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Mechanism of developing myocarditis after mRNA COVID-19 vaccines

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Abstract:

There have been studies which show that SARS-CoV-2 vaccinations and the development of myocarditis are related predominantly after the second dose of vaccination. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of coronavirus that causes COVID-19. This is a single stranded RNA virus which is very infectious in humans. SARS-CoV-2 vaccinations help develop immunity by imitating an infection.This activates the immune system to produce antibodies. In addition, COVID-19 vaccines reduce the risk of SARS-CoV-2 infection by working with the body's natural defense to develop immunity to the disease. Myocarditis, which is caused by Covid-19 mRNA can be severely extreme, especially in adolescent males. This is mostly caused by viral inflammation leading to strong social awareness. Factors contributing to hormones and antibodies are linked to the observed sex differences in myocarditis where there have been more cases across males compared to females. Covid-19 mRNA vaccines contain nucleoside-modified mRNA that encodes extreme spike glycoprotein of SARS-CoV-2 rather than the DNA or the virus itself. Some individuals develop myocarditis since the body's defense system may recognised the mRNA vaccine as an antigen so this activates the proinflammatory rapidly along with an immunologic pathway that may be associated with the formation of myocarditis. The mRNA vaccines for an antigen may be mistaken by the immune system so this may stimulate the pro-inflammatory cascades and the immune system's direction towards the heart.

Keywords: myocarditis, mRNA COVID-19 vaccines, SARS-CoV-2

Introduction:

SARS-CoV-2 vaccinations and the development of myocarditis has been reported to be correlated (1, 2). This link is clearly seen following the 2nd additional dose of both mRNA vaccines (BNT 162b2 and mRNA-1273) (3-5). Chronic heart failure is thought to be caused by myocarditis which to an extent can lead to death (5, 6). There is still not many information provided of the mechanism resulting in the heart disease but it has been seen that smallpox vaccines in adults also have similar adverse effects (7). Covid-19 mRNA vaccinations eventuating in myocarditis is thought to be a rare complication especially in youthful adults and adolescent males (3, 8, 9). Usually there is a 2 to 3 days gap period after the second dose of mRNA vaccine then myocarditis symptoms such as chest pain starts to appear (10, 11). This causes high cardiac troponin levels. Severe myocarditis is usually caused by viral infection including the infection of SARS-CoV-2 which is the coronavirus disease (12). There has been strong social media awareness of the risks of myocarditis after mRNA vaccinations. Even though the risk of developing myocarditis is low, there has been acknowledgement of the vaccine

causing severe effects since it is made from mRNA technology (13). However, an important thing to be noted is that the risks associated with the mRNA vaccines are lower than the risks of high healthcare provision and death from COVID-19 virus (14). In addition, the relative risk of myocarditis and arrhythmia manifold can be reduced once more boosters of the mRNA vaccines have been ejected into individuals (7, 15). This decrease in risk can be more significant in adolescents. This review aims to compare the age differences in individuals who developed myocarditis after mRNA vaccines along with identifying mechanisms which lead to heart disease.

Two COVID-19 mRNA vaccines in comparison:

