Editorials

Thrombosis after covid-19 vaccination

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Rapid Response:

Might post-injection distribution of CoViD vaccines to the brain explain the rare fatal events of cerebral venous sinus thrombosis (CVST)?

Dear Editor

The recent reports of cerebral venous sinus thrombosis (CVST) following administration of CoViD-19 viral vector vaccines (AZ/Oxford and J&J/Janssen) have a peculiar clinical presentation exhibiting haemorrhage, blood clots and thrombocytopenia.

We previously proposed a mechanism [1-2] to explain the vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) and reported that the genetic CoViD-19 vaccines (both viral and non-viral vector-based) may directly infect platelets or megakaryocytes triggering mRNA translation and consequent spike protein synthesis intracellularly. This may potentially result in an autoimmune response against platelets and megakaryocytes. The consequent thrombocytopaenia may lead to internal bleeding and spontaneous blood clots. We also proposed that the increased circulatory levels of acute-phase proteins, as observed in the pre-clinical vaccine studies in animals, may also be a contributory factor in putting the haemostatic system at an increased thrombotic potential [3].

The pharmacovigilance data confirmed the CVST incidences with all genetic vaccines (viral or non-viral vector), however, the regulatory authorities in their recent investigations reported that the CVST was unusually accompanied with thrombocytopenia in subjects injected with CoViD-19 viral vector vaccines (such as AstraZeneca and J&J/Janssen) than those injected with mRNA vaccines. We, therefore, looked at the preclinical

studies of these vaccines to ascertain their biodistribution to body tissues (for instance brain) beyond the injection site for a possible explanation of the rare fatal clots formed in the brain.

Although, the modern viral vectors that are used in CoViD vaccines are silenced (replication-deficient), each dose of the vaccine contains a very high viral load (e.g., 50 billion viral particles per dose in Ox/AZ or J&J/Janssen CoViD-19 vaccines whereas 100 billion viral particles per dose in the Sputnik-V). The viral particles are unlikely to be confined to the muscles at the injection site; they are free to distribute across the body and drain through the lymphatic system; their apparent volume of distribution is likely to be very high. The biodistribution of ChaAdOx1 containing HBV in BALB/c mice (study 0841MV38.001) indicated the highest viral levels at the injection site, but low levels of virus were still detected after 24 hours of injection in all other tissues (including blood, brain, heart, inguinal lymph node, kidney, liver, lung, gonads, and spleen). The proportional tissue distribution of viral vectors in the body tissues away from the injection site was likely to increase with time, however, biodistribution beyond 24h post-dose was not studied. The biodistribution of ChAdOx1 encoding nCoV-19 following intramuscular injection in mice (study 514559) was ongoing at the time of its regulatory approval [4]. The study 514559 was aimed to examine the biodistribution of ChAdOx1 nCoV-19 in bone marrow, brain, spinal cord, sciatic nerve, and other body tissues. The data from this study is not yet available in the public domain but this might provide evidence of vaccine delivery in the brain. We, therefore, agree with your comments that all vaccine-related data and analyses in possession of the regulatory authorities must be published in full without any further delays.

However, in the absence of the results of study 514559, the biodistribution of ChaAdOx1 HBV in mice (study 0841MV38.001) confirms the delivery of vaccine into the brain tissues. The vaccine may therefore spur the brain cells to produce CoViD spike proteins that may lead to an immune response against brain cells, or it may spark a spike protein-induced thrombosis. This may explain the peculiar incidences of the fatal CVST observed with viral vector-based CoViD-19 vaccines. There is very little information in the public domain to assess the biodistribution of all genetic vaccines, however, it is anticipated that if it is characteristic to the viral vector employed in the vaccine, then the other vaccines using similar technology may also lead to the same safety concerns. Some examples of these vaccines include AstraZeneca/Oxford (Chimp adenoviral vector), J&J/Janssen (Human adenoviral vector 26), CanSinoBio (Human adenoviral vector 5), and Sputnik V (Human adenoviral vectors 26 and 5).

For COVID-19 mRNA Vaccine (Pfizer or Moderna), the biodistribution studies in animals were not conducted. The surrogate studies with luciferase and solid-lipid nanoparticles (Pfizer) confirm a biodistribution to the liver and other body tissues beyond the administration site [5]. For Moderna, the biodistribution of mRNA-1647 (encoding CMV genes) formulated in a similar lipid nanoparticulate delivery system confirms a biodistribution beyond the injection site, in particular, the distribution to the lymph nodes, spleen and the eye was noted [6]. However, the detailed tissue-specific distribution of mRNA vaccines encoding SARS-CoV-2 spike proteins (Pfizer or Moderna) is not fully known that can offer invaluable insights into the potential safety of these vaccines in peoples with pre-existing conditions or those on certain medications.

The detailed biodistribution data including pharmacokinetics of various CoViD vaccines were not conducted by the vaccine manufacturers because the studies demonstrating biodistribution of antigens were considered ‘not required' by the regulatory authorities on the premise that vaccines work by an immunological response than the classic pharmacological approach. However, such an exemption may barely justify the conventional vaccines such as those incorporating whole inactivated virus, split virion, or the sub-unit vaccines, that directly attracts an immune response post-injection.

On the contrary, modern genetic vaccines work on the premise of gene delivery, therefore, a detailed biodistribution and pharmacokinetic evaluation of the formulated product is invaluable in understanding the potential impact of vaccine encoding gene transfection to various body tissues beyond the site of injection. Vaccines are one of the great discoveries in medicine that has improved life expectancy dramatically. However, if

genetic vaccines were to be sustained beyond the CoViD19 pandemic, a tissue targeted approach may be the way forward to limit the antigen (the encoding gene) distribution to the intended tissues only to improve the vaccine safety profile for a global mass public rollout. In comparison, the conventional vaccine approaches (classic non-genetic formulations) have a long history of human use across much wider age groups (infants to elderly) and have an established safety profile despite the current challenges in antigen propagation and large-scale production in a timely manner using conventional methods.

References:

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Competing interests: No competing interests

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