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EDITORIAL

Aducanumab and adenoviral COVID-19 vaccines: increased cerebral hemorrhage risk?

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1. Introduction

The U.S. Food and Drug Administration's approval of aducanumab – an anti-amyloid human immunoglobulin G1 (IgG1) monoclonal antibody for treating Alzheimer's disease – has ignited a firestorm of debate [1]. Proponents of the FDA approval suggest that aducanumab promises a disease-modifying therapy for AD. Opponents (including the Peripheral and Central Nervous System Drugs Advisory Committee of FDA) are mainly concerned about uncertain clinical benefits and the risk of harm. Amyloid-related imaging abnormalities (ARIA) and its two presentation types of microhemorrhage and superficial siderosis (ARIA-H), and edema (ARIA-E) are the principal adverse reactions of aducanumab that might be more pronounced and serious in real-world scenarios [2,3]. Besides, due to the lack of post-marketing experience, there is very scarce knowledge about interactions with other drugs; so far, no contraindications have been registered [3]. Thus, it is quintessential to foresee any significant interactions with widely used drugs. Worsening of the side effect profile could further jeopardize the already questioned risk/benefit profile of this treatment.

In the light of the ongoing coronavirus disease 2019 (COVID-19) pandemic, vaccine-induced immune thrombotic thrombocytopenia (VITT) has emerged as one of the rare but devastating complications associated with adenoviral vector ChAdOx1 nCoV-19 and Ad26.COV2 vaccines [4]. To broadly define such cases, the Brighton collaboration coined the term – thrombosis with thrombocytopenia syndrome (TTS) [5].

Notably, cerebral hemorrhage is a potentially fatal manifestation of VITT (TTS). The concomitant administration of COVID-19 vaccine and aducanumab in elderly patients might increase their hemorrhagic risk. Although VITT mostly affects younger patients [6,7], occurrence in older adults of up to 79 years old has been reported [8]. This population overlaps with the target group of aducanumab therapy. Hence, we speculate that administration of aducanumab after a recent vaccination with the adenoviral COVID-19 vaccine might have an additive effect on the cerebral hemorrhage risk. Consequently, we discuss the possible underlying mechanisms and mitigation strategies.

2. Aducanumab-induced ARIA

A recent investigator-led secondary analysis found that 19.1% and 35.2% of the aducanumab-treated patients demonstrated microhemorrhage (ARIA-H) and edema (ARIA-E), respectively [9]. In the clinical trials with aducanumab, perhaps due to controlled and highly-selective recruitment of AD patients, no fatal cases were reported. However, in early Aβ immunization trials, after the death of two subjects, advanced cerebral amyloid angiopathy (CAA) was identified. CAA is a well-characterized and common small vessel disease in older adults that is defined by vascular amyloid-β (Aβ) accumulation, perivascular inflammation, and vascular leakage [10]. Due to the high prevalence of CAA in older adults, the possibility of increased ARIA-associated morbidity and mortality in the real-world setting may be higher.

Although the pathological mechanisms underlying the adverse reactions of aducanumab remain poorly understood, existing literature suggests that aducanumab binds with Aβ (amyloid-beta) aggregates (plaques, fibrils, and oligomers) and microglial Fcγ-receptor, and triggers the phagocytosis of β-amyloid plaques by microglial cells [11]. Furthermore, the binding of aducanumab with C1q (a complement protein subcomponent) and the interaction of C1q with Aβ may trigger microgliosis and astrogliosis, leading to chronic inflammation and neurodegeneration [11–13]. In this line, Xiong et al. proposed that aducanumab, via C1q-mediated astrogliosis, might disrupt the blood-brain barrier, thereby contributing to chronic cerebrovascular inflammation and ARIA [14].

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Nevertheless, whether astrogliosis directly causes microhemorrhage or defective clearance of aducanumab-Aβ complex triggers inflammation and culminates in microhemorrhage, or whether both mechanisms are involved remains to be investigated. Aducanumab is not known to cause thrombocytopenia, in contrast to adenoviral COVID-19 vaccines.

3. COVID-19 vaccines and vaccine-induced immune thrombotic thrombocytopenia (VITT)

A prospective cohort study found that the patients may present the symptoms of VITT (TTS) between 5–48 days after the first dose of the vaccine [8]. The study showed that the overall mortality rate was 22% and that the presence of intracranial hemorrhage and thrombocytopenia were independently associated with death. Although VITT mostly affects younger patients [6,7], occurrence in older adults of up to 79 years old has been reported [8].

It is important to note that intracranial hemorrhage typically occurs secondary to cerebral venous sinus thrombosis (CVST) in patients with TTS. A recent study demonstrated that sixty-eight percent of the cases presented intracranial hemorrhage secondary to CVST in the context of TTS [15]. Another study reported that 36% of the patients with VITT presented secondary intracranial hemorrhage due to CVST [8]. Hence, there is a lack of adequate evidence to directly link TTS with primary intracranial hemorrhage. Elevated venous pressure due to outflow obstruction might be the reason underpinning the occurrence of secondary hemorrhage in CVST patients with TTS.

