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Systemic lupus erythematosus following SARS-CoV-2 vaccination; a review of literature

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ABSTRACT

From March 2020, the coronavirus disease 2019 (COVID-19) pandemic challenged public health and healthcare systems worldwide. Viral infection is one of the environmental factors that has been associated with the development, relapse, or exacerbation of systemic lupus erythematosus (SLE). SLE patients are at an increased risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) because of immune system dysfunction related to their disease as well as immunosuppression medications. So far, the most effective way to reduce SARS-CoV-2 infection-induced hospitalization and death is vaccination. On the other hand, SLE patients present distinct challenges related to the safety and effectiveness of SARS-CoV-2 vaccination. We have reviewed some reports on the onset or flare of SLE post-COVID-19 vaccination. Of note, the mRNA COVID-19 vaccines are associated with increased SLE disease activity, more frequently than the other types of COVID-19 vaccines.

Review

Implication for health policy/practice/research/medical education:
There is no clear mechanism for describing systemic lupus erythematosus (SLE) development or flare after COVID-19 vaccinations, however, numerous hypotheses might elucidate this association. The increased concentration of type I interferon especially after the mRNA COVID-19 vaccination may explain the higher rate of SLE and SLE flares following vaccination.

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Introduction

Since March 2020, the coronavirus disease 2019 (COVID-19) pandemic has challenged public health and healthcare systems worldwide. The most effective way to reduce severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-induced hospitalization and death remains vaccination. Several vaccines have been developed and used, with extensive investigation on their adverse consequences and efficiency.

The various types of SARS-CoV-2 vaccines are developed based on messenger ribonucleic acid (mRNA)-based vaccines (such as Pfizer-BioNTech and mRNA 1273 (Moderna), Comirnaty), DNA-based vaccines (such as Janssen, AstraZeneca/Oxford, and Sputnik V), inactivated viruses (such as CoronaVac, BBIBP-CoV and Wuhan) and recombinant subunit vaccines (such as Novavax vaccine) (1).

Systemic lupus erythematosus (SLE) is a chronic

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autoimmune multisystem disease, more common in females. It is distinguished by immune system dysfunction and inflammation that affects connective tissue and almost any of the body's organs. Many autoantibodies are seen in SLE and some such as ant SM and anti dsDNA are known to be very specific for the SLE.

The pathogenesis of SLE implicates interaction between genetic and environmental factors including air pollution, ultraviolet light exposure, pesticides, cigarette smoking, heavy metals, drugs, and infections. Viral infection is one of the most important environmental factors. SLE patients are at an increased risk of SARS-CoV-2 viruses due to immune, dysfunction, the presence of autoantibodies and immune complexes development, and diminished clearance of apoptotic cells (2), and use of immunosuppressing medications. Therefore, vaccination against SARS-CoV-2 for patients with SLE is crucial. On the other hand, SLE patients present distinct challenges related to the safety and effectiveness of vaccination due to their immune system dysregulation and treatment with immunomodulators and immunosuppressants. The patients treated with immunosuppressants or immune-modifying drugs were excluded from some phases of vaccine trials such as Moderna (NCT04470427) and Pfizer/BioNTech, resulting in ambiguity about the safety and efficacy of SARS-CoV-2 vaccines in patients with autoimmune inflammatory rheumatic diseases especially SLE (3,4). This has raised concerns about adverse events associated with the COVID-19 vaccine and its effectiveness in these patient populations

It is well known that some viral vaccines including hepatitis B, human papillomavirus, and measles vaccines can cause SLE flares in some genetically predisposed populations (5-7).

