

*Review Article*

## Exploring the Safety and Effects of COVID-19 Vaccination in Patients with Autoimmune Disease

Kirttna Solai Vairavan<sup>1</sup>, Loh Teng-Hern Tan<sup>1,2</sup>, Jodi Woan-Fei Law<sup>1</sup>, Priyia Pusparajah<sup>1</sup>, Vengadesh Letchumanan<sup>1\*</sup>

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<sup>1</sup>Novel Bacteria and Drug Discovery Research Group (NBDD), Microbiome and Bioresource Research Strength (MBRS), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, 47500, Selangor Darul Ehsan, Malaysia. kvai0001@student.monash.edu (KSV) loh.teng.hern@monash.edu (LT-HT); jodi.law1@monash.edu (JW-FL); priyia.pusparajah@monash.edu (PP)

<sup>2</sup>Clinical School Johor Bahru, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Johor Bahru 80100, Malaysia

\*Corresponding author: Vengadesh Letchumanan, Novel Bacteria and Drug Discovery Research Group (NBDD), Microbiome and Bioresource Research Strength (MBRS), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, 47500, Selangor Darul Ehsan, Malaysia; vengadesh.letchumanan1@monash.edu (VL)

**Abstract:** The COVID-19 pandemic has quickly become the most significant public health phenomenon, effectively eclipsing the H1N1 and Ebola crises that came before it. It can spread rapidly and has caused the death and disability of many worldwide. Vaccines are our most effective line of defense against the rapidly spreading and mutating virion. Still, there is significant vaccine hesitancy among those with autoimmune conditions who fear the vaccine may cause them more harm than good. This scoping review explores the safety, outcomes, and effects of COVID-19 vaccines in autoimmune patients. Online databases; Pubmed, Ovid Medline, and Scopus were used to search published literature evaluating the effectiveness and side effects of COVID-19 vaccines in patients with autoimmune conditions. The search results were limited to 4 distinct autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and myasthenia gravis). Thirty-seven studies were retrieved and assessed on the safety, effects, and outcomes of COVID-19 vaccination in patients with the chosen autoimmune conditions. Overall, the risk of flares and the development of severe side effects after vaccination was low. Most autoimmune patients showed a good antibody response to vaccination, especially after the second dose. This review provides a favorable impact of vaccination in patients with autoimmune conditions.

**Keywords:** COVID-19; vaccines; autoimmune patients; rheumatoid arthritis; systemic lupus erythematosus; psoriasis; myasthenia gravis

## 1. Introduction

The COVID-19 outbreak, which emerged in China late in 2019, has since quickly spread worldwide to become the most infamous health crisis of our time<sup>[1–8]</sup>. World Health Organization (WHO) declared COVID-19 a pandemic caused by severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2)<sup>[9–11]</sup>. COVID-19 has caused high morbidity and mortality, socioeconomic burden, and pressure on healthcare systems. All these factors can only be reduced by achieving herd immunity against COVID-19 thru vaccination. The virus attacks the host respiratory system and causes flu-like symptoms upon exposure. The disease manifests with a mild respiratory infection, cough, headache, and fatigue at the early stage<sup>[12]</sup>. Still, as the disease progresses, it may lead to acute respiratory failure with severe complications such as multiorgan failure<sup>[13–15]</sup>. There is a greater risk of infection among the elderly, patients with autoimmune diseases, and immunocompromised patients<sup>[15,16]</sup>. Given the severity of illness in autoimmune patients, clinicians and healthcare professionals have been advocating the importance of being vaccinated.

Pharmaceutical companies raced against time to develop COVID-19 vaccines. The most common COVID-19 vaccine platforms that are currently in use include inactivated virus vaccines (Sinovac, Covaxin, Sinopharm), mRNA (Pfizer-BioNTech and Moderna), and adenovirus vector (AstraZeneca, CanSino, Sputnik V)<sup>[17–19]</sup>. These vaccines have produced robust humoral responses and presented good outcomes in most vaccinated populations<sup>[20]</sup>. Vaccinations help to protect the host by creating an antibody response without having the person experience severe illness or post-COVID-19 conditions.

Existing literature suggests that autoimmune patients are at high risk of contracting severe COVID-19 and emphasizes the need for vaccination<sup>[21,22]</sup>. However, hesitancy has increased in patients with autoimmune diseases since there is limited data on the safety of COVID-19 vaccines in autoimmune patients. Studies comparing the consequences of different vaccine types between patients and healthy controls are also unavailable<sup>[21]</sup>. In addition, the disease onset and vaccination can trigger flares. Flares are cumbersome to the patient and would thus discourage them from taking the vaccine; the simple possibility is enough to make them wary of the vaccine roll-out. On top of that, many patients with autoimmune conditions are also on immunosuppressants to keep their conditions at bay. This immunosuppressed state may impair their ability to mount an immune response and even increase their risk of vaccine side effects.

