Review

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Review

mRNA Vaccines and the Potential Risk of Connective Tissue Diseases

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Abstract: The emergence of mRNA vaccines represents a significant advancement in public health by conferring protection against a variety of infectious diseases. However, concerns regarding the potential risk of inducing or exacerbating autoimmune disorders, particularly connective tissue diseases (CTDs), have arisen. This paper explores the mechanisms by which mRNA vaccines may lead to the onset or worsening of CTDs, focusing on the immune responses induced by Pathogen-Associated Molecular Patterns (PAMPs), the interactions between Toll-like receptors 7/8 and 9 (TLR7/8 and TLR9), and the activation of self-reactive B cells. Furthermore, guidelines are suggested for administering vaccines to individuals at elevated risk, such as those with a positive antinuclear antibody (ANA) test or specific rheumatic disease genes. Our findings underscore the necessity for targeted vaccination strategies that mitigate risks while maintaining public health efficacy.

Keywords: mRNA vaccines; COVID-19; connective tissue diseases (CTD); systemic lupus erythematosus (SLE); Autoimmune diseases

1. Introduction

Connective Tissue Disease (CTD) is an autoimmune disorder that affects multiple organ systems throughout the body, leading to tissue damage, collagen deposition, and potential loss of function in affected organs [1]. CTDs encompass a diverse group of heterogeneous disorders and inflammatory conditions including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), dermatomyositis (DM) and polymyositis (PM), ankylosing spondylitis (AS), Sjögren's syndrome (SS), and mixed connective tissue disease (MCTD) [1,2]. The primary pathological features of CTD include chronic inflammation of blood vessels and connective tissues, which can further affect organs and lead to multi-system damage.

Vaccines have significantly advanced public health by providing an efficacious means to prevent and control infectious diseases. From conventional vaccines to the state-of-the-art mRNA technology utilized in recent developments, these medical interventions have substantially reduced mortality rates and enhanced global health outcomes[3]. The emergence of mRNA vaccines represents a significant advancement in immunization technology. These innovative prophylactic agents demonstrate remarkable efficacy across a broad spectrum of health challenges, ranging from safeguarding against common infectious diseases such as influenza to potentially addressing serious conditions like cancer[4]. Ko et al. conducted an anonymous online survey of rheumatology patients at a large suburban health network and found that, out of 641 respondents, 65% were willing to receive the SARS-CoV-2 vaccine, while 34.4% exhibited vaccine hesitancy (unwilling or undecided). Among those who were hesitant, 39.2% indicated they would be more likely to accept vaccination if given a choice of which vaccine to receive, and 54.5% stated they would be more willing to get vaccinated if recommended by their rheumatologist. Therefore, physician recommendations and

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guidance on vaccination can address individuals' concerns and promote vaccine acceptance among rheumatology population [5]. Understanding the potential impact of vaccines on CTDs is crucial for both patient care and public health policy.

In this review, we emphasize the necessity for continued research and the development of tailored guidelines to optimize the benefits of mRNA vaccines while minimizing potential risks for patients with CTDs. The insights provided herein will be valuable for researchers, healthcare providers, and policymakers working in the fields of immunology, rheumatology, and public health. By addressing these critical knowledge gaps, this research aims to contribute to the safe and effective use of mRNA vaccines in diverse patient populations.

2. Connective Tissue Diseases

The classification of various Connective Tissue Disease (CTD) subtypes relies primarily on their distinct clinical presentations, specific laboratory findings, and characteristic tissue pathology [6]. The hallmark pathological characteristics of these autoimmune-mediated CTDs include chronic inflammation of blood vessels and connective tissues, which can result in multi-system damage affecting various organs [7]. Women are disproportionately affected by CTDs, with female-to-male ratios ranging from 2:1 to 15:1. Furthermore, an individual's racial background can sometimes impact the frequency or severity of these disorders [8–10].

According to data from 2006, the prevalence of SS ranges from 0.5 to 3% within the general population. SLE has an estimated prevalence of 15 to 50 cases per 100,000 individuals, with a female-to-male ratio of 6 to 10:1 in individuals aged 15 to 40 years. SSc exhibits a lower prevalence, which varies significantly across different studies and geographic regions. The prevalence of overlap syndromes, particularly MCTD, remains unknown. PM and DM are categorized as very rare rheumatic diseases [8]. In the geriatric population, CTDs are typically accompanied by age-related comorbidities and complications related to both the disease and its treatments, contributing to significant morbidity and mortality and complicating treatment decisions [2].