Search strategy

For this review, we searched Web of Science, EBSCO, Scopus, PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase, and Google Scholar, using various keywords including; SARS-CoV-2, vaccination, COVID-19, systemic lupus erythematosus, flare, and immune system

Review of published cases of SLE or SLE-like syndromes following COVID-19 vaccination

The flares or new onsets of immune-mediated diseases post- COVID-19 vaccination is investigated in the 27 cases in which 21 cases had at least one underlying autoimmune disease in the first large report by Watad et al, in three different countries. Out of 27 cases, 23 cases received the Pfizer-BioNTech vaccine, two cases received Moderna and two cases received the AZD1222, while only seven cases are reported with severe adverse effects (8). Among severe cases, six cases received the Pfizer-BioNTech vaccine, and one case received the AZD1222 vaccine.

Ntouros et al demonstrated that the SARS-CoV-2 vaccine, is characterized by acute immune system activation, and it can activate the DNA damage response network, while the SLE disease is characterized by chronic immune system activation that reveals abnormal DNA damage and activation response. It seems that the SARS-CoV-2 vaccines in SLE cases could lead to a sudden increase in DNA damage response activation and therefore SLE flare (9).

Jin et al reported a case of ocular adverse effects including conjunctival congestion, eyelid swelling with itchy, and intense headaches, three days after COVID-19 vaccination in a 28-year-old female with the previous medical history of SLE for 6 years (10).

The first international large-scale cross-sectional study (VACOLUP) in France examined COVID-19 vaccine tolerability in SLE patients. They found, that 49% of participants had some mild to moderate side effects after the first or second dose of the vaccine. This study showed that 3% had a disease flare-up in 21 out of 696 vaccinated patients (11).

A recent multi-racial/ethnic cohort at New York University with 90 SLE patients demonstrated that 30% of the patients had a low-response post-COVID-19 vaccination. Around 11.4% of patients had a mild to moderate worsening of the disease after vaccination. Additionally, 1.3% of the patients had a severe flare (12).

Recently, a 22-year-old single Saudi female was diagnosed with SLE without previous history. She had acute pancreatitis and cutaneous vasculitis on the hands and feet, seven days after the first dose of the Pfizer-BioNTech COVID-19 vaccine was reported (13).

Nune et al also described the development of SLE based on clinical findings of polyarthritis, oral ulcers, leukopenia, lymphopenia, and positive laboratory results in a 24-year-old Caucasian man after the Pfizer-BioNTech COVID-19 vaccine (14).

Further, Patil and Patil described a 22-year-old woman who felt knee pain while climbing or descending the stairs two weeks after getting the first dose of the COVID-19 vaccine. Following the second dose of an adenoviral vector vaccine of AZD1222 nCoV-19 vaccine, this patient developed fever, edema, petechiae, and polyarthralgia in the ankles, feet, and lower legs, and was found to have albuminuria, thrombocytopenia, positive ANA, and anti-dsDNA antibodies emphasized meeting the criteria for SLE. The patient's condition improved after the administration of hydroxychloroquine, prednisolone, and mycophenolate mofetil for one month (15).

Recently, Zavala-Miranda et al reported a 23-year-old woman with membranous lupus nephritis, low C3 levels, positive ANA and anti-dsDNA antibodies, alopecia, and lymphopenia, seven days after the first dose of the AZD1222 adenoviral vector vaccine. The patient's condition improved in 21 days following treatment with

hydroxychloroquine, mycophenolate mofetil, diuretics, and glucocorticosteroids (16).

Likewise, Tuschen et al described a case of relapse of mesangial and membranous lupus nephritis in a 41-year-old woman with the previous medical history of membranous lupus nephritis, one week after taking the first dose of the mRNA vaccine of Pfizer–BioNTech vaccine (17).

Molina et al described a life-threatening lupus pneumonitis after vaccination requiring intensive care unit (ICU) in a 42-year-old woman, without the previous medical history of SLE. She presented with elevated antiphospholipid antibodies, dyspnea, hypoxemia, and pulmonary embolism. This patient presented as the first case of SLE with antiphospholipid syndrome along with inflammatory arthritis, high erythrocyte sedimentation rate and C-reactive protein levels, after receiving the first dose of Pfizer/BioNTech vaccine. Treatment with anticoagulation, hydroxychloroquine, azathioprine, and corticosteroids, resulted in the improvement of all her manifestations (18).