Localized pain on the injection site, fever, body aches, and headaches are among the typical COVID-19 vaccine side effects that people have reported worldwide<sup>[23]</sup>. Esquivel-Valerio and colleagues studied the impact of six different COVID-19 vaccines on patients with autoimmune rheumatic diseases. They found that localized pain, fatigue, headache, and muscle ache are the most prevalent adverse effects in this group of patients<sup>[24]</sup>. It is also reported hepatitis B, and influenza vaccines trigger the flares of autoimmune diseases by molecular mimicry inducing autoimmunity<sup>[25–27]</sup>. This review explores the safety, outcomes, and effects of COVID-19 vaccines in autoimmune patients.

## 2. Methodology

Three databases (PubMed, Ovid Medline, and Scopus) were searched using search keywords ‘*rheumatoid arthritis, systemic lupus erythematosus, psoriasis, myasthenia gravis, and COVID-19 vaccines*’ to retrieve studies evaluating the effectiveness and side effects of COVID-19 vaccines in patients with autoimmune conditions. This review search was focus to four distinct autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and myasthenia gravis). The included studies were published in English between January 2020 and January 2022. Conference proceedings, editorials, dissertations, literature reviews, commentaries, and conference abstracts were excluded. Articles were then screened using Covidence based on the inclusion and exclusion criteria (Table 1).

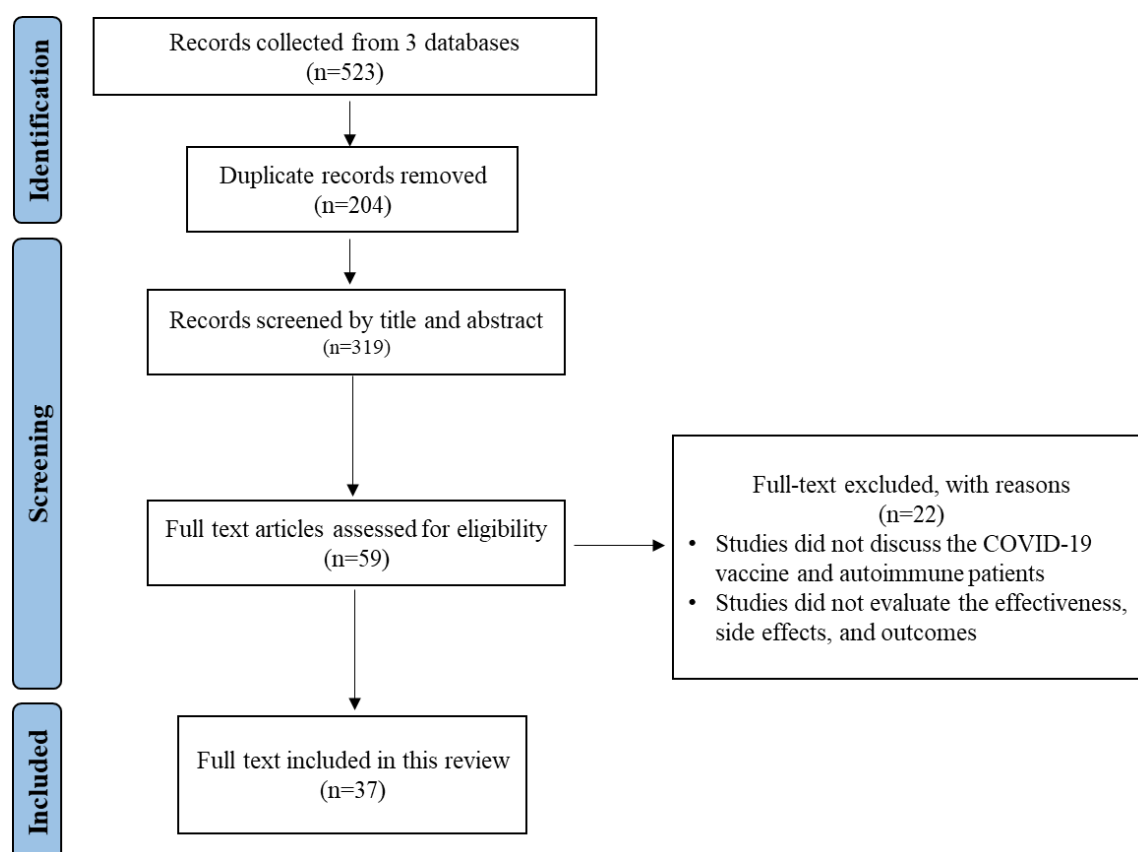
**Table 1.** The inclusion and exclusion criteria.

Criteria	Specific criteria
Inclusion	<ul style="list-style-type: none"> <li>• Studies evaluate the effectiveness and side effects of COVID-19 vaccines in patients with autoimmune diseases.</li> <li>• Population: Patients with rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and myasthenia gravis.</li> </ul>
Exclusion	<ul style="list-style-type: none"> <li>• Studies related other than COVID-19 vaccines and autoimmune diseases.</li> <li>• Conference proceedings, commentaries, editorials, dissertations, literature reviews, and conference abstracts.</li> </ul>

## 3. Results

### 3.1. Search Results

Three electronic databases were chosen to conduct the search process with search terms. The search retrieved 523 studies from PubMed, Ovid Medline, and Scopus. A total of 204 duplicates were removed from the resulting studies, and 319 articles were kept for the title and abstract screening. Based on the inclusion and exclusion criteria, 59 full-text articles met the eligibility criteria, and 260 articles were excluded. In the end, 37 articles were chosen and included in this review. The scoping review process is shown in Figure 1.