The pathogenesis of CTDs involves a complex interplay between genetic and environmental factors, leading to a variety of clinical manifestations such as malar rash, alopecia, oral ulcers, plaques, hyperpigmentation, and muscle atrophy [11]. These conditions can manifest as isolated irregularities, causing only aesthetic concerns, or they might lead to severe systemic issues that significantly impair function.

The human lung is especially susceptible to such damage because it contains abundant collagen fibers and extensive vascular network [2,3]. Among patients with CTD, the prevalence of ILD was observed to be higher in individuals diagnosed with SSc, idiopathic inflammatory myositis (primarily PM and DM), and MCTD (combined prevalence of 47%, 41%, and 56%, respectively) [4,5]. Connective tissue disease related interstitial lung disease (CTD-ILD) becomes a significant cause of morbidity and mortality among patients with CTD [3,6]. Infections are a major cause of death in SLE. Disease-related activity and cardiovascular complications are the most frequent causes of death in patients with SSc [7]. In patients diagnosed with DM, PM, or clinically amyopathic dermatomyositis (CADM), hemophagocytic lymphohistiocytosis (HLH) presented as an uncommon (4.2%) yet highly lethal (77.8%) complication [4].

3. Overview of Vaccines

Vaccines, including the recently developed mRNA vaccines, play a critical role in preventing infectious diseases and have been widely administered globally. To provide protection against infections or diseases, a vaccine works by activating the immune system through the introduction of specific antigens. these antigens, which can either be synthetically produced or derived from the pathogen itself, help the body recognize and respond to the pathogen upon future exposure [3]. Vaccines have played a critical role in reducing the global burden of various infectious diseases, particularly in low- and middle-income countries. Key vaccines include the measles vaccine, which has significantly reduced cases worldwide despite recent resurgences due to gaps in immunization, and the polio vaccine (OPV and IPV), which has brought the world close to eradicating polio. The

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pneumococcal and rotavirus vaccines have been instrumental in preventing pneumonia and severe diarrhea, particularly in children, while the HPV vaccine protects against cervical and other cancers caused by human papillomavirus. The Hib vaccine prevents bacterial infections that can cause severe pneumonia and meningitis, and the DTP vaccine continues to control diphtheria, tetanus, and pertussis in low-income regions. Additionally, the hepatitis B vaccine reduces liver infections and associated cancers, and the yellow fever vaccine remains vital for controlling outbreaks in Africa and South America. These vaccines collectively demonstrate the profound impact of immunization on global public health by preventing severe diseases and reducing mortality [12].

3.1. Categories

Vaccines can be classified into different categories based on how they stimulate the immune response. Live-attenuated vaccines contain a weakened version of the pathogen, allowing it to replicate without causing disease. This type of vaccine closely mimics a natural infection, resulting in strong and long-lasting immunity [13]. On the other hand, inactivated vaccines consist of pathogens that have been killed or inactivated, meaning they cannot replicate. These vaccines elicit an immune response without the risk of infection but may require booster doses for sustained protection [14]. Subunit vaccines include only specific components of a pathogen, such as proteins or polysaccharides, which are sufficient to trigger an immune response [15]. They do not contain the entire pathogen, making them safer, though they often need adjuvants to enhance effectiveness. Similarly, Virus-like particle (VLP) vaccines, a subtype of subunit vaccines, mimic the structure of viruses but do not contain genetic material, thus they are non-infectious [3]. VLPs effectively stimulate the immune system due to their resemblance to real viruses, as seen in vaccines like the HPV vaccine [16].

3.2. mRNA Vaccines

mRNA vaccines represent a new class of vaccines that utilize messenger RNA (mRNA) to instruct cells in the body to produce a protein that triggers an immune response, once inside, the mRNA is translated into a viral protein by the cellular machinery, prompting the immune system to recognize and respond by producing antibodies and activating T-cells[4]. Unlike traditional vaccines, which use inactivated pathogens or protein subunits, mRNA vaccines provide genetic instructions for cells to make specific viral proteins, such as the spike protein of SARS-CoV-2 [17]. There are two main types of mRNA vaccines: non-replicating mRNA vaccines, which deliver the mRNA that is translated into the target protein without the ability to replicate, and self-amplifying RNA (saRNA) vaccines, which include additional machinery that enables the mRNA to replicate, producing more antigen with smaller doses of RNA [18]. The mRNA is delivered to cells via lipid nanoparticles, which protect it and facilitate its entry into cells [19]. Importantly, mRNA does not enter the nucleus or alter the DNA of the recipient, and it is naturally degraded after translation.