A 30-year-old African-American male with a known past medical history of mesangial and membranous lupus nephritis had a flare-up of glomerulonephritis three days after getting the first dose of the Moderna vaccine (19).

Kreuter et al reported a 79-year-old man with subacute cutaneous lupus erythematosus by along with fatigue, 10 days after the first dose of the BNT162b2 vaccine. Again, treatment with hydroxychloroquine and glucocorticosteroid resulted in the disappearance of all skin symptoms after one month (20). There is another case of post-vaccination cutaneous lupus erythematosus in a 73-year-old woman with erythematous patches that rapidly improved by using systemic and topical corticosteroids (21).

Lemoine et al reported an SLE patient presenting with inflammatory arthritis, positive ANA and elevated dsDNA in a 68-year-old woman without previous history of autoimmune diseases, around seven days following receiving the first dose of the Pfizer-BioNTech COVID-19 vaccine. This patient recovered significantly after the use of steroids (22).

There is a case report of a 54-year-old male who developed high-grade fever, cervical lymphadenopathy, and palpable purpuric lesions on his feet that, two weeks after receiving the second dose of the Pfizer COVID-19 vaccine (23).

In another report, a case of symmetric inflammatory polyarthritis and new-onset SLE is described in a 27-year-old woman with type I diabetes mellitus and a family history of SLE, two weeks after receiving the second dose of the SARS-CoV-2 mRNA-1273 vaccine (24).

A recent report also described a 24-year-old male who presented with positive ANA, and polyarthritis with joint pains with morning stiffness without a past medical history of autoimmune diseases, ten days following the first dose of the SARS-CoV-2 Pfizer-BioNTech mRNA vaccine (25).

Antibody response following COVID-19 vaccination in COVID-19 vaccination

The COPANARD (Corona Pandemic Autoimmune Rheumatic Disease) cohort looked at antibody response in 134 patients with SLE or rheumatoid arthritis. 61 of them had SLE, 73 patients had rheumatoid arthritis and they all had received the Pfizer–BioNTech vaccines. Only 77% developed measurable antibodies against COVID-19, compared with healthy individuals this number is about 95%. Among those who had received rituximab, only 24% developed positive antibodies against COVID-19.

Such data raises concern about the efficiency of vaccines for patients treated with B cell depletion therapy with rituximab (26). Hence, delaying or interrupting B cell depletion therapy to improve COVID-19 vaccine efficacy should be evaluated.

The study by Gerosa et al showed out of 452 SLE patients, 26% of them demonstrated adverse events after the first and or the second dose of COVID-19 vaccines. They found only 4% of patients had a flare after the vaccination, without any reported hospitalization or death. Patients with constitutional symptoms (including weight loss, fever, and fatigue) and those on immunosuppressive drugs (especially belimumab) displayed more side effects after vaccination (27).

In a prospective, single-arm, open-labelled study in Thailand, 100 patients with 71 SLE and 29 patients with rheumatoid arthritis (93% women), were evaluated for the safety and immunogenicity of third and fourth mRNA (Pfizer–BioNTech) vaccine booster doses. All patients had previously been vaccinated with different SARS-CoV-2 vaccines. Vaccine administration was more correspondingly arranged among SLE patients by inactivated, ADZ1222, and BNT162b2 vaccines. Two severe SLE flares occurred shortly following the fourth booster dose. The intensity of immunosuppressive treatment and the type of primary vaccine seemed to influence the humoral immune response to the third and fourth BNT162b2 boosters (28). Fifty-four patients had suboptimal humoral responses to the third booster (28).