**Figure 1.** The PRISMA flowchart

### 3.2. Characteristics of Included Studies

Of the 37 articles reviewed, the findings were divided into 15 studies on rheumatoid arthritis, 11 studies about psoriasis, seven on systemic lupus erythematosus (SLE), and four on myasthenia gravis.

#### 3.2.1. Rheumatoid arthritis

Of the 15 Rheumatoid arthritis studies, ten evaluated the administration of mRNA vaccines; two discussed mRNA vaccines and viral vector vaccines; one looked at mRNA vaccines and inactivated vaccines; the remaining two explored inactivated either alone or with viral vector vaccines (Table 2). All the study participants were adults (>18 years old). The number of participants varied from 5493 patients in one of the cohort studies to 1 patient in the case report. Spinelli *et al.*<sup>[28]</sup> and Geisen *et al.*<sup>[29]</sup> found that the vaccine side effects in those with rheumatoid arthritis were similar to those without autoimmune conditions. Local injection site pain was the most common complaint by the patients. Furer and colleagues studied the flare of herpes zoster following BNT162b2 mRNA COVID-19 vaccination in patients with rheumatic diseases. The study found six patients with AIIRD (autoimmune inflammatory rheumatic diseases) developed mild herpes zoster after the first dose of the vaccine and were given oral antiviral therapy with a resolution of herpes zoster symptoms. Five patients completed the second COVID-19 vaccine dose without other adverse effects.

They concluded that further studies are required to assess the safety of the mRNA-based COVID-19 vaccines in patients with AIIRD and the reactivation of zoster<sup>[30]</sup>.

**Table 2.** Summary of studies related to rheumatoid arthritis (RA).

Study	Vaccine given	Population	Therapies Used	Response
Cherian <i>et al.</i> <sup>[31]</sup>	ChAdOx1 nCoV-19 (Viral vector vaccine) or BBV152 (Inactivated vaccine)	724 patients with rheumatoid and musculoskeletal disease (RMD). 523 had autoimmune rheumatic disease (AIRD) and 201 had non-AIRD	In AIRD group, Steroids ( $n=97$ ) csDMARDs ( $n=468$ ) BioDMARDs ( $n=27$ )	436 (60.22%) participants had at least one adverse effect (AE). Four patients reported a flare of arthritis that resolved in 5 days.
Geisen <i>et al.</i> <sup>[29]</sup>	BioNtech/Pfizer or Moderna (mRNA vaccine)	42 healthy controls and 26 patients with chronic inflammatory disease (CID)	In CID group, BioDMARDs ( $n=20$ ) csDMARDs ( $n=8$ ) Steroids ( $n=7$ )	SARS-CoV-2 antibodies and neutralising activity detected in all participants. No severe adverse effects were observed.
Ferri <i>et al.</i> <sup>[32]</sup>	BNT162b2 and mRNA-1273 (mRNA vaccines)	478 unselected ASD patients (mean age $59 \pm 15$ years), namely 101 RA, 38 SLE, 265 SSc, and a miscellanea of 74 systemic vasculitis. The control group included 502 healthy individuals.	In ASD group, Glucocorticoids, Mycophenolate-mofetil, Rituximab	Increased prevalence of non-response to vaccines was observed in patients with ASD-related interstitial lung disease and those treated with glucocorticoids, mycophenolate-mofetil, or rituximab.
Furer <i>et al.</i> <sup>[30]</sup>	BNT162b2 (mRNA vaccination)	491 patients with rheumatoid disease and 99 healthy controls	Not available	Prevalence of herpes zoster was 1.2% in patients with the rheumatic disease compared with none in controls.

Study	Vaccine given	Population	Therapies Used	Response
Watah <i>et al.</i> <sup>[33]</sup>	ChAdOx1 nCoV-19 (viral vector vaccine), BNT162b2 (mRNA vaccine), or mRNA-1273 (mRNA vaccine)	Collection of cases ( $n=27$ , 17 flares, and 10 new-onset IMID) in patients with IMID in 28 days following COVID vaccination	Mixed group including biologics, steroids, and DMARDs	Flares were temporally associated with vaccination, but no way to determine causation.
Iancovici <i>et al.</i> <sup>[34]</sup>	BNT162b2 (mRNA vaccine)	12 rheumatoid arthritis patients who were treated with Janus kinase inhibitors. 26 healthy controls.	Janus kinase inhibitors	Reduced levels of anti-spike antibodies in patients taking Janus kinase inhibitors. B cell responsiveness to SARS-CoV-2 in patients with rheumatoid arthritis was low.
Simander <i>et al.</i> <sup>[35]</sup>	mRNA vaccine	53 patients with RA, 46 patients with spondyloarthritis and 169 healthy participants	DMARDs (disease-modifying anti-rheumatic drug)	Seroconversion rates after 1st immunisation was 54% in patients with inflammatory arthritis compared with 98% in control group. Seroconversion was 100% in both groups after second dose. Seroconversion was reduced in individuals receiving DMARD therapy.
Spinelli <i>et al.</i> <sup>[28]</sup>	mRNA vaccine	126 patients with RMD and 85 controls.	70 patients were taking immunosuppressants and/or biologics.	5 patients had confirmed arthritis flares. Most common side effect was injection site pain.