3.3. Applications of mRNA Vaccines

3.3.1. COVID-19

mRNA vaccines, such as the Pfizer - BioNTech and Moderna vaccines, have shown high efficacy in preventing symptomatic COVID - 19 [20]. Clinical trials demonstrated that they could reduce the risk of developing COVID - 19 symptoms by around 90 - 95% after a full course of vaccination [21,22]. This is achieved through the activation of the immune system to recognize and mount a defense against the SARS - CoV - 2 virus [23]. One of the most significant benefits of mRNA vaccines in the COVID - 19 pandemic has been their ability to significantly reduce the risk of severe illness, hospitalization, and death [24]. Even with the emergence of new variants such as Delta and Omicron, vaccinated individuals were much less likely to experience severe COVID - 19 symptoms compared to unvaccinated individual [25]. For example, in many studies, vaccination reduced the risk of hospitalization due to COVID - 19 by more than 70 - 80% [24,26] .

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3.3.2. Influenza

The progress of mRNA vaccines continues to advance steadily. In preclinical assessments with mice, a universal influenza mRNA vaccine encoding influenza hemagglutinin (HA), nucleoprotein (NP), and three tandem repeats of matrix protein 2 (3M2e) demonstrated promising results [27]. Quadrivalent mRNA vaccines targeting hemagglutinin (HA) proteins from four seasonal influenza subtypes have demonstrated robust antibody responses and effective protection in preclinical studies, such as those conducted in mice [28]. These early results suggest the potential for strong immunity against multiple influenza strains. Currently, clinical trials are advancing new quadrivalent influenza vaccines alongside combined mRNA vaccines targeting both influenza and COVID-19 [29,30].

3.3.3. Cancer

In cancer therapy, mRNA vaccines operate by delivering specific tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) into cells, particularly antigen-presenting cells (APCs), the mRNA is translated into antigenic proteins, which are then presented on the cell surface via major histocompatibility complexes (MHCs). This presentation process activates both innate and adaptive immune responses, engaging T-cells and B-cells to target and destroy cancer cells that express these antigens [17].

Personalized mRNA vaccines are emerging as promising cancer treatments and have been administered to patients with advanced melanoma in several phase I/II clinical trials[31]. Notable examples include mRNA-4157/V940, developed by Moderna and Merck, which encodes up to 20 tumor-specific neoantigens and is currently being evaluated in combination with pembrolizumab in the KEYNOTE-942 phase 2b trial [32]. Additionally, Moderna also tested mRNA-4157 both alone and in combination with other therapies in a phase I trial for participants with solid tumors [33]. Similarly, combined Autogene Cevumeran vaccine is a hopeful therapy for tumors that are in advanced or metastatic stages [34,35]. BNT116 is also an innovative, personalized mRNA-based cancer vaccine designed to activate the immune system to identify and eliminate cancer cells [34,36].

However, cancers like Hepatocellular Carcinoma needs further research and clinical trials to assess their safety, efficacy, and potential as complementary therapies[37].

3.3.4. Respiratory Syncytial Virus (RSV)

The RSV F protein (Respiratory Syncytial Virus Fusion protein) is essential for viral entry into host cells, in its pre-fusion (pre-F) conformation, the F protein is in an “activated” state, poised to initiate fusion with the host cell membrane [38]. This pre-F structure is metastable, meaning it can easily shift conformation under certain conditions, if prematurely triggered by environmental factors before reaching the host cell, the F protein rearranges into a stable post-fusion (post-F) form, which loses the ability to mediate cell entry, thus, the pre-F conformation is active and primed for infection, while the post-F form is stable but ineffective for viral entry, however, many vaccine candidates, including an earlier inactivated RSV vaccine, contained predominantly post-F protein, limiting their efficacy [38]. However, the discovery of the atomic-level structure of the pre-F conformation provided critical insights, enabling the development of a stabilized, immunologically relevant pre-F protein that can now be expressed as a stable recombinant in vaccines [39]. Currently, an mRNA-based RSV vaccine, mRNA-1345, encoding the stabilized RSV prefusion F glycoprotein, is under clinical investigation in a phase 2–3 trial, leveraging this stabilized pre-F structure to enhance immune response and vaccine efficacy [40].