Although intracranial hemorrhage secondary to CVST has been described primarily after ChAdOx1 nCov-19 vaccine, incremental risk of arterial thromboembolism and stroke after other types of COVID-19 vaccine should not be overlooked [16]. A review by Sharifian-Dorche et al. described that nearly half of the cases with post-vaccine VITT and CVST presented cerebral hemorrhage and/or subarachnoid hemorrhage [4]. Of note, the authors proposed a possible mechanism of post- vaccine VITT due to adenoviral vaccine constituents. Accordingly, the free DNA or adenoviral capsid component may bind with platelet factor-4 (PF4) and elicit anti-PF4 antibodies [4].

Despite the presence of immune response in VITT, there does not seem to be a rationale to test for anti-PF4 antibodies before administering aducanumab. Emerging reports show that anti-PF4 antibodies detected in patients with VITT do not interact with epitopes on the spike protein [17]. Moreover, patients with VITT receiving the second dose of COVID-19 vaccination do not seem to have a relapse of VITT [18]. These data suggest that the autoimmune response is independent of the spike antibody response nor is there any evidence of a link between anti-PF4 antibodies and aducanumab; thus, these findings do not support the anti-PF4 screening before administering anti-amyloid immunotherapy.

The anti-PF4 immune complex triggers Fcγ receptor-mediated platelet activation and the formation of platelet-derived microparticles. These microparticles kick off the prothrombotic cascade leading to thrombocytopenia [4]. In this line, Mastellos et al. [19] proposed that complement activation is the pivotal mechanism underpinning VITT in the patients presenting high titers of anti-PF4 autoantibodies. First, the complexation of vaccine constituents with PF4 triggers the activation of C3 leading to the production of pro-inflammatory components and effectors (C3a, C5a, etc.). In addition, human complement C1q (a pattern recognition molecule)–via Fcγ receptor-mediated activation of platelets, monocytes, and neutrophils–triggers thrombosis/thromboinflammation and VITT [19], which might culminate in brain hemorrhage.

4. Possible increased brain hemorrhage risk

Alzheimer's patients under aducanumab therapy are at higher risk of a brain hemorrhage. First, AD very often co-occurs with cerebral amyloid angiopathy that causes vascular accumulation of β-amyloid, causing perivascular inflammation, vessel leakage, rupture, and intracranial hemorrhage [10]. Second, aducanumab therapy is associated with a high rate of microhemorrhages (ARIA-H) [2, 9]. Both mechanisms may have an additive effect on brain hemorrhage risk. Similar to humans, murine models experience microhemorrhages in an age-related fashion and are a valuable source for studying mechanisms related to microhemorrhages [20,21]. In murine studies, intravenous administration of ^{ch}12F6A, a chimeric version of aducanumab, was found to provoke cerebrovascular inflammation, thrombosis, and cerebral hemorrhage [11].

Although possible that the mechanisms of brain hemorrhage due to COVID-19 vaccines and aducanumab follow independent pathways, clinicians should be cautious of possible exacerbation of the hemorrhagic risk when these treatments are concomitant. Even though VITT is rare, it is associated with devastating morbidity and mortality. It is possible that the platelet activation – a pivotal event in the VITT pathology – could trigger an inflammatory reaction and lead to aggravation of microvascular injury and brain hemorrhage caused by aducanumab [14,19]. In addition, the stimulation of Iba-1-positive microglia directly by aducanumab and indirectly by COVID-19 vaccines via platelet activation may increase the risk and severity of brain hemorrhage when compared to the risk of these treatments alone [4,11,14]. Considering the odds of exacerbated cerebrovascular adverse reactions and consequent brain hemorrhage due to combined effects of COVID-19 vaccine (i.e. VITT) and aducanumab (i.e. ARIA) (Figure 1) in the fragile AD population, clinicians must be vigilant of this scenario in clinical trials and real-world settings. Given that aducanumab trials were carried out before the COVID-19 pandemic, the clinical evidence of the additive effects of COVID-19 vaccination and aducanumab therapy is not yet available. However, clinicians and investigators should be aware of possible interaction and increased risk of hemorrhagic events, based on the outlined mechanistic explanations. More longitudinal clinical data will be needed to fully understand the potential additive hemorrhage-inducing effects of COVID-19 vaccines and aducanumab immunotherapy.