Study	Vaccine given	Population	Therapies Used	Response
			30 patients were taking hydroxychloroquine.	
Li <i>et al.</i> <sup>[36]</sup>	CoronaVac, BNT162b2	5493 patients with rheumatoid arthritis	Immunosuppressants, corticosteroids, NSAIDs, cs/bDMARDS	No significant link between rheumatoid arthritis flares and vaccination.
Lukaszuk <i>et al.</i> <sup>[37]</sup>	BNT162b2 vaccine (mRNA vaccine)	50-year-old female with rheumatoid arthritis	Methotrexate	Antibody levels kept increasing but at a lower rate than in patients not receiving immunomodulatory therapies.
Madelon <i>et al.</i> <sup>[38]</sup>	mRNA vaccine	37 patients with rheumatoid arthritis (RA) or multiple sclerosis (MS), 22 healthy controls	Rituximab in patients with RA and Ocrelizumab in patients with MS	Patients on anti-CD20 treatment can mount potent T-cell responses to mRNA COVID-19 vaccines.
Picchianti-Diamanti <i>et al.</i> <sup>[39]</sup>	BNT162b2 vaccine (mRNA vaccine)	167 controls and 35 rheumatoid arthritis patients	CTLA-4-inhibitors, IL-6 inhibitors	Sufficient immune responses induced by the COVID-19 mRNA vaccine were present in majority of RA patients who underwent temporary suspension of immunosuppressive treatment during vaccination.
Schreiber <i>et al.</i> <sup>[40]</sup>	BNT162b2 and mRNA-1273 (mRNA vaccines)	243 patients with rheumatoid arthritis, spondyloarthritis or psoriatic arthritis	cs/bDMARDS	Seventy-two patients (32%) had an insufficient IgG response. The median IgG level in patients treated with cs/bDMARD

Study	Vaccine given	Population	Therapies Used	Response
				combination therapy was significantly lower compared to patients without any DMARD treatment.
Schumacher <i>et al.</i> <sup>[41]</sup>	BNT162b2 (mRNA vaccine), mRNA-1273 (mRNA vaccine), AstraZeneca/Oxford (viral vector vaccine), Ad26.COV2.S (viral vector vaccine)	102 patients with idiopathic rheumatic disease on treatment with Rituximab	Rituximab (RTX) <ul style="list-style-type: none"> <li>• Prednisone (<i>n</i>=81)</li> <li>• Methotrexate (<i>n</i>=23)</li> </ul>	65 patients (64%) showed a negative antibody level after vaccination.
Seyahi <i>et al.</i> <sup>[42]</sup>	CoronaVac (inactivated vaccine)	82 hospital workers with RMD and 300 controls.	Rituximab (RTX), DMARDs	Among RMD patients, those using immunosuppressive drugs were significantly less likely to have detectable antibodies than those of treatment.

### 3.2.2. Psoriasis

Of the 11 psoriasis studies, ten focused on mRNA vaccines, and one focused on inactivated vaccines (Table 3). One of the above studies included results from patients taking viral vector vaccines, but no studies focused on that subset of vaccines. Participants were all adults above 18, and the study population ranged from 1 to 436. Five studies focused on the immune response following vaccination, while the remaining 6 explored the risk of exacerbation following anti-COVID-19 vaccination. No studies looked specifically into the side effects of vaccination in psoriatic patients. Generally, the risk of psoriatic flare following vaccination seems very low, but it can happen. Usually, it is not severe and easily managed. The outcomes of vaccination are promising; most patients can mount a detectable immune response even if it is not as significant as that seen in the normal population. Methotrexate has shown itself to reduce the immune response produced by the body.



**Table 3.** Summary of studies related to psoriasis.

Study	Vaccine given	Population	Therapies Used	Response
Haberman <i>et al.</i> <sup>[43]</sup>	BNT162b2 (mRNA vaccination)	Patients with IMID ( $n=51$ ). 24 subjects had psoriasis, 22 had rheumatoid arthritis and 5 had other IMIDs. Healthy subjects as controls ( $n=26$ ). A second independent a validation cohort of controls ( $n=182$ ) and patients with IMID ( $n=31$ )	In IMID group, Methotrexate Anticytokine biologics TNF inhibitors In controls, Nil	Those patients with IMID on background methotrexate ( $n=45$ ) achieve an adequate response in only 62.2% of cases. Patients with IMID on methotrexate do not demonstrate increased CD8+ T-cell activation after vaccination.
Huang <i>et al.</i> <sup>[44]</sup>	Moderna mRNA-1273, AstraZeneca-Oxford AZD1222	32 unimmunized controls and 51 vaccinated psoriasis patients	49 patients with psoriasis were on biologics.	Fifteen episodes of exacerbation in the vaccinated group, which is higher than two episodes in the control group.
Skroza <i>et al.</i> <sup>[45]</sup>	mRNA vaccine	436 patients with moderate-severe psoriasis, both male and female, in treatment with biologics	Biologics.	None of the vaccinated patients in concomitant therapy with anti-psoriatic immunomodulating agents developed adverse events (ADR).
Musumeci <i>et al.</i> <sup>[46]</sup>	Pfizer mRNA BNT162b2 (mRNA vaccine) and Moderna M1273 (mRNA vaccine)	50 patients with stable plaque psoriasis	24 patients were treated with anti-TNF, 14 with anti-IL 17, 7 with anti-IL 12-23 (ustekinumab), and 5 with anti-IL 23 (guselkumab).	None of the patients experienced any side effects or a psoriatic flare. Only one patient treated with infliximab reported an exacerbation of psoriasis after the vaccine.
Venerito <i>et al.</i> <sup>[47]</sup>	BNT162b2 vaccine (mRNA vaccine)	40 patients with psoriasis	TNF inhibitors	Continuing TNFi throughout the vaccination did not hamper immunogenicity.

