard dose, resulting in an overall effectiveness of 70.4% in preventing symptomatic COVID-19.\(^1\)

Despite the effectiveness of COVID-19 vaccines in reducing mortality and morbidity, reported side effects, particularly with AstraZeneca, include mild reactions such as fatigue, pain at the injection site, and myalgia. Severe reactions, though extremely rare, involve anaphylaxis, blood clots, angioedema, and Guillain-Barré syndrome.\(^3,4\)

Notably, concerns have arisen regarding AstraZeneca’s association with abnormal clot formation, specifically cerebral thrombosis and low platelet count leading to vaccine-induced thrombotic thrombocytopenia (VITT) or thrombotic thrombocytopenia syndrome (TTS). European countries temporarily suspended AstraZeneca’s use in March 2021 due to thrombosis concerns, but subsequently, vaccine distribution resumed with assurances from the World Health Organization (WHO) and European Medicine Agency (EMA) that the benefits outweigh the risks.\(^5\) Reports indicated rare instances of cerebral venous thrombosis (CVT) and other thrombosis cases in the European Union and the United Kingdom.

The mechanism of VITT remains unknown, but molecular mimicry is proposed, with antibodies against spike proteins potentially cross-reacting against platelet antigens, leading to platelet activation and aggregation, resulting in thrombocytopenia and thrombus formation. This phenomenon parallels heparin-induced thrombocytopenia and is supported by the detection of anti-platelet antibodies in VITT patients.\(^6,7\) VITT typically manifests 4 to 30 days post-vaccination with symptoms like severe headache, abdominal pain, and shortness of breath. Prompt medical evaluation, including CBC, imaging for thrombosis, and assessing anti-PF4, fibrinogen, and D-dimer levels, is crucial when VITT is suspected.\(^8,9\)

Considering that clinical trials primarily assess vaccine efficacy, post-marketing surveillance and pharmacovigilance are vital to identifying rare side effects. This study aims to comprehensively review thrombotic reactions associated with the AstraZeneca vaccine, providing insights for understanding and managing this syndrome based on current knowledge.

### Methods

A literature search was conducted utilizing PubMed, Google Scholar, and an internal database to accomplish these objectives to identify resources and articles. The search process was carried out on June 20, 2021, and was updated on March 25, 2023, using the following Keywords: "AstraZeneca", "COVID-19 Vaccine", "Clot", "Clots", "Thrombosis", and "Thrombus formation" in isolation as well in different combinations. The literature search was limited to the articles available in English and published in peer-reviewed journals. Papers were excluded if they were written in any language other than English, had a duplicate study population, and were not peer-reviewed. We reviewed all relevant sources and decided which sources to include by consensus.

### Results

A total of 34 resources were found in the literature search, and 11 of these contained primary data. A total of 28 cases of Vaccine-Induced Thrombotic Thrombocytopenia (VITT) were identified in these studies. Among these cases, 28.6% (n=8) were male, while 71.4% (n=20) were female. The age range of the patients spanned from 22 to 74 years, with a median age of 36 years. The onset of VITT symptoms after vaccination varied, occurring anywhere from 1 day to 17 days post-vaccination. The most prevalent thrombotic site observed in these patients were Central Venous Thrombosis, followed by Splenic Vein Thrombosis and Pulmonary Embolism. Within the scope of the included studies, 46.4% (n=13) of the cases showed signs of improvement, while 53.6% (n=15) of them resulted in fatalities.

A summary of these studies is given in Table 1.

### Discussion

The incidence of clot formation post-AstraZeneca vaccination is exceptionally rare, estimated at around 6 per 100,000 vaccinations, with 28 reported cases in Europe and the United Kingdom, involving nearly 17 million doses.\(^10\) Data from Denmark and Norway, covering 280,000 vaccinated individuals, reported 11 adverse events per 100,000 vaccinations.\(^11\) Case series from Norway, Germany, and Austria outlined patients developing clotting abnormalities and thrombocytopenia within 5-30 days of AstraZeneca vaccination.\(^6,12\) Compared to AstraZeneca, other vaccines like Moderna...
and Pfizer reported fewer cases of deep vein thrombosis, with 29 and 13 cases, respectively, from February 17 to March 12, 2021.\textsuperscript{13} However, considering the background incidence of clot formation (56-182 per 100,000 population), establishing a clear causal link between AstraZeneca and thrombosis is challenging due to limited data, under-reporting, and confounding factors.\textsuperscript{13} Larger cohort studies are needed for a comprehensive understanding.

Vaccine-Induced Thrombotic Thrombocytopenia (VITT) symptoms typically onset 1 to 17 days post-vaccination, presenting as severe or recurrent headache, vomiting, abdominal pain, shortness of breath, chest pain, limb pain or swelling, or visual changes within 4-30 days.\textsuperscript{8,9} Symptoms within 24-48 hours post-vaccination, like fever or headache, are normal immune responses and not indicative of VITT.