3.3.5. HIV

The mechanism of mRNA vaccines for HIV aims to induce broadly neutralizing antibodies (bnAbs) by sustaining germinal center activity, activating rare B-cell precursors, and following a sequential immunization strategy [41]. This approach also includes developing mRNA vaccines targeting various HIV antigens to elicit strong immune responses by activating both CD4+ and CD8+

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T-cells, while guiding B cells through maturation to recognize conserved HIV epitopes [42]. However, several challenges complicate bnAb development: immune tolerance limits the activation of bnAb-producing B cells, extensive mutations are required for bnAbs to be effective, and a series of sequential immunogens is necessary to guide B-cell maturation properly [43]. Three relatively small Phase I trials have demonstrated that this approach can produce a good range of bnAbs, and efforts are ongoing to broaden this response and advance towards Phase II trials, yet, as outlined in the latest findings, unexpected side effects, such as skin reactions (including hives) in ten to fifteen percent of vaccine recipients, have slowed progress [44–47].

3.3.6. Zika Virus

The mechanism of mRNA vaccines targeting Zika virus involves using lipid nanoparticle (LNP)-encapsulated modified mRNA that encodes the Zika virus prM and E structural proteins, once delivered into cells, this mRNA directs the host's cellular machinery to produce virus-like particles resembling the Zika virus, thereby eliciting an immune response [48]. The mRNA-1893, an mRNA-based Zika vaccine, demonstrates promising potential [49]. In the development of mRNA-based Zika vaccine, modifications to the mRNA sequence were incorporated to reduce potential adverse cross-reactivity with dengue virus by eliminating specific cross-reactive epitopes [50]. In phase I trials, mRNA-1893 was well tolerated at all evaluated dose levels and successfully induced strong Zika virus-specific serum neutralizing antibody (nAb) responses after a two-dose regimen, underscoring its potential in Zika virus protection [51].

3.3.7. Human Cytomegalovirus (CMV) and Rabies

This novel technology also brings hope to some intractable, for which efficient methods are lacking, such as CMV and rabies. Cytomegalovirus (CMV), a common pathogen from the β-herpesvirus family, can replicate extensively and lead to severe end-organ disease [52]. The mRNA-1647 vaccine induces high titers of neutralizing antibodies with broad coverage, generates long-lasting memory B cells, and elicits robust, polyfunctional T-cell responses [53]. Additionally, mRNA-1647 produces durable, CMV-specific antibody responses compared to the gB/MF59 subunit vaccine. For the horrible disease rabies, the CV7201 prophylactic mRNA-based vaccine candidate, featuring the rabies viral antigen RABV-G, effectively induces functional antibodies that can be boosted over time [54]. Studies in dogs have demonstrated that it significantly raises antibody titers, leading to an extended duration of immune protection [55].

3.4. Potential Side Effects on Vaccines

The majority of vaccine-related side effects are typically mild, short-lived, and temporary, there are instances where rare and severe reactions can occur. These uncommon but serious responses may include hypersensitivity, the triggering of infections, and autoimmune disorders, which in extreme cases can be life-threatening or even result in death [56]. Researchers have identified potential connections between mRNA vaccines and certain systemic autoimmune conditions, such as autoimmune hepatitis and nephritis. Autoimmune conditions may emerge after receiving vaccines that are not mRNA-based, including those for human papillomavirus, hepatitis B, and influenza. This newly developed autoimmunity could potentially be initiated by a process known as molecular mimicry [50,51].

Effective delivery of mRNA into target cells requires a diverse array of mechanisms. These encompass widely utilized transfection agents, as well as specialized systems such as protamine-based formulations, polysaccharide-derived particles, and various nanoparticle compositions. Among these are cationic nanoemulsion, polymers, and lipid-based nanoparticles. Each of these delivery methods exhibits distinct characteristics and advantages, rendering them suitable for specific applications within the domain of mRNA therapeutics [55]. The Pfizer–BioNtech and Moderna mRNA vaccines employ a nanoparticle delivery system based on lipids. This system serves two crucial functions: it shields the mRNA from rapid breakdown by enzymes and enables effective

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delivery within the body [45,53–55]. The stability of this nanoparticle carrier system is enhanced through the incorporation of a polyethylene glycol (PEG) 2000 lipid conjugate. This conjugate generates a hydrophilic outer layer that prolongs the half-life of the system [56]. There is a hypothesis that certain adjuvant components integrated in the vaccine's lipid layer, such as polyethylene glycol (PEG) 2000, may trigger anaphylaxis following BNT162b2 and mRNA-1273 vaccinations [44].