Study	Vaccine given	Population	Therapies Used	Response
Wei <i>et al.</i> <sup>[48]</sup>	Moderna mRNA-1273 (mRNA vaccine)	8 patients	Biologics	7 patients experienced an acute exacerbation of psoriasis and 1 had new-onset psoriasis.
Lopez <i>et al.</i> <sup>[49]</sup>	Pfizer (mRNA vaccine)	58-year-old man with a history of psoriasis 4 days post-second dose of vaccine	Not available	Acute exacerbation of psoriasis.
Mahil <i>et al.</i> <sup>[50]</sup>	BNT162b2 (mRNA vaccine)	82 participants after second vaccination.	Methotrexate ( <i>n</i> =14), TNF-inhibitors ( <i>n</i> =19), IL-7 inhibitors ( <i>n</i> =14), IL-23 inhibitors ( <i>n</i> =20)	All participants had detectable spike-specific antibodies following the second dose, and all groups demonstrated similar neutralising antibody titres against wild-type, alpha, and delta variants. By contrast, a lower proportion of participants on methotrexate had detectable T-cell responses following the second vaccine dose, compared with controls.
Mahil <i>et al.</i> <sup>[51]</sup>	BNT162b2 (mRNA vaccine)	121 participants were enrolled, 84 with psoriasis receiving immunosuppressive treatment and 17 controls.	Methotrexate ( <i>n</i> =17), TNF-inhibitors ( <i>n</i> =27), IL-7 inhibitors ( <i>n</i> =15), IL-23 inhibitors ( <i>n</i> =25)	Seroconversion rates were lower in patients receiving immunosuppressants than in controls, with the lowest rate in that receiving methotrexate.
Onsun <i>et al.</i> <sup>[52]</sup>	CoronaVac (Inactivated vaccine)	A 72-year-old male psoriasis patient 4 days post-vaccination	Not available	Generalised pustular psoriasis flare.
Pavlostsky <i>et al.</i> <sup>[53]</sup>	BNT162b2 (mRNA vaccine)	51 psoriasis patients on treatment with	Systemic immune modifiers,	Forty-nine patients had a positive antibody response.

Study	Vaccine given	Population	Therapies Used	Response
		systemic immune modifiers	especially biologics	

### 3.3.3. Systemic lupus erythematosus (SLE)

Of the 7 SLE studies, 3 were case reports, 2 were cohort studies, and the remaining two were case series and case-control studies (Table 4). Six studies focused on mRNA vaccines alone, and only 1 study focused on mRNA vaccines and viral vector vaccines. There is a distinct lack of studies looking into the effect of viral vector vaccines and inactivated vaccines in patients with SLE. The results of the studies looking at vaccination outcomes in patients with SLE were similar to those found in rheumatoid arthritis and psoriasis. Patients with SLE could produce an immune response to the vaccine, but it was weaker than that seen in healthy controls. Assawaksakul *et al.*<sup>[54]</sup> added on the potency of the booster in stimulating a stronger immune response and suggested that the viral vector vaccine may not be as effective as the mRNA vaccine in patients with SLE. Regarding disease exacerbations, multiple studies found that the vaccination triggers SLE flares but is not severe enough to warrant hospitalization or emergency care. They have commonly identified side effects of the vaccine, including headache, fatigue, muscle pain, and local injection site pain, similar to that seen in non-autoimmune patients.

**Table 4.** Summary of studies related to systemic lupus erythematosus (SLE).

Study	Vaccine Given	Population	Therapies used	Response
Assawasaksakul <i>et al.</i> <sup>[54]</sup>	Pfizer/BioNTech (mRNA vaccine) or ChAdOx1 (viral vector vaccine) booster	8 healthcare workers in Thailand with known SLE who had previously completed the CoronaVac series (2 doses of inactivated vaccine)	Mycophenolate mofetil Azathioprine Calcineurin inhibitor	6 patients had a strong immune response to the booster. 1 patient was heavily immunosuppressed, and the other had taken the viral vector vaccine rather than the mRNA vaccine. During the study period of 2 months, no SLE flares were recorded. Most common side effects reported were