Both BNT162b2 (Pfizer), and mRNA-1273 (Moderna) were seen to be effective in trials in phase 3 (3, 16). Therefore, the comparisons between the two mRNA vaccines can be quite controversial (17, 18). There would need to be a large sample size to directly compare the two types of vaccines in detail and to outline differences since both vaccines have greater than 90% efficiency in preventing the development of COVID-19 virus (3, 16, 19). However, it is possible to estimate the effectiveness of both vaccines due to the hundreds of millions doses of mRNA vaccines that have been given out to citizens (20). There has been a study reported by Dickerman and colleagues about the two mRNA vaccines effectiveness (3). In this study, data have been collected from the Department of Veterans Affairs (VA) hospitals in the United States where people who acquired both doses of the vaccination were included (3). These groups of people were to go to a follow-up date during two distinct periods, one was when the SARS-CoV-2 B.1.1.7 (alpha variant) was the main spread and the second was wehn B.1.617.2 (delta) variant was spreading significantly (3). There has been evidence which shows that the delta variant is more resistant to vaccines (21, 22). The differences in the effectiveness of vaccines was able to be detected due to the large sample size of the study (23). During the time when the B.1.1.7 (alpha) variant was the significant spreader which was about 24 weeks, there have been two groups conducted which were 219,842 persons each of participants who received a mRNA vaccine (3, 24-26). These participants were matched for factors such as age, gender, race, date of vaccination and their location. In each group several measures have been considered which were symptomatic infection, hospitalization with high provision or intensive care unit (ICU), and death in each group (16, 27). During the 24-week period, results have shown that 5.75 events per 1000 persons were related to the BNT162b2 in a documented SARS-Cov-2 infection (3, 27). On the other hand, 4.52 events per 1000 persons were related to mRNA-1273 (28). The two groups had a difference of 1.23 events. Distinctions between the groups preserved for symptomatic infection was 0.44 events per 1000, hospitalization was 0.55 per 1000, ICU admission was 0.1 per 1000 and death was 0.02 per 1000 (28). During the 12-week interval which was influenced by the delta variant, the between-category distinction regarding documented infection grew to 6.54 events per 1000 persons (29, 30). Both of the vaccines use a different network for the pathway of mRNA which affect each type of vaccine's effectiveness. The number of doses for each mRNA vaccine are not the same, so as the gap period between each dose (31). To determine specific information for each mRNA vaccine, there were some variations tested in the second phase of the trials of the development (32, 33). It would be hard to see if each regimen would be more or less effective with a different dose of vaccine or time period between doses, each could also be improved (34). Regardless, to improve the vaccines it would be demanding since there need to be large trials with large sample sizes and with a reliable biomarker of protection. At the moment there are no such biomarkers that exist (13). These vaccines are also very productive so the use of biomarkers might not be worth it (35). It is clear enough to say that both vaccines are significantly implicit (35, 36). However, when we compare large sample sizes, it can be seen that mRNA-1273 is more efficacious than BNT162b2 (37). This is because the death rate in vaccinated people is lower. The risk difference between the two types of mRNA was roughly 0.2 per 10,000 vaccines during the peak of the alpha variant (20). It can be hard to determine how both vaccines were compared due to side effects (19, 28, 38). Comparison of vaccine efficacy between mRNA-1273 and BNT162b2 is unmeasurable (27). The high demand for mRNA vaccines in countries outside the United States means that they require both mRNA vaccines including vaccines that are developing (20). Other

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vaccination types are also in high demand in some countries which don't have much access to vaccines. This includes vaccines which are not mRNA as well because they can still be beneficial to protect against the Covid-19 virus (20). A study by Dickerman et al suggests that it will be difficult to compare effectiveness of vannines after the booster dose (3).

Potential mechanism caused myocarditis:

Myocarditis caused by enteroviruses or human herpesviruses (HHV4 and HHV6) tend to be more extreme in children and men (7, 39). Myocarditis caused by enteroviruses or human herpesviruses may be correlated with background with a genetic immunity that raises the risk of severe heart myocarditis following extreme accidents, including genetic variants coding for HLA factors and, in a small group of cases, genetic variants coding for desmosomal, cytoskeletal, or sarcomeric proteins (40). Recent publications describe similar risk factors for extreme myocarditis following mRNA vaccinations for the Covid-19 virus (16, 35). Factors contributing with hormones and antibodies are linked to the observed sex differences in myocarditis caused by primary infections of COVID-19 mRNA and non-COVID-19 vigorous myocarditis (41).

Contrasting to live virus or DNA vaccines, vaccinations for SARS-CoV-2 mRNA contains nucleoside-modified mRNA that encodes the extreme spike glycoprotein of SARS-CoV-2, rather than the DNA or the virus itself (40, 42, 43). They are enclosed in nanoparticles made from lipids that serve as a pathway for mRNA to make way into cells (44). They can also contain stagnant components such as buffers and salts (44). Spike protein triggers immune cells to produce IgG antibodies to neutralise SARS-CoV-2 (33). Spike protein has the ability to bind to angiotensin-converting enzyme 2 receptors so this prevents host cell binding to it (45, 46). A virus that expresses spike protein can be identified and destroyed by an adaptive immune response triggered by the mRNA vaccine once it plunges into the host cells (47, 48).