4. Potential Risk of mRNA-Based Vaccines to CTD Patients

Although vaccines are generally safe and efficacious, concerns have been raised regarding their potential to initiate or exacerbate CTDs [57]. The mechanisms by which vaccines, particularly mRNA vaccines, may induce or aggravate CTDs are multifaceted and require further examinations. In general, typical manifestations after vaccinations include local pain, redness, and swelling at the injection site, as well as mild systemic symptoms like fever, headache, and fatigue [50]. For patients with pre-existing CTDs, these reactions might be exacerbated due to their already heightened immune response. Also, case studies have shown that vaccinations can trigger the onset of undifferentiated connective tissue disease (UCTD) in individuals without prior CTD diagnoses [58], highlighting the importance of monitoring post-vaccination in the potential high-risk population.

4.1. Reactions of CTD Patients Following Vaccination

Jung et al. found that the risk of developing most CTDs did not increase after mRNA vaccination, except for systemic lupus erythematosus (SLE), which showed a 1.16 times higher risk compared to the control group [57]. A study based on data from the European League Against Rheumatism (EULAR) Coronavirus Vaccine Physician Reporting Registry found that disease flares after SARS-CoV-2 vaccination are not common among patients with inflammatory/autoimmune rheumatic and musculoskeletal diseases (I-RMD) (70% received Pfizer/BioNTech, 8% received Moderna) [59]. I-RMD encompasses multiple autoimmune conditions, some of which can be classified as connective tissue diseases, such as SLE, scleroderma, Sjögren's syndrome, polymyositis/dermatomyositis, and others [60]. The study demonstrated the safety of SARS-CoV-2 vaccines in patients with inflammatory/autoimmune rheumatic and musculoskeletal diseases, including those with CTD (18% of the study population) [59]. Ou et al. conducted a retrospective analysis on 78 hospitalized patients who developed immune - mediated diseases (IMDs) within 120 days after receiving the AZD1222, BNT - 162b2, and/or mRNA - 1273 vaccines. They used a two - tailed Kolmogorov - Smirnov (KS) test to analyze the time from vaccination to the onset of IMD. The results showed that, compared with CTDs, non - CTDs had a shorter period from vaccination to the appearance of symptoms [55].

4.2. Mechanisms of mRNA Vaccines on CTD

The ability of mRNA vaccines to function as pathogen-associated molecular patterns can initiate an inflammatory response, potentially impacting individuals with CTDs. These vaccines introduce genetic material that directs cells to create viral proteins, which can serve as pathogen-associated molecular patterns (PAMPs) [4]. PAMPs have the capacity to stimulate innate immune responses, including the generation of type I interferons, which are recognized for their involvement in autoimmune disorders [61]. The activation of the innate immune system by mRNA vaccines can result in an inflammatory reaction characterized by enhanced interferon activity. For individuals predisposed to autoimmune conditions, this intensified immune response may exacerbate existing CTDs or trigger the onset of new autoimmune disorders.

Also, the cause of autoimmune/inflammatory phenomena observed after (SARS-CoV-2) vaccination may be attributed to the use of Toll-Like Receptor 7/8 (TLR7/8) and TLR9 agonists as adjuvants in the vaccines [62]. These new-generation vaccines, by stimulating TLR-7 and TLR-9, are likely to upregulate interferon-stimulated genes (ISGs) and contribute to strong early innate immune responses, including robust type-I interferon (IFN) responses. Stimulation of TLR7 and TLR9 can subsequently trigger the generation of type I interferon, a crucial cytokine in the pathogenesis of SLE and other rheumatic disorders [63,64]. This may explain the cutaneous and potentially other related

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symptoms. Moreover, dysregulated nucleic acid metabolism is linked to interferonopathies and systemic lupus erythematosus (SLE), as well as other conditions associated with antinuclear antibodies (ANAs) [62]. Additionally, the interaction of TLR7/8 and TLR9 can result in the TLR7-mediated overstimulation of age-related CD11c+ T-bet+ B cells (ABCs). These ABCs are associated with the generation of self-reactive immunoglobulin G, enhanced antigen presentation to T cells, and the spontaneous development of germinal centers [65]. In individuals who are genetically and immunologically susceptible, ABCs can accumulate prematurely in autoimmune conditions like SLE. This premature accumulation can lead to the production of self-reactive antibody-secreting plasma blasts, potentially triggering autoimmunity [66,67].