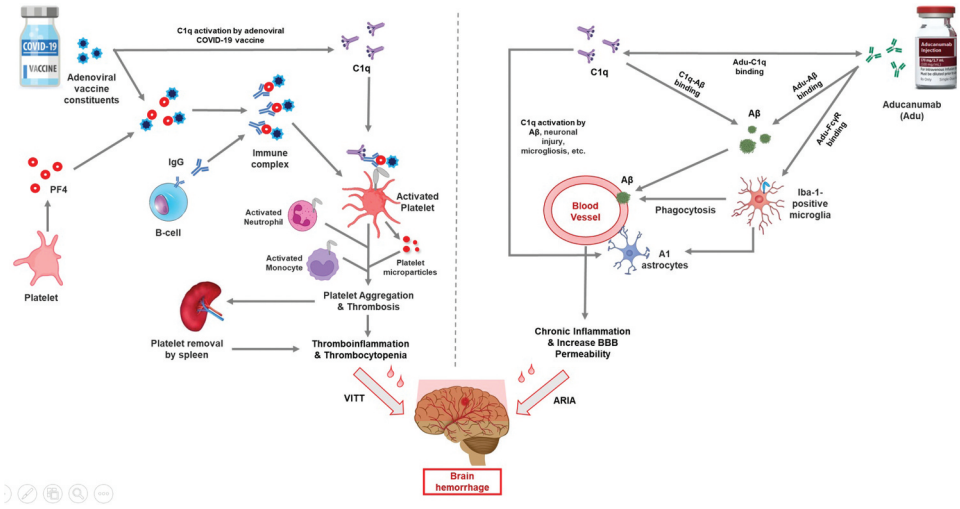

Figure 1. A schematic representation of the possible risk for an increased brain hemorrhage caused by the concomitant administration of aducanumab and adenoviral COVID-19 vaccines. The possible mechanisms of VITT (elicited by adenoviral COVID-19 vaccines) and ARIA (provoked by aducanumab) are outlined. Aducanumab may trigger astrogliosis – via Fcγ receptor-mediated activation of Iba-1+ microglia and C1q-mediated complement activation. In addition, the binding of aducanumab with Aβ and compromised perivascular clearance triggers chronic inflammation. These intricate events may collectively contribute to blood vessel leakage and ARIA (microhemorrhage and edema) in AD patients under aducanumab therapy. Besides, the adenoviral vaccine constituents – via Fcγ receptor-mediated activation of platelets (fueled by C1q-mediated complement activation) and other immune effector cells (e.g. neutrophils and monocytes) may lead to thrombosis and inflammation. Increased thrombotic reactions can contribute to thrombocytopenia (VITT) and may ultimately lead to brain hemorrhage. These additive interactions between aducanumab (i.e. ARIA) or COVID-19 vaccines (i.e. VITT) may exacerbate the associated hemorrhagic risk and mitigation strategies should be considered.

5. Mitigation of hemorrhagic risk

If the future provides evidence of increased risk of a cerebral hemorrhage after concomitant COVID-19 vaccination and anti-β-amyloid therapy, there could be several possible clinical scenarios where mitigation strategies would be useful. To avert the occurrence of such 'exacerbated' adverse reactions, the following bespoke approaches could be considered: i) aducanumab therapy should not be initiated earlier than 48 days after vaccination (as the risk of VITT seems to be attenuated thereafter) [8]; ii) AD patients under aducanumab therapy should be vaccinated with an mRNA-based vaccine whenever such choice is possible (as the risk of VITT seems to be lesser after mRNA-based vaccines [16]); iii) bloodwork could be performed before aducanumab administration to exclude thrombocytopenia iv) additional brain imaging (preferably MRI with iron-sensitive T2* or susceptibility-weighted images) could be performed in the interval between the COVID-19 vaccination and initiating/resuming aducanumab treatment to exclude incidental hemorrhage. Although, additional brain imaging could be a supplementary mitigation measure in certain higher-risk populations (patients with microbleeds, apolipoprotein E4 allele carriers, or previous cerebral venous thrombosis), the cost-effectiveness and clinical benefit of such measure remain to be investigated. Overall, these strategies will need further assessment if the outlined theoretical interaction mechanisms prove to be translated into the clinical setting. Meanwhile, clinicians should be cautious of the possible additive hemorrhage-inducing effects of COVID-19 vaccines and anti-β-amyloid immunotherapy.

In summary, aducanumab therapy predisposes the fragile AD population to the risk of cerebral hemorrhage (ARIA-H). On the other hand, adenovirus-based COVID-19 vaccines might trigger the rare syndrome, VITT – which may culminate in cerebral hemorrhage. We hypothesize that Fcγ receptor-mediated activation of platelets, microglia, and other immune-effector cells and the stimulation of inflammatory reactions by aducanumab (i.e. ARIA) or COVID-19 vaccines (i.e. VITT) may exacerbate the cerebrovascular injury. Nevertheless, if the suspected additive risk of cerebral hemorrhage becomes evident in the real-world setting, the outlined mitigation strategies should be considered.

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Declaration of interests

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