Some RNA molecules which have been chosen can produce an immune response and trigger immune systems of mammals (49). This inhibits the mRNA from reaching selected cells, forbid the production of spike protein and the creation of antibodies will also be neutralised. Researchers have discovered that nucleoside modifications of mRNA can reduce innate immunogenicity while also resulting in less activation of cytokines (50). This discovery has paved the way for the development of mRNA vaccines (43). In many big trials, mRNA vaccines for COVID-19 have been shown to be both powerful and secure (42). However, there are findings that in children they have high chances to have side effects from the vaccine after the second dose has been vaccinated (46, 51). Only a rate of 0.05% that were found to have extreme cardiovascular events (14, 52).

Although adjustments of nucleoside to mRNA can lower their immunogenicity but in some people with genetic predispositions, the immune response to mRNA may not be reduced and this can lead to obtained immune response (48). Dendritic cells or cells expressing Toll-like receptors revealed to RNA hold onto their ability to demonstrate cytokines and activation markers in some people (53). On the other hand, the capacity may be significantly reduced when revealed to mRNA with adjustments of nucleoside compared to unmodified RNA (42). Some people develop myocarditis since the immune system may recognise the mRNA vaccine as an antigen, activating proinflammatory rapidly along with immunologic passageway that may be associated with the formation of myocarditis (14, 48). It will be hard to monitor the probability of these situations since the use of mRNA vaccines is still being considered (48).

The mRNA vaccines for an antigen may be mistaken by the immune system so this may stimulate the pro-inflammatory cascades and the immune system's direction towards the heart. Even though adjustments of nucleoside may lower the intrinsic immunity of mRNA, the stimulation of an aberrant innate and acquired immune response will still be driven by the immune response caused by mRNA (47). This indicates the reason why mRNA vaccines induce a more vigorous immune response compared to other vaccines for COVID-19 (42, 54). Regardless, this theory is contradicted by the missing extreme effects where vaccines of mRNA have been occupied (44). Another possibility is that the cardiac self-antigens and SARS-CoV-2 spike proteins are similar in molecular structure. Immune defences which are raised in opposition to spike glycoproteins

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of SARS-CoV-2 may cross-react with protein sequences of humans such as myocardial-myosin heavy chain (14, 40). These antibodies which are produced by humans may be unintentional due to myocardial inflammation and this may mirror a particular immune genetic background that leads to hyperimmune and myocarditis (40). Lastly, distinction in the signalling of hormones which are associated with myocarditis of mRNA vaccinations may be due to the rise in prevalence of male patients (40). Testosterone has been shown to suppress reduction in inflammation, immune cells and encourage a violet T helper 1 cell-type immune response (40). In comparison, oestrogen suppresses T cells which are pro-inflammatory which leads to a depletion in immune responses which are cell-mediated (55).

SARS-COV-2 polymerase ongoing reaction and vigorous scientific studies for distinct causes such as hepatitis, Epstein-Barr virus, cytomegalovirus, parvovirus, mycoplasma, HIV influenza A/B, respiratory syncytial virus, rhinovirus, enterovirus (Coxsackie A, Coxsackie B), adenovirus, etc were offset, arguing against myocarditis (14). In diseases such as autoimmune, antinuclear antibodies and rheumatoid factor serology were offset and there was no proof of a predisposition towards people with beginning disorders of autoimmune (13). Additionally, no high white blood cell count, high levels of eosinophils, anaemia, low platelet count, or transaminase elevation were observed (56). d-Dimer was quite high and red blood cell sedimentation estimate was also moderately high in two patients who did not have pulmonary embolism or venous thromboembolic events (14, 57, 58). One of the cases had a negative result in a predetermined medical test for alternatives in 121 genes which were correlated to cardiomyopathy (57). This suggests that known gene variants may have led to underlying predisposition to cardiomyopathy.