In 2021, Barbhaiya et al investigated 136 patients with SLE who received SARs-CoV-2 vaccination, including 81 (59.6%) receiving Pfizer, 48 (39.3%) receiving Moderna, and four (2.9%) receiving Janssen. They found 100 patients (74%) with adverse events and 11 patients (8.1%) with SLE flares. SLE flares occurred in 12.5% receiving Moderna and 6.2% receiving the Pfizer vaccine (29).

The immunogenicity of the COVID-19 vaccines of Comirnaty (mRNA-based vaccine) and CoronaVac (inactivated virus) was evaluated by a surrogate neutralization assay at 28 days following the second dose

in 65 SLE patients (38 Comirnaty and 27 CoronaVac). The antibody response, reactogenicity, and disease activity were evaluated in patients with SLE in comparison with the control. Humoral immunity in SLE patients was impaired compared to control subjects, as well. This impairment was associated with the type of received vaccines and the immunosuppressive treatments. The study also showed that adverse events in SLE patients were more frequent after the mRNA-based vaccine of the Comirnaty group (30).

A cross-sectional survey by Tang et al investigated post-vaccination adverse events and SLE flares in 188 cases with SLE and 190 healthy individuals who received at least one dose of the SARS-CoV-2 inactivated vaccine. The adverse events were negligible and there were no severe adverse events in both groups of SLE cases and healthy individuals after SARS-CoV-2 inactivated vaccine (31). This is in sharp contrast to other mentioned reports with increased side effects and flares with use of mRNA COVID-19 vaccines such as Pfizer/BioNTech (BNT162b2) (12-14,17,18,20-23,25,26), AZD1222 vaccine (15,16) and Moderna (19,24).

Discussion

Currently, the pathogenesis of post-vaccination SLE is not clear, however, numerous hypotheses have been hypothesized. It seems the association between the COVID-19 vaccine and SLE flare or development is more than accidental.

Type I interferon is involved in the antiviral activity and contributes to immune responses for antiviral immunity, such as COVID-19 infection. COVID-19 vaccination (especially mRNA and adenovirus vaccines) activates type I interferon. On the other hand, type I interferon increases in SLE patients at baseline and is indicative of disease activity. Theoretically, the increased type I interferon in both SLE disease and COVID-19 vaccination can cause similar aggravation of SLE disease (32). The proposed mechanism for adverse events following vaccination such as SLE can be molecular mimicry, immune hyper-activation including B and T cells activation, and the production of particular autoantibodies and inflammasomes, epitope spreading, that be simulated by vaccine adjuvants like lipid nanoparticles, especially in genetically susceptible individuals (14,33).

Several studies have shown that the mRNA, as a single-stranded RNA contained in mRNA vaccine, binding to endosomal Toll-like receptors (TLRs), leads to the production of type I interferon and potentially autoimmune diseases such as SLE. On the other hand, in SLE, TLRS especially TLR7 and TLR9 have complex roles associated with levels of serum type I interferon and can influence DNA autoantibody production as an important component of lupus nephritis (34). It is conceivable by this action, the mRNA vaccines are associated with the aggravation of SLE disease, more than any type of other COVID-19 vaccines.

Conclusion

There is no clear mechanism for describing SLE development or flare after COVID-19 vaccinations, however, numerous hypotheses might elucidate this association. The increased concentration of type I interferon especially after the mRNA COVID-19 vaccination may explain the higher rate of SLE and SLE flares after them.

Patients with SLE and rheumatoid arthritis have less immune antibody response to COVID-19 vaccinations. Treatment with immunosuppressive agents especially B cell depletion therapy even further impairs the antibody response to COVID-19 vaccines. The delaying or interrupting B cell depletion therapy to improve COVID-19 vaccine efficacy should be further evaluated.

Authors' contribution

Conceptualization and Methodology: LM, TS and MRKF; Validation, Investigation, Resources, Data Curation: LM and MRKF; Writing—Original Draft Preparation and Writing—Reviewing and Editing: BR, HRG, OFBM and TS; Visualization, Supervision, Project Management and Funding Acquisition: LM and MRKF.

Conflicts of interests

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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