5. Ongoing Studies and Reported Case Studies

Currently, there are ongoing clinical trials investigating the safety and efficacy of various vaccines in patients with pre-existing CTDs. These trials aim to better understand the risk-benefit profile of vaccinations in this vulnerable population. A typical case report involves a

There have been cases in which SLE has developed following mRNA vaccination [54]. A case study by Baez-Negro'n et al. detailed a 27-year-old woman who experienced fatigue and symmetrical joint inflammation two weeks after receiving her second Moderna mRNA-1273 vaccine dose [68]. In the months that followed, she developed mild protein excretion in her urine (urine protein creatinine ratio 640 mg) and was administered prednisone and mycophenolate as treatment. Despite the absence of a kidney biopsy, the patient exhibited elevated anti-dsDNA antibodies, reduced C4 levels, and proteinuria, suggesting a potential diagnosis of lupus nephritis [69]. A 22-year-old woman sought medical attention one week after receiving the Pfizer BNT162b2 mRNA vaccine. She exhibited symptoms of pancytopenia, cutaneous vasculitis, and pancreatitis. Her treatment regimen included high doses of glucocorticoids, along with hydroxychloroquine and azathioprine [69]. The remaining two cases did not show significant organ involvement, with symptoms limited to fever, arthritis, and cytopenias [70,71].

Watad et al. evaluated the incidence of exacerbations or initial symptoms immune-mediated diseases (IMDs) occurring within 28 days of receiving the SARS-CoV-2 vaccine at five major tertiary health facilities in Israel, UK, and USA. Out of the total 28 cases, 23 individuals (85.2%) received the BNT-162b2 vaccines [62]. Two cases are reported in Israel. A 78-year-old female with a history of laboratory-confirmed SLE but no prior clinical manifestations received the first dose of the BNT162b2 vaccine in January 2021. Two days post-vaccination, she developed symptoms including pyrexia, erythematous rash consistent with generalized acute cutaneous lupus, purpura, oral aphthous ulcers, and arthritis. These symptoms were classified as mild and diagnosed as new-onset IMD. Relevant laboratory tests revealed positive ANA, elevated CRP and ESR, and a skin biopsy from the purpura indicated leukocytoclastic vasculitis. Treatment with hydroxychloroquine resulted in a rapid response and prompt symptom improvement. The temporal relationship between vaccination and symptom onset was considered compatible. A 62-year-old female with a history of immune-mediated disease (IMD) and dermatomyositis (DM), who was undergoing treatment with methotrexate (MTX) and 200 mg of plaquenil (PLQ) twice daily, received her initial dose of the BNT162b2 vaccine in January 2021. Seven days post-administration of the first dose, the patient experienced a mild IMD exacerbation characterized by a cutaneous eruption similar to that observed during her initial DM diagnosis. The exacerbation was managed with topical corticosteroid therapy and spontaneously resolved after one week. Subsequently, the patient received the second dose of the vaccine without experiencing additional adverse effects. The temporal relationship between vaccine administration and symptom onset suggests a potential association between the vaccination and the observed IMD exacerbation [62].

Macrophage activation syndrome (MAS) is a potentially life-threatening complication of CTDs such as Still's disease and SLE [72,73]. Several case reports patients develop MAS after COVID-19 vaccine [74,75]. Frédéric reported on the case of a 20-year-old woman diagnosed with adult-onset Still's disease (AOSD), who experienced a macrophage activation syndrome (MAS) six days post-

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administration of her initial dose of the BNT162b2 COVID-19 vaccine, with remarkably elevated ferritin levels reaching 136,680 μg/l [11].

Ongoing clinical trials and reported case studies provide critical evidence for the potential link between mRNA vaccines and various CTDs.

6. Management and Prevention Strategies

Effective management and prevention strategies are essential for CTD patients who receive vaccinations, including careful risk assessment and close monitoring. Current vaccination advice and guidelines aim to minimize the risks while ensuring the benefits of vaccination.