Another possible mechanism of myocarditis is molecular mimicry (theoretical possibility that sequence similarities between foreign and self-peptides are sufficient to result in cross-activation of B/T cells) linking SARS-CoV-2 spike protein and conventional substance which induce immune response in the body of an individual (13, 57). Human peptide protein sequences such as myosin cross-react with antibodies which were made against SARS-CoV-2 spike glycoproteins (40, 57). Acute extreme incidents, on the other hand, have been sporadic (59). mRNA COVID-19 vaccines may stimulate early existent dysregulated pathways in susceptible people, even though it does not seem to cause severe immune effects but this can still result in cell expansion of polyclonal B, formation of immune complex systems and inflammation (40, 57, 60).

Additionally, there is no evidence to suggest a slowed hypersensitivity response including serum sickness-like reaction or eosinophil infiltration of the myocardium that can be a origin of myocarditis as an effect from COVID-19 mRNA vaccinations (5, 61, 62). Even though it is uncommon, skin intolerance reactions were reported after the mRNA vaccine for COVID-19 with a seven days median latency whereas myocarditis had a three to four days latency (63). In the cases which have been reported, there was no proof of high-level eosinophils in blood that flows through vessels, prominent feature of several autoimmune diseases or infiltration of eosinophil in idiopathic disorder biopsy sampling (14, 57). Lipid nanoparticles that have been used in mRNA vaccinations were not seen to generate reactions of cells to the presence of substances and it also is not yet linked to myocarditis (7, 44).

Vaccine-instigate immune thrombotic thrombocytopenia has been reported infrequently following vaccination with the recombinant adenoviral vector encoding the SARS-COV-2 spike protein antigen (64, 65). After many of the mRNA COVID-19 vaccines, there are some patients who have thrombotic complications (66). Individuals involved in these cases have thrombocytopenia and antiplatelet antibodies deficiency (67, 68). Thrombotic events, thrombocytopenia or disseminated intravascular coagulation was not found in patients with myocarditis (61, 68). Furthermore, there were no verification of a cytokine storm, hemophagocytosis, macrophage activation syndrome, lymphadenopathy, hepatosplenomegaly, cytopenias (anaemia, leukopenia, and thrombocytopenia), hypofibrinogenemia, transaminitis, extremely elevated ferritin, or multiorgan impairment contributed in these cases (14, 53). Tenacious fever across the first couple of days of the infection was also not detected (14).

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In many clinical studies, myocarditis cases seem to have developed more across males compared to females but the underlying mechanisms remain undetermined (41, 46). A significant possibility is that the differences in sex hormones exist (69). This could be caused by testosterone where it is considered to be part of the combination of anti-inflammatory cell inhibition and devotion to a Th1-type immune response (68, 70). Postmenopausal women also has a higher chance of developing pericarditis due to the hormone estrogen that inhibits pro-inflammatory T cells which cause a decline in cell-mediated immune response (14). Another of one of the causes could be female underdiagnoses (14). In accordance to the VAERS database of June 6, 2021, where there were 6235 cases reported involving chest pain including 69% of the cases which were women whereas men was 30% of the cases (14). Statistics have shown that women have higher chances of chest pain after COVID-18 vaccine administration (14, 71, 72). However, after diagnostic evaluation which includes electrocardiograms, laboratory biomarkers, echocardiography, etc, results have shown that the case was often found in males than females who had chest pain after the vaccine (14, 70, 73).

Conclusion:

COVID-19 vaccines from medical studies have shown that they are exceptionally successful at inhibiting symbolic diseases. The epidemiology curve goes to plateau (flattens the curve) due to vaccination and this also reduces the chances of extreme cases in hospitals with high healthcare provision. In addition, the death related to COVID-19 also decreased since the probability of acute kidney injury, arrhythmia and thrombosis has declined. Extending from this, the risk of developing myocarditis decreased in correlation to the administration of COVID-19 vaccine. There is a decrease of 1,000-fold in the population with a 1-5 fold increase in risk of mild myocarditis in adolescents. In consequence of the high risk ratio of myocarditis, teenagers and adults are advised to take the COVID-19 vaccine. However myocarditis resulting from the vaccine still requires more research on the side effects, risk factors, potential mechanisms, treatment methods, reasons for sex differences.

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