In cases of suspected VITT, urgent medical evaluation is crucial, involving a complete blood count (CBC), peripheral smear, and imaging for thrombosis. VITT patients exhibit thrombocytopenia, high anti-PF4 levels, decreased fibrinogen, and elevated D-dimers. Imaging depends on specific symptoms, with CT or MR venography for headaches or visual changes and contrast-enhanced abdominal CT for abdominal complaints.\textsuperscript{8,14} The proposed mechanism involves molecular mimicry, where spike protein antibodies cross-react with platelet antigens, aligning with the observed timing of VITT occurrence and associations with other autoimmune diseases linked to COVID-19.\textsuperscript{6}

While resembling Heparin-Induced Thrombocytopenia (HIT) in platelet activation and consumption, VITT presents unique features. No prior heparin exposure is noted, and thrombotic events occur at unusual sites. Research is warranted to identify risk factors and understand genetic predisposition in VITT pathogenesis.\textsuperscript{8,15} Treatment recommendations for VITT, extrapolated from HIT, include avoiding heparin, platelet transfusion,

### Table 1: CVT, Cerebral venous thrombosis; SVT, splanchic venous thrombosis; PE, pulmonary embolism.

<table>
<thead>
<tr>
<th>Sr #</th>
<th>Authors</th>
<th>Sample size</th>
<th>Age</th>
<th>Sex</th>
<th>Days after vaccination</th>
<th>Clinical Site of Thrombosis</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>J. Helms et al</td>
<td>01</td>
<td>74</td>
<td>M</td>
<td>1</td>
<td>CVT</td>
<td>Improved</td>
</tr>
<tr>
<td>2</td>
<td>Bjørnstad-Tuven et al</td>
<td>01</td>
<td>30</td>
<td>F</td>
<td>3</td>
<td>CVT</td>
<td>Expired</td>
</tr>
<tr>
<td>3</td>
<td>Andreas Grünacher et al</td>
<td>11</td>
<td>Median age e36 years (range 22-49)</td>
<td>9=female 2=male</td>
<td>5-16 days</td>
<td>CVT=09 SVT=03 PE=03</td>
<td>6 expired 5 improved</td>
</tr>
<tr>
<td>4</td>
<td>Nina H. Schultz et al.</td>
<td>05</td>
<td>37</td>
<td>M</td>
<td>8</td>
<td>CVT</td>
<td>Expired</td>
</tr>
<tr>
<td>5</td>
<td>Marc E Wolf et al.</td>
<td>03</td>
<td>22</td>
<td>F</td>
<td>10</td>
<td>CVT</td>
<td>Improved</td>
</tr>
<tr>
<td>6</td>
<td>Puja R. Mehta</td>
<td>02</td>
<td>32</td>
<td>M</td>
<td>7</td>
<td>CVT</td>
<td>Expired</td>
</tr>
<tr>
<td>7</td>
<td>Massimo Franchini</td>
<td>01</td>
<td>50</td>
<td>M</td>
<td>7</td>
<td>CVT</td>
<td>Expired</td>
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<tr>
<td>8</td>
<td>Vincenzo D’Agostino</td>
<td>01</td>
<td>54</td>
<td>F</td>
<td>7</td>
<td>CVT</td>
<td>Expired</td>
</tr>
<tr>
<td>9</td>
<td>RA Blauenfeldt et al</td>
<td>01</td>
<td>60</td>
<td>F</td>
<td>9</td>
<td>MCA</td>
<td>Expired</td>
</tr>
<tr>
<td>10</td>
<td>Antonios Bayas</td>
<td>01</td>
<td>55</td>
<td>F</td>
<td>10</td>
<td>Ophthalmic vein MCA</td>
<td>Improved</td>
</tr>
<tr>
<td>11</td>
<td>Maaike Vierstraete et al</td>
<td>01</td>
<td>49</td>
<td>M</td>
<td>9</td>
<td>Aortic Right femoral</td>
<td>Improved</td>
</tr>
</tbody>
</table>

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anticoagulation, and intravenous immunoglobulin (IVIG). Non-heparin anticoagulants like fondaparinux, argatroban, and apixaban are options. Treatment initiation based on pending anti-PF4 results is acceptable if suggestive clinical presentation, CBC, and imaging are present, but confirmatory testing before IVIG is essential. No data supports corticosteroid administration; plasma exchange may be considered if no improvement is seen despite anticoagulation and IVIG. Outcomes for described patients were generally favorable.\textsuperscript{8,9,14}

Acknowledging limitations, including a limited number of documented events, under-reporting, and confounders, this review provides valuable insights into AstraZeneca vaccine-related thrombosis. We conclude that, weighing benefits and risks, AstraZeneca COVID-19 vaccine administration should continue due to its overall benefits outweighing risks. Careful consideration for patients with thrombotic history is advised. Prompt symptom recognition, urgent evaluation, and collaboration with experts are crucial. Enhanced adverse effects reporting and further research are needed to refine our understanding of this rare phenomenon.

Conclusion

AstraZeneca COVID-19 vaccine developed by Oxford is a very safe and effective vaccine against COVID-19. Most of the side effects are mild and do not require any treatment. Therefore, it is being used on a very large scale. However, concerns have been raised against the development of vaccine-induced thrombotic thrombocytopenia. This side effect is very serious but extremely rare and presents with thrombosis at unusual sites, and low platelets count.

Conflict of Interest: The authors declare no conflict of interest.

Funding Source: None

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