At the time of immunization, a patient treated with low-dose hydroxychloroquine (HCQ) was found to be beneficial both for active therapy as well as for prevention of SLE exacerbations. Therefore, appropriately administered immunomodulatory therapy at the time of immunization may offer protection to patients at high risk of adverse reactions following immunization [76].

Vaccine surveillance registers are recommended to track the safety, effectiveness, and real-world performance of vaccines [77]. A Worldwide Registration System is a global registration system used to collect and analyze vaccine administration data from different countries. Its key feature is its broad coverage, allowing for data aggregation and analysis across regions and nations. An example is the global vaccine safety monitoring platform (GVSI) coordinated by the World Health Organization (WHO). Local Active Surveillance Registries are proactive monitoring systems that operate within specific geographic areas, collecting detailed data through regular and continuous tracking to monitor vaccine safety. These systems are highly targeted and typically conduct detailed data collection and analysis in one or a few specific locations. Examples include the Vaccine Safety Datalink (VSD) and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM). Additionally, some existing systems help customize the safest and most effective vaccines at individuals and populations level [78], such as Vaccine Adverse Event Reporting System (VAERS), a national reporting system designed to detect safety concerns in licensed vaccines at an early stage. The Clinical Immunization Safety Assessment (CISA) Project comprises vaccine safety experts from the Centers for Disease Control and Prevention (CDC), research centers, and other collaborators. CISA offers consultations to U.S. healthcare providers with complex questions about vaccine safety for individual patients in the United States [79]. V-safe allows individuals to report their conditions to CDC after receiving the COVID-19 or RSV vaccine. V-safe health check-ins are brief and maintained in a confidential manner [80]. This strategy could aid in identifying genetic markers for populations at high risk of autoimmune reactions following vaccination and contribute to the development of more effective, safe, and personalized vaccines [22].

7. Future Perspectives

Further research is needed to fully understand the precise mechanisms of mRNA vaccine-induced CTD and to develop more targeted study designs. To establish a clear causal relationship between vaccination and CTDs, we propose conducting cohort studies involving participants with known autoimmune predispositions. Longitudinal data collection, biobanking, and genetic analysis will be crucial for differentiating between natural disease progression and vaccine-related onset. Animal studies can further elucidate immune mechanisms in a controlled environment.

Equally important, proposed vaccination guidelines, such as those for patients with positive antinuclear antibody tests or specific rheumatic disease genes, will be crucial in guiding future practices, particularly in individuals who may have a genetic predisposition exacerbated by environmental triggers. Individualized guidelines are essential for ensuring patient safety in cases of positive ANA tests of rheumatic diseases[81] or specific genetic markers such as ECM genes associated with connective tissue disorders [82]. Customized vaccination protocols, including the monitoring of antibody and autoimmune marker levels.

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8. Conclusions

The advent of mRNA vaccines has revolutionized public health by providing rapid, effective protection against infectious diseases, notably during the COVID-19 pandemic. However, the connection between COVID-19 immunization and connective tissue diseases (CTDs) is still unclear, with researchers proposing various hypothetical mechanisms to explain a potential link. This review analyzes current evidence, highlighting the complex interplay between CTDs and vaccination and stressing the need for meticulous risk assessment and monitoring. Findings suggest that while mRNA vaccines are beneficial, targeted research and risk assessments are crucial, especially for individuals with pre-existing autoimmune disorders. Potential mechanisms linking mRNA vaccines to CTDs include PAMP-induced immune responses, TLR7/8 and TLR9 interactions, and activation of self-reactive B cells.

Integrating clinical case studies into the context of vaccine-induced CTDs provides concrete examples of mRNA vaccines' impacts on autoimmune conditions, offering empirical insights. Suggested guidelines for vaccinating high-risk individuals, such as those with positive antinuclear antibody (ANA) tests or specific rheumatic disease genes, highlight the importance of individualized approaches for safety and efficacy.

Establishing robust vaccine surveillance systems, like global registration platforms and local active surveillance registries, is essential for monitoring vaccine safety and effectiveness. These systems can help identify genetic markers associated with heightened risk of autoimmune reactions post-vaccination, contributing to the development of safer, more personalized vaccines.

This review underscores the need for continued research and tailored guidelines to optimize mRNA vaccines' benefits while minimizing risks for patients with CTDs. The insights provided will be valuable for researchers, healthcare providers, and policymakers in immunology, rheumatology, and public health, addressing knowledge gaps to ensure the safe and effective use of mRNA vaccines in diverse populations.

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