Study	Vaccine Given	Population	Therapies used	Response
				injection site pain, fatigue and fever.
Bartels <i>et al.</i> <sup>[55]</sup>	BNT162b2 (mRNA vaccine)	285 subjects with either SLE or RA. 128 patients with SLE and 154 patients with RA.	Biologics	5 patients had severe adverse events (1.8%). No patients were hospitalized or died. Fatigue, headache, muscle pain and joint pain were the most reported side effects.
Hidaka <i>et al.</i> <sup>[56]</sup>	BNT162b2 (mRNA vaccine)	53-year-old Japanese woman 2 weeks post-second dose of vaccine	Not available.	New Onset Evans Syndrome.
Izmirly <i>et al.</i> <sup>[57]</sup>	BNT162b2 (mRNA vaccine) or mRNA-1273 (mRNA vaccine)	90 SLE patients and 20 healthy controls.	Hydroxychloroquine Prednisone Immunosuppressants (ex. Azathioprine, Mycophenolate Mofetil, Methotrexate, etc.)	SLE patients produced significantly lower antibodies compared to healthy controls. The use of any immunosuppressant or prednisone was associated with decreased vaccine response. Post-vaccination flares occurred in 11.4% of patients, 1.3% were severe.
Joseph <i>et al.</i> <sup>[58]</sup>	Moderna (mRNA vaccine)	54-year-old woman 4 days post-second dose of vaccine	Mycophenolate Mofetil	Subacute cutaneous lupus erythematosus flare.
Zavala-Flores <i>et al.</i> <sup>[59]</sup>	BNT162b2 (mRNA vaccine)	100 patients with SLE	Hydroxychloroquine Azathioprine	27 patients experienced SLE flares. The

Study	Vaccine Given	Population	Therapies used	Response
				predominant type of flare was arthritis, followed by dermal manifestations. Pain at the inoculation site was the most common side effect. All side effects were mild.
Nune <i>et al.</i> <sup>[60]</sup>	BNT162b2 (mRNA vaccine)	24-year-old previously well male 2 weeks post-second dose of vaccine	Nil	New onset of SLE

### 3.3.4. Myasthenia gravis

Of the 4 Myasthenia gravis studies, 1 was a single center case series, while the remaining 3 were single case reports (Table 5). The case series was conducted for one month and looked at 22 participants registered on an MG database. All 3 case reports looked at the elderly population (age > 60 years old). The participants of the case series ranged from 25 to 73 years old. Three studies looked at the worsening/onset of myasthenia gravis symptoms<sup>[61–63]</sup>, whereas one looked at the immune response elicited by vaccination<sup>[64]</sup>. Tagliaferri *et al.*<sup>[62]</sup> and Chavez *et al.*<sup>[63]</sup> reported a myasthenia gravis crisis in a patient following a second vaccination dose. These two articles suggest that COVID-19 vaccination may be a potential trigger for myasthenia gravis, especially the second dose. Plymate and colleagues showed that immune response was minimal in a myasthenia gravis patient after receiving two doses of the mRNA vaccine, but she then demonstrated an excellent response to the third dose given 85 days later<sup>[64]</sup>. This suggests that patients with myasthenia gravis may require booster shots to mount an adequate immune response. Ruan *et al.*<sup>[61]</sup> reported a retrospective case series demonstrating the safety of inactivated vaccines in patients with myasthenia gravis, defined as mild/absent worsening of symptoms.

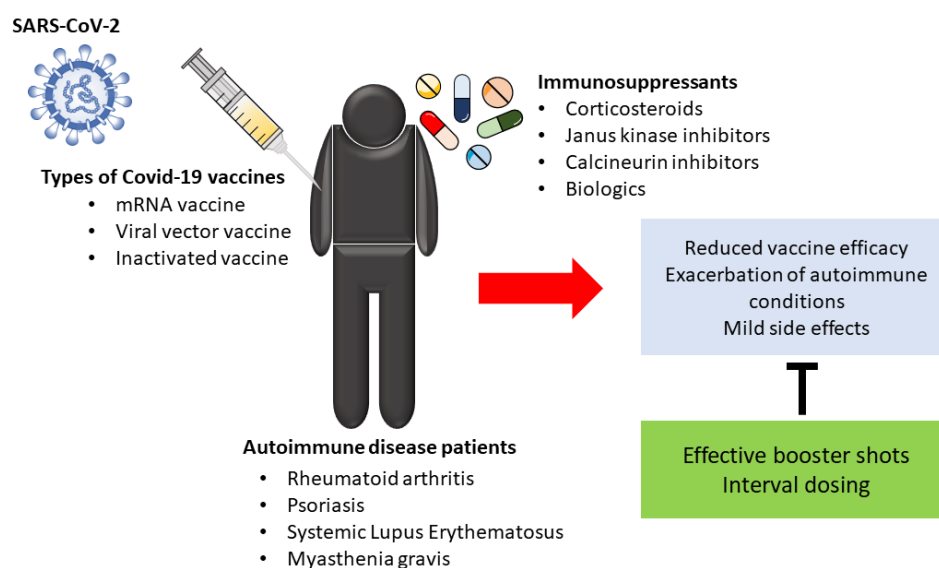
**Table 5.** Summary of studies related to myasthenia gravis.

