

# Spotlight on Adenovirus-Based Vaccines and Rare Thrombotic Events

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A recent paper from Moonla et al addressed the huge concern of coagulation disorders in COVID-19.<sup>1</sup> The current debate about blood clots, following administration of some vaccine formulas, is harassing the scientific community. Experts in the field are striving to make people trusted about the negligible hazard associated with those vaccines. Yet, truth is hidden within some fundamental evidence, which deserves further research. A paper from Stone et al, published on 2007, showed that the delivery of the recombinant adenovirus-based vectors (serotype 5) used for therapy, caused platelet sequestering, thus triggering their activation and also aggregation, which were followed by their entrapment in the liver and finally their capture by Kupffer cells.<sup>2</sup> Adenovirus serotype 5 (Ad5) is widely used as a recombinant, non replicative vector even for COVID-19 vaccine formulations<sup>3,4</sup> and the ability of Ad5 vectors to sequestering platelets, causing temporary thrombocytopenia, has been widely demonstrated.<sup>5,6</sup> Moreover, it seems that Ad5 binds the platelets CD62 and increases D-dimer for at least 6 hours following Ad5 introduction.<sup>2</sup> Recombinant Ad5 therefore can activate platelets. Despite this *in vitro* evidence may suggest some criticism about Ad5-based therapy and support caution in addressing Ad5 vaccine based safety, the rate of thrombogenic adverse effects is negligible, amounting to less than 0.00034%.<sup>7,8</sup>

Driving a car is much more hazardous, taking a flight is much more hazardous, therefore why fueling an outcry and enhancing the amount of reluctant people by sequestering Ad5-based vaccines? The real question is why this occurs and which subjects are involved.

In the elderly, that is, subjects aged over 65 yrs, a study from Msaouel et al reported a significant association of thrombocytopenia (HR = 1.45; 95% CI: 1.36-1.56) with a decrease in overall survival respect to individuals with normal platelets count.<sup>9</sup> To prevent this event, though particularly rare, physicians recommending to associate vaccination with salicylate therapy should be aware that salicylate may be associated with autoimmunity,<sup>10</sup> whereas, very recently, Bruton tyrosine

kinase (BTK) inhibitors are widely recommended to prevent immune thrombotic thrombocytopenia caused by vaccine-related adverse effects.<sup>11</sup> Common knowledge about thrombotic mechanism does not associate thrombosis risk with thrombocytopenia, yet with thrombocytosis, i.e. a platelets count higher than the normal range is alarming for blood clots, never the contrary. Yet, it seems that this consideration might be even flawed.

Blood clots appeared to occur much more frequently in relatively young women ( $\leq 45$ -50 yrs) undergoing Ad5-based vaccination,<sup>8</sup> in female subjects thrombocytopenia and micro-thrombotic events are often associated with hormonal estrogenic therapy,<sup>12</sup> therefore, some news about how come adverse effects in the coagulation pathway may occur with Ad5 vaccines, should find any possible, though anecdotal, explanation. Briefly speaking, as negligible and very rare are events associated with anaphylactic responses toward polyethylenglycole (PEG), in some vaccine formulation, the same can be argued about thrombotic very rare occurrences. After reading the very recent literature, it seems that thrombocytopenia may be one the leading causes of blood clots causing the rate of mortality observed upon some vaccination formulas.

For example, immune thrombocytopenia (ITP), contrarily to the majority of opinions, may cause sporadic cases of thrombosis.<sup>13</sup> Some authors reported that at least 20 events on 36 ITP patients resulted in micro-thrombotic events (55.6%), aside from age distribution and sex, and with a platelet count  $\leq 100 \times 10^3/\mu\text{l}$ .<sup>13</sup> The hypothesis is that platelet microparticles (PMPs), which are particularly frequent in ITP and very hard

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to be detected by routine blood count, may cause thrombotic events in these subjects.<sup>12</sup> PMPs, which can be yet detected by flow cytometry,<sup>14</sup> are generated also in heparin-induced thrombocytopenia,<sup>15</sup> therefore a thrombocytopenic condition may be causative of thrombotic events, though anecdotal and paradoxical.

ITP is very rare, with about 200,000 people worldwide, increases with increasing ages (over 60) and involves 2.6 times female subjects than males. Obviously, if this is one of the possible concern related to Ad5-employing vaccines, an anamnestic and pre-diagnostic panel should be debated within the scientific and medical community. The conclusion one could forward is that platelets count may be an early warning to access Ad5-based vaccination with the highest safety and anamnesis of heparin used as therapy considered a critical issue.

Pragmatism, urgency in vaccinating people during this COVID-19 emergency and burdensome managing may prevail. Anyway, this debate should be expanded within experts in the field and further investigation is needed to improve vaccine safety and greatly reduce thrombotic events in people.

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