Study	Vaccine Given	Population	Therapies used	Response
Ruan <i>et al.</i> <sup>[61]</sup>	CoronaVac vaccine (Inactivated vaccine)	22 patients with MG receiving the COVID-19 vaccine. 10 have Ocular MG and	Azathioprine (n=12) Mycophenolate mofetil (n=3) Steroid and Azathioprine (n=3)	20 patients did not have any worsening of MG symptoms.

Study	Vaccine Given	Population	Therapies used	Response
		12 have generalized MG.	None ( $n=4$ )	2 patients reported mild MG symptoms worsening.
Tagliaferri <i>et al.</i> <sup>[62]</sup>	Moderna COVID-19 vaccine (mRNA vaccine)	A 77-year-old man with a five-year history of MG 1 week post-second dose of vaccine	Prednisone and pyridostigmine	Myasthenia gravis crisis
Plymate <i>et al.</i> <sup>[64]</sup>	BNT162b2 COVID-19 vaccine (mRNA vaccine)	A 74-year-old woman diagnosed with generalized MG 44 months before the initial SARS-CoV-2 vaccination	1440 mg mycophenolate sodium and prednisone 11 mg daily.	2 doses of mRNA vaccination failed to elicit detectable circulating vaccine-specific IgG or IFN- $\gamma$ T cell responses.
Chavez <i>et al.</i> <sup>[63]</sup>	BNT162b2 COVID-19 vaccine (mRNA vaccine)	82-year-old man, two days post-second dose of vaccine	Nil.	New late-onset myasthenia gravis.

#### 4. Discussion

There is a distinct lack of studies focusing on viral vectors and inactivated vaccines in these four different autoimmune disease patients. Each vaccine has a different mechanism of action and, therefore, will have other interactions and effects on the human body, even if they aim to accomplish the same outcome. As such, it isn't easy to conclude the outcomes, safety, and side effects of the vaccines (Figure 2).



**Figure 2.** The outcome, side-effect and safety of COVID-19 vaccine on autoimmune disease patients.

#### 4.1. Outcomes

Overall, most autoimmune patients can mount a significant immune response to the vaccine even if the potency is less than that of healthy participants. Several studies also seem to show a reduced response after the first dose but a much better response after the following doses. For example, a study by Simander *et al.*<sup>[35]</sup>, wherein the seroconversion rate after the first dose was only 54% amongst participants with rheumatoid arthritis as opposed to 98% in the control group, but the seroconversion rates in both groups were 100% after the second dose. A case series by Assawaksakul *et al.* that looks at 8 SLE patients found a much stronger immune response in patients following a booster dose of the vaccine<sup>[54]</sup>. The case report by Plymate *et al.* depicted an older woman who received two doses of the Pfizer/BioNTech vaccine but mounted a negligible immune response following vaccination. She then took a third booster dose 85 days later and showed significant improvement<sup>[64]</sup>. These studies indicate that patients with autoimmune conditions may benefit more from multiple doses of vaccination than the general population.

As mentioned above, taking Rituximab and DMARDs reduces the immune response in patients with rheumatoid arthritis. Schreiber *et al.*<sup>[40]</sup> identified a 32% non-response rate in patients taking DMARDs to manage their arthritis. Picchianti-Diamanti *et al.*<sup>[39]</sup> found that suspending the medication during vaccination allowed all patients in their study to develop a strong and sufficient immune response to the vaccine. Patients are taking their medication for a reason. While we want them to get the most out of their vaccination, any decision to stop or modify treatment should be discussed and decided with the advice and guidance of a clinician lest they end up with chronic pain or severe flares.

Rituximab is a form of B-cell-depleting therapy. The study by Madelon et al. found that patients taking Rituximab could still produce good immune responses<sup>[38]</sup>. Still, the study by Schumacher *et al.*<sup>[41]</sup> found that 64% of patients taking Rituximab were vaccine non-responders. Schumacher's study had a larger population of 102 participants and found a correlation between the antibody response elicited and the interval since Rituximab administration<sup>[41]</sup>. Interval dosing may allow clinicians to optimize vaccine outcomes without stopping the medication that keeps the patient's arthritis in remission. However, there is still a small risk of non-response, which should be considered. Since a booster dose seems to offer some benefit in improving outcomes in patients with SLE and myasthenia gravis, it can be considered to optimize vaccine efficacy in patients with Rheumatoid arthritis as well, barring any contraindications.

Prednisone, Janus kinase inhibitors, and Methotrexate hamper the immune response produced by the vaccine, but they don't seem to cause non-response. As such, it is still beneficial for patients taking these medications to take the anti-COVID-19 vaccine. Venerito et al. find that TNF inhibitors do not impair the vaccine's efficacy<sup>[47]</sup>. A review by Wack et al. finds that TNF inhibitors may still cause some impairment compared to healthy controls, and therefore the immune response may still be less robust<sup>[65]</sup>. Interval dosing or suspension of the medication may play a part in all autoimmune patients taking immunosuppressants. Still, the decision should be on a case-by-case basis and with the advice and guidance of a clinician.

#### 4.2. Safety

Myasthenia gravis is an autoimmune neuromuscular junction disorder caused by antibodies to the acetylcholine receptor<sup>[66]</sup>. It causes fatigable weakness, most evident after repeated muscle use or with the day's progression. Exacerbations of the condition are usually caused by infection, especially since the advent of this pandemic. Since infection with SARS-CoV-2 can cause a worsening, it warrants the suggestion that vaccination against SARS-CoV-2 could also trigger an exacerbation. Studies suggest vaccination is unlikely to trigger an exacerbation, with only 2 participants reporting slight worsening symptoms that quickly resolved within a few days<sup>[61–63]</sup>. More studies with bigger sample sizes must be conducted before establishing a solid link between symptom flares and vaccination. There is also a lack of studies looking into different types of vaccines and their potential link to myasthenia gravis exacerbations.

Spinelli et al. studied 126 participants, and five rheumatoid arthritis patients had arthritic flare after vaccination<sup>[28]</sup>. Thankfully, the flares were self-limiting and resolved within a few days with some symptomatic management. The study by Izmirly et al. looked at the risk of SLE flares and found the risk to be about 11.4%, only 1.3% were severe, and none were so severe that they required hospital care<sup>[57]</sup>. Huang and Tsai studied 32 unimmunized psoriatic patients and 51 immunized patients. They reported that the immunized group patients presented exacerbations compared to the non-immunized group<sup>[44]</sup>. The mean Psoriatic Arthritis Severity Index (PASI) score also increased from 3.1



to 8 following vaccination. As such, there is undoubtedly some correlation between the vaccine and autoimmune conditions worsening or fluctuating across the board. Flares can be triggered by various factors, from infections to stress to poor medication adherence. Hence, it is difficult to determine whether a flare has resulted from vaccination, disease progression, or perhaps even a combination.

Overall, we can see that the risk of disease flares post-COVID-19 vaccination is significant. Still, the risk of a flare severe enough to require hospitalization or emergency care remains rare and almost exclusive to the odd case report. Most of the flares are mild and self-limiting. Given the increased risk of morbidity and mortality in patients with comorbidities, it may be better for autoimmune patients to be vaccinated rather than remain unvaccinated. The final decision should be discussed and well-thought-out, considering the patient's risk factors and disease severity. For patients with mild autoimmune conditions in remission, getting vaccinated is likely the lesser of two evils.

#### 4.3. Side Effects

Herpes zoster virus activation was identified as a potential side effect of vaccination in patients with rheumatoid arthritis by Furer *et al.*<sup>[30]</sup>. This study documents six patients who developed their first episode of herpes zoster shortly after vaccination. The prevalence amounted to roughly 1.2% in patients with autoimmune rheumatic conditions as opposed to none in the healthy controls. Herpes Zoster viral activation has been reported in connection to other vaccines, such as trivalent influenza, hepatitis A, and rabies vaccines. Potential mechanisms that might explain the link between mRNA-COVID-19 vaccination and herpes zoster reactivation are related to the stimulation of innate immunity through toll-like receptors (TLRs) by mRNA-based vaccines. TLR signaling has been implicated during the reactivation of herpesviruses, a process essential for these viruses to maintain themselves in the host. TLRs are much more highly expressed in patients with rheumatic disease compared to the general population. This might be why the prevalence of herpes zoster activation following vaccination is much higher in this group compared to the controls.

Hidaka *et al.* document a case of Evans Syndrome following COVID-19 vaccination<sup>[56]</sup>. Evans syndrome, a rare condition characterized by the coexistence of autoimmune hemolytic anemia (AHA) and Idiopathic Thrombocytic Purpura (ITP), is associated with SLE. Interestingly, a case of Evans Syndrome following the influenza vaccine has also been reported. Looking at this, we can conclude that an overactive immune response following vaccination is the most likely trigger causing these SLE patients to progress to Evans Syndrome. It is rare, and there has only been one case so far, but it is worth keeping in mind.

Geisen *et al.* discussed side effects in vaccinated patients with chronic autoimmune conditions, but the side effects identified are quite similar to those seen in the general population; headache, malaise, body aches, injection site pain, fever, etc.<sup>[29]</sup>. A few other studies in this review have come to a similar conclusion. As mentioned, there is a lack of

studies looking into specific side effects elicited by vaccination in patients with myasthenia gravis and other autoimmune conditions. It would be essential to establish if there are any condition-specific side effects that clinicians should investigate when counseling these patients on vaccination.

## 5. Conclusions

With COVID-19 vaccines becoming widely available and the pandemic once again proving itself to be more resilient than the pandemics that came before it, clinicians need to be prepared to discuss the risks and benefits of vaccination with their autoimmune patients. Based on the information available, we can deduce that the benefits of vaccination in this population group still outweigh the risks and severe complications are rare if present. Neither an autoimmune condition nor any concurrent treatment is a contraindication for the vaccination, but immunosuppressants have shown to reduce the vaccine's efficacy. This can be countered by interval dosing or temporary suspension of the medication, but these are not solutions that would work for everyone. A third vaccination dose to boost immune response appears safe and effective. The decision should be made after viewing each patient as a whole and considering their needs and wants, the severity of their condition, and any limitations they may have. The decision to be vaccinated should not be rushed, especially if patients are hesitant. Patients should be monitored for any undesirable side effects and be able to return to the hospital if they face any severe adverse events. It is also essential that more studies should be carried on to understand better the safety and efficacy of different vaccines in various autoimmune